SKIN DISEASES OF THE DOG AND CAT

Clinical and Histopathologic Diagnosis

Second Edition
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Preface and acknowledgements

Much has occurred in the world of veterinary dermatology and veterinary dermatopathology since the publication of *Veterinary Dermatopathology: A Macroscopic and Microscopic Evaluation of Canine and Feline Skin Disease* in 1992. Since then, four additional world congresses devoted to our specialty discipline, many textbooks, an exponential explosion of publications in refereed journals, and international listservs have added substantially to the body of knowledge.

We elected to change the name of this book to *Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis* to more accurately reflect the scope of the content and the goals of this text. Pathogenesis, clinical and histopathologic description, and clinical and histopathologic differential diagnosis have all been expanded to reflect the growth of our discipline. This book sees the addition of over three dozen new inflammatory diseases alone, as well as numerous neoplastic entities. We also introduce our new co-author, Verena Affolter, the principal author of the chapters describing mesenchymal neoplasia.

As in the first book, inflammatory diseases are grouped by histologic pattern. However, since histopathologic classification usually reflects changes observed clinically, clinically relevant groupings often result. The authors have striven to present information in a diagnostically relevant way for clinicians and pathologists alike. Etiopathogenesis (where known), clinical features, and the histopathologic lesions are described for each disease; methods of optimal biopsy are included for inflammatory diseases as well.

Classification systems for skin tumors were established early in veterinary pathology with sporadic additions of newer entities over the years. Standardized international nomenclature was adopted over 25 years ago, and the long-awaited, revised World Health Organization classifications were published in 1998. The authors are gratified that these new WHO fascicles incorporated many of the changes in terminology proposed in the first edition of *Veterinary Dermatopathology*. New information has warranted the extensive revision and expansion of the chapters covering neoplastic diseases, including the addition of immunohistochemical diagnosis. Much of the enhanced precision with which neoplastic lesions are categorized as to cell of origin or path of differentiation reflects the application of immunohistochemistry for cell markers. This is especially true for single cytokeratin markers and hematopoietic cell markers, many of which have become readily available for use on formalin-fixed tissue only in the past few years. The failure of many immunohistochemical reagents developed for use in humans to stain specimens from other animal species continues to be a source of frustration; the authors are hopeful that the development of additional clones or animal-specific clones will allow continued advances. This new book also expands relevant information on analogous tumors from the human dermatopathology literature. The authors believe that comparative dermatopathology is an invaluable tool for the understanding of pathogenesis, the recognition of new diseases, and the advance of research.

It is well to remember that nomenclature is man-made and diseases are biologic aberrations; there will always be lesions that refuse to fit neatly into any given classification system. Large gaps in our knowledge certainly still exist. It is precisely those gaps that the authors hope will serve as inspiration for current and future colleagues to engage in continued critical thinking, clinical studies, and research in the field of dermatology and dermatopathology.

We owe David Lloyd a special tribute as we consider him to be the initial force behind this book. His constant encouragement and early contact with Blackwell Publishing helped initiate the launch of this project. The authors thank Danny Scott, Bill Miller, and Craig Griffin for providing the 6th edition of *Muller & Kirk's Small Animal Dermatology*. Our task was made much easier by having available such a complete and well-referenced textbook. The authors also thank Michael Goldschmidt and Fran Shofer for providing numeric data in such an easily accessible format in *Skin Tumors of the Dog & Cat*.

As for the first edition, we thank M. Donald McGavin for his role as photomicrographic mentor. His talents are

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unequaled and we can hope to have achieved only some semblance of his proficiency in these pages.

We are indebted to the dermatologists and pathologists from around the world who gave generously of their clinical photographs, tissue blocks, and knowledge on our behalf. We offer special thanks to Thierry Olivry, Jan Declercq, and Ann Hargis for their unselfish gifts of time, case material, and opinions. Thierry Olivry contributed substantially as a reviewer of Chapter 2 in his capacity as expert in the field of autoimmune subepidermal bullous diseases, and Jan Declercq provided excellent clinical photographs for many diseases as well as blocks and slides of uncommon diseases for histopathologic study. We would be remiss not to single out Zeineb Alhaidari, Kim Boyanowski, Didier Carlotti, Jacques Fontaine, Amy Grooters, Richard Malik, Peter Moore, Claudia Nett, Manon Paradis, Helen Power, Michelle Rosenbaum, Danny Scott, Sheila Torres, Carlo Vitale, and Stephen White for their invaluable assistance. In addition, we thank our many other colleagues, too numerous to mention individually, who responded graciously via the VetDerm listserv to our global plea for material about uncommon, rare, or regional skin diseases.

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SECTION ONE

INFLAMMATORY, DYSPLASTIC, AND DEGENERATIVE DISEASES

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PART I

Diseases of the Epidermis

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Chapter 1

Pustular diseases of the epidermis

Pustular diseases are characterized by the formation of pustules in the epidermis and may range from subcorneal to panepidermal. Pustules result from breakdown in the integrity of the keratinocytes by spongiosis or acantholysis, as well as the accumulation of inflammatory cells that migrate from the underlying dermal vasculature in response to superficial infectious agents or epidermal damage. Pustules may be discrete or poorly defined, and may contain neutrophils, eosinophils, and acantholytic or apoptotic keratinocytes.

IMPETIGO

Clinical features (Figures 1.1 and 1.2)

Impetigo is a common canine bacterial skin disease characterized by superficial nonfollicular pustules. As in other forms of canine pyoderma, *Staphylococcus intermedius* is the primary pathogen. Underlying causes usually are not documented in the most common form of impetigo presenting in prepubescent and pubescent dogs. However, inflammation secondary to fecal debris, urine scalding, hair coat matting, and ectoparasitism may enhance susceptibility; poor environmental hygiene or poor nutrition may be contributory. A much less common bullous form of impetigo, sometimes seen in conjunction with underlying immunosuppression, is most frequently observed in older dogs.

The pathogenesis of impetigo may involve staphylococcal exfoliative toxins, as seen in human bullous impetigo (Prevost et al., 2003). These toxins may also be involved in exfoliative staphylococcal infections such as superficial spreading pyoderma (see p. 6). Exfoliative toxins have recently been identified in dogs with staphylococcal pyoderma (Terauchi et al., 2003). Interestingly, desmoglein 1 is the target of both exfoliative toxins of staphylococci and the antibodies of pemphigus foliaceus in humans (Amagai et al., 2000), which explains morphologic similarities in lesions. Other nonstaphylococcal bacteria such as *Pseudomonas* spp., *Enterobacter* spp., and *Escherichia coli* occasionally may be the primary pathogens in bullous impetigo (Ihrke, 1996).

The primary lesions of canine impetigo in young dogs are nonfollicular pustules. Pustular contents vary from creamy white to yellow. Since intact pustules are fragile and rupture readily, yellowish crusts adherent to mildly erythematous papules may be the predominant clinical feature. Peripheral epidermal collarettes may remain as an additional 'footprint' of pyoderma. Follicular pustules have central protruding hairs in contrast to the interfollicular pustules of impetigo; a hand lens is useful for differentiation. Differentiation is important clinically since impetigo responds more readily to therapy than superficial folliculitis. Occasionally, a small number of follicular pustules (folliculitis) may coexist with impetigo; however, either impetigo or folliculitis will predominate clinically. Impetigo is seen predominantly in the glabrous or sparsely-haired regions of the groin and axillae in young dogs. Partial bilateral symmetry is common. Pruritus, if present, is mild and lesions are non-painful and otherwise asymptomatic.

In bullous impetigo of older dogs due to underlying immune suppression, pustules are larger and range from 5 to 15 mm in diameter. These pustules are flaccid and may span multiple follicles. Pustular contents can vary from white to yellow or even light green. Unusual color in a pustule indicates the likelihood of a less common Gram-negative bacterial infection, and thus warrants bacterial culture. Bullous impetigo is seen most frequently with naturally occurring or iatrogenic hyperglucocorticoidism, but has also been seen in conjunction with diabetes mellitus, hypothyroidism, lymphoid neoplasia, and other debilitating diseases associated with immunosuppression. This subgroup of impetigo usually begins in the glabrous regions of the groin and axillae, but is much more likely to generalize than the impetigo seen in young dogs. Pruritus is uncommon.

Canine impetigo is seen most commonly in prepubescent and pubescent dogs. Impetigo of adult or senile onset is uncommon and suggests underlying disease. Breed or sex predilections have not been noted.

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Fig. 1.1 Impetigo of the ventral abdomen of a pubescent dog. Note the multiple crusted papules and the sparse intact pustules.



Fig. 1.2 Bullous impetigo of the ventral abdomen of a Boxer with hyperadrenocorticism. A single large, intact, asymmetrical pustule is surrounded by an erythematous halo. The nipple exhibits calcinosis cutis.

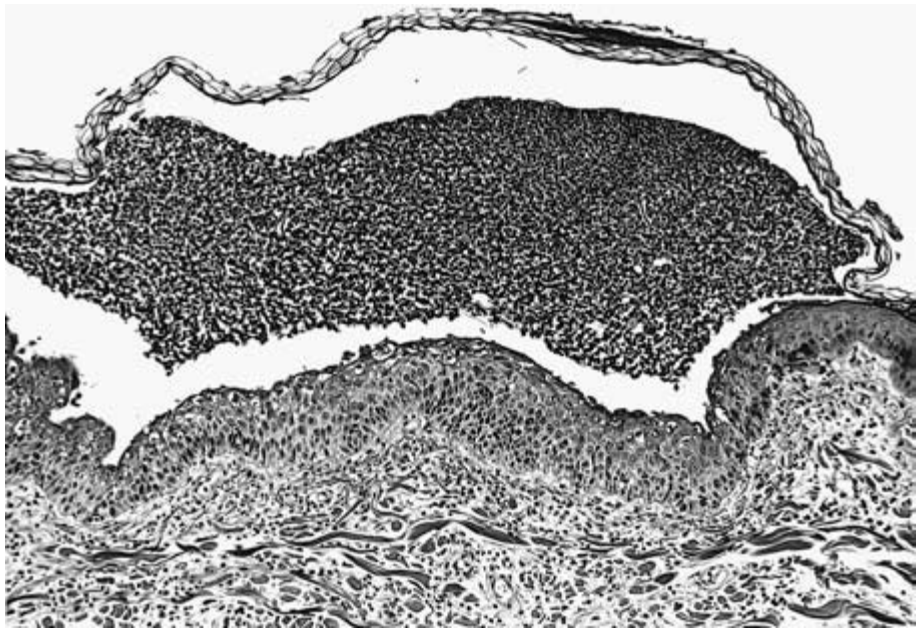


Fig. 1.3 Impetigo in a dog. Note the large, discrete subcorneal pustule with subjacent mild spongiosis.

Clinical differential diagnoses for impetigo of young dogs include early onset flea allergy dermatitis and superficial folliculitis. Pruritus should be evident even with mild flea allergy dermatitis, in contrast to the relatively mild or absent pruritus of impetigo. In folliculitis, the pustules are oriented around hairs and their follicles, rather than between them as in impetigo of young dogs. An uncommon variant of pemphigus foliaceus characterized by intermittent waves of truncal pustules, ranging from 2 to 10 mm in diameter, can mimic bullous impetigo of adult dogs.

Biopsy site selection

Skin biopsy specimens should be obtained from intact pustules, if available. Crusted papules are not ideal as they represent pustules in advanced stages of degeneration.

Histopathology (Figure 1.3)

The typical microscopic lesion is a discrete subcorneal or intragranular pustule that is composed predominantly of neutrophils. Generally, pustules are elevated above the

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epidermal surface and are located between hair follicles. In bullous impetigo, broader pustules span one or two hair follicles. Spongiosis often occurs beneath pustules; mild separation of keratinocytes (acantholysis) may be present at the base, or there may be a few intrapustular acantholytic cells. Rarely, there is marked acantholysis, mimicking pemphigus foliaceus (see p. 13). Pustules become crusts as inflammatory cells degenerate, and new stratum corneum often develops at the base of these older lesions. The epidermis is mildly to moderately acanthotic. A bacterial stain often reveals Gram-positive cocci within pustules. Stains are useful diagnostically only if the pustule is intact, as any ruptured pustule may develop secondary bacterial colonization.

The dermis has superficial perivascular to interstitial, mixed inflammation with neutrophils predominating. Mild to moderate dermal edema is common. There may be concurrent folliculitis (see Chapter 16).

The principal differential diagnosis is pemphigus foliaceus, particularly in the case of bullous impetigo, or when acantholysis is prominent. Acantholysis usually is absent or minimal in impetigo and intact pustules reveal bacteria, in contrast to the sterile intact pustules of pemphigus foliaceus. In pemphigus foliaceus, immunoglobulin and frequently C3 may be found in the intercellular spaces of the epidermis and often superficial follicular epithelium with immunofluorescence or immunohistochemical testing (see p. 13). Clinical differentiation may be required if acantholysis is severe and/or if immunohistochemical or immunofluorescence testing is negative or not performed.



Fig. 1.4 Superficial spreading pyoderma in a dog. Two asymmetrical erythematous macules have slight peripheral collarettes.

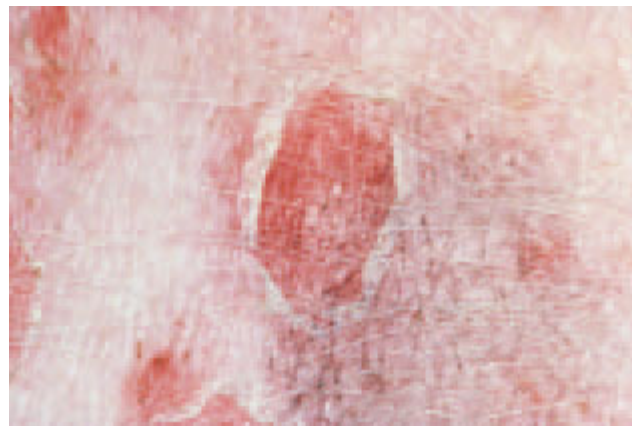


Fig. 1.5 Superficial spreading pyoderma in the glabrous skin of the ventral abdomen of a dog. A large collarette peels peripherally from the border of the erythematous macule.

SUPERFICIAL SPREADING PYODERMA

(Synonym: exfoliative pyoderma)

Clinical features (Figures 1.4 and 1.5)

Superficial spreading pyoderma is a superficial bacterial skin disease seen commonly in the dog and rarely in the cat. *Staphylococcus intermedius* is the primary pathogen, as in other forms of pyoderma. Superficial spreading pyoderma may be seen alone or more commonly in conjunction with superficial bacterial folliculitis (see Chapter 16). Exfoliative toxin has been isolated from strains of *Staphylococcus intermedius* from dogs with pyoderma; the isolated toxin caused exfoliation of the skin of dogs and other species (Terauchi et al., 2003). Similar toxins have also been recovered from pigs with exudative epidermitis, an exfoliative *Staphylococcus hyicus* infection (Tanabe et al., 1996), and are recognized in staphylococcal scalded skin, a severe form of exfoliative staphylococcal infection in humans (Prevost et al., 2003). Superficial spreading pyoderma frequently occurs secondary to other underlying diseases such as canine atopic dermatitis and other allergic skin diseases. In humans, there is a high prevalence of certain staphylococcal superantigens on the skin of patients with atopic dermatitis (Mempel et al., 2003). Recently, staphylococcal superantigens with marked T cell blastogenesis potential have been isolated from *Staphylococcus intermedius* strains obtained from canine pyoderma (Hendricks et al., 2002). The marked inflammation and pruritus seen with canine superficial spreading pyoderma in the setting of atopic dermatitis may be due to superantigen production from inappropriate staphylococcal bacterial colonization in susceptible dogs. Frequent localization of lesions to the glabrous intertriginous regions of the groin and axillae suggests that anatomic factors leading to moisture, heat retention, and frictional micro-trauma may be contributory to bacterial overgrowth and infection (Ihrke, 1996).

The more florid form of superficial spreading pyoderma, seen most commonly in the Shetland Sheepdog, usually is idiopathic; a breed predisposition to coloniza-

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tion by exfoliative toxin-producing staphylococci is possible. A cat with chronic feline immunodeficiency virus (FIV) infection presented with antibiotic-responsive lesions that clinically were strikingly similar to canine superficial spreading pyoderma (Radowicz, S., personal communication, 2003).

Erythematous macules enlarge centripetally from tiny transient pustules and create expanding coalescing erythematous rings. At the margins of the expanding macules, superficial keratin layers lift and peel peripherally forming distinctive collarettes with well-demarcated borders. Individual macules commonly achieve diameters of 1 to 2.5 cm. Subtle central crusting may be present. Expanding macules with peripheral collarettes impinge upon each other creating irregular arciform patterns that resemble interconnecting ripples. In well-haired areas, alopecia may occur in ring-like patterns within the confines of the macules. Postinflammatory hyperpigmentation marks the site of previously active lesions. Lesions often are confined to the glabrous skin of the ventrum, but may be more generalized on the trunk. Pruritus is variable and may not correlate with the magnitude of erythema. Superficial bacterial folliculitis may occur in conjunction with superficial spreading pyoderma; one of the two syndromes usually predominates (Ihrke & Gross, 1994) (see Chapter 16). A particularly striking subgroup of combined superficial spreading pyoderma and superficial folliculitis occurs predominantly in Shetland Sheepdogs. In this highly characteristic subgroup, individual coalescing collarettes emanating from sheet-like exfoliation may reach 5 cm in diameter, leading to widespread truncal alopecia.

Age, breed, or sex predilections have not been reported. Shetland Sheepdogs, Border Collies, Australian Shepherds, and Collies may be predisposed to exceptionally florid lesions.

The expanding macules with peripheral coalescing collarettes of superficial spreading pyoderma are distinctive and visually striking. Generalized truncal exfoliation may be seen initially with thyroid hormone supplementation, but is not accompanied by macules, papules, erythema, or collarettes. Clinical differential diagnoses for lesions with peripheral epidermal collarettes include superficial bacterial folliculitis, pemphigus foliaceus, erythema multiforme, and sterile eosinophilic pustulosis. If pruritus and self-trauma are marked, lesions may be considerably less diagnostic and may resemble flea allergy dermatitis or dermatophytosis. History, clinical features, distribution of lesions, and often response to appropriate therapy allow definitive diagnosis.

Biopsy site selection

Specimens for skin biopsy should be obtained from the advancing edge of the collarette. Biopsy of the central region of an erythematous macule is less likely to yield diagnostic results. If pustules are present, they also should be sampled. When performing the skin biopsy, care should be taken not to dislodge the scale present at the margin of the epidermal collarette since this material is most likely to yield a definitive diagnosis.

Histopathology (Figures 1.6 through 1.8)

The microscopic appearance is variable and is highly dependent on the stage and site of lesions obtained for biopsy. Because lesions evolve rapidly in an outward direction, it may be difficult to obtain a diagnostic biopsy.

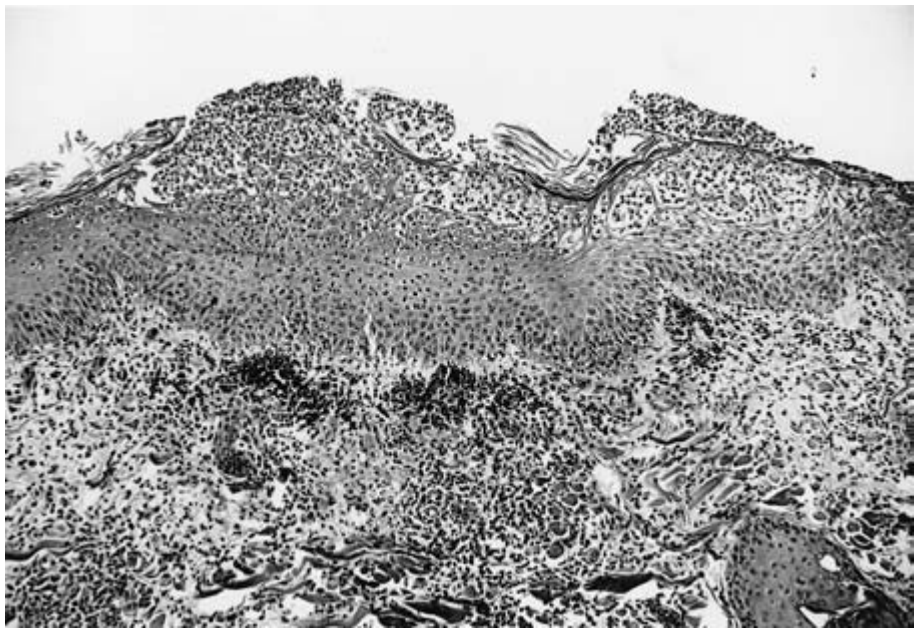


Fig. 1.6 Superficial spreading pyoderma in a dog. A large spongiotic pustule is loosely organized in the superficial epidermis.

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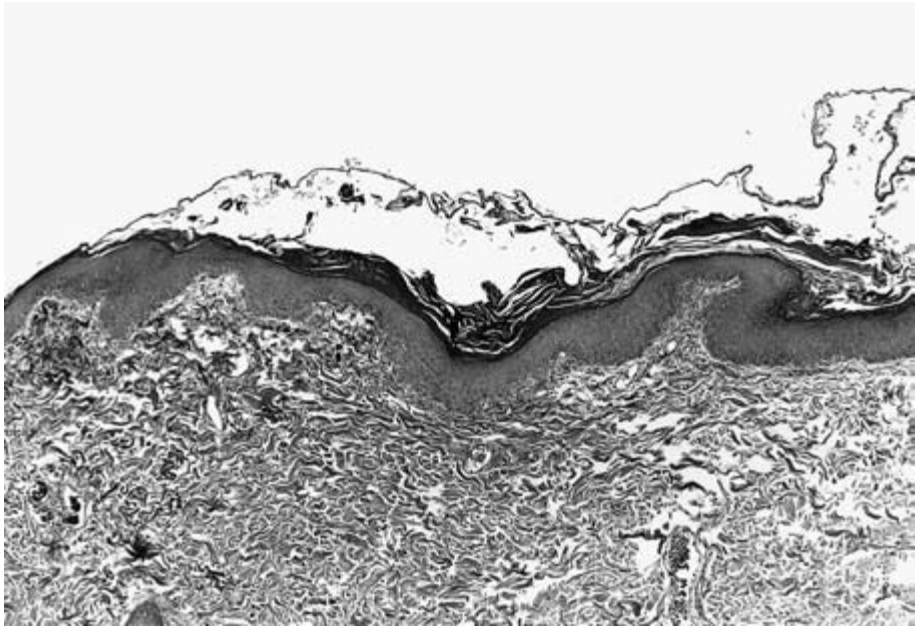


Fig. 1.7 Dunstan's blue line characterized by dark subcorneal deposits of degenerating cellular debris. Note lifting of stratum corneum.

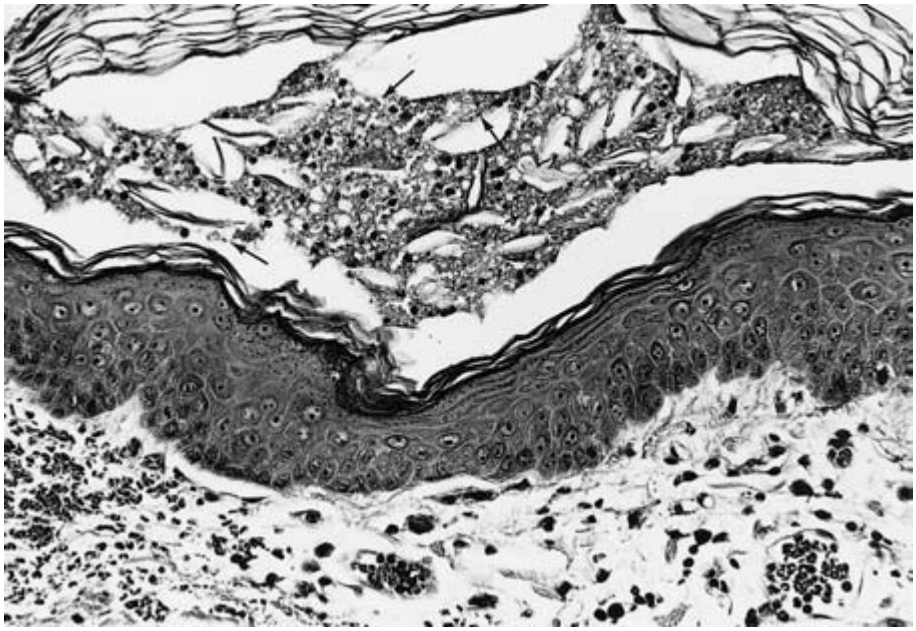


Fig. 1.8 Dunstan's blue line. Degenerating nuclear debris, fragments of keratin, and numerous small cocci (arrows) are intermingled at the advancing edge of a pustule. Note the elevated stratum corneum.

In less optimal specimens, such as those obtained from the center rather than the advancing periphery, epidermal lesions may be absent, making differentiation from chronic dermatitis difficult.

The most characteristic epidermal lesions, obtained from the periphery of an advancing collarette, consist of small, loosely organized and spongiotic, superficial epidermal pustules that rapidly form crusts, accompanied by lifting of the overlying stratum corneum from the epidermal surface. Occasionally, the lifting of the stratum corneum predominates and subjacent epidermal inflammation is subtle; however, a close search usually reveals small crusts within the stratum corneum. The lifted stratum corneum is generally of basketweave appearance.

Gram-positive cocci may be seen within superficial layers of keratin and may be accompanied by granular basophilic cellular debris, collectively referred to as 'Dunstan's blue line'. In cases of minimal inflammation, staphylococci may be distributed in exfoliating keratin in a looser pattern. Lifting of keratin is evident above or just adjacent to the blue line, and this corresponds to the peripheral scaling, or advancing epidermal collarette, seen

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clinically. In this respect, lesions of superficial spreading pyoderma resemble those of very early exudative epidermitis, a *Staphylococcus hyicus* infection seen in pigs. Early macroscopic skin lesions of scaling in gnotobiotic pigs correspond to microscopic splitting of the keratin layer and superficial colonization by staphylococci (Lloyd, D.H., Allaker, R.A. & Gross, T.L., unpublished data, 1986). The exfoliative lesions also resemble those of staphylococcal scalded skin in man, from which staphylococcal exotoxins have been isolated, although the canine lesions are clinically not as severe.

The dermis has a superficial perivascular to interstitial admixture of neutrophils, plasma cells, lymphocytes, eosinophils and mast cells. Neutrophils may predominate in some lesions. Mild to moderate dermal edema is common (see Chapter 9).

In the cat with clinical lesions resembling superficial spreading pyoderma (see above) there were large subcorneal pustules that dipped into superficial hair follicles. Mild acantholysis was seen, as in impetigo (see p. 4). The stratum corneum was lifted, but blue line formation was not observed. Dermal inflammation was more severe than observed in dogs, and neutrophils and eosinophils were prominent.

Differential diagnoses include impetigo and impetiginization due to self-trauma from pruritus. Ichthyosis and exfoliation due to thyroid hormone supplementation also must be considered for lesions in which inflammation is subtle. Pustules of superficial spreading pyoderma are rarely as discrete as those of impetigo and do not confine themselves as neatly to the subcorneal space. Lesions of impetiginization found in chronic hyperplastic dermatitis due to allergy (see Chapter 7) are compact neutrophilic crusts, often admixed with parakeratosis or hyperkeratosis, and sometimes accompanied by erosion; frank pustules usually are not seen and lifting of the stratum corneum is not a feature. Lifting of the stratum corneum is a feature of ichthyosis and thyroid hormone supplementation; the lifted keratin is of lamellar rather than basketweave appearance in ichthyosis, but of normal basketweave appearance in thyroid hormone supplementation. Careful searching usually will reveal small crusts within the stratum corneum of lesions of superficial spreading pyoderma, in contrast to the noninflamed stratum corneum of ichthyosis and exfoliation due to thyroid hormone supplementation.

CANDIDIASIS

Clinical features (Figures 1.9 and 1.10)

Candidiasis is a very rare fungal disease reported in dogs and cats that is caused by species of the genus *Candida*. Although *Candida albicans* is the most commonly reported pathogen, many other species have been identified as causative agents in individual cases. Candidiasis usually is seen as an opportunistic infection secondary to underlying immunosuppressive or debilitating systemic disease (Greene & Chandler, 1998). Reported initiators include hyperadrenocorticism, diabetes mellitus, hypothyroidism, cancer, inherited defects of the immune system, and immunosuppressive drug therapy. Disruption of normal barrier function and factors that disturb the normal endogenous microflora may contribute.

Ulcers and erosions are coated with adherent, tenacious, foul-smelling gray exudate. The oral mucosa, mucocutaneous junctions and distal extremities are the most frequently involved sites. Lesions also may be seen in the external ear, perineum, nares, vulva, scrotum, and glabrous intertriginous skin. Pruritus and pain are variable but may be intense. Canine *Candida* pododermatitis may involve single or multiple paws and is characterized by erythema, oozing, pruritus, and pain (Carlotti & Pinn,



Fig. 1.9 Perioral candidiasis in an elderly Poodle with superficial necrolytic dermatitis.



Fig. 1.10 Closer view of Fig 1.9. Dark crusts and tenacious mucoid deposits adhere to erosions and mat the surrounding hair.

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1999). In all forms of candidiasis, secondary bacterial invasion may contribute to morbidity, pruritus, and pain.

Sex or breed predilections have not been noted. Candidiasis may be seen more frequently in adult and elderly animals with immunosuppression or debilitation as contributing factors.

Clinical differential diagnoses reflect the site affected. Mucosal and mucocutaneous lesions may mimic autoimmune skin disease (pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus), other immunologic diseases (erythema multiforme, epidermolysis bullosa acquisita), epitheliotropic lymphoma (mycosis fungoides), uremic stomatitis, and superficial necrolytic dermatitis. Cutaneous lesions may mimic pyotraumatic dermatitis, and intertriginous candidiasis must be differentiated from bacterial intertrigo. As a further complication, candidiasis may occur secondary to any of the diseases mentioned above, especially if immunosuppression is present. Stained smears from exudate demonstrating blastoconidia and pseudohyphae are a diagnostic aid, but definitive diagnosis cannot be made without biopsy and culture.

Biopsy site selection

Intact crusted lesions should be selected. Care should be taken to leave crusts attached to the specimens. The pathology service should be instructed to include any separated crusts in the slide preparation. Ulcers should not be sampled alone since an intact epidermis or mucosa may be essential for the identification of organisms in tissue.

Histopathology (Figures 1.11 and 1.12)

Microscopic findings consist of moderate to severe, superficial epidermal pustulation, generally composed of neutrophils. Large areas of surface pustulation and serocellular crusting with parakeratosis may be present; discrete small pustules generally are not seen. Subjacent spongiosis is often prominent. Secondary erosion and ulceration are common. Intact epidermis is moderately acanthotic.

Discovery of yeast and pseudohyphae or hyphae of *Candida* species in superficial crusts or pustules is critical diagnostically. Organisms may be found on routine examination with hematoxylin and eosin (HE), but are more obvious with the use of periodic acid–Schiff (PAS) stain which reveals brilliant magenta, oval-shaped, budding yeast, measuring 3 to 4 μm in diameter, as well as tangled pseudohyphae. Inflammation and yeast colonization may extend to superficial hair follicles (Scott et al., 2001).

Dermal inflammation is superficial perivascular to interstitial, and mixed, and includes a prominent component of neutrophils, with mixtures of lymphocytes, plasma cells and macrophages. Dermal edema is variable but is usually mild to moderate.

The pustular and crusting inflammation of candidiasis is reminiscent of superficial spreading pyoderma but is generally more severe. Discovery of yeast is required for definitive diagnosis. Superficial pustular dermatophytosis may resemble candidiasis. It may be difficult to differentiate pseudohyphae and hyphae of candidiasis from hyphae of dermatophytic origin. The concurrent presence of budding yeast indicates likely candidiasis; however,

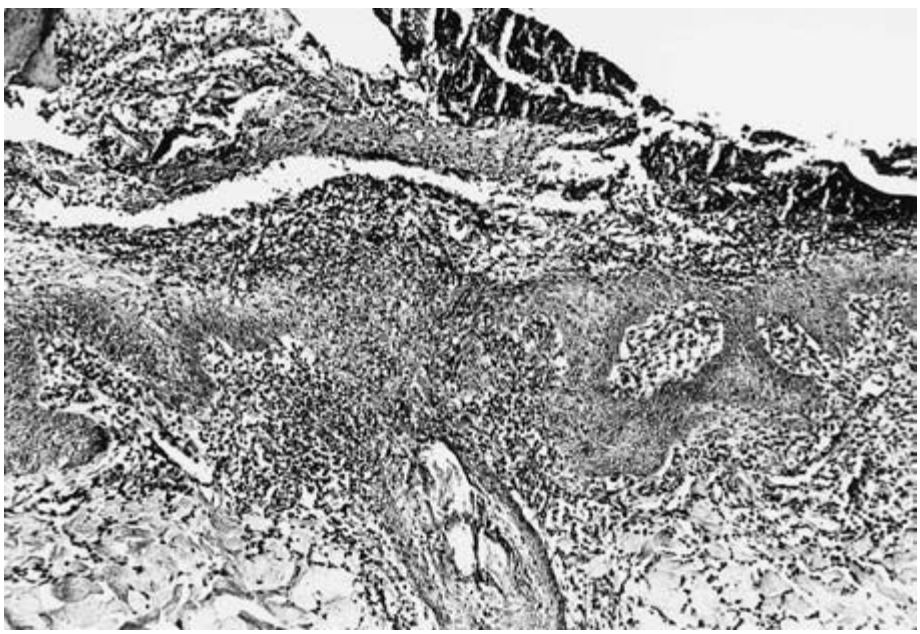


Fig. 1.11 Candidiasis in a dog. A large superficial pustule is accompanied by marked epidermal edema.

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Fig. 1.12 *Candida* sp. in superficial keratin (periodic acid–Schiff).

culture is required for definitive differentiation. Candidiasis can complicate superficial necrolytic dermatitis; lesions compatible with superficial necrolytic dermatitis (see Chapter 4) should be searched for in specimens with superficial yeast colonization.

SUPERFICIAL PUSTULAR DERMATOPHYTOSIS

(Synonym: keratin-colonizing dermatophytosis)

Clinical features (Figure 1.13)

Superficial pustular dermatophytosis is an uncommon, predominantly facially-oriented skin disease seen occasionally in the dog. It is caused by keratin-colonizing dermatophytes that affect the surface stratum corneum or superficial follicular keratin preferentially over hair. A similar but even more rare syndrome is seen in cats. The zoophilic dermatophyte *Trichophyton mentagrophytes* is isolated in most reported cases. *Trichophyton mentagrophytes* var. *erinacei* may be the most common keratinophilic dermatophyte seen in the dog (Fairley, 2001). The European hedgehog is the natural host for *Trichophyton mentagrophytes* var. *erinacei*, which has been reported to cause facially-oriented dermatophytosis in dogs in Europe, Great Britain, and New Zealand (Fairley, 2001). However, other dermatophytes (*Trichophyton terrestre*, *Microsporum persicolor*, and *Epidermophyton floccosum*) also have been cultured less frequently.

This syndrome is distinct from most cases of dermatophytosis. Clinically it mimics facially oriented autoimmune skin disease, and histologically it is characterized in part by superficial neutrophilic pustules, sometimes with acantholysis. It has been theorized that in humans and in dogs, acantholysis results from complement-mediated, transepidermal neutrophilic chemotaxis, as well as proteolytic enzymes secreted by the dermatophyte (Poisson et al., 1998). Also, these dermatophytes may be less well adapted to canine and feline hosts, and thus induce a more florid cell-mediated response (Parker & Yager,

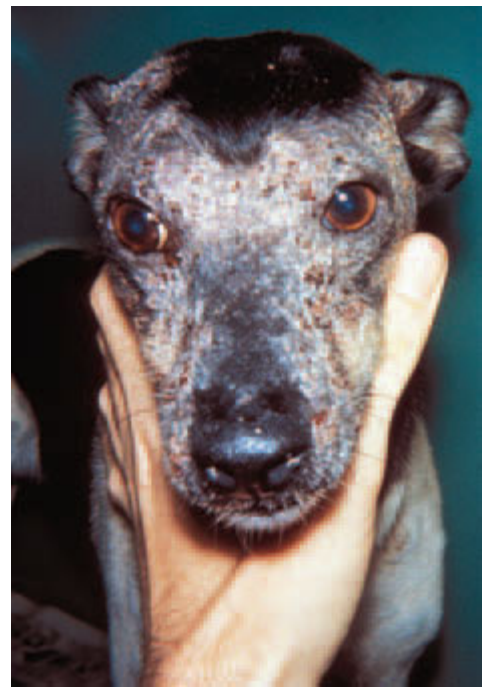


Fig. 1.13 Superficial pustular dermatophytosis in a dog. Lesions are bilaterally symmetric affecting both the haired skin and the planum nasale of the muzzle. (Photograph courtesy A.A. Stannard.)

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1997). Superficial pustular dermatophytosis has also been seen occasionally as a more generalized disease in dogs with severe systemic illness that may have been immunosuppressed: these dogs have shown a poor response to therapy. Severe, generalized superficial pustular dermatophytosis has been reported secondary to pituitary dependent hyperadrenocorticism (Chen & Su, 2002).

Clinical features include pustules that rapidly rupture, giving rise to inflamed erythematous papules and plaques with copious adherent crusts. Intact pustules, when present, vary in size from 1 to 5 mm. Larger pustules may be asymmetric and not completely circular. Erosions and ulceration may be present. Lichenification, alopecia, and hyperpigmentation occur rapidly with chronicity. Lesions gradually extend into adjacent normal skin. Rarely, similar lesions have been seen in cats.

The most common site of involvement is the face, including the dorsal and lateral muzzle, and the periorbital region. Unlike other facial dermatophyte infections, the planum nasale may occasionally be affected. Bilateral symmetry is common with facial orientation. Other regions of the body may be affected. Pawpads and the margins of pawpads may be affected in dogs with superficial necrolytic dermatitis (see Chapter 4).

The Fox Terrier and Manchester Terrier may be at increased risk. Three of four affected dogs reported recently from New Zealand were Bull Terriers (Fairley, 2001). Age and sex predilections have not been noted.

Clinical differential diagnoses include facially-oriented autoimmune skin diseases such as pemphigus foliaceus and pemphigus erythematosus, demodicosis, and other dermatophyte infections. In contrast to facially-oriented autoimmune skin disease, superficial pustular dermatophytosis usually does not violate the planum nasale and alter the normal cobblestone appearance. Facial superficial pustular dermatophytosis is much more likely to be bilaterally symmetric than demodicosis. Dermatophyte culture and skin biopsy are recommended for definitive diagnosis.

Biopsy site selection

Intact pustules should be sampled if present. If only chronic crusted lesions remain, care should be taken to include the crusts. The pathology service should be instructed to process any nonadherent crusts.

Histopathology (Figures 1.14 and 1.15)

This form of dermatophytosis is characterized by superficial epidermal pustules. Although most often small, they may be large and broad, resembling those of pemphigus foliaceus. The degree of acantholysis is relatively mild in most cases, but in some canine cases it may be prominent. Superficial pustular dermatophytosis with minimal to no acantholytic cells has been seen in cats. There is variable, sometimes severe, hyperkeratosis of the epidermis and superficial hair follicles; keratin is colonized by dermatophytic spores and hyphae. Organisms may be difficult to identify with hematoxylin and eosin (HE), and are best found using periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) stains. These demonstrate typical magenta (PAS) or black (GMS) dermatophytic hyphae and spores within keratin of the epidermis and hair follicles, sometimes in small numbers, but often numerous. In dogs, the dermatophytes very rarely invade hair shafts, leading to the alternate designation of this

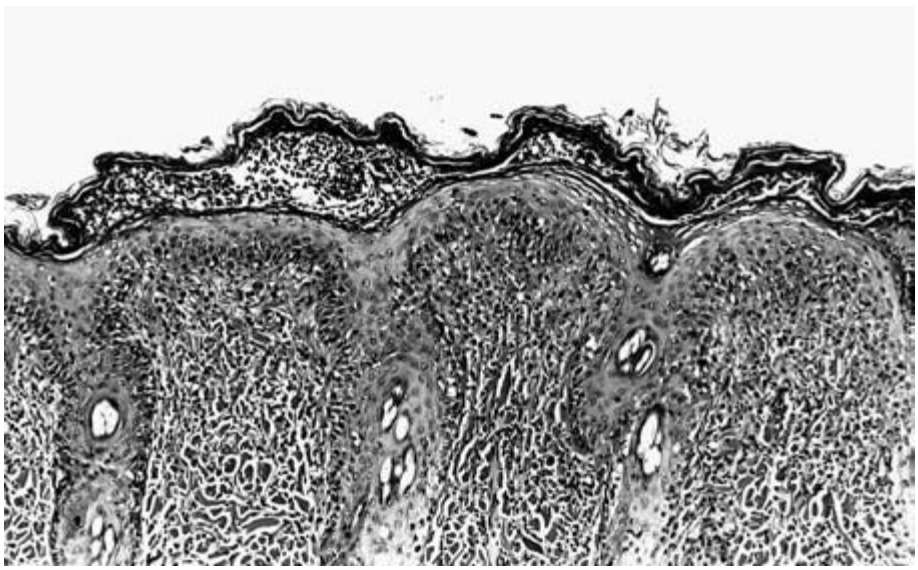


Fig. 1.14 Superficial pustular dermatophytosis in a cat. Note broad subcorneal pustule.

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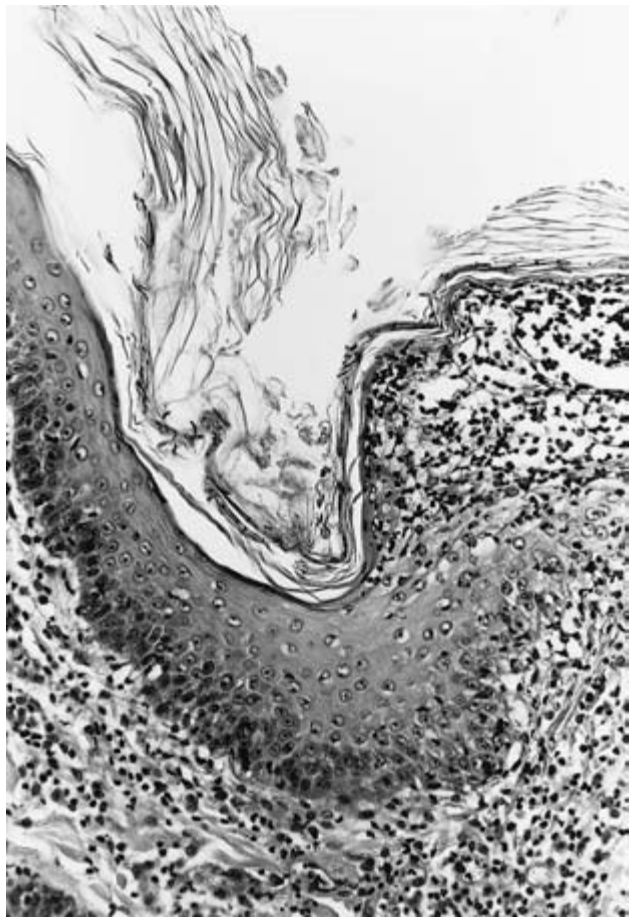


Fig. 1.15 High magnification of superficial pustular dermatophytosis in a cat. Keratin-colonizing dermatophytes are within a follicular ostium adjacent to the edge of a superficial pustule (periodic acid–Schiff).

form of dermatophytosis as 'keratin-colonizing dermatophytosis'. In cats, typical invasion of hair shafts usually is present and organisms are generally easier to see, even on HE evaluation (see Chapter 16).

There may be hyperkeratosis without inflammation in rare biopsy specimens, notably in cats. Dermatophytes may be sparse in these cases; careful search using a PAS or GMS stain, if necessary, should always be made, particularly when obtained from a cat with scaling or alopecia reported as clinical findings.

Superficial dermal inflammation is perivascular to interstitial, and includes neutrophils and mixed mononuclear cells. In some canine cases there may be a band-like pattern of dermal inflammation, including lymphocytes and plasma cells, that may be either lichenoid (without basal cell damage) or interface (with basal cell damage; see Chapters 3 and 11) (Parker & Yager, 1997). Inflammation often extends to the wall of the hair follicles (mural folliculitis; see Chapter 18). In addition, pustular



Fig. 1.16 Pemphigus foliaceus in a cat. Note symmetrical crusting and alopecia. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

folliculitis or pyogranulomatous furunculosis may be observed.

Differential diagnoses include pemphigus foliaceus, superficial spreading pyoderma, and candidiasis. Pemphigus foliaceus features more acantholysis than most cases of superficial pustular dermatophytosis. Superficial spreading pyoderma demonstrates blue line formation (see p. 6), which is absent in superficial pustular dermatophytosis. Pustular folliculitis, when present, is suggestive of dermatophytosis, particularly in cats. The presence of concomitant mural follicular inflammation also is a feature of this type of dermatophyte infection (see Chapter 18). In all cases demonstration of fungi is required for definitive diagnosis. Culture may be required to differentiate superficial pustular dermatophytosis from candidiasis.

PEMPHIGUS FOLIACEUS

Clinical features (Figures 1.16 through 1.18)

Pemphigus foliaceus (PF) is an uncommon bullous autoimmune skin disease of dogs and cats that affects the epidermis and hair follicles. Desmoglein 1 (Dsg 1) is the primary targeted autoantigen in canine PF, as in humans (Suter et al., 1993; Iwasaki et al., 1997); other antigens in addition to Dsg 1 may be targeted. Autoantibodies bind to Dsg 1, which is a prominent component of the desmosomes in the superficial layers of the epidermis and hair follicles. In humans, the clinical phenotype of the pemphigus group of diseases is defined by the antidesmoglein autoantibody profile; mucosal-dominant pemphigus

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Fig. 1.17 Pemphigus foliaceus in a dog. Multiple intact and recently ruptured vesicopustules are more irregular in contour than most pustules caused by bacterial pyoderma.



Fig. 1.18 Canine pemphigus foliaceus restricted to the pawpads. Keratinous crusts peel away from intact normal-appearing pad, demonstrating the wave-like progression of the disease.

vulgaris, mucocutaneous pemphigus vulgaris, and PF all have different and distinctive antidesmoglein autoantibody profiles (Amagai et al., 1999). A similar circumstance probably exists in the dog. Pemphigus foliaceus is likely a heterogeneous immunological disease, which may explain the clinical and histological variations observed (Olivry, T.O., personal communication, 2001).

The exact pathomechanism of vesicle and bulla formation is not known. However, loss of intercellular cohesion leads to acantholysis resulting in superficial vesicles and bullae. Plakoglobin may conceivably play a role, as has been demonstrated in the similarly acantholytic disease, pemphigus vulgaris, in dogs (Calhedari et al., 2001). Antikeratinocyte IgG4 autoantibodies may be relevant to the pathogenesis of PF in dogs, as circulating IgG4 antibodies were noted in 80% of dogs with the disease and decreased in 67% of dogs in remission due to immunosuppressive therapy (Hogan et al., 2002). In humans, apoptosis following cellular detachment (termed 'anoikis') characterizes pemphigus, and may be related to increased Fas ligand (FasL) in patients' sera; FasL/Fas interaction on keratinocytes is a major trigger of the extrinsic apoptotic pathway (Puviani et al., 2003). Apoptosis is characteristic of PF in animals as well (see below).

Drug-related, PF-like disease can occur. The term 'pemphigus foliaceus-like drug reaction' may be used when clinical, histopathologic, and immunopathologic features mirror naturally occurring PF, and the disease disappears when the offending drug is discontinued. The term 'drug-induced pemphigus foliaceus' may be used when clinical, histopathologic, and immunopathologic features mirror naturally occurring PF, and the disease continues after drug withdrawal. Drug-related PF (both PF-like drug reaction and drug-induced PF) is reported as a sequela to the administration of various antibiotics (trimethoprim-potentiated sulfonamides, cephalexin) (White et al., 2002). The authors have seen methimazole initiate drug-related PF in cats. To qualify for categorization as drug-related PF, the skin disease must closely mimic the naturally occurring disease, clinically, histopathologically, and immunopathologically. However, possible markers for drug-related PF include unusually rapid onset, very early age of onset, oral lesions, and any other features atypical for naturally occurring disease. Some overlap occurs between drug-related PF and superficial pustular drug reactions (see p. 23). If clinical, histopathological and immunopathological parameters stray too far from those seen with naturally occurring PF, then the term 'superficial pustular drug reaction' may be more appropriate.

Transient superficial pustules (or vesicopustules) develop in waves. Individual pustules may be large (2 to 6 mm in diameter) and vary in color from translucent, to gray-white, to yellow. Coalescence of pustules leads to visually distinct intact pustules or vesicopustules with irregular, asymmetric, polycyclic borders. Pustules frequently span multiple hair follicles, and multiple hairs may protrude from individual pustules. Animals may progress from absence of lesions to sudden development of dozens of pustules. Pustules quickly eventuate in thick, adherent crusts with marked exfoliation. These exfoliative crusts are the most common clinical lesions of PF. Rarely, erosions from ruptured pustules may exhibit targetoid or polycyclic patterns. Alopecia is variable. Generalized erythroderma may be seen. Characteristic pawpad lesions in dogs consist of erythematous swelling at the pad margins, and cracking and villous hypertrophy of the pads. Whitish discoloration beneath the surface of the pad may indicate an intact subcorneal pustule. Pruritus is noted in less than one-half of affected dogs. Photophobia may be noted but is unexplained. In contrast to

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canine lesions, feline lesions usually are much milder in severity. In the cat, pustules and vesicles eventuate very rapidly in erosions with adherent yellowish crusts.

The most common sites of involvement in the dog are the dorsal muzzle, planum nasale, pinnae, periorbital skin, and pawpads. Pawpad lesions vary considerably in severity but almost always are present. Truncal lesions are variable but may be diffuse. Striking bilateral symmetry is a common and key feature. Occasionally, the disease may be predominantly confined to the face (see below) or pawpads. Less commonly, mucocutaneous junctions can be affected. One author (P.J.I.) has seen two dogs with lesions of PF confined to the lip folds; another dog had lesions confined to the medial surface of both pinnae. In cats, lesions are less widespread and often are restricted to the muzzle, planum nasale, ear pinnae, around the nipples, and the distal extremities, especially affecting the ungual folds of the claws and pawpad margins. As in dogs, one author (T.L.G.) has seen perioral lesions just at the juncture of the lips. The authors have also seen two cats with histologically typical lesions confined to one extremity.

A clinically distinctive subset of PF, termed 'facially-predominant pemphigus foliaceus', is seen in the Chow Chow, Akita, and occasionally in other breeds. One author (E.J.W.) has observed several cases in Siberian Huskies. Bilaterally symmetric facial lesions are characterized by increased severity with ulceration. Lesions of lesser severity may be seen on the trunk and elsewhere. An additional clinically distinctive subset characterized by widespread truncal pustules with or without facial or pedal involvement may occur more commonly in the Cocker Spaniel and the Chihuahua.

The Bearded Collie, Akita, Chow Chow, Newfoundland, Schipperke, and Doberman Pinscher are genetically predisposed. More recently, the English Springer Spaniel, Chinese Shar Pei, and Collie also have been shown to be at increased risk (Kuhl et al., 1994). Facially-predominant PF is seen more commonly in the Chow Chow and Akita. Canine PF usually is a disease of middle age, but dogs of any age may be affected. The mean age of onset is 4 years with two-thirds of dogs developing lesions at or before 5 years of age (Ihrke et al., 1985). Sex predilections have not been noted. Age, sex, or breed predilections have not been reported for the cat. Some cases of PF may occur as a consequence of chronic, on-going inflammatory skin disease; dogs that developed PF often had a history of long-term inflammatory skin disease (Pascal et al., 1995).

Superficial bacterial folliculitis is the major clinical differential diagnosis for PF. Pustules seen with PF usually are larger and more irregular in contour than the pustules seen with superficial bacterial folliculitis, which tend to be more circular. Pemphigus foliaceus also can appear visually similar to other crusting, pustular and exfoliative skin diseases, such as superficial pustular dermatophytosis, (follicular) dermatophytosis, lupus erythematosus, demodicosis, zinc-responsive dermatosis, sebaceous adenitis, and mycosis fungoides (epitheliotropic malignant T cell lymphoma; see Chapter 37). However, the frequent bilateral symmetry and periodic 'waves' of pustules observed in PF are important differentiating features. When bilaterally symmetric facial lesions are present, the involvement of both haired skin and the non-haired planum nasale is a key differentiating feature of PF. Drug-induced PF may be indistinguishable from classic PF; other superficial pustular drug reactions (not histologically compatible with PF) may partially resemble PF (see p. 23). Superficial pustular dermatophytosis may be the most difficult disease to distinguish from canine PF, and dermatophytosis also may be the most problematic differential diagnosis in the cat. Positive Tzanck preparations from intact vesicopustules or pale central regions on pawpads may document the presence of individual acantholytic cells or rafts of acantholytic cells. Histopathology is required to confirm the diagnosis.

Biopsy site selection

Because of the fragile and transient nature of primary lesions in PF, early lesions (pustules and vesicopustules) should be obtained promptly. Diagnostic histopathology may not be forthcoming from older crusted lesions. If only crusted lesions are available, these should be procured carefully, and the pathology service should be instructed to include any dissociated crusts in the slide preparation. Sites directly adjacent to early pustules should be sampled for direct immunofluorescence or immunohistochemical testing.

Histopathology (Figures 1.19 and 1.20)

Broad, discrete, subcorneal or intragranular pustules within a variably acanthotic epidermis are the typical histopathologic lesions of PF. Pustules often span several follicles and may extend into the follicular infundibula. Mural pustular follicular inflammation may occur (see Chapter 16). Pustules are composed of neutrophils and often eosinophils. Individualized, rounded, often brightly eosinophilic, acantholytic keratinocytes are present in small to large numbers within pustules. Free floating 'rafts' of partially adherent acantholytic cells and adherence of acantholytic cells to the overlying stratum corneum are both characteristic histopathologic features of PF. Neutrophils may encircle and cling to individual acantholytic cells. Active acantholysis, characterized by rounding up of keratinocytes, which appear to be 'springing' from the underlying epidermis, are found beneath pustules. Rarely, acantholysis without pustule formation

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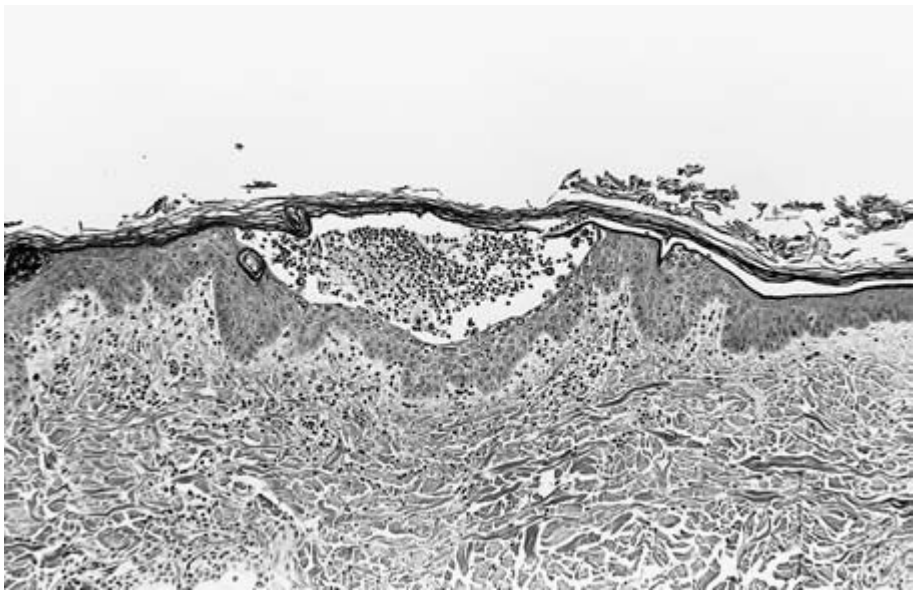


Fig. 1.19 Canine pemphigus foliaceus. A subcorneal pustule contains acantholytic cells.

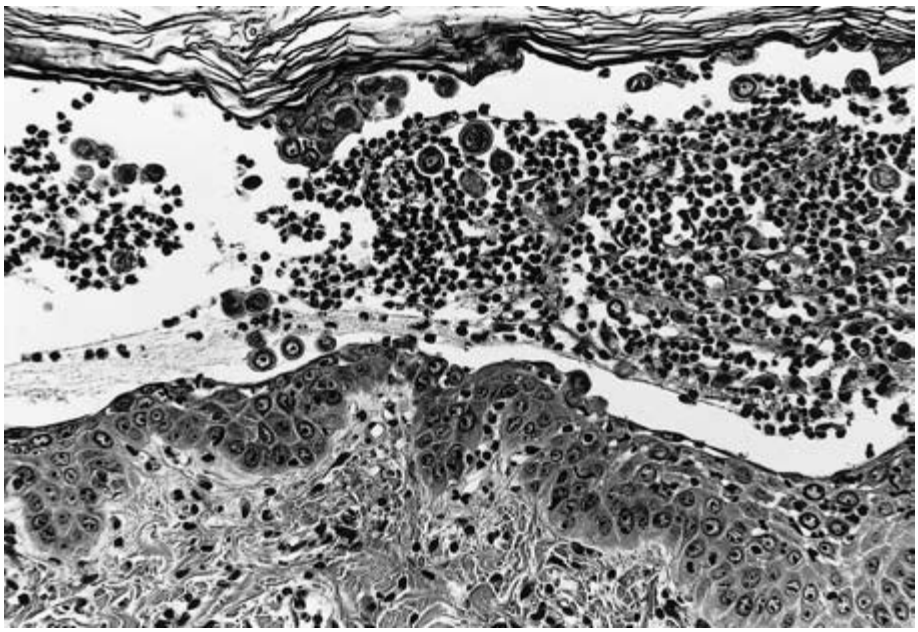


Fig. 1.20 High magnification of subcorneal pustule from a dog with pemphigus foliaceus. Prominent acantholytic cells are free-floating; partially acantholytic cells are adhered to the roof of the pustule.

may be seen in the superficial epidermis; these lesions resemble a 'crumbling brick wall'. In these lesions, affected keratinocytes are hypereosinophilic, slightly rounded, and separated from the underlying epidermis.

Because pustules are transient, active acantholysis and pustulation often are not present in biopsy specimens; the diagnosis may then depend upon the demonstration of degenerated free keratinocytes in crusts. Some caution is warranted in relying on free keratinocytes alone for the diagnosis of PF since spongiosis, as seen in superficial pyoderma and other inflammatory diseases of the epidermis, can also result in separation of keratinocytes from the underlying epidermis, and their ultimate shedding into crusts. Keratinocytes that are disconnected via spongiotic mechanisms may appear less rounded and more ragged or angular than typical acantholytic cells in early stages, but may be indistinguishable once they are within aged crusts. As a further complication, spongiosis rather than acantholysis may be prominent at the base of otherwise typical pustules of PF.

Facially-predominant PF, as seen in Chow Chows, Akitas, and other breeds, is a deeper inflammatory process that frequently involves the wall of hair follicles, often in full thickness distribution ('panfollicular pem-

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phigus'; see Chapter 16). Similarly, pustules may extend through the epidermis and be found at all levels rather than just superficially. In addition to acantholysis, brightly eosinophilic, contracted, apoptotic keratinocytes are often prominent in this form of PF, particularly in deeper epidermal or mural follicular pustules. Confirmation of apoptosis in PF lesions in dogs was performed using immunohistochemistry for the detection of free 3′ DNA ends (resulting from endonuclease activity in apoptosis) (Noli et al., 1998). These apoptotic cells are surrounded by neutrophils and sometimes a few lymphocytes or histiocytes. Early lesions are often characterized by one or two apoptotic keratinocytes surrounded by a few neutrophils; these lesions may be subtle, but are nevertheless diagnostic.

Deep follicular pustulation in hair follicles may mimic lesions of pemphigus vegetans because the pustules may lie in a suprabasilar location, thus mimicking suprabasilar clefting of pemphigus vegetans (a variant of pemphigus vulgaris). The case in the first edition of this textbook was most likely panfollicular PF (see Chapter 16) and not pemphigus vegetans. The authors have not seen a convincing case of pemphigus vegetans in the dog or cat.

Drug-related PF may be indistinguishable histologically. Transepidermal apoptosis, as seen in erythema multiforme (see Chapter 4), with or without neutrophilic satellitosis was reported in two of four cases of drug related PF in dogs (White et al., 2002). Those cases may represent collision of two distinct immunoreactive, drug-related processes rather than PF with excessive apoptosis.

Pemphigus foliaceus of the pawpads often shows degenerating pustules and crusts entrapped in thick layers of dense hyperkeratotic or focally parakeratotic keratin. Acantholytic keratinocytes are easily demonstrated within lesions. The thick keratin layer of the pawpad is more difficult to disrupt, and acts as a sturdier roof over the pustules; thus, they are maintained intact for longer periods of time than in lesions elsewhere.

A rare variant of PF is characterized by prominent spongiotic eosinophilic pustulation of the epidermis or superficial hair follicles. Acantholysis is not a feature. Affected animals develop typical histopathologic lesions of PF in later stages of the disease.

Dermal inflammation is superficial, mixed, and perivascular to interstitial, and is accompanied by edema, vascular ectasia and congestion. Neutrophils and eosinophils usually are prominent, and are intermingled with macrophages, lymphocytes or plasma cells. In the cat, eosinophils may be absent or sparse in dermal inflammation; neutrophilic predominance in dermal inflammation is characteristic of feline PF. In facially predominant PF of dogs, lesions of the dorsal muzzle and planum nasale usually have band-like or lichenoid dermal inflammation with absent or minimal interface damage (see Chapter 11). Lichenoid inflammation is most likely a reflection of anatomic location rather than a specific feature of PF; chronic lesions of the planum such as mucocutaneous pyoderma and discoid lupus erythematosus also feature lichenoid dermatitis (see Chapter 11). Pigmentary incontinence, or the accumulation of melanophages in the superficial dermis, may be prominent.

IgG, frequently C3, and less commonly IgM, may be found in the intercellular spaces of the epidermis and often superficial follicular epithelium with immunofluorescence or immunohistochemical testing (Ihrke et al., 1985). Findings in drug-related PF were similar (White et al., 2002). In contrast to pemphigus vulgaris, immunoglobulin deposition may be confined to the superficial epidermis. Only 40–50% of random biopsy specimens are positive for immunoglobulin deposition, but sequential biopsy specimens from affected animals may increase the likelihood of a positive result.

In a recent report, immunohistochemical staining for desmoglein 1 in 62% of dogs with PF demonstrated alteration of expression of this molecule from the uniform finely granular delineation found in normal keratinocytes, as observed in some human cases. Alterations included clumped staining at the periphery of keratinocytes and/or dark cytoplasmic staining characterized by streaked or perinuclear deposits (Steeves et al., 2002).

The principal histopathologic differential diagnoses for PF include bullous impetigo, superficial pustular drug reactions, and superficial pustular dermatophytosis. Intact pustules of impetigo may contain cocci, and variable free keratinocytes; however, active acantholysis is usually absent. Drug-related PF is essentially indistinguishable histologically; in addition, other clinically superficial pustular drug reactions may resemble PF histologically. Clinical differentiation may be required. Superficial pustular dermatophytosis should be carefully considered, particularly for those lesions that have epidermal and follicular hyperkeratosis or folliculocentric pustular or mural inflammation. A periodic acid–Schiff (PAS) stain is required for differentiation and should be utilized liberally in all cases for which even slight suspicion for dermatophytosis exists.

Combined interface dermatitis and superficial pustular lesions characterize pemphigus erythematosus, a rare variant of pemphigus (see p. 18). These findings are similar to facially-predominant PF, but basal cell damage, or true interface dermatitis, is a feature of pemphigus erythematosus, whereas lichenoid inflammation (with absent to minimal interface change) is generally more prominent in facially-predominant PF. The principal microscopic method for differentiating these two diseases is through immunofluorescence or immunohistochemical techniques; pemphigus erythematosus exhibits deposition of immunoglobulin along the basement membrane in

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Fig. 1.21 Pemphigus erythematosus in an Airedale Terrier. Lesions are confined to the dorsal muzzle, planum nasale, periorbital region, and the pinnae. (From Ihrke, P.J. et al. (1985) Pemphigus foliaceus in dogs: a review of 37 cases. *J Am Vet Med Assoc* **186**, 59–66. Reprinted with permission.)



Fig. 1.22 Pemphigus erythematosus in a Spitz-crossbreed. Adherent, thick crusts symmetrically cover the dorsal muzzle and planum nasale.

addition to the intercellular spaces of the epidermis. Clinical differentiation (including a positive antinuclear antibody (ANA) test) is also required. Prominent apoptosis in facially-predominant PF may be confused with erythema multiforme (see Chapter 4). However, apoptotic cells in facially-predominant PF are surrounded by neutrophils, while in erythema multiforme they are surrounded by lymphocytes (satellitosis).

PEMPHIGUS ERYTHEMATOSUS

Clinical features (Figures 1.21 and 1.22)

Pemphigus erythematosus (PE) is a very rare variant of pemphigus foliaceus reported in the dog and cat. This disease has been characterized as either a benign form of pemphigus foliaceus or a crossover syndrome between pemphigus foliaceus and systemic lupus erythematosus (see Chapter 3). Lesions have been exacerbated in a dog by ultraviolet light, both *in vivo* and *in vitro* (Iwasaki & Maeda, 1997).

Clinical signs are very similar to those of pemphigus foliaceus, but usually are less severe. The lesions of PE are confined to the face. Bilaterally symmetric crusting, exudation, and alopecia of the face are as seen with pemphigus foliaceus. Depigmentation of the dorsal muzzle and planum nasale, with attendant marked photoaggravation, are possible differentiating features. Clinical features coupled with a positive antinuclear antibody (ANA) test suggest a diagnosis of PE.

The Collie and the German Shepherd Dog may be at increased risk (Scott et al., 1987). Canine age or sex predilections have not been noted. Statistical predilections have not been reported for the cat.

Clinical differential diagnoses should include facially-predominant pemphigus foliaceus, discoid lupus erythematosus, superficial pustular dermatophytosis, epitheliotropic T cell lymphoma (mycosis fungoides), and Vogt–Koyanagi–Harada-like disease. Careful examination of dogs with facially-predominant pemphigus foliaceus generally reveals lesions at other sites. Facially-predominant pemphigus foliaceus is a more severely ulcerative disease than PE. A positive ANA test and direct immunofluorescence testing are prerequisites for a confirmatory diagnosis of PE in the dog.

Biopsy site selection

See Pemphigus foliaceus, p. 13.

Histopathology (Figure 1.23)

In man, PE is indistinguishable from pemphigus foliaceus. In dogs, lesions of PE, although similar to facially-predominant pemphigus foliaceus (see p. 13), are less

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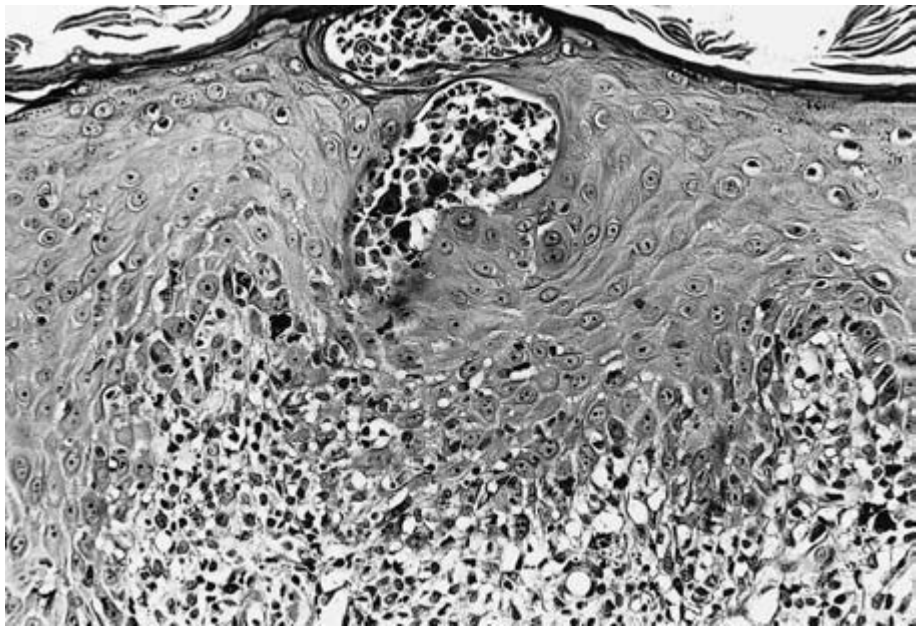


Fig. 1.23 Canine pemphigus erythematosus. Two small intraepidermal pustules contain acantholytic cells. Note interface infiltrate with basal cell vacuolation.

severe. Lichenoid, or band-like, inflammation is not as prominent as it is in facially-predominant pemphigus foliaceus. Also, basal cell damage (interface dermatitis) occurs prominently in PE, and resembles the interface dermatitis of lupus erythematosus (see Chapter 3). However, in order to make a definitive diagnosis of PE, immunofluorescence or immunohistochemical testing should demonstrate deposition of IgG in the intercellular spaces of the epidermis as well as at the basement membrane zone. This represents a combination of the patterns of immunoglobulin deposition seen in both pemphigus foliaceus and lupus erythematosus.

The differential diagnosis is facially-predominant pemphigus foliaceus and its attendant differential diagnoses (see p. 13). Interface degeneration is a feature of PE, but generally is absent in facially-predomimant pemphigus foliaceus. Without confirmatory immunologic findings, assignment of a diagnosis of PE may be difficult. Adherence to the immunologic criteria of PE requires that the diagnosis be made only when immunohistochemical or immunofluorescence testing is compatible, and when other clinical testing (including a positive ANA test) is supportive.

SUBCORNEAL PUSTULAR DERMATOSIS

Clinical features (Figure 1.24)

Subcorneal pustular dermatosis is a very rare, controversial superficial pustular skin disease in the dog. It is the authors' belief that this syndrome has been over-diagnosed in the past; some reported cases may represent



Fig. 1.24 Subcorneal pustular dermatosis in a dog. Yellow pustules, crusting, and collarettes are present on the ventral abdomen. (Photograph courtesy S.D. White; case material University of California, Davis.)

superficial pustular drug reactions or superficial pustular dermatophytosis. The etiology of subcorneal pustular dermatosis is not known.

Affected dogs are reported to have a generalized or multifocal, pustular and exfoliative dermatitis (McKeever & Dahl, 1977; Kalaher & Scott, 1990; Scott et al., 2001). The face and ears are commonly involved. The pustules may be green or yellow (Scott et al., 2001). Pustules are transient and are accompanied by crusting, scaling, alopecia, erythema, and epidermal collarettes. Pruritus is variable but may be extreme.

Miniature Schnauzers are reported as a breed at high risk (McKeever & Dahl, 1977). Age or sex predilections

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have not been noted. Some affected dogs have been puppies (under 6 months of age). One author (T.L.G.) has seen several cases of nonantibiotic-responsive subcorneal pustular skin disease in Dachshunds.

Major clinical differential diagnoses include superficial bacterial folliculitis, pemphigus foliaceus, superficial pustular dermatophytosis, or pruritic skin disease with secondary superficial bacterial folliculitis. Repeated bacterial cultures of intact pustules and dermatophyte cultures of crusts are negative in subcorneal pustular dermatosis. Subcorneal pustular dermatosis should be considered a diagnosis of exclusion based on both clinical and histopathologic parameters.

Biopsy site selection

Care should be taken to biopsy new intact pustules. The differentiating features of subcorneal pustular diseases cannot be distinguished in disrupted or aged lesions.

Histopathology (Figures 1.25 and 1.26)

Subcorneal pustules without bacterial or dermatophytic colonization or significant acantholysis are the principal histopathologic prerequisites for the diagnosis. Pustules range from small to broad; some pustules are greatly elevated above the adjacent epidermal surface. Pustules are usually accompanied by underlying spongiosis. Neutrophils and variable eosinophils compose the pustules. Acantholysis is absent or very mild.

The dermis has superficial perivascular to interstitial, mixed inflammation with neutrophils predominating. Mild to moderate dermal edema is common.

Immunofluorescence or immunohistochemical testing for IgG is negative. It is unknown if some cases of subcorneal pustular dermatosis are IgA-associated, as in humans, since IgA testing is not routinely performed in diagnostic laboratory settings. IgA assays on several cases observed by the authors, and others (Olivry, T.O., personal communication, 2001) have been negative. In general, subcorneal pustular dermatosis has been diagnosed histopathologically by exclusion; results of clinical response to therapy have been as important as histopathologic findings in obtaining a diagnosis. Subcorneal pustular dermatosis may represent a heterogeneous group of diseases, including pustular drug reactions (see p. 23). Subcategorization awaits further investigation.

Differential diagnoses include impetigo and pemphigus foliaceus, both of which are more common than subcorneal pustular dermatosis. Pustules of pemphigus foliaceus demonstrate prominent acantholysis; intact pustules of impetigo should contain bacteria.

STERILE PUSTULAR ERYTHRODERMA OF MINIATURE SCHNAUZERS

(Synonyms: superficial suppurative necrolytic dermatitis of Miniature Schnauzers, Schnauzer syndrome)

Clinical features (Figures 1.27 and 1.28)

Sterile pustular erythroderma of Miniature Schnauzers is a rare, severe cutaneous and visceral reaction pattern seen exclusively in Miniature Schnauzers. The syndrome was first noted by Walder and Rosenkrantz and occurred within 48 hours after the use of various shampoos (Gross & Schick, 1993). Multiple cases have



Fig. 1.25 Subcorneal pustular dermatosis demonstrating broad superficial pustule.

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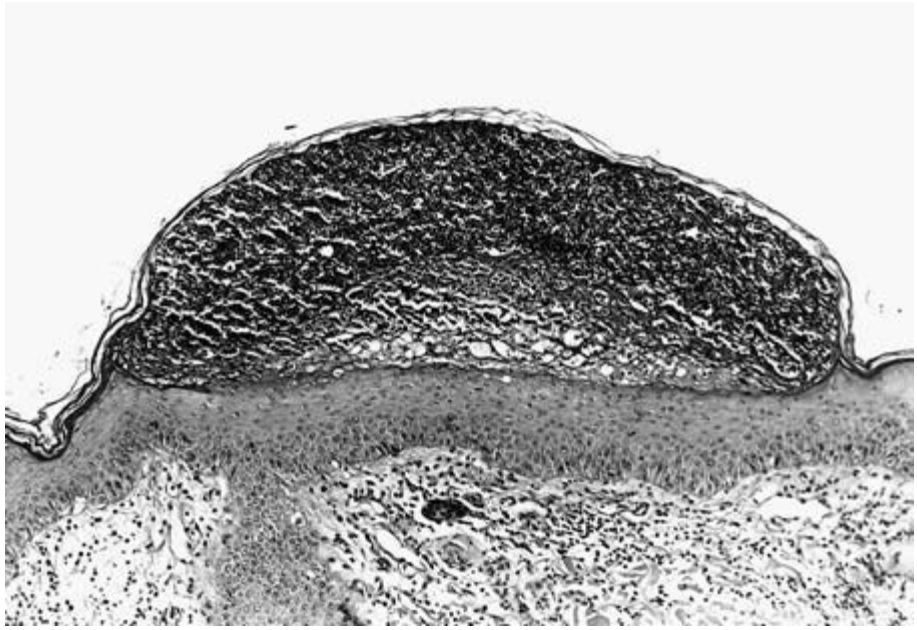


Fig. 1.26 Pustule of subcorneal pustular dermatosis. Note elevation above surface of epidermis.



Fig. 1.27 Sterile pustular erythroderma of Miniature Schnauzers. Note erythema and focal areas of erosion and ulceration. (Photograph courtesy L.P. Schmeitzel; case material University of California, Davis.)

been seen after the use of various 'herbal' shampoos. However, a seemingly identical clinical syndrome has been noted in several dogs with no confirmatory history of recent shampooing (Vitale, C. B., personal communication, 2003).



Fig. 1.28 Sterile pustular erythroderma of Miniature Schnauzers in the same dog as in Fig 1.27 photographed later in the course of disease. Note that macular erythema, erosion, and ulceration have increased in severity. (Photograph courtesy L.P. Schmeitzel; case material University of California, Davis.)

The etiology is unknown, but is suspected to be associated with an adverse drug reaction or exposure to other unusual allergens or immunogens, including, possibly, systemically absorbed components of certain shampoos or other chemical products. The presence of pyrexia and depression, neutrophilic leukocytosis, as well as heart, lung, and liver lesions in some cases, indicates systemic involvement. Marked clinical and histopathologic similarities to canine sterile neutrophilic dermatosis (Sweet's syndrome; see Chapter 14) suggest that this syndrome may be a related phenomenon.

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The characteristic clinical features include erythematous papules and macular erythema which coalesce to form highly erythematous edematous plaques with suppurative crusts. The magnitude of erythema may be visually striking. Concurrent small pustules or vesicles may be present transiently. Expanding areas of marked erythema and erosion can rapidly lead to profound ulceration with exfoliation. Lesions initially may be localized, but rapidly generalize. Alopecia develops in conjunction with ulceration. The trunk is affected preferentially, but lesions may occur anywhere. The authors are aware of several cases in which pinnal lesions were prominent. Lesional areas are markedly painful, even before ulceration occurs. Fever, depression, and leukocytosis are common. Visceral lesions have been observed (see below). Very low serum albumin levels may be present (Vitale, C.B., personal communication, 2003). Many affected dogs die.

Sterile pustular erythroderma of Miniature Schnauzers occurs only in this breed. Affected dogs have been adults; sex predilections have not been noted.

Clinical differential diagnoses are few; the syndrome is highly characteristic, largely due to its confinement to the Miniature Schnauzer. Most likely clinical differential diagnoses include toxic epidermal necrolysis, severe erythema multiforme, toxic shock syndrome, and canine sterile neutrophilic dermatosis (Sweet's syndrome). The recognition of rapid onset, generalizing ulcerative skin disease in a Miniature Schnauzer heightens suspicion, as does a history of shampooing within 24 to 48 hours.

Biopsy site selection

Multiple areas of erythema, papules and plaques without evidence of ulceration should be sampled. Well-developed lesions may show more characteristic histopathologic changes.

Histopathology (Figures 1.29 and 1.30)

In sterile pustular erythroderma of Miniature Schnauzers, the epidermis often contains extensive broad pustules evolving to crusts; these may be more apparent in late-stage fully formed lesions of this syndrome. Pustules may be subcorneal to panepidermal. There may be ulceration and exudation. Pustular inflammation may extend to superficial hair follicles. In some specimens there is acanthosis and variable spongiosis with only small pustules. Apoptotic-appearing keratinocytes which appear shrunken and brightly eosinophilic may be observed rarely in some lesions, and may be secondary to ischemia from vascular damage (Binder, S., personal communication, 2002). Dermal lesions include neutrophilic and eosinophilic inflammation with variable edema; vasculopathic and vasculitic changes may be observed (see Chapter 14).

As in some dogs with sterile neutrophilic dermatosis (see Chapter 14), pulmonary interstitial neutrophilic infiltrates may occur. Myocardial and hepatic necrosis has been observed; hepatic lesions suggest terminal disseminated intravascular coagulation (DIC).

Differential diagnoses for the epidermal pustular lesions of this syndrome include severe impetigo, subcorneal pustular dermatosis, and superficial pustular drug reactions that do not feature acantholysis. In contrast to the other diseases, the dermal inflammatory lesions of toxic pustular erythroderma may be more intense, more eosinophilic, and include vasculitic change (see Chapter 14). Clinical differentiation may be required. Apoptosis with epidermal neutrophilic infiltrates are seen in toxic shock syndrome, and may be severe and diffuse in later stages of that disease. Pustules are generally larger and epidermal apoptotic necrosis much milder in sterile pustular erythroderma of Miniature Schnauzers than in late stage toxic shock syndrome.

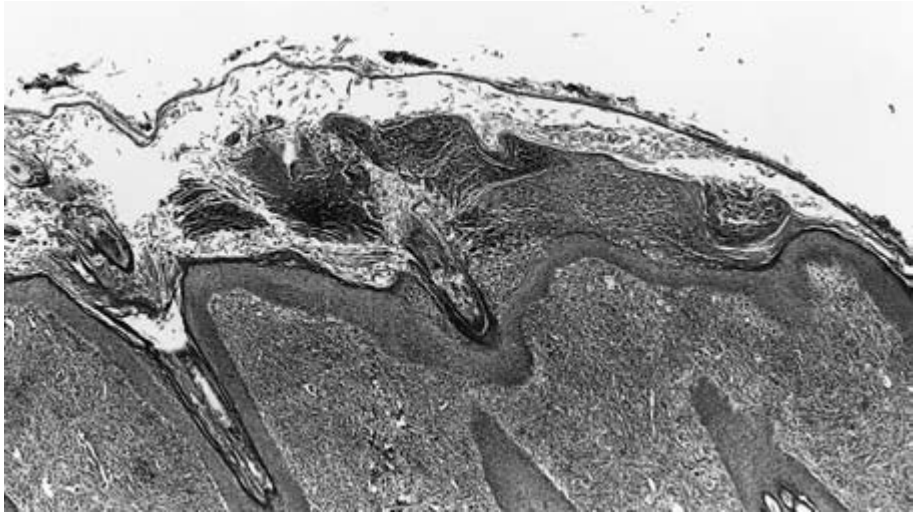


Fig. 1.29 Large superficial pustule of sterile pustular erythroderma. Note extension to follicles and severe dermal inflammation.

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Fig. 1.30 High magnification of pustule in sterile pustular erythroderma. Pustulation is accompanied by extensive spongiosis; note extension to follicular infundibula.

SUPERFICIAL PUSTULAR DRUG REACTIONS

Clinical features (Figure 1.31)

Superficial pustular drug reactions occur as adverse reactions to various drugs. Some overlap occurs between superficial pustular drug reactions and drug-related pemphigus foliaceus (see p. 13). The term 'superficial pustular drug reaction' is advisable if clinical, histopathological, and immunopathological parameters stray too far from those seen with naturally occurring pemphigus foliaceus. Superficial pustular drug reactions, clinically divergent from classical pemphigus foliaceus, have been noted by one author (P.J.I.) as a sequela to the administration of various drugs, including antibiotics (trimethoprim-potentiated sulfonamides, cephalexin, ampicillin, amoxicillin, ormetoprim-potentiated sulfonamides) and antihistamines (diphenhydramine). The authors have seen superficial pustular drug reactions to methimazole in cats.

Clinical features include transient superficial pustules or vesicopustules. Similar to pemphigus foliaceus, pustules may occur in waves. Individual pustules may be markedly pleomorphic, and vary considerably in size and shape, being either circular or irregular. As in other canine and feline pustular skin diseases, primary lesions may eventuate rapidly in adherent crusts with marked exfoliation. Alopecia may be present. Pruritus is variable. Sites of involvement vary considerably; lesions may localize to discrete regions such as the head or pinnae, or may be more generalized. In general, the pustules or vesicopustules seen with superficial pustular drug reactions tend to be less bilaterally symmetric than those seen with pemphigus foliaceus. Oral cavity lesions may be seen.



Fig. 1.31 Superficial pustular drug reaction in a dog due to amoxicillin. Individual pustules are markedly pleomorphic. (Photograph courtesy M. Rosenbaum.)

Major clinical differential diagnoses include superficial bacterial folliculitis, pemphigus foliaceus, and superficial pustular dermatophytosis. Clinical features not compatible with these diseases (oral ulceration, unusual patterns of distribution) should alert the clinician to the possibility of a superficial pustular drug reaction. Pemphigus foliaceus may be the most difficult disease to differentiate from superficial pustular drug reactions. In cases that clinically, histologically, and immunologically mimic pemphigus foliaceus exactly, the designation of 'drug-related

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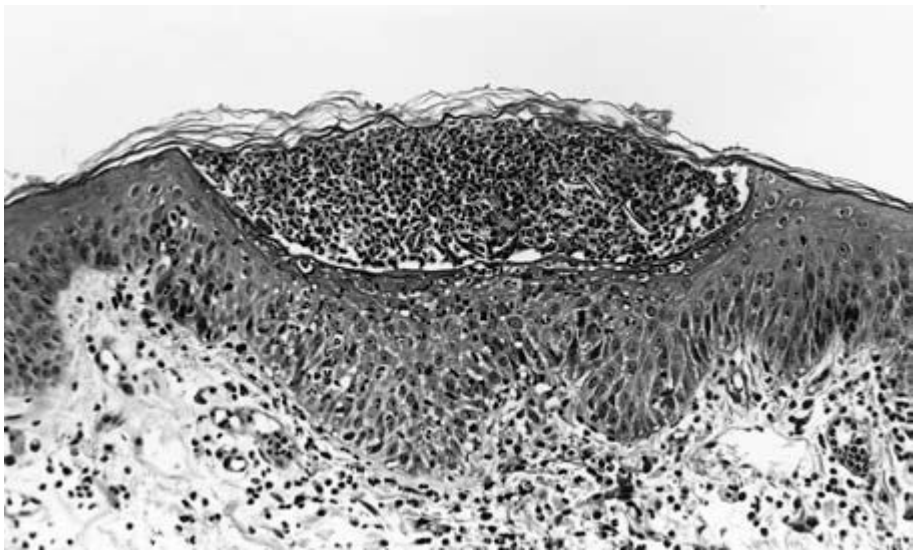


Fig. 1.32 Superficial pustular drug reaction in a dog due to trimethoprim-sulfa.

pemphigus foliaceus' rather than superficial pustular drug reaction may be more appropriate.

Biopsy site selection

As in other superficial pustular disease, intact pustules are fragile and should be sampled promptly. Early lesions are more likely to yield diagnostically helpful results. Sites directly adjacent to early pustules should be sampled for direct immunofluorescence or immunohistochemical testing.

Histopathology (Figures 1.32 and 1.33)

Superficial pustulation is the principal histologic pattern of this type of drug eruption. If acantholysis is a prominent feature, then drug-related pemphigus foliaceus is the preferred diagnosis (see above). In other cases, superficial pustulation without prominent acantholysis is observed in association with variable crusting. There may be variable apoptosis, as seen in erythema multiforme (see Chapter 4). Apoptosis of keratinocytes has been reported in drug-related pemphigus foliaceus in dogs (White et al., 2002). Those cases may represent collision of two immunoreactive drug-related processes rather than pemphigus foliaceus with excessive apoptosis.

The dermis has superficial perivascular to interstitial, mixed inflammation with neutrophils predominating. Eosinophils may be prominent. Mild to moderate dermal edema is common.

Differential diagnoses include non drug-induced pemphigus foliaceus, superficial pustular bacterial infections (impetigo and superficial spreading pyoderma), and

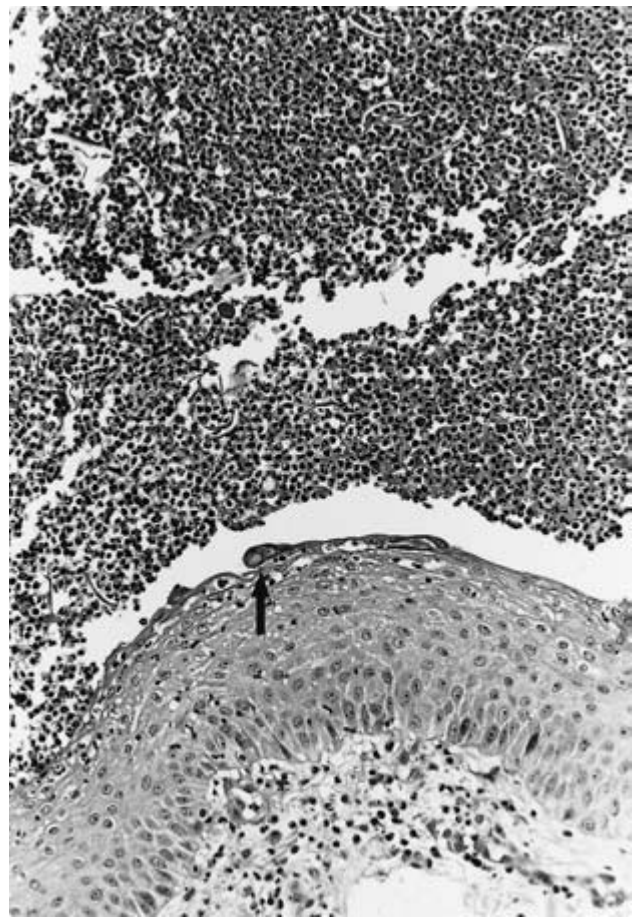


Fig. 1.33 High magnification of pustule from the same dog as in Fig. 1.32. Note mild acantholysis at base of pustule (arrow).

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subcorneal pustular dermatosis. Microscopic delineation often is not possible; instead response to drug withdrawal may be required for definitive diagnosis.

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Chapter 2

Bullous and acantholytic diseases of the epidermis and the dermal–epidermal junction

Bullous and acantholytic diseases are characterized by the formation of clefts, leading to vesicles or bullae. In bullous diseases, separation most commonly occurs between the dermis and epidermis, and results from loss of structural integrity of the basement membrane zone. In acantholytic disease, adhesion between keratinocytes is degraded, resulting in separation and cleft formation. Some diseases in this chapter may not be characterized by obvious clinical vesicles or bullae; for simplicity and clarity, diseases that show microscopic bullous or acantholytic degeneration of the epidermis, or of the basement membrane zone, are included regardless of clinical presentation. Bullous and acantholytic diseases frequently are the result of autoimmune processes which create autoantibodies that damage the basement membrane zone, basal cells, or the intercellular adhesion structures of the keratinocytes. Genetic defects in the structural integrity of these regions also characterize some diseases of this group.

Subepidermal bullous diseases have variable clinical presentations, as well as differences in histologic characteristics. These include the shape of bullae, the degree and type of accompanying dermal inflammation, and the presence or absence of immunoglobulin or complement at the basement membrane zone. However, it is not usually possible histologically to specify individual diseases beyond 'subepidermal blistering or bullous'. Immunologic studies for detection of *in situ* and circulating autoantibodies directed against basement membrane components, as well as immunoblotting, enzyme-linked immunosorbent assay (ELISA) testing, and other studies to characterize the targeted antigens specifically are required.

BULLOUS PEMPHIGOID

Clinical features (Figures 2.1 and 2.2)

Bullous pemphigoid (BP) is a very rare vesiculobullous subepithelial autoimmune skin and mucosal disease of the dog and cat. Autoantibodies are directed against the 180 kDa bullous pemphigoid antigen (BP180/BPAG2) which is a constitutive transmembrane glycoprotein present in basal keratinocytes. IgG autoantibodies target antigenic epitopes located in the NC16A ectodomain of type XVII collagen, similar to bullous pemphigoid in humans (Iwasaki et al., 1995; Olivry et al., 1999). Since the lesion is subepidermal, intact vesicles or bullae are seen more commonly than with other bullous autoimmune skin diseases such as pemphigus vulgaris, in which lesions form intraepidermally and are thus more fragile.

The wide variation in clinical presentation of formerly reported cases probably indicates that multiple subepidermal bullous diseases were identified incorrectly as BP. Definitive differentiation among the subepidermal bullous diseases requires the identification of the antigen targeted by the pathogenic antibodies. Consequently, case data published prior to the documentation of canine and feline autoantibodies directed against the BP antigen (1995 and 1999, respectively) are suspect, and may represent various subepidermal bullous diseases. In a recent study, BP accounted for 12% of 59 dogs and 50% of eight cats diagnosed as having antibasement membrane circulating autoantibodies (Olivry, T., personal communication, 2004).

Erythematous macules eventuate in multifocal vesicles that progress to variably sized bullae with irregular borders. Smaller vesicles and bullae may remain intact in protected sites such as the pinnae, axillae, and buccal gingiva. Since canine and feline epidermis is relatively thin, most bullae rupture, leading to multifocal ulceration as the most common clinical sign. Generally, the ulcers do not coalesce and spread, and tend to remain the same size as the previous bullae. Scarring is common, but variable in severity. New vesicles and bullae frequently develop within scarred lesions. Secondary bacterial infection is frequent. The typical clinical course of true BP seems to be chronic but relatively mild (Olivry & Chan, 2001).

Even though the diagnosis of BP has been confirmed immunologically in only seven canine patients, the review of this small case series permits useful clinical observa-

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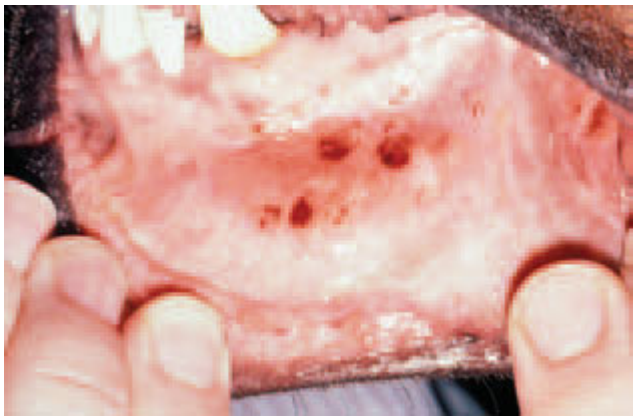


Fig. 2.1 Bullous pemphigoid affecting the buccal mucosa of a Doberman Pinscher. Multiple intact bullae are present amid well-demarcated ulcers resulting from ruptured bullae. (Photograph courtesy L.P. Schmeitzel; case material University of California, Davis.)



Fig. 2.2 Bullous pemphigoid of the inner surface of the pinna of the dog seen in Fig 2.1. Note the centrally located large, intact bulla and multiple smaller bullae. (Photograph courtesy L.P. Schmeitzel; case material University of California, Davis.)

tions (Olivry, 2003). In this series, skin lesions of canine BP consisted of erythematous macules, patches or plaques (4/7; 57%); tense vesicles or bullae (3/7; 43%); ulcers (6/7; 86%); as well as crusts (5/7; 71%). In these dogs, lesions of BP occurred first on the head, ears, or trunk. At the time of diagnosis, lesions could be seen on the back (4/7; 57%), axillae (2/7; 29%), and abdomen (2/7; 29%). Pawpads were rarely affected in dogs with BP. Lesions at mucosal or mucocutaneous junctional sites were detected in four dogs (57%), with a median number of one such site being affected. Lesions involved primarily the oral cavity (3/7; 43%), lip margins (4/7; 57%), and sparsely-haired skin of the concave pinnae (4/7; 57%). In most patients, there were no systemic signs associated with blistering episodes. Although some dogs have oral and perioral involvement, oral lesions may occur in less than one-half of the dogs with well characterized disease (Olivry & Chan, 2001). Other sites include mucocutaneous junctions of the anus, as well as the skin of the clawbeds. In the cat, the lips, pinnae, and both the hard and soft palate may be predilection sites.

Subepidermal bullae arising in and restricted to scar tissue from presumptively traumatic etiology (including burns) have been observed rarely in dogs by the authors. Immunologic studies confirming BP have not been performed for these lesions, and thus the true nature of this phenomenon has yet to be determined. In humans, physical trauma, notably burns, has provoked BP, presumably by exposing BP antigen in the basement membrane (Wagner & Paraskevopoulos, 1995). However, bullous lesions usually spread to other cutaneous sites due to the presence of circulating autoantibodies (Wagner & Paraskevopoulos, 1995).

Previously published signalment predilections may be inaccurate, as previously reported cases may have been other subepidermal bullous diseases. The Doberman Pinscher and Collie are reported to be at increased risk. However, at least some of the Collies reported as having BP may have had vesicular cutaneous lupus erythematosus of Collies and Shetland Sheepdogs (see Chapter 3). The Dachshund also may be at increased risk. Unlike the human homologue, canine and feline BP may affect animals of any age (Olivry & Chan, 2001). Genetic factors have been postulated to explain the occurrence of autoimmune skin disease in younger domestic animals (Olivry, 2002). Sex predilections are not reported.

Major clinical differential diagnoses include epidermolysis bullosa acquisita, mucous membrane pemphigoid, vesicular cutaneous lupus erythematosus of Collies and Shetland Sheepdogs, pemphigus vulgaris, erythema multiforme, and bullous drug eruptions. In dogs with BP, there are usually no systemic signs associated with blistering episodes and pawpads are rarely affected, in marked contrast to canine epidermolysis bullosa acquisita (Olivry, 2003). Differentiation from genetic diseases of structural integrity such as hereditary epidermolysis bullosa usually should not be problematical since these occur either at birth or in very young animals. In comparison to pemphigus vulgaris, the ulcers of BP do not coalesce and spread, and tend to remain the same size as the previous bullae; furthermore, oral lesions are less common in BP than in pemphigus vulgaris (Olivry, 2003). Compatible histopathology and further immunologic testing, including target antigen identification, are required for definitive diagnosis.

Biopsy site selection

If present, an intact bulla or vesicle should be removed in its entirety, preferably by excisional biopsy.

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Shearing forces created during punch biopsy may rupture fragile lesions. Biopsy should be performed as soon as possible, because intact lesions may be transient and ruptured lesions are less likely to yield diagnostic specimens. If an intact lesion is not available, tissue from the immediate margin of a recently ruptured bulla may be adequate for histopathologic interpretation.

Histopathology (Figures 2.3 and 2.4)

A small to large, often turgid vesicle or bulla develops at the dermal–epidermal junction. In early lesions there is intact epidermis above a clean separation between dermis and epidermis. Cleft formation may extend to follicular infundibula. Within and along the base of the bullae there are eosinophils and neutrophils, often intermingled with fibrin. There may be a relative lack of inflammatory cells within bullae of the feline disease (Olivry et al., 1999). As the lesion ages, the epidermal roof of the bulla may be spongiotic; degeneration eventuates in ulceration. Eosinophilic spongiosis has been described (Tomlinson et al., 2001).

The dermis is generally only minimally to mildly inflamed beneath early bullae. Characteristically, although not consistently, eosinophils line up in rows and clusters just beneath the basement membrane of intact skin as well as beneath blisters. Eosinophils may be degranulated (Iwasaki et al., 1995), requiring demonstration with a Luna stain in some cases. Eosinophils, neutrophils, and mixed mononuclear cells may be found superficially in a perivascular and interstitial pattern. Edema usually is present. Advanced lesions may have more intense dermal edema and inflammation that is eosinophil rich (Iwasaki et al., 1995). Secondary ulceration results in severe neutrophilic dermatitis and fibrinosuppurative exudation.

Antigen immunomapping with a collagen IV-specific monoclonal antibody demonstrates vesiculation above collagen IV (a major component of the lamina densa), confirming cleavage through the lamina lucida (Olivry et al., 2000). Direct immunofluorescence (or immunohistochemistry) detects fine linear deposition of IgG in dogs and cats. In rare instances, faint staining extends around basal keratinocytes, representing recycled BP180 antigen (Olivry et al., 1999). IgM and C3 also have been demonstrated in dogs (Iwasaki et al., 1995).

Indirect immunofluorescence testing identified circulating IgG antibodies that were directed to the epidermal side of salt-split skin (the artificial split occurs through the lamina lucida of the basement membrane) (Iwasaki et al., 1995; Olivry et al., 1999). Immunoblotting identified the targeted antigen in dogs and cats as a 180 kDa protein, BP antigen 2 (BPAG2), which was further characterized as type XVII collagen (Olivry et al., 1999).

Differential diagnoses principally include epidermolysis bullosa acquisita, inherited epidermolysis bullosa, mucous membrane pemphigoid, and linear IgA dermatosis. Inherited epidermolysis bullosa is generally sparsely inflamed, as may be linear IgA dermatosis. When present, intense accumulations of eosinophils at the base of a bulla, or along the basement membrane in intact skin, favor a diagnosis of BP, while numerous neutrophils in the same location favor epidermolysis bullosa acquisita. Mucous membrane pemphigoid may feature lichenoid



Fig. 2.3 Subepidermal bulla of canine bullous pemphigoid. (Case material courtesy R.W. Dunstan.)

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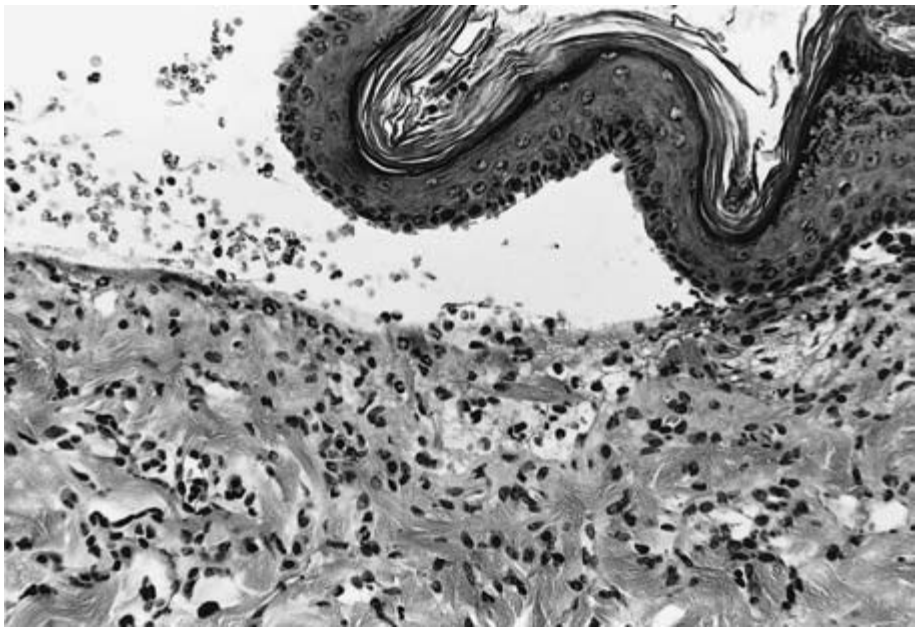


Fig. 2.4 Higher magnification of Fig. 2.3. Note red blood cells and small numbers of granulocytes in bulla.

dermatitis, which is not generally seen in other subepidermal vesicular diseases. Although a tentative histologic diagnosis may be possible, confirmatory immunologic studies are required for definitive diagnosis. Clinical features may be supportive, including breed and sites affected, and clinical severity. Knowledge of clinical distribution of lesions is particularly important in the differential diagnosis of this entity from mucous membrane pemphigoid, which is immunologically similar (see below).

MUCOUS MEMBRANE PEMPHIGOID

(Synonym: cicatricial pemphigoid)

Clinical features (Figures 2.5 and 2.6)

Mucous membrane pemphigoid (MMP) is a rare, chronic vesicobullous subepithelial autoimmune disease affecting mucous membranes, mucocutaneous junctions, and haired skin in the dog and cat. Circulating basement membrane-specific IgG autoantibodies are present (Olivry & Chan, 2001). In MMP of dogs and cats (as also seen in humans), the targeted autoantibodies are more heterogeneous than in bullous pemphigoid (Olivry et al., 2001; Olivry et al., 2002). The circulating autoantibodies target different antigenic epitopes, including the NC16A segment of collagen XVII and the 30 kDa carboxy-terminal segment of collagen XVII (Olivry et al., 2001). In one dog, autoantibodies were shown to recognize the three chains of purified human laminin-5 instead (Olivry, 2003); antibodies against the alpha-3 chain of laminin-5 only were identified in a cat (Olivry et al., 2002).



Fig. 2.5 Mucous membrane pemphigoid in a dog. Ulceration is partially bilaterally symmetric and restricted to the planum nasale. (Photograph courtesy T. Olivry.)

Previously, cases of MMP probably were published as bullous pemphigoid. In a recent study, MMP accounted for 53% of 59 dogs and 50% of eight cats diagnosed with antibasement membrane circulating autoantibodies, making MMP the most common autoimmune disease of the basement membrane zone in the dog and cat (Olivry, 2003). One cat initially reported as having bullous pemphigoid was later determined to have MMP (Olivry et al., 1999; Olivry, T., personal communication, 2002).

Erosive and ulcerative lesions are the predominant clinical features, although intact flaccid or turgid vesicles may be present in protected areas. Adherent crusts may be

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found, especially when lesions are located on haired skin. Scarring, when present, may be atrophic. Hypopigmented macules are seen periorbitally in a minority of dogs (Olivry et al., 2001). In one study the most commonly affected sites included, in descending order, the oral cavity, lips, planum nasale, perinasal skin, periorbital region, concave pinnae, genitalia, and anus (Olivry et al., 2001). Oral lesions most commonly affect the gums, hard palate, and tongue. The bulbar conjunctiva is affected in only a small number of dogs, and pawpad lesions are similarly uncommon (Olivry et al., 2001). Similar lesions have been seen in six cats to date (Olivry et al., 2002; Olivry, T., personal communication, 2003). One author (E.J.W.) has seen esophageal lesions in a cat with MMP.



Fig. 2.6 Mucous membrane pemphigoid in a cat. Ulceration is present on the lips, philtrum, and planum nasale. (Photograph courtesy T. Olivry.)

A reference population was not available for statistical comparison, but the German Shepherd Dog may be at increased risk, as it comprised 12 of 42 reported cases (Olivry, 2003). Siberian Huskies, Border Collies, Dachshunds, Poodles, and Cocker Spaniels also may be over-represented as more than one case per breed has been diagnosed with this rare disease (Olivry, 2003). The median age for the initial development of lesions was 5 years (Olivry, 2003). One-third more males than females were affected (Olivry, 2003).

Clinical differential diagnoses for MMP include bullous pemphigoid, epidermolysis bullosa acquisita, vesicular cutaneous lupus erythematosus of Collies and Shetland Sheepdogs, pemphigus vulgaris, erythema multiforme, and bullous drug eruptions. Clinical distribution may be useful diagnostically, due to the marked mucocutaneous predilection of MMP. Histopathology and immunologic studies, including identification of targeted antigens, are required for differentiation.

Biopsy site selection

As in bullous pemphigoid, intact vesicles, if present, should be removed entirely, preferably by excisional biopsy. If an intact lesion is not available, tissue from the margins of recently ruptured bullae may be sampled.

Histopathology (Figures 2.7 and 2.8)

A bulla develops at the dermal–epidermal junction beneath an intact epidermis, as seen in bullous pemphigoid (see p. 27). Some bullae may feature retention of the irregular or peg-like lower contour of the epidermis. Bullae are usually devoid of inflammatory cells but may



Fig. 2.7 Mucous membrane pemphigoid in a dog demonstrating large subepidermal bulla.

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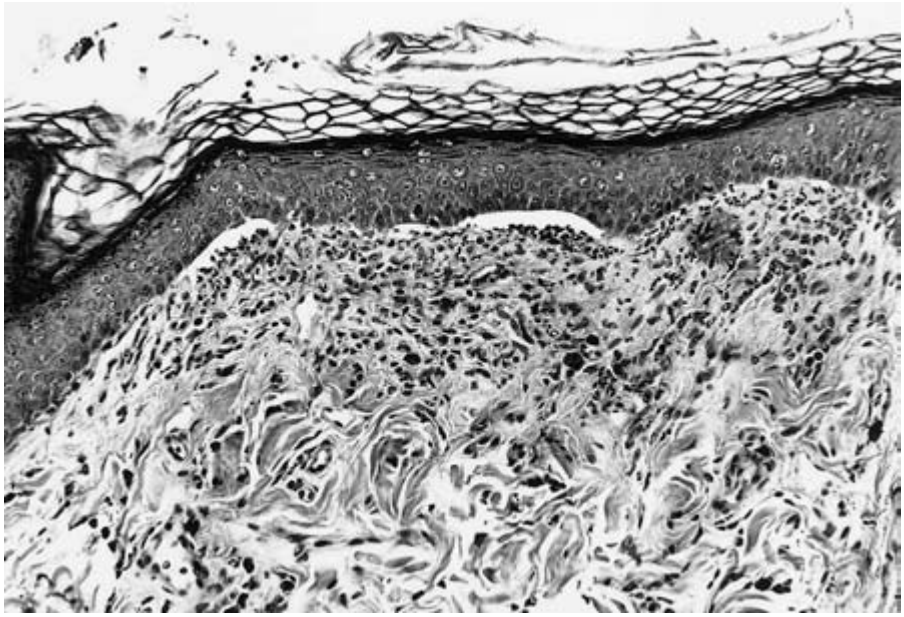


Fig. 2.8 High magnification of early bulla in canine mucous membrane pemphigoid. Note granulocytes in early cleft and subjacent superficial dermis.

contain red blood cells, eosinophils, or neutrophils. Intravesicular eosinophils, neutrophils, and mononuclear cells have been reported in dogs; 52% of 66 skin biopsies contained uninflamed vesicles (Olivry, 2003).

In dogs, the superficial dermis contains neutrophils, eosinophils, and often lymphocytes and plasma cells. Inflammation is usually lichenoid in putatively chronic lesions and may be found in the absence of subepidermal bulla formation. This pattern of inflammation is attributed to the anatomic location of the mucocutaneous lesions, and is as observed in other lichenoid dermatoses of mucous membranes or mucocutaneous junctions, such as mucocutaneous pyoderma (see Chapter 11). There may be a fibrovascular reaction beneath some bullae, suggesting that they are redeveloping at the site of previous lesions. Ulceration is accompanied by more intense neutrophilic inflammation and fibrinosuppurative exudation. In cats, minimal subvesicular inflammation is reported (Olivry et al., 2002).

In dogs, direct immunofluorescence testing detects IgG at the basement membrane of skin or mucosa, and less consistently, C3, IgM, and IgA (Olivry et al., 2001). Direct immunofluorescence testing was negative in one cat reported (Olivry et al., 2002). Indirect immunofluorescence testing identifies circulating IgG antibodies directed to the epidermal side of salt-split skin in most cases in dogs (the artificial split occurs through the lamina lucida of the basement membrane). In addition, IgG autoantibodies were directed to the dermal aspect of the split in one dog and one cat (Olivry et al., 2001, 2002).

Differential diagnoses include epidermolysis bullosa acquisita, inherited epidermolysis bullosa, bullous pemphigoid, and linear IgA dermatosis. Inherited epidermolysis bullosa is generally sparsely inflamed, as may be linear IgA dermatosis. When present, intense accumulations of eosinophils at the base of a bulla, or along the basement membrane in intact skin, favor a diagnosis of bullous pemphigoid, while intense neutrophils in the same location support epidermolysis bullosa acquisita. MMP in dogs may feature lichenoid dermatitis, which is not generally seen in other subepidermal vesicular diseases. Chronic lesions with lichenoid inflammation only may not be distinguishable from mucocutaneous pyoderma. Although a tentative histologic diagnosis may be possible, confirmatory immunologic studies are required for definitive diagnosis. Knowledge of clinical distribution of lesions is important in the differential diagnosis of this entity from bullous pemphigoid, which is immunologically similar (see p. 27).

PEMPHIGUS VULGARIS

(Synonym: suprabasilar pemphigus)

Clinical features (Figures 2.9 and 2.10)

Pemphigus vulgaris (PV) is a very rare, severe vesicobullous and ulcerative autoimmune disease reported in the dog and cat. Desmoglein 3 (Dsg3), a 130 kDa, transmembrane desmosomal cadherin of keratinocytes, is more strongly expressed in the suprabasilar keratinocytes of the oral mucosa, and has been identified as the targeted antigen in canine PV, as occurs in humans (Olivry et al., 2003). However, when lesions of PV affect the haired skin

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Fig. 2.9 Pemphigus vulgaris in an adult Great Dane. Extensive erosion and secondary ulceration are present on the tongue, oral mucous membranes, and muzzle.



Fig. 2.10 Pemphigus vulgaris involving the pawpad of the dog in Fig. 2.9. Note the pad epithelium has been shed to expose dermal tissue.

as well as mucous membranes, other antigens such as desmoglein 1 (Dsg1), which is more strongly expressed in superficial keratinocytes of haired skin, may be targeted. Thus, the clinical phenotype of PV in humans is defined by the antidesmoglein autoantibody profile (Amagai et al., 1999). This variation in or progression of the clinical phenotype may be explained by the phenomenon of 'epitope spreading', in which the primary autoimmune inflammatory process exposes previously sequestered antigens, resulting in a secondary autoimmune response (Chan et al., 1998). A similar circumstance probably exists in animals. The targeted autoantigen in canine PV is Dsg3 (Foster & Olivry, 2001; Olivry et al., 2003). Targeted autoantigens in the case of alopecic PV were Dsg1 and Dsg3 (Olivry & Jackson, 2001).

Drug-induced PV may occur in humans; removal of the offending drug leads to reversal of the lesions (Brenner et al., 1998). PV-like skin reactions putatively due to drug therapy (including sulfasalazine) have been observed sporadically in both dogs and cats. Also, transient, often orally confined, cases not explained by adverse drug reactions have been seen by the authors in these species.

The exact pathomechanism of vesicle and bulla formation is not known. Autoantibodies in the epidermis or mucosal epithelium bind to Dsg3, leading to suprabasilar acantholysis. However, it has recently been shown that autoantibody binding to Dsg3 alone is insufficient for lesion formation; plakoglobin, a submembranous plaque protein in the desmosomal complex, appears critical for the formation of lesions, as demonstrated in mice (Calhedari et al., 2001). Further, upregulation of P-cadherin, an important Ca^{2+} dependent adhesion molecule in the epidermis, occurs in both autoimmune and hereditary acantholytic disorders in humans, and is suggested to be involved in the development of acantholysis (Hakuno et al., 2001).

Suprabasilar acantholysis creates fragile, transient vesicles and bullae that rapidly progress to ulcers. Partial bilateral symmetry, especially facial, can be striking. Fragile, irregularly shaped vesicles and bullae develop in groups. Erythema may precede vesicle formation, especially in haired skin areas (Olivry, 2003). Rupture of vesicles and bullae rapidly leads to erosions; secondary surface bacterial overgrowth then results in widespread ulceration. Crusting is a feature of nonmucosal ulcerations. Ulcers expand, creating lesions that are substantially larger than the previously existent intact bullae. These ulcers are irregularly shaped and may coalesce further. A positive Nikolsky sign (the artificial extension of a blister or ulcer induced by digital pressure to adjacent mucous membrane or skin) may be elicited. In a recent meta-analysis of all published dogs with PV, trauma to eroded areas resulted in deeper ulceration in 71% of cases (37/52) (Olivry, 2003).

Most dogs and cats have lesions affecting the oral cavity and mucocutaneous junctions. Coalescing ulcers on the tongue, palate, and gingiva which are not contiguous with the teeth should increase clinical suspicion for PV. Lip involvement usually is seen with extensive oral disease. Thick, ropy, tenacious, odorous saliva is an additional feature.

Pemphigus vulgaris commonly evolves from a mucosal predominant to a mucocutaneous phenotype (Olivry, 2003). Affected body regions in the dog include the oral

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cavity (31/40; 78%), concave pinnae and auditory orifices (20/40; 50%), nasal planum (18/40; 45%), lip margins (14/40; 35%), genitalia (13/40; 33%), anus (10/40; 25%) or periocular skin (9/40; 23%) (Olivry, 2003). Erosive perionyxis/paronychia can occur (6/40; 15%), usually in conjunction with onychomadesis (shedding of claws) (5/40; 13%) (Olivry, 2003). Corneal ulcers and esophageal involvement may be present. Haired skin lesions occur most commonly (18/35; 51%) in regions of friction and trauma such as the axillae, groin, and lateral pressure points of the limbs (hocks, stifles, and digits) (Olivry, 2003). Pawpads may slough in a minority of cases. Lethargy, anorexia and depression may be seen in more severe cases (Carlotti et al., 2000). Transient cases, whether drug-induced or idiopathic, may be clinically atypical in distribution and severity; for example, oral involvement may be lacking and the affected animal may not show signs of systemic ill health.

A variant affecting only the planum nasale and the adjacent haired muzzle has been reported (Olivry et al., 1992; Foster & Olivry, 2001). Well demarcated, severe erosions and ulcerations characterize this subgroup. A single case of a dog affected with an alopecic phenotype of PV, characterized by multifocal predominantly truncal alopecia, has been reported (Olivry & Jackson, 2001).

Although reference populations are lacking, the German Shepherd Dog and the Collie appear to be overrepresented by meta-analysis of data from 52 dogs (Olivry, 2003). The median age at onset is 6 years, with 48% developing the disease at more than 7 years of age (Olivry, 2003). Dogs less than 1 year of age may be affected (Carlotti et al., 2000). Males outnumbered females by approximately three to two (Olivry, 2003). Age, breed, or sex predilections have not been noted for the cat.

Major clinical differential diagnoses include paraneoplastic pemphigus, mucous membrane pemphigoid, bullous pemphigoid, epidermolysis bullosa acquisita, erythema multiforme, and mycosis fungoides, all of which may cause similar oral ulcers. If lesions are limited to the oral cavity, the many causes of feline and canine ulcerative stomatitis must also be considered. Superficial necrolytic dermatitis and mucocutaneous candidiasis can present with perioral skin disease; however, frank oral ulceration is not a feature. Differentiation from genetic diseases of structural integrity, such as hereditary epidermolysis bullosa, should not be problematical since those conditions occur either at birth or in very young animals. Most dogs that develop PV are adult or aged. In contrast to bullous pemphigoid, the ulcers of PV coalesce and expand, leading to lesions that are substantially larger than previously existent intact bullae. Histopathology should allow differentiation.

Biopsy site selection

Intact vesicles or margins of recent ulcers should be removed for biopsy. In general, specimens from the lips or other cutaneous sites are more likely to yield diagnostic results, because lesions of the oral mucosa are extremely fragile. Rapid natural degradation of vesicles or bullae also makes sampling difficult. Due to the frailty of the lesions, wedge biopsy more commonly yields diagnostic specimens than does punch biopsy.

Histopathology (Figures 2.11 and 2.12)

The typical lesion of PV is a suprabasilar cleft or separation due to acantholysis, leading to formation of a bulla. Often the roof of the bulla detaches from a specimen, leaving a row of basal cells attached to the basement membrane. This row of plump or rounded basal cells, commonly called 'tombstone' cells, remains at the base of the cleft. Active acantholysis may be seen above the cleft, and free acantholytic cells may be present within the lumen. Bubble-like vacuoles may occur in basal and suprabasilar locations, and delineate the sites of future clefts. Inflammation is absent from intact bullae. Neutrophils and acantholytic cells intermingle on the surface of deroofed bullae. Secondary ulceration and fibrinosuppurative exudation are common sequelae.

Lesions involve the mucosal epithelium or epidermis, and frequently extend to superficial and sometimes deep hair follicles. Follicular lesions are often characterized by drop-out of follicular root sheath cells beyond the retained outermost cell layer, creating a striking suprabasilar cleft or space that does not disturb the central hair shaft. In the alopecic form of PV, suprabasilar cleft formation was confined to the isthmus and inferior segments of the hair follicle. The epidermis was not affected (Olivry & Jackson, 2001).

Deep follicular pustulation in hair follicles, as seen in 'panfollicular' pemphigus foliaceus (see Chapter 16), may mimic lesions of pemphigus vegetans (a variant of PV) because the pustules may lie in suprabasilar location, thus mimicking the suprabasilar clefting of pemphigus vegetans. The case in the first edition of this textbook was most likely panfollicular pemphigus foliaceus and not pemphigus vegetans. The authors have not seen a convincing case of pemphigus vegetans in the dog or cat.

Superficial dermal inflammation is variable, and includes lymphocytes, plasma cells, and neutrophils. Extension around hair follicles may be present. The composition and severity of the infiltrate are contingent partly upon the presence of deroofed bullae or ulcers, the latter of which are associated with more intense neutrophilic inflammation. In nasally predominant PV,

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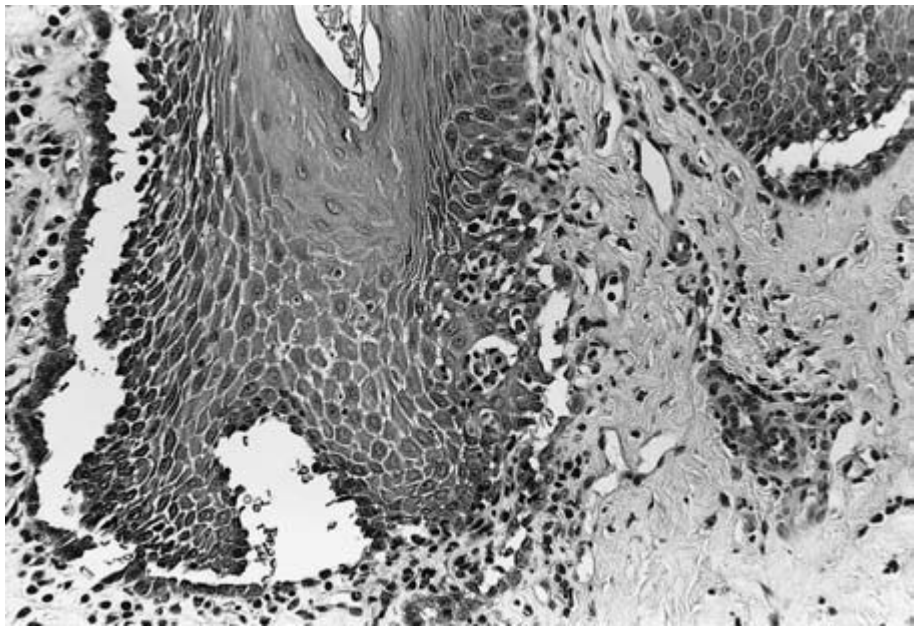


Fig. 2.11 Suprabasilar cleft in canine pemphigus vulgaris. Note involvement of superficial hair follicle. (Case material courtesy M.B. Calderwood Mays.)

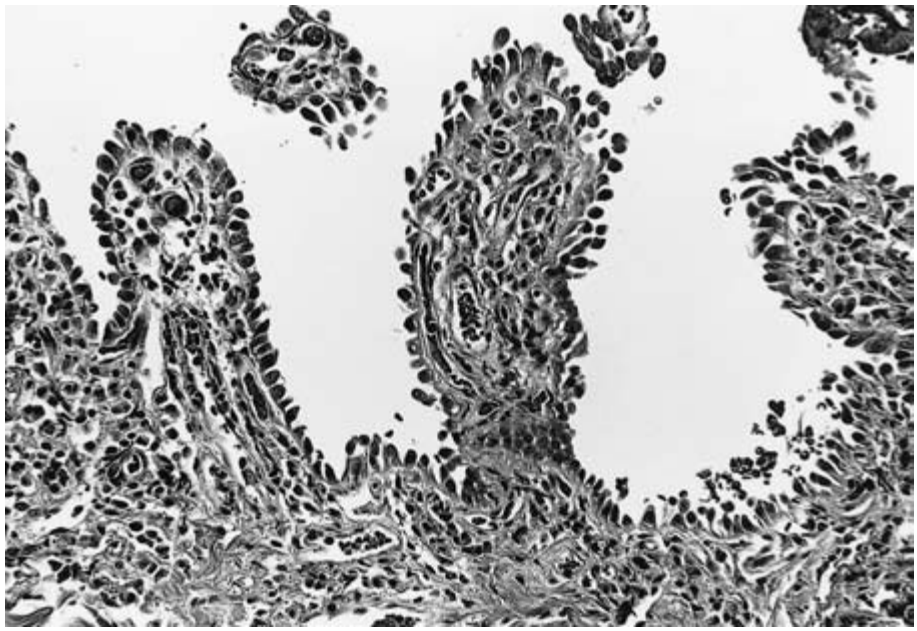


Fig. 2.12 Canine pemphigus vulgaris. Residual basal cells are in tombstone-like configuration along the base of the cleft.

inflammation is often lichenoid, reflecting mucocutaneous (planum) location. Pigmentary incontinence may be present.

Immunofluorescence or immunohistochemical findings are transepidermal and superficial follicular intercellular deposition of immunoglobulin, usually IgG, and occasionally C3. Direct immunofluorescence testing of nasally predominant PV revealed IgG (Foster & Olivry, 2001). As in pemphigus foliaceus, a positive result is not always forthcoming from random biopsy. Obtaining multiple sequential specimens for immunohistologic evaluation may increase the chances of a positive result. Indirect immunofluorescence testing has identified circulating IgG antikeratinocyte antibodies (Olivry et al., 2003); these antibodies mostly target Dsg3.

Differential diagnosis is uncomplicated in cases where characteristic suprabasilar clefting is found. Paraneoplastic pemphigus often has the suprabasilar cleft formation of PV, but is more profoundly pustular (see p. 36), and includes apoptosis of keratinocytes.

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PARANEOPLASTIC PEMPHIGUS

Clinical features (Figures 2.13 and 2.14)

Paraneoplastic pemphigus (PNP) is a very rare, severe autoimmune blistering disease affecting the mucosa and mucocutaneous junctions that is seen in conjunction with neoplasia. Lesions resemble pemphigus vulgaris. In humans with PNP, a mixed and variable panel of targeted antibodies includes multiple plakin family proteins (such as multiple recombinant proteins of envoplakin and periplakin) and various antidesmoglein antibodies (Nagata et al., 2001; Ohyama et al., 2001). A dog with thymic lymphoma and skin lesions homologous to PNP in humans has been reported (Lemmens et al., 1998). Immunologically, the disease was characterized by autoantibodies directed against envoplakin and periplakin (de Bruin et al., 1999). Interestingly, the first of three dogs reported with pemphigus foliaceus by Stannard et al. (1975) had clinical and histological features more commensurate with a diagnosis of PNP; a thymoma was discovered in that patient. Recently, PNP has been documented in a dog with a splenic sarcoma (Elmore et al., 2003). In that dog, antibodies targeted bullous pemphigoid antigen 1 (BPAG1), desmoplakins I and II, envoplakin, and periplakin, as well as extracellular segments of human desmoglein 3 (Dsg 3) and canine desmoglein 1 (Dsg 1) (Elmore et al., 2003). Dsg 1 is the usual targeted autoantigen in pemphigus foliaceus (see Chapter 1), but also has been identified in an alopecic form of pemphigus vulgaris (see p. 32). Dsg 3 is the usual targeted autoantigen in pemphigus vulgaris (see p. 32). As plakin autoantibodies also have been found in human cases of pemphigus foliaceus and pemphigus vulgaris, they are not considered unique or specific for the identification of PNP (Nagata et al., 2001; Ohyama et al., 2001). The exact immunologic mechanism for this entity remains undiscovered. T cell mediated keratinocyte apoptosis has been demonstrated in human PNP (Reich et al., 1999), and likely is a major contributor to the disease.



Fig. 2.13 Paraneoplastic pemphigus in a dog. Bilaterally symmetric facial ulceration is present on the dorsal muzzle and periorbitally. (Photograph courtesy T. Olivry.)

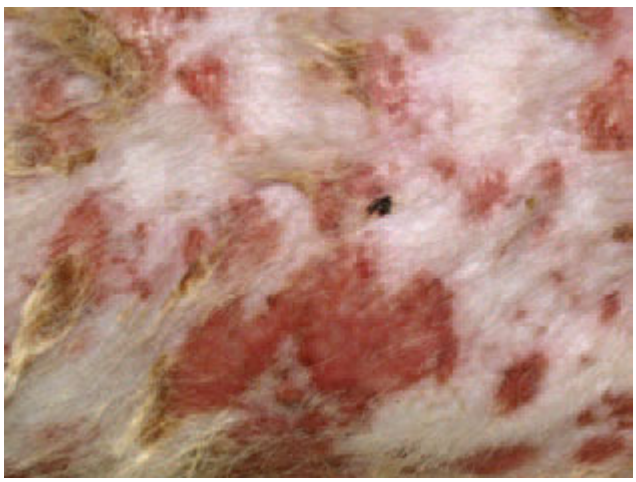


Fig. 2.14 Paraneoplastic pemphigus in a dog. Multifocal severe ulceration is present. (Photograph courtesy T. Olivry.)

An additional published case shares many clinical, histopathologic and immunologic features of PNP, including autoantibodies directed against envoplakin, periplakin, Dsg1, and Dsg3; however, underlying neoplasia was not identified (Olivry et al., 2000). This case may be a variant of pemphigus vulgaris that mimics PNP both clinically and histologically (Olivry, T., personal communication, 2003). The authors have observed a dog in which typical clinical and histological features of PNP were transient; this dog had no evidence of neoplasia upon systemic evaluation. Thus, other syndromes with mixed immunologic features exist, and caution is warranted regarding automatic association with occult neoplasia. Drug reaction should be ruled out and was suspected in the case observed by the authors.

Paraneoplastic pemphigus was reported in a 7-year-old female Bouvier des Flandres (Lemmens et al., 1998). Severe ulceration of the oral cavity and mucocutaneous junctions of the planum nasale, vagina, and anus, plus severe cutaneous ulceration of the muzzle, pinnal margins and clawbeds, was observed. Skin lesions were partially bilaterally symmetric. Postmortem revealed thymic lymphoma with hepatic metastases (Lemmens et al., 1998). In the additional dog with immunopathologic features of PNP, but without confirmed neoplasia, similar clinical features plus pressure-point involvement were noted (Olivry et al., 2000). In the putative case reported by Stannard et al. (1975), there was severe ulcerative stomatitis and cheilitis, accompanied by weight loss, lethargy, purulent

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nasal discharge, and a cough; post mortem examination revealed a thymoma.

Major clinical differential diagnoses include pemphigus vulgaris, epidermolysis bullosa acquisita, mucous membrane pemphigoid, bullous pemphigoid, vesicular cutaneous lupus erythematosus of Collies and Shetland Sheepdogs, systemic lupus erythematosus, severe erythema multiforme, toxic epidermal necrolysis, and bullous drug eruptions. Histopathology and immunologic studies, including identification of targeted antigens, as well as the documentation of underlying neoplasia, are required for definitive diagnosis.

Biopsy site selection

See Pemphigus vulgaris, p. 32.

Histopathology (Figures 2.15 and 2.16)

Epidermal or mucosal epithelial features include suprabasilar acantholysis, variable intraepidermal pustulation with free (apoptotic) keratinocytes, and keratinocyte apoptosis. Thus, the lesions present features of pemphigus vulgaris (suprabasilar clefting), erythema multiforme (apoptosis), and to a lesser extent pemphigus foliaceus (intraepidermal pustulation with free keratinocytes). It is this confounding mixed morphologic presentation that is the key to the diagnosis of PNP. However, based on the reported case for which underlying neoplasia was not discovered (Olivry et al., 2000), and the putative drug-associated case observed by the authors, other immunologic triggers besides neoplasia may produce a similar morphologic pattern in the skin.

Suprabasilar acantholysis may not always be tidily above the basal cell layer, as in classic pemphigus vulgaris (see p. 32), but can affect the lower spinosum, leaving multiple layers of keratinocytes on the floor of the cleft. Neutrophils fill the cleft to form variably sized, often panepidermal pustules. Suprabasilar clefting without significant pustule formation has been reported (Lemmens et al., 1998). Individual keratinocytes at all levels of the epidermis are apoptotic and are contracted and brightly eosinophilic. There may be lymphocytic satellitosis of apoptotic keratinocytes. The putative case of PNP reported by Stannard et al. (1975) featured acantholysis of salivary ducts and the esophagus, with bulla formation in the latter.

The dermis or submucosa contains a mixed mononuclear infiltrate of lymphocytes, macrophages, and plasma cells. Neutrophils are variably present and may be numerous.

Direct immunofluorescence testing showed intercellular deposition of only IgG at all levels of mucosal epithelium in the case without underlying neoplasia (Olivry et al., 2000), and in the epidermis and follicles in the case with splenic sarcoma (Elmore et al., 2003). Indirect immunofluorescence testing revealed high titers of IgG autoantibodies (Lemmens et al., 1998; Olivry et al., 2000; Elmore et al., 2003). Specific targeted antigens are multiple and variable (see clinical features, above).

Differential diagnoses include erythema multiforme, pemphigus foliaceus, and pemphigus vulgaris. As stated, features of all three typify PNP. Erythema multiforme and pemphigus foliaceus do not feature suprabasilar acantholysis. Classical pemphigus vulgaris is not characterized by apoptosis. Facially predominant pemphigus foliaceus

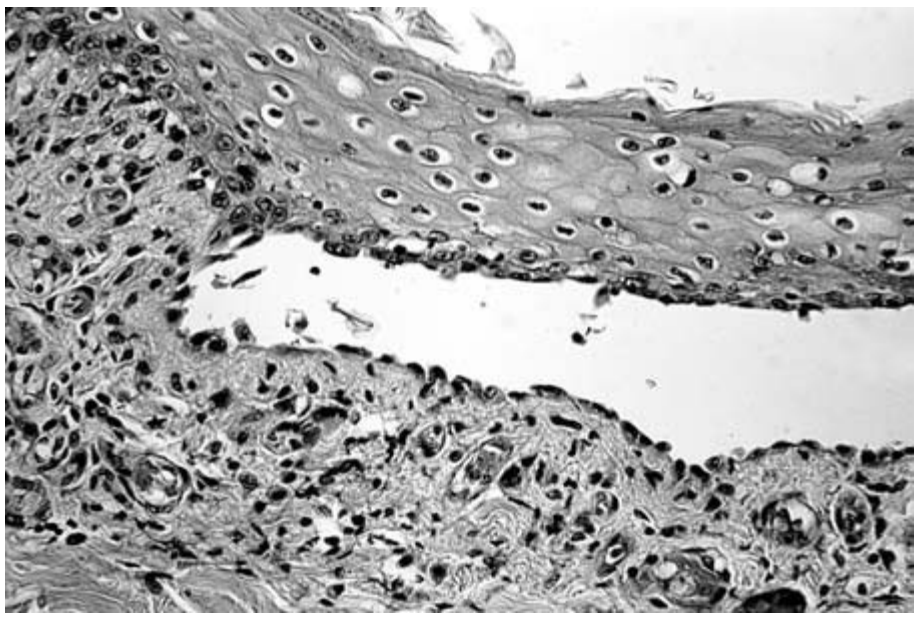


Fig. 2.15 Canine paraneoplastic pemphigus, featuring an irregular, suprabasilar cleft with lifting of the overlying epidermis. (Photograph courtesy T. Olivry.)

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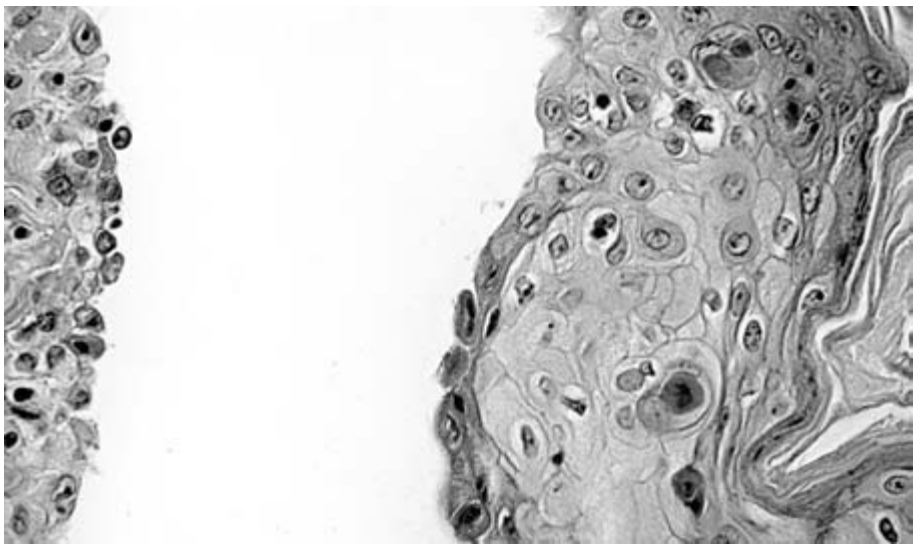


Fig. 2.16 Higher magnification of canine paraneoplastic pemphigus. There is apoptosis of keratinocytes of the epidermis overlying the cleft (at right). Note residual basal cells at base of cleft (at left). (From Lemmens, P., De Bruin, A., De Meulemeester, J. et al. (1998) Paraneoplastic pemphigus in a dog. *Vet Dermatol* 9, 127–34. Reprinted with permission.)

may include apoptosis, but generally apoptotic keratinocytes are surrounded by neutrophils to form small pustules. Due to the observed and reported cases that mimic PNP both clinically and histologically, definitive linking of this entity to neoplasia may not be prudent. Other underlying causes, including drug reaction, should be considered. Other similar histological overlap syndromes may be observed and may be drug-related. For example, in some cases of drug related pemphigus foliaceus, apoptosis may be severe, suggesting concurrence of both pemphigus foliaceus-like immunoreaction and erythema multiforme (see Chapter 1).

HEREDITARY EPIDERMOLYSIS BULLOSA

(Synonyms: congenital epidermolysis bullosa, epidermolysis bullosa congenita)



Fig. 2.17 Hereditary junctional epidermolysis bullosa in a German Shorthaired Pointer. Note tiny vesicles and ulcers of the inner pinna. (Photograph courtesy B. Gay-Bataille.)

Clinical features (Figure 2.17)

Epidermolysis bullosa (EB) is a term used to describe a group of mechanobullous diseases of variable etiology that are recognized in humans, dogs, and cats. In the hereditary form, structural defects occur in the basal cell layer or at various levels of the basement membrane zone, resulting in loss of epithelial integrity, blister formation, and clinical disease of variable severity. Acquired EB is due to antibody targeting of these same structures (see p. 40). Hereditary (congenital) forms have been described in humans, dogs, and cats, and acquired forms (EB acquisita) have been described in humans and dogs.

Hereditary EB in humans is divided into three subcategories (based on depth of defect moving from superficial to deep): EB simplex (epidermolytic EB), junctional EB, and dystrophic EB (dermolytic EB) (Fine et al., 2000). In EB simplex, fragility and clefting occur through the basal cell layer of the epidermis. Convincing evidence of EB simplex has not been published for the dog or cat. Junctional and dystrophic EB have been reported in the dog and cat (Dunstan et al., 1988; Koch & Walder, 1990; Johnstone et al., 1992; White et al., 1993; O'Dair & Henderson, 1994; Nagata et al., 1995; Rakich et al., 1996; Guaguère et al., 1997; Olivry et al., 1997, 1999; Olivry & Mason, 1998; Palazzi et al., 2000; Guaguère et al., 2002; Olivry, 2002).

Fragility and cleavage within the lamina lucida of the basement membrane zone characterize junctional EB. In humans, this junctional fragility is due to defective expression of hemidesmosome/anchoring filament proteins, including collagen XVII (bullous pemphigoid antigens BPAG2, BP180), integrin alpha-6, and laminin-5 (Uitto &

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Pulkkinen, 2001). An absence of collagen XVII was first demonstrated in German Shorthaired Pointers with nonlethal junctional epidermolysis bullosa (Guaguère et al., 1997; Olivry et al., 1997), but normal secretion of this protein was found *in vitro*. A mutation in the gene encoding laminin-5 has been shown to be the defect underlying junctional EB in this breed (Spirito et al., 1999). Dystrophic EB is characterized by fragility and separation beneath the lamina densa. Dystrophic EB occurs from defects in the anchoring fibrils that include diminished or absent expression of type VII collagen (Olivry et al., 1999).

In junctional EB, multiple oral and cutaneous vesicles and bullae lead to ulceration. Skin over bony prominences of the face and legs, pawpads, pinnae, intertriginous skin, and other frictional sites are affected preferentially. Ulcers may occur in the oral cavity, and dystrophic claws may be present. Friction may produce lesions iatrogenically. Lethal and nonlethal variants have been seen; severity is proportionate to the body area affected.

Published cases of junctional EB include a Toy Poodle, Beaucerons, German Shorthaired Pointers, a mixed breed dog and Siamese cats (Dunstan et al., 1988; Rakich et al., 1996; Guaguère et al., 1997, 2002; Olivry et al., 1997; Olivry & Mason, 1998; Olivry, 2002). Autosomal recessive inheritance was hypothesized in the Beaucerons and German Shorthaired Pointers (Dunstan et al., 1988; Guaguère et al., 1997, 2002; Olivry et al., 1997; Olivry, 2002). Putative junctional EB has been reported only twice in the cat in related Siamese cats and in a domestic longhaired cat (Johnstone et al., 1992; O'Dair & Henderson, 1994). Age of onset is early, with affected animals presenting between birth and 2 months of age.

Lesions of dystrophic EB are more severe than the junctional form of the disease. Ulcerations are deeper and may be more widespread. More extensive oral and oropharyngeal lesions are seen. Skin lesions occur on the pawpads, clawbeds, pressure points, and areas overlying bony prominences such as the metacarpal and metatarsal joints, and the tail tip. Claws may be sloughed. Defective tooth enamel and growth retardation may be seen. The syndrome has been noted in Akitas, Golden Retrievers, and in a Persian cat (White et al., 1993; Nagata et al., 1995; Olivry et al., 1999; Palazzi et al., 2000). Age of onset is before 2 months.

Clinical differential diagnoses include bullous autoimmune skin diseases such as epidermolysis bullosa acquisita, toxic epidermal necrolysis, and chemical or thermal burns. Differentiation usually should not be problematic since inherited EB occurs either at birth or in very young animals. A history of probable exposure generally accompanies chemical or thermal burns. Toxic epidermal necrolysis and bullous autoimmune diseases commonly occur in adult or older animals.

Biopsy site selection

Bullae or vesicles should be obtained carefully by wedge biopsy to preserve the integrity of these fragile lesions. Margins of early ulcers may show diagnostic changes at the dermal–epidermal junction.

Histopathology (Figures 2.18 and 2.19)

Three general categories of inherited EB have been identified in humans; only junctional and dystrophic forms

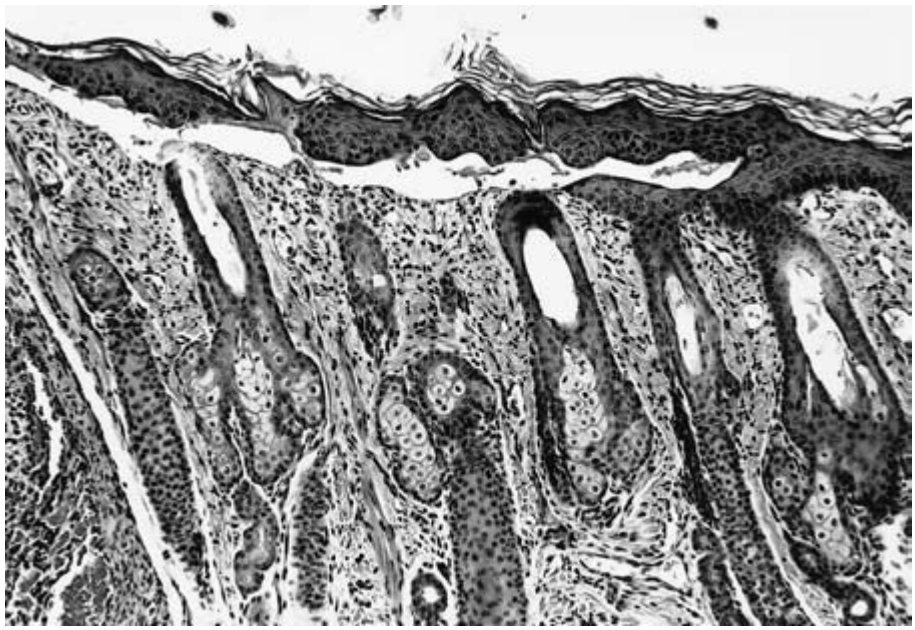


Fig. 2.18 Canine junctional epidermolysis bullosa. Note the large subepidermal bulla. (Case material courtesy R.W. Dunstan.)

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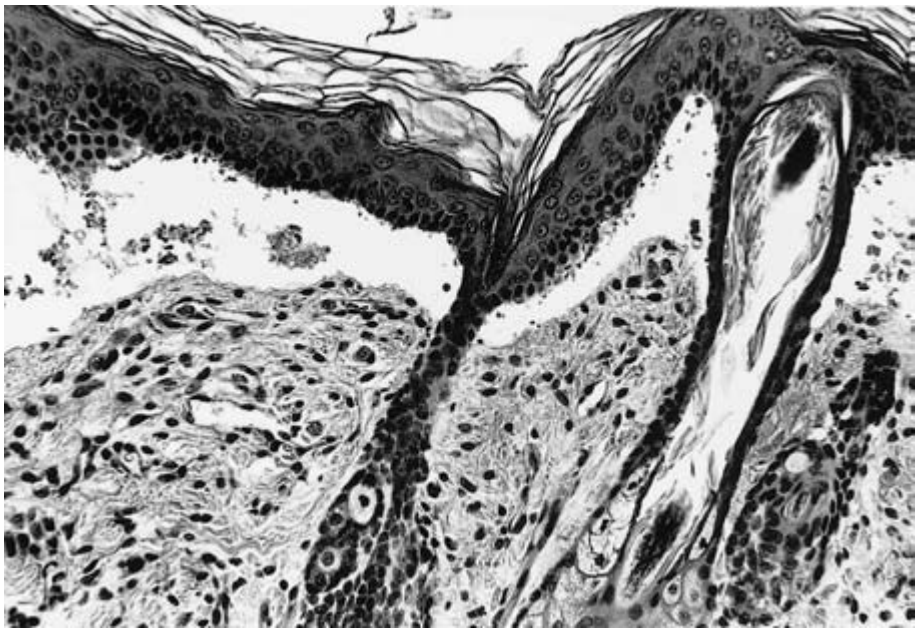


Fig. 2.19 Higher magnification of canine junctional epidermolysis bullosa in the dog of Fig. 2.18. Basal cells remain intact in the roof of the bulla.

have been convincingly identified in dogs and cats (see clinical features, above). In both junctional and dystrophic EB, the epidermis is cleanly separated from the underlying dermis to form a bulla or vesicle. Inflammation is not present within early bullae, and dermal inflammation is sparse. The earliest lesions of junctional EB in a Poodle occurred as vacuoles along the basement membrane (Dunstan et al., 1988). A periodic acid–Schiff (PAS) stain may color the lamina densa along the floor of the bulla in junctional EB and on the roof of the bulla in the dystrophic form. As the bullae evolve to ulcers there is secondary severe fibrinosuppurative exudation and neutrophilic dermal inflammation, often accompanied by a fibrovascular reaction in the dystrophic form. A clean separation of the epidermis from an underlying bed of granulation tissue has also been observed, suggesting that there may be new splitting at the site of previous lesions. Direct and indirect immunofluorescence testing for autoantibodies is negative.

Electron microscopy demonstrated the formation of clefts below the lamina densa of the basement membrane zone in Golden Retrievers with dystrophic EB (Palazzi et al., 2000). Antigen immunomapping with a collagen IV-specific monoclonal antibody demonstrated collagen IV (a major component of the lamina densa) above sites of dermal–epidermal separation in feline dystrophic EB, also indicative of clefting below the lamina densa (Olivry et al., 1999). Electron microscopy and immunostaining identified a decrease in anchoring fibrils, due to reduction in their main component collagen VII, in cats with dystrophic EB (Olivry et al., 1999). Although anchoring fibrils were ultrastructurally normal in Golden Retrievers with dystrophic EB, immunostaining of collagen VII was reduced in skin (Palazzi et al., 2000). Conversely to dystrophic EB, immunomapping showed the separation above the lamina densa in dogs with junctional EB, indicative of cleavage through the lamina lucida (Olivry et al., 1997).

Histopathologically, inherited EB resembles epidermolysis bullosa acquisita, bullous pemphigoid, mucous membrane pemphigoid, and linear IgA disease. Knowledge of an early age of onset is important in the differentiation of inherited EB from the other three diseases. Inflammation within and beneath the intact cleft of inherited EB is generally sparse in comparison to the other subepidermal bullous dermatoses, except for some cases of linear IgA disease (see p. 45). Autoantibodies are not present in inherited EB, in contrast to the other diseases. Immunomapping studies are required for definitive diagnosis.

EPIDERMOLYSIS BULLOSA ACQUISITA

(Synonym: acquired epidermolysis bullosa)

Clinical features (Figure 2.20)

Epidermolysis bullosa is a term used to describe a group of mechanobullous diseases of variable etiology that are recognized in humans, dogs and cats. In the hereditary form, structural defects occur in the basal cell layer or at various levels of the basement membrane zone, resulting in loss of epithelial integrity and blister formation (see p. 38).

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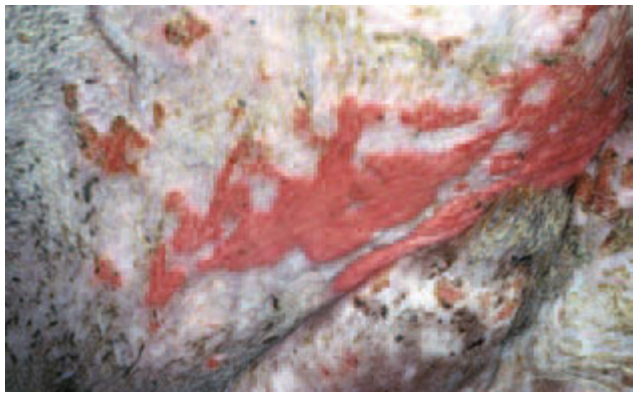


Fig. 2.20 Epidermolysis bullosa acquisita in a Great Dane. Multifocal ulcers are coalescing. (Photograph courtesy T. Olivry.)

Epidermolysis bullosa acquisita (EBA), an autoimmune blistering disease due to antibody targeting of these same structures, can present with either a generalized or a localized phenotype. EBA has been described only in humans and dogs. In humans, EBA is a very rare disease. Formerly, canine EBA also was thought to be very rare. However, according to Olivry (2003), generalized inflammatory EBA (to distinguish from the predominantly mechanobullous form observed in humans) is among the most common subsets of subepidermal autoimmune blistering diseases, and represents up to 25% of autoimmune blistering dermatoses associated with antibasement membrane autoantibodies. Only one dog has been reported with localized disease (Olivry et al., 2000).

In EBA, autoantibodies are directed against the aminoterminal, noncollagenous (NC1) domain of type VII collagen, a major component of dermal anchoring fibrils that bind to the basement membrane zone (Olivry et al., 1998). In a series of 12 dogs, IgG serum autoantibodies targeted recombinant human NC1 (12/12) and NC2 segments (3/12) of collagen VII (Olivry et al., 2002). Two additional dogs with indistinguishable clinical features had autoantibodies directed against laminin-5 (Olivry, 2002), making them the acquired counterpart of junctional epidermolysis bullosa.

In generalized inflammatory EBA, erythematous macules and urticarial plaques and patches eventuate in transient tense vesicles that evolve rapidly into widespread well-demarcated ulcers. Epithelial sloughing occurs in the oral cavity, mucocutaneous junctions, and intertriginous or frictional regions such as the face, axillae, and abdomen (Olivry & Chan, 2001; Olivry, 2003). Oral involvement results in severe halitosis, hypersalivation, and anorexia (Olivry, 2003). The nasal planum and pawpads also may be affected (Olivry, 2003). Affected dogs are lethargic, depressed and febrile. Lymphadenopathy is common (Olivry, 2003). Sepsis secondary to widespread ulceration may be seen.

A solitary case of mild, localized EBA similar to the 'Brunsting–Perry' form of EBA in humans has been reported (Olivry et al., 2000). Vesicles and ulcers gave rise to scarring. Lesions affected predominantly the head, including the pinnae; lesser lesions occurred on the trunk (Olivry et al., 2000).

Young adult Great Danes appear to be predisposed to the development of generalized EBA (6/12; 50%) (Olivry et al., 2002). Inbreeding has been proposed as the reason for this predilection (Olivry & Chan, 2001). The male to female ratio in reported dogs is 2 : 1 (Olivry, 2003). In this same study, the age of onset was surprisingly young with a median of 1 year; 8 of 12 dogs developed the disease by 15 months of age (Olivry, 2003).

Major clinical differential diagnoses for generalized EBA include bullous pemphigoid, mucous membrane pemphigoid, vesicular cutaneous lupus erythematosus of Collies and Shetland Sheepdogs, pemphigus vulgaris, severe erythema multiforme, and bullous drug eruptions. Hereditary epidermolysis bullosa should be easily differentiated from EBA based on age of onset, as lesions are noted before 2 months of age. EBA is more likely to have pawpad involvement and systemic signs than bullous or mucous membrane pemphigoid. Histopathology and further immunological testing, including identification of targeted antigens, are required for differentiation.

Biopsy site selection

See Hereditary epidermolysis bullosa, p. 38.

Histopathology (Figures 2.21 through 2.23)

In EBA, usually large and flat subepidermal bullae are present, and these may be filled with blood. A few strands of dermal collagen may cling to the roof of the bulla. Neutrophils accumulate along the base or within the cleft, sometimes intensely. Eosinophils may be observed but are less common. Noninflammatory blisters may be seen. Neutrophils often line up beneath the basement membrane and may degenerate, resulting in the presence of nuclear fragments in this location (leukocytoclasia). Small subepidermal vesicles filled with polymorphonuclear cells, or subepidermal microabscesses, may be reminiscent of human dermatitis herpetiformis.

Neutrophils, fewer eosinophils, lymphocytes and plasma cells are found in the superficial and occasionally the periadnexal dermis. Inflammation is usually mild to moderate and is accompanied by some dermal edema. Ulceration is common and is accompanied by more intense neutrophilic inflammation and fibrinosuppurative exudation.

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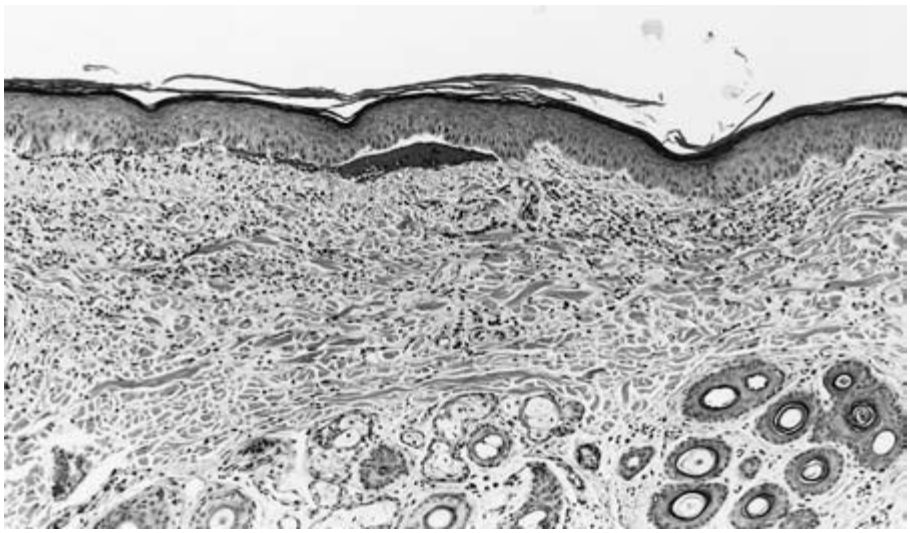


Fig. 2.21 Epidermolysis bullosa acquisita in a dog. Note hemorrhage in flaccid subepidermal bulla.

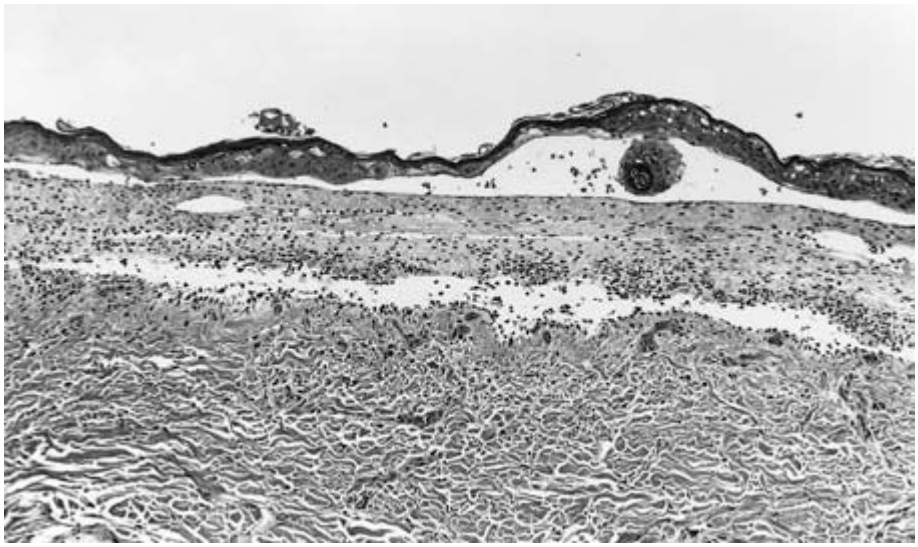


Fig. 2.22 Epidermolysis bullosa acquisita in a German Shorthaired Pointer. Fibrin and neutrophils are in a large flaccid bulla.

Antigen immunomapping with a collagen IV-specific monoclonal antibody demonstrates collagen IV (a major component of the lamina densa) on the epidermal side of the split, indicating cleavage below the basement membrane (Olivry et al., 1998, 2000). Direct immunofluorescence studies predominantly identify IgG in a linear pattern along the basement membrane zone; fewer dogs have IgA, IgM, and C3 (Olivry et al., 1998). Deposition of IgG is more intense and thick than in other autoimmune blistering skin diseases (Olivry et al., 2002). In blistered skin, IgG often segregates with the epidermis; remnants of stained basement membrane may be seen on the floor of the blister or within it (Olivry et al., 2002). Only IgG was found in the localized form (Olivry et al., 2000).

Indirect immunofluorescence testing detected circulating IgG in the localized form of EBA (Olivry et al., 2000), and IgG and IgA antibodies in the generalized form (Olivry et al., 1998). These autoantibodies are directed to the dermal side of salt-split skin (the artificial split occurs through the lamina lucida of the basement membrane). Immunogold electron microscopy of one case showed autoantibodies targeting the extremity of anchoring fibrils in the sublamina densa (Olivry et al., 1998).

Differential diagnoses include bullous pemphigoid, mucous membrane pemphigoid, inherited epidermolysis bullosa, linear IgA dermatosis, and type I bullous systemic lupus erythematosus. Bullous pemphigoid may feature eosinophilic infiltrates along the basement membrane zone; in contrast, neutrophilic infiltrates may characterize EBA. Intact lesions of inherited epidermolysis bullosa and linear IgA dermatosis often are only minimally inflamed. Immunologic studies are required for definitive differentiation. Type I bullous systemic lupus erythematosus may

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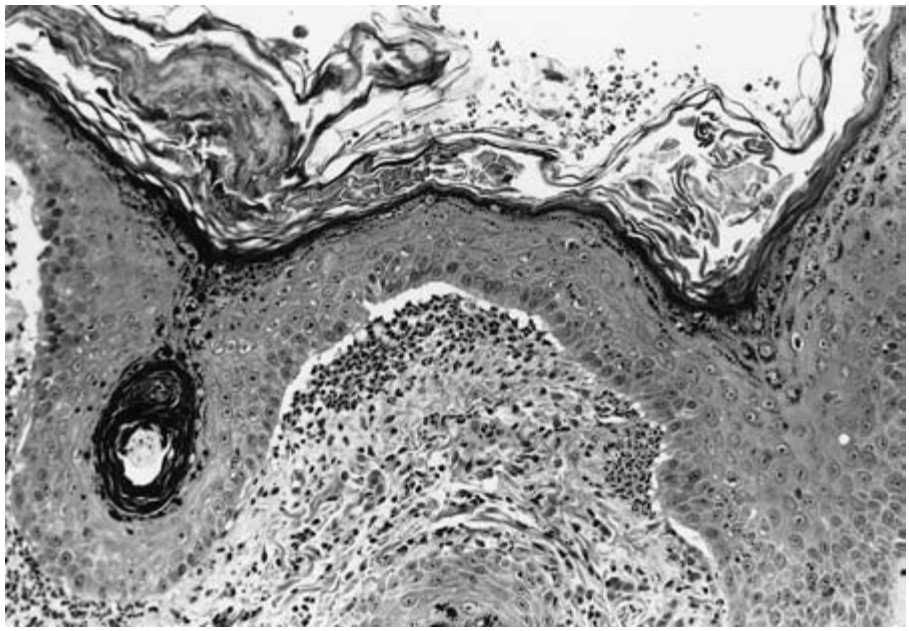


Fig. 2.23 Higher magnification of early subepidermal vesicle of epidermolysis bullosa acquisita with accumulations of neutrophils in a dermatitis herpetiformis-like morphology.

be histologically and immunologically identical to EBA; identification of criteria compatible with systemic lupus erythematosus is required for differentiation (see Chapter 3).

CANINE DARIER'S DISEASE

(Previous name: canine Hailey–Hailey disease)

Clinical features

A rare genodermatosis characterized by a defect of epithelial cohesion was originally reported in three related English Setters as a canine counterpart of Hailey–Hailey (HH) disease (benign familial chronic pemphigus), as seen in humans (Shanley et al., 1993). Subsequent breeding experiments with an affected English Setter and a Beagle bitch indicated the likelihood of autosomal dominant inheritance with incomplete expression (Sueki et al., 1997). The syndrome showed many similarities to human HH disease, an uncommon hereditary defect of epithelial cell cohesion due to the formation of weak desmosomal connections (Metze et al., 1996). The defect leads to recurrent vesicles and bullae, and has an autosomal dominant mode of inheritance. Recent unpublished work by Suter and her group indicates that these dogs probably have a canine counterpart to Darier's disease of humans instead (Suter, M., personal communication, 2002).

In humans, HH disease and Darier's disease are clinically and histologically similar genodermatoses that result from different, but similar, genetic mutations in Ca^{2+} pumps. In Darier's disease, the SERCA2 (ATP2A2) gene, which codes for the SERCA2 pump located in the endoplasmic reticulum, is mutated, while in HH disease the mutation affects the SPCA1 (ATP2C1) gene for the pump located in the Golgi apparatus (Shull et al., 2003). Both pumps restore the calcium stores within the endoplasmic reticulum and Golgi apparatus, respectively, after a transient increase of intracellular free calcium occurs after multiple signals. The drug thapsigargin inhibits the SERCA2, but not the Golgi pump. Using thapsigargin, Suter has demonstrated that the SERCA2 pump and not the Golgi pump was affected in dogs with this syndrome (Suter, M., personal communication, 2002). Subsequent cloning of the SERCA2 gene did not reveal a specific mutation; however, this failure to reveal a specific mutation has occurred in 50% of the human Darier's patients tested as well (Suter, M., personal communication, 2004). Upregulation of P-cadherin, an important Ca^{2+} dependent adhesion molecule in the epidermis, occurs in both autoimmune and hereditary acantholytic disorders in humans, and is suggested to be involved in the development of acantholysis of both HH disease and Darier's disease (Hakuno et al., 2001).

In English Setters distinctive, well-demarcated, erythematous, crusted, alopecic, and hypertrophic plaques formed on the trunk, head, and extremities, including at pressure points. The lesions remained localized and did not seem to enlarge over time. Pruritus or pain were not obvious features (Shanley et al., 1993; Sueki et al., 1997). A similar disease was noted in a young Doberman Pinscher, but details were not provided (Scott et al., 2001). Lesions developed at approximately 6 months of age in the English Setters.

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Clinical differential diagnoses may include multifocal demodicosis, superficial pyoderma, or dermatophytosis. Skin biopsy is required for definitive diagnosis.

Biopsy site selection

Representative specimens should be acquired from multiple lesions. Care should be taken in procuring the specimen as affected tissue is easily damaged.

Histopathology (Figures 2.24 and 2.25)

Loss of keratinocyte cohesion, or acantholysis, occurring throughout the epidermis and follicular infundibula, creates the image of the so-called 'crumbling brick wall'. Affected keratinocytes are more densely staining, and as they progress to the surface, become flattened and cornified. Increased mean size of suprabasal keratinocytes in lesional sites was reported (Sueki et al., 1997). There is often a thick layer of parakeratotic or orthokeratotic keratin which extends to superficial hair follicles. The granular layer is prominent. There is severe epidermal and follicular infundibular hyperplasia, and frequently superficial pustulation and crusting. Dermal inflammation is mild except in areas with secondary superficial pustulation, and includes neutrophils, lymphocytes and macrophages.

Direct immunofluorescence testing for autoantibodies was negative (Sueki et al., 1997). Monoclonal antibody studies of affected English Setters demonstrated a lack of E cadherin within intercellular adhesion structures in some reports (Shanley et al., 1993; Suter et al., 1996), but not in a later report of the same group of dogs (Sueki et al., 1997).

The principal differential diagnosis is pemphigus vulgaris, which in some cases may demonstrate numerous acantholytic cells within epidermal clefts. In pemphigus vulgaris there is often loss of the roof of the bullae leaving a characteristic row of prominent basal cells. In contrast to pemphigus vulgaris, canine Darier's disease features



Fig. 2.24 Canine Darier's disease. Acantholysis and premature cornification of keratinocytes creates a 'crumbling brick wall'.

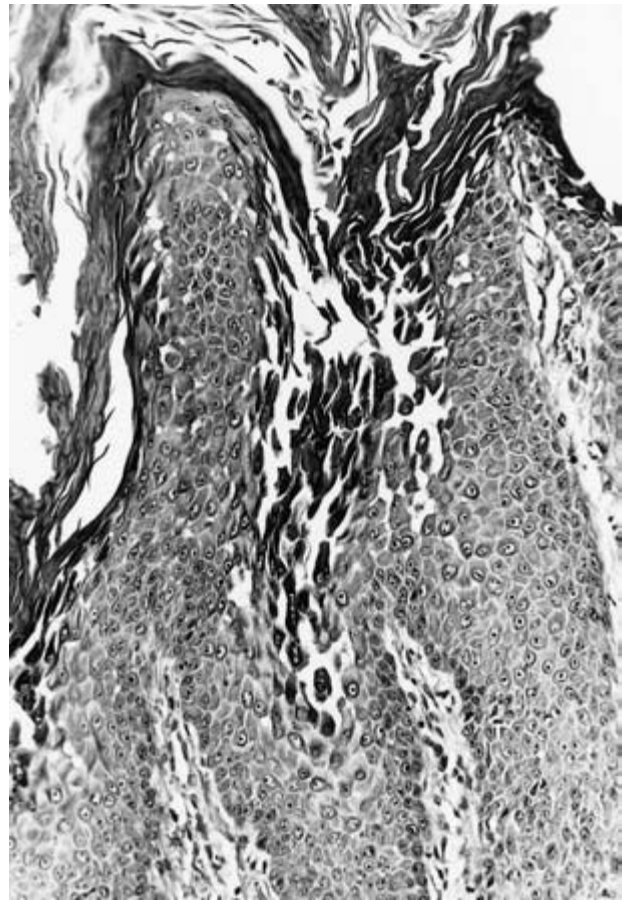


Fig. 2.25 Higher magnification of Darier's disease in the dog of Fig. 2.24. Note flattening of cornified acantholytic keratinocytes as they approach the surface.

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cornification of dissociated keratinocytes, as well as severe epidermal and follicular infundibular hyperplasia. Immunofluorescence studies reveal antikeratinocyte autoantibodies in pemphigus vulgaris but not in canine Darier's disease.

LINEAR IgA DISEASE

Clinical features

Linear IgA disease (LAD) is a very rare, vesiculobullous subepithelial blistering autoimmune disease affecting mucous membranes, mucocutaneous junctions, and skin of humans and dogs. Both skin-fixed and circulating IgA autoantibodies target LAD-1, the processed extracellular segment of type XVII collagen (Olivry et al., 2000; Olivry & Chan, 2001). This disease is not similar to the disease previously reported by Scott et al. (1982).

In the two dogs reported by Olivry et al. (2000), ulcers were present in the oral cavity, face, and extremities; pawpads and the intertriginous regions of the axillae and groin also were affected; intact vesicles were not seen grossly. In humans, either children or adults may be affected. Signalment predilection data are not available for the dog.

Clinical differential diagnoses include mucous membrane pemphigoid, bullous pemphigoid, epidermolysis bullosa acquisita, vesicular cutaneous lupus erythematosus of Collies and Shetland Sheepdogs, pemphigus vulgaris, systemic lupus erythematosus, severe erythema multiforme, toxic epidermal necrolysis, and other bullous drug eruptions. As in all of the subepithelial bullous dermatoses, histopathology and further immunological testing, including identification of targeted antigens, are required for differentiation.

Biopsy site selection

As in all bullous dermatoses affecting the basement membrane zone, intact vesicles, if present, should be removed in their entirety, preferably by excisional biopsy. If an intact lesion is not available, tissue from the margins of recently ruptured bullae may be sampled.

Histopathology (Figure 2.26)

There is subepidermal vesiculation leading to the formation of large bullae. Bullae may be somewhat flaccid, resulting in retention of the irregular or peg-like lower contour of the epidermis. Turgid bullae are also observed. Bullae are either devoid of luminal inflammation, or contain fibrin and small numbers of neutrophils. Eosinophils are not observed within bullae and have not been reported (Olivry et al., 2000).

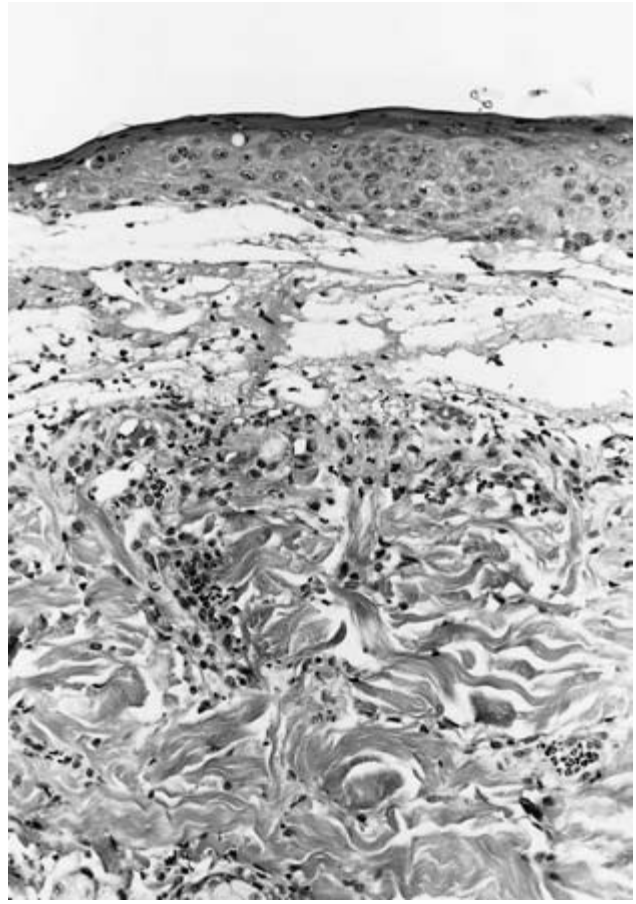


Fig. 2.26 Linear IgA disease in a dog. A subepidermal bulla contains fibrin and small numbers of neutrophils.

Ulceration is accompanied by severe fibrinosuppurative exudation.

Dermal inflammation beneath intact bullae is generally mild and includes neutrophils, lymphocytes, plasma cells, and macrophages. Eosinophils may be present in small numbers, but do not line up along the basement membrane of intact skin or beneath bullae. A fibrovascular proliferation may be present in the superficial dermis beneath ulcers or intact skin.

Antigen immunomapping with a collagen IV-specific monoclonal antibody demonstrated collagen IV (a major component of the lamina densa) on the dermal side of the split, indicating cleavage through the lamina lucida (Olivry et al., 2000). Direct immunofluorescence studies identified IgG, IgA, IgM, and C3 in a continuous linear pattern along the basement membrane zone (Olivry et al., 2000). Indirect immunofluorescence testing detected circulating IgG and IgA antibodies (Olivry et al., 2000). These autoantibodies were directed to the epidermal side of salt-split skin (the artificial split occurs through the lamina lucida of the basement membrane). Immunoblot-

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ting identified the target as a 120 kDa antigen consisting of the processed extracellular domain of collagen XVII, also called LAD-1 (Olivry et al., 2000).

Differential diagnoses include bullous pemphigoid, mucous membrane pemphigoid, inherited epidermolysis bullosa, and epidermolysis bullosa acquisita. Bullous pemphigoid may feature intense eosinophilic infiltrates along the basement membrane zone; intense neutrophilic infiltrates may characterize epidermolysis bullosa acquisita. Intact lesions of inherited epidermolysis bullosa and linear IgA dermatosis often are only minimally inflamed. Immunologic studies are required for definitive differentiation.

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Chapter 3

Interface diseases of the dermal–epidermal junction

The terms 'lichenoid' and 'interface' are often used interchangeably by others. For descriptive clarity, the authors prefer to define interface dermatitis as generally minimal to mild superficial dermal inflammation that is oriented tightly to and often obscures the dermal–epidermal junction. Interface diseases affect the epidermis and usually the infundibulum of hair follicles. Basal cell damage, usually apoptosis (see introduction to Chapter 4), is a consistent feature of interface dermatitis; in some diseases interface damage occurs, but without significant interface inflammation. Interface change with minimal to mild inflammation is considered 'cell poor' interface dermatitis; most of the diseases of this chapter conform to this pattern. Vacuolar degeneration of basal cells may be a feature of interface change, but is only significant when pronounced; scattered and mild basal cell vacuolation is normal.

Intense, band-like subepidermal inflammation defines lichenoid dermatitis. Lichenoid dermatitis may occur with or without interface change. Lichenoid inflammation with interface damage may be termed 'lichenoid-interface' dermatitis. Lichenoid dermatoses are described in Chapter 11.

ISCHEMIC DERMATOPATHY/CANINE DERMATOMYOSITIS

Clinical features (Figures 3.1 and 3.2)

Ischemic dermatopathy is a general designation for multiple vasculopathic syndromes that are unified by similar clinical and histopathologic features (Ihrke & Gross, 1993). This group includes: (1) canine familial dermatomyositis (DM) (seen predominantly in the Collie and Shetland Sheepdog, but also reported in other breeds); (2) dogs with a juvenile-onset ischemic dermatopathy that is identical to DM but without proven breed predilection and therefore without known familial predisposition; (3) postrabies vaccination panniculitis (see Chapter 21); (4) dogs with more severe generalized postrabies vaccination-associated disease, termed 'generalized vaccine-induced ischemic dermatopathy' (GVIID); and (5) dogs with adult-onset generalized ischemic dermatopathy but without a correlative history indicating the likelihood of vaccine reaction induction. The last group (5) is termed 'generalized idiopathic ischemic dermatopathy' (GIID). Some Group 2 dogs have temporal association with multivalent puppy vaccines (not rabies).

Clinical and histopathologic similarities unite these five syndromes. Groups 1 and 2 develop as juvenile-onset disease and are clinically indistinguishable from each other. Group 3 develops as focal skin disease (see Chapter 21). Groups 4 and 5 develop as generalized, more severe, and usually adult-onset skin disease. The lesions noted in Groups 4 and 5 may be generalized beyond the expected distribution pattern of DM (Group 1) and DM-like disease (Group 2). The presence of either a hereditary or an individual predisposition, coupled with a secondary environmental trigger has long been hypothesized for DM in humans (Kovacs & Kovacs, 1998; Sontheimer, 1999). It is likely that similar factors are operant in canine ischemic dermatopathy.

The term 'canine familial dermatomyositis' currently is reserved for those dogs with clinical and histopathologic evidence of a juvenile onset heritable inflammatory disease affecting skin and muscle in a breed at known increased risk. The etiopathogenesis is not known. Autoimmune and viral etiologies in conjunction with hereditary predilection have been postulated for DM in humans (Sontheimer, 1999).

Both the clinical and histopathologic features of ischemic dermatopathies correlate with lesions likely to result from long-term lack of cutaneous vascular sustenance (Vitale et al., 1999). Indeed, a cell poor vasculitis unites the syndromes (see Chapter 10). Cutaneous hypoxia leads to follicular atrophy and, clinically, alopecia and associated chronic skin changes. Lesions occur over bony prominences due to susceptibility to trauma, and on distal extremities where collateral circulation does not allow appropriate vascular sustenance.

The unifying clinical features of all five subgroups of canine ischemic dermatopathy include alopecia with crusting and post-inflammatory, mottled pigmentary

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Fig. 3.1 Canine familial dermatomyositis in a young Shetland Sheepdog. Alopecia and scaling are present on the dorsal muzzle and periorbitally over bony prominences.



Fig. 3.2 Chronic canine familial dermatomyositis in an adult Shetland Sheepdog. Extensive alopecia and crusting are present on the face and pinnae.

change. Hyperpigmentation may be seen in breeds predisposed to enhanced pigmentation as a sequela to inflammation; in other breeds, hypopigmentation can occur. Erosion and ulceration may occur in more severe cases, especially if trauma or secondary pyoderma is present. Scarring may or may not be apparent clinically. Lesions of skin and muscle vary markedly in severity.

Dogs with DM and DM-like disease (Groups 1 and 2) present with identical clinical features. Earliest lesions include rare transient papules, pustules, and vesicles eventuating in the more commonly noted crusted erosions, ulcers, and alopecia. Scarring is a feature of chronicity; some lesions may become atrophic. Pigmentary aberrations give rise to poikilodermatous change with either hyper- or hypopigmentation, or both. Initial lesions usually occur over bony prominences (sites of mild trauma), especially on the muzzle, in periorbital and perioral locations, and on the dorsum of the distal phalanges. Later, similar lesions are seen on distal extremities with poor collateral circulation, and on pressure points that are susceptible to shearing injury and trauma. The pinnae (especially the tips), pinnal folds, claw folds, tip of the tail, plus other bony prominences of the distal extremities and other pressure points may be affected. Inflammation of the clawbed may lead to claw dystrophy and claw sloughing. Familial cutaneous vasculopathy of German Shepherd Dogs is characterized by swelling of the pawpads and histopathologic features distinct from ischemic dermatopathy (see Chapter 10), but also may feature signs of juvenile-onset ischemic dermatopathy. This suggests a close relationship between these two diseases, particularly as similar pawpad lesions consistent with familial cutaneous vasculopathy have been observed in Fox Terriers with otherwise typical juvenile-onset ischemic dermatopathy. In contrast, lesions histologically compatible with ischemic dermatopathy have been seen by the authors in the pawpads only in two Welsh Corgis.

Pain and pruritus are not common unless ulceration or secondary pyoderma is present. Photo-aggravation occurs, and trauma or estrus may trigger relapse.

Muscle involvement often is subtle, and may be limited to temporal and masseter muscle atrophy. Difficulties with mastication and swallowing may occur. Severely affected dogs show growth retardation, megaesophagus, lameness, and widespread muscle atrophy. Muscles of the tongue may fasciculate causing difficulty in prehension. Infertility is an additional feature of severe DM. Mildly affected dogs may achieve clinical remission with time. Severely affected dogs with generalized disease exhibit lifelong disease with cyclical recrudescence.

The clinical and histopathologic features of dogs with GVIID (Group 4) and GIID (Group 5) are very similar. However, vaccine-induced ischemic dermatopathies also often have a focal lesion at the vaccine site compatible with postrabies vaccination panniculitis (see Chapter 21). Even dogs without a correlative history of recent rabies vaccination should have likely vaccination sites checked for compatible lesions, as the focal lesions may have been previously missed, particularly in long-haired dogs. Specific lesions are those of DM and DM-like disease (see above), but may be more severe and more widespread in

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distribution. The most severe lesions are located over bony prominences and on distal extremities; this distribution mirrors that of DM. However, similar but usually less severe lesions are seen over much of the skin surface. Varying degrees of muscle atrophy are noted. Generalized vaccine-induced ischemic dermatopathy may gradually diminish in severity over time. Dogs with GIID usually exhibit lifelong disease with some cyclical recrudescence.

Canine familial DM is seen most commonly in Shetland Sheepdogs, Collies, and their related crossbreeds. DM-like disease (Group 2) has been reported occasionally in the Chow Chow, Beauceron Shepherd, Welsh Corgi, Lakeland Terrier, German Shepherd Dog, and Kuvasz, as compiled by Scott (Scott et al., 2001), and has been seen by the authors in Miniature Schnauzers, Miniature Dachshunds, Fox Terriers, and other breeds. Both groups are juvenile-onset diseases; initial lesions usually occur by 6 months of age. Sex predilection has not been noted.

Signalment predilections for GVIID (Group 4) and GIID (Group 5) are not available. Clinical impressions suggest that the Miniature and Toy Poodle, Shih Tzu, Shetland Sheepdog, Lhasa Apso, Pomeranian, and Yorkshire Terrier may be at increased risk for adult-onset generalized ischemic dermatopathy. As in post-rabies vaccination panniculitis (see Chapter 21), long-haired toy or miniature breeds seem to be at greater risk. However, the syndromes can be seen in any breed. Age or sex predilections have not been noted.

The authors believe that a syndrome reported in five Jack Russell Terriers is, in fact, canine ischemic dermatopathy (Parker & Foster, 1996); however, the wide range of age of onset and clinical features do not allow further subcategorization. The most prominent histologic feature of these cases was a cell-poor vasculitis (see Chapter 10). Restriction of the syndrome to Jack Russell Terriers likely indicates familial predisposition.

Major clinical differential diagnoses for canine DM and DM-like disease (Groups 1 and 2) include juvenile-onset demodicosis, dermatophytosis, facial pyoderma, and discoid lupus erythematosus. Concurrent clinical, electromyographic, or histologic evidence of muscle disease is suggestive of DM. Skin scrapings should be performed to rule out demodicosis, and fungal culture should be performed to rule out dermatophytosis. If small numbers of *Demodex* mites are found on scrapings, skin biopsy should still be performed as the authors have seen mites localized to DM lesions. Breed predilections and association with a prior vaccination site simplify the diagnosis of post-rabies vaccination panniculitis (Group 3) (see Chapter 21). GVIID and GIID (Groups 4 and 5) must be differentiated from many other inflammatory diseases where extensive alopecia and pigmentary changes are seen. Most vaccine-induced ischemic dermatopathies have a focal lesion at a prior vaccine site. Skin biopsy is required for definitive diagnosis.

Biopsy site selection

Lesions showing erythema and alopecia are preferred sites for biopsy. If skin biopsy is performed on the face, there may be fortuitous inclusion of lesional skeletal muscle. Secondarily infected or scarred lesions are suboptimal for the demonstration of typical microscopic lesions.

Histopathology (Figure 3.3)

Histopathologic features of all forms of ischemic dermatopathy are similar. Lesions overlying postrabies vaccination panniculitis are identical to those of ischemic dermatopathy, as they represent a localized form of the same condition (see Chapter 21).

Scattered degeneration of individual basal cells is the typical epidermal feature, but may be sparsely evident in many cases. Follicular basal cell degeneration to the level of the isthmus is generally more consistently observed than basal cell lesions of the epidermis (see Chapter 19). Affected basal cells may be either vacuolated, or shrunken and brightly eosinophilic, consistent with apoptosis. Secondary dermal–epidermal vesiculation is present occasionally, particularly in severely affected animals. In the authors' experience, Collies are more likely to demonstrate prominent basal cell degeneration and subepidermal vesicles. Vesicles often contain red blood cells and occur above the basement membrane, as demonstrated by laminin staining of the basement membrane along the floor of the separation. Also, artifactual dermal–epidermal separation (due to basal cell damage) may occur at the margin of the specimen. Only tissue weakened through the dermal–epidermal junction will separate in this manner during processing and consequently this 'usable artifact of Stannard' is valid evidence of interface damage (Stannard, A.A., personal communication, 1986). Secondary ulceration may occur if vesicular lesions are extensive. Superficial crusting is variable.

Dermal inflammation is generally diffuse and very mild, and often loosely encircles follicles. Lymphocytes and histiocytes predominate; mast cells, plasma cells, and neutrophils also may be observed. Intense inflammation, which includes prominent neutrophils, may be seen accompanying ulceration in severe lesions. Dermal scarring leading to cicatricial alopecia is rare, but can occur in the wake of severe ulceration and inflammation. Increased prominence of the connective tissue of the external root sheath of the atrophic hair follicle should not be misinterpreted as perifollicular scarring.

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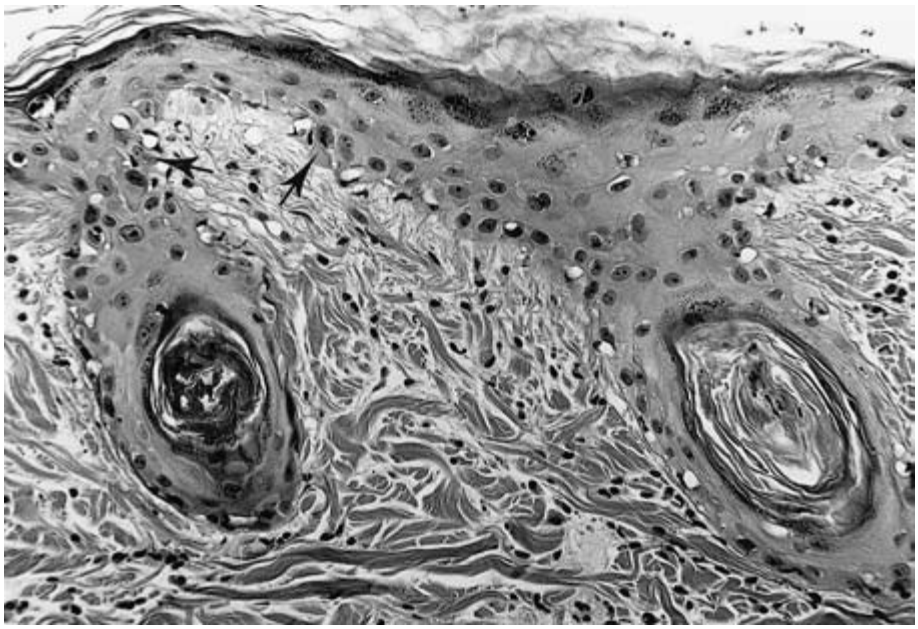


Fig. 3.3 Canine familial dermatomyositis. Basal cells are mildly vacuolated and occasionally shrunken and apoptotic (arrows); the outer follicle also is affected.

There is typically diffuse pallor of the dermis, characterized by pale-staining, 'smudged', or rarified collagen that has lost its fibrillar character. This change is believed to result from tissue ischemia. There may be mild to moderate mucin deposition and/or edema. Lymphocytes and/or macrophages may surround collagen fibers to form small putatively ischemic granulomas as seen in cell poor vasculitis (see Chapter 10). Blood vessels show features of cell-poor vasculitis (see Chapter 10). Complement has been demonstrated intravascularly in the muscle of dogs with GVIID (Vitale et al., 1999). Hair follicles are severely atrophic or 'faded'; this atrophy may represent a combination of direct ischemia and basal cell degeneration.

Deeper biopsies, particularly in periocular or perioral location, occasionally will show inflammation of skeletal muscle. Myositis is characterized by mixed inflammation, including lymphocytes, macrophages, plasma cells, and sparse neutrophils, myofiber degeneration (fragmentation, vacuolation, increased eosinophilia), regeneration, fibrosis, and atrophy. In general, random biopsy of clinically affected muscle groups, such as the temporal or masseter muscles, may not show lesions. Electromyography is a more reliable method of documenting muscle disease and locating appropriate sites for muscle biopsy.

Systemic, discoid, and cutaneous lupus erythematosus are the principal differential diagnoses. Epidermal basal cell degeneration is generally more severe in all forms of lupus erythematosus, with the exception of DM (ischemic dermatopathy) in Collies. Lichenoid dermal inflammation, as seen predominantly in discoid lupus erythematosus, is not a feature of DM. Most forms of lupus erythematosus do not feature follicular atrophy; further, ischemic change of dermal collagen is also generally absent unless there is accompanying vascular disease, as may occur in systemic lupus erythematosus.

DISCOID LUPUS ERYTHEMATOSUS

Clinical features (Figures 3.4 through 3.6)

Discoid lupus erythematosus (DLE) is a relatively common autoimmune skin disease of the dog. It is likely that some dogs previously diagnosed as having nasal solar dermatitis or 'Collie nose' actually had DLE. However, solar vasculopathy may complicate depigmenting skin diseases of the dorsal muzzle such as DLE (see Chapter 10). In humans, actinic radiation is postulated to be instrumental in altering the antigenic nature of keratinocytes, thus inducing an autoimmune response. Since canine DLE is at least photo-aggravated if not photo-induced, lesions often are more severe in the summer and in parts of the world with high solar intensity. The authors do not believe that DLE has been diagnosed convincingly in the cat.

Lesions are commonly restricted to the face (Griffin et al., 1979). Early lesions, characterized by depigmentation, erythema, and scaling, frequently are confined to the planum nasale and occur in a bilaterally symmetrical pattern. The planum often exhibits a loss of the normal 'cobblestone' architecture. Alopecia, crusting, erosion, ulceration, and scarring occur in more severe cases. Chronic scarred and atrophic lesions are fragile and may be abraded easily, resulting in episodic hemorrhage. Lesions may be present on the dorsum of the muzzle, lips, periorbitally, and on the ears. Loss of pigmentation also

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Fig. 3.4 Mild canine discoid lupus erythematosus in a Bearded Collie. The distal dorsal muzzle and planum are depigmented and erythematous.



Fig. 3.5 Closer view of Fig 3.4. Note the depigmentation and erosion of the planum nasale.

has been noted within the oral cavity. Rarely, focal oral ulcers, and lesions on the genitals and distal extremities have been reported. This phenomenon could result from epitope spreading in the autoimmune process, as in pemphigus vulgaris (see Chapter 2). On very rare occasions, squamous cell carcinoma may develop in chronic lesions of the dorsal muzzle (Scott & Miller, 1995) (see Chapter 22).



Fig. 3.6 Severe canine discoid lupus erythematosus in an Old English Sheepdog. Ulceration and scarring deface the entire dorsal muzzle.

The Collie, Shetland Sheepdog, German Shepherd Dog, and Siberian Husky exhibit a breed predilection for DLE. As a subgroup, white German Shepherd Dogs are at greater risk and may exhibit especially severe lesions. These dogs may have coexistent solar vasculopathy (see Chapter 10). Affected siblings and mother–daughter cohorts have been recognized. Sex or age predilections have not been substantiated.

Major clinical differential diagnoses include systemic lupus erythematosus, mucocutaneous pyoderma, dermatophytosis, pemphigus foliaceus, pemphigus erythematosus, vitiligo, trauma, and Vogt–Koyanagi–Harada-like syndrome. An antinuclear antibody (ANA) test and a chemistry screening profile should be performed to aid in differentiation from systemic lupus erythematosus. Lesions usually do not violate the planum nasale in dermatophytosis. Poliosis and uveitis usually are prominent coexistent features of Vogt–Koyanagi–Harada-like syndrome. Histopathology is useful in differentiating all of these diseases except for systemic lupus erythematosus since the histopathology of systemic lupus erythematosus and DLE may be identical. ANA testing and further systemic evaluation may be performed to rule out systemic lupus erythematosus.

Biopsy site selection

Recent sites of depigmentation, characterized by graying or partial loss of pigment, are optimal sites for skin biopsy. Traumatized lesions, or lesions with severe crusting, ulceration, or scarring should be avoided. Lesions of the lip and dorsal muzzle are more likely to yield diagnostic results. Potential difficulties with hemostasis and scarring are reasons to avoid the planum nasale or pinnae, unless other more suitable sites for biopsy are not affected.

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Histopathology (Figures 3.7 and 3.8)

Basal cell apoptosis, characterized by shrinkage and eosinophilia of basal keratinocytes, is a highly characteristic, but sometimes sparse, lesion of DLE. Basal cell degeneration, both apoptotic and vacuolar, creates an irregular and indistinct dermal–epidermal junction that is further obscured by interface inflammation. Apoptosis of keratinocytes of the stratum spinosum with variable lymphocyte satellitosis is observed randomly in biopsy specimens from dogs with otherwise typical clinical and histologic features of DLE. The significance of this feature is not known. It may represent 'spillover' lymphocyte-mediated damage beyond the basal cell layer. Suprabasilar apoptosis also may represent direct solar damage to keratinocytes ('sunburn' cells).

Artifactual dermal–epidermal separation may occur at the margin of the specimen. Only tissue weakened through the dermal–epidermal junction will separate in this manner during processing, and consequently this 'usable artifact of Stannard' is valid evidence of interface damage (Stannard, A.A., personal communication, 1986).

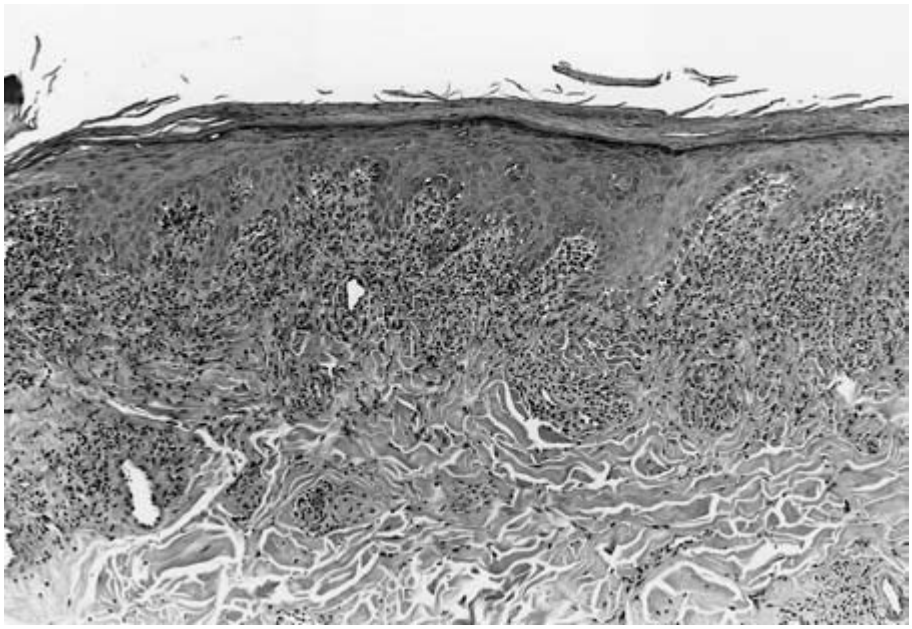


Fig. 3.7 Lichenoid-interface inflammation of discoid lupus erythematosus. The sharp demarcation between epidermis and dermis is partially obscured by interface inflammation, seen most prominently at the left.

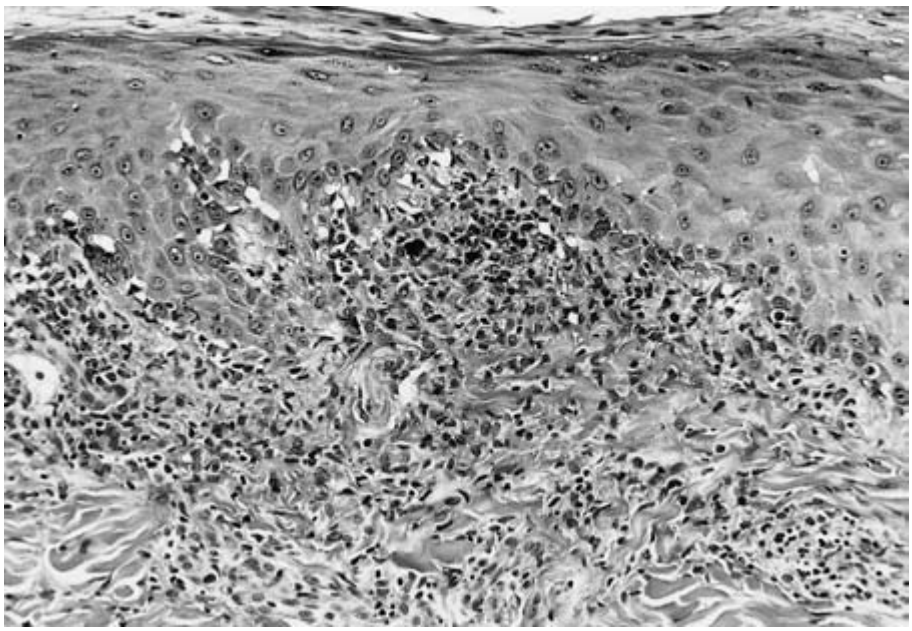


Fig. 3.8 Higher magnification of interface dermatitis in discoid lupus erythematosus. There is prominent basal cell degeneration, creating an indistinct dermal–epidermal junction.

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Secondary erosion or ulceration, and superficial pustulation and crusting are observed in severe cases. Moderate acanthosis usually occurs; epidermal atrophy may be present, particularly in areas of previous ulceration that have re-epithelialized. The basement membrane may be markedly thickened in some cases; this is a nonspecific finding, however, and can be observed in other chronic inflammatory dermatoses.

The dermis usually has a lichenoid, or band-like, mild to moderate inflammatory infiltrate that includes lymphocytes, macrophages, plasma cells, and fewer neutrophils (see Chapter 11). Inflammation often obscures the dermal–epidermal junction, and thus is best termed 'lichenoid-interface', when accompanied by basal cell degeneration. Mild interface and/or superficial perivascular inflammation, without a lichenoid band, may be observed in some cases, particularly in early lesions. Pigmentary incontinence usually is present and reflects loss of melanin by damaged basal cells and its incorporation into macrophages in the superficial dermis. Chronically inflamed lesions with prominent plasma cell infiltrates often lack obvious basal cell damage and are more purely lichenoid. In some putative chronic lesions, there may be a zone of superficial laminar hypocellularity with or without laminar fibrosis. This is subtended by a deeper zone of lichenoid inflammation. Superficial neutrophilic vasculitis and fibrinoid vasculopathy may be present in some of these hypocellular lesions, suggesting secondary solar vasculopathy in the face of chronic depigmentation and alopecia (see Chapter 10).

Direct immunofluorescence or immunohistochemistry shows deposition of granular deposits of immunoglobulin, usually IgG (occasionally IgM), and often complement, at the dermal–epidermal junction (positive lupus band). One reported case demonstrated circulating autoantibody; indirect immunofluorescence showed linear deposition at the basement membrane zone (Iwasaki et al., 1995). Positive results are not automatically forthcoming in random biopsy specimens, and a negative result should not exclude the diagnosis if clinical findings and histopathology are characteristic.

Other forms of lupus erythematosus are the principal differential diagnoses in cases with obvious basal cell apoptosis. Discoid lupus erythematosus may have a more intense, band-like or lichenoid dermal infiltrate and less severe basal cell degeneration than systemic lupus erythematosus; however, these two diseases can be indistinguishable histologically, and clinical differentiation, including adjunctive testing for ANA, may be required. Discoid lupus erythematosus with prominent basal cell degeneration must also be distinguished from exfoliative cutaneous lupus erythematosus of the German Shorthaired Pointer, and vesicular cutaneous lupus erythematosus of the Shetland Sheepdog and Collie. Knowledge of signalment is therefore important in differentiation.

Discoid lupus erythematosus exhibiting suprabasilar apoptosis may resemble erythema multiforme. Apoptosis is generally more severe in erythema multiforme than in DLE, and features satellitosis more prominently (see p. 65). Chronic lesions of DLE in which basal cell degeneration is lacking resemble other lichenoid conditions, notably mucocutaneous pyoderma. Clinical differentiation is required (see Chapter 11).

SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical features (Figures 3.9 and 3.10)

Systemic lupus erythematosus (SLE) is a rare, multisystemic autoimmune disease reported in the dog and cat. Both organ-specific and nonorgan-specific circulating autoantibodies are directed against a wide variety of

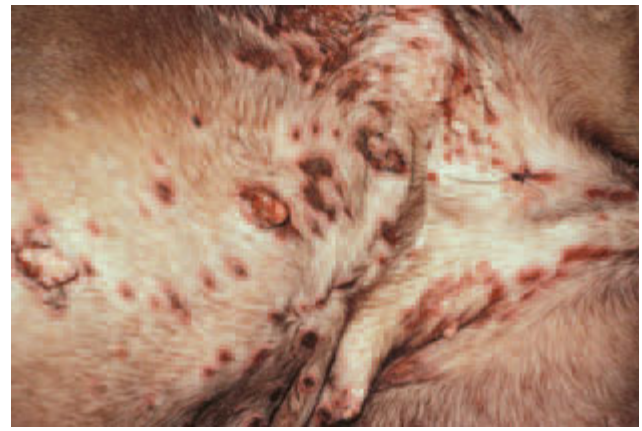


Fig. 3.9 Canine systemic lupus erythematosus. Widespread focal erosions and ulcerations of the ventral abdomen have erythematous, thickened margins and necrotic crusts.

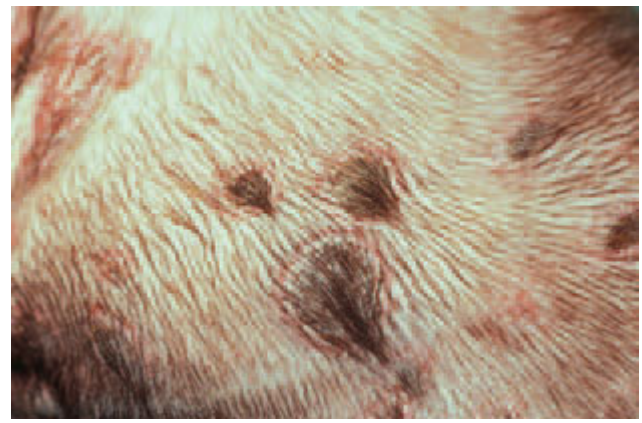


Fig. 3.10 Closer view of Fig. 3.9. Adherent crusts entrap remaining hair in the lesions.

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tissue antigens. The antinuclear antibody (ANA) test should be positive. Tissue damage may be due to immune complex deposition (Gel and Combs Type III), direct cytotoxic action (Type II), or even cell-mediated immunity (Type IV) as in lupus-induced autoimmune thyroiditis. A wide spectrum of disease is associated with multifactorial immunologic injury to a variety of organ systems (Olivry & Chan, 2001). Reported abnormalities in the dog include fever of unknown origin, polyarthritis, glomerulonephritis and proteinuria, anemia, thrombocytopenia, skin disease, neutropenia, and central nervous system disease (Fournel et al., 1992; Chabanne et al., 1995). Fever of unknown origin, weight loss, glomerulonephritis, hemolytic anemia, and skin disease are signs of SLE in the cat (Pedersen & Barlough, 1991; Vitale et al., 1997). Leukocytoclastic vasculitis is reported as an uncommon finding in SLE (Scott et al., 2001). Recognition of multisystemic disease should increase the index of suspicion for SLE.

The frequency of lupus-related skin disease in the dog is controversial. The opinion of the authors is that skin disease is seen in less than 20% of dogs with SLE. The diagnosis of skin disease due to SLE should be reserved for animals with compatible cutaneous signs, a positive ANA test, and evidence of additional organ system involvement in addition to skin lesions. The authors reserve the term 'discoid lupus erythematosus with a positive ANA' for the rare problematic cases in dogs exhibiting only cutaneous signs consistent with discoid lupus erythematosus but with positive serology consistent with SLE. However, evidence of other organ system involvement may occur later in the course of disease. Cases demonstrating histologic features of lupus erythematosus may be drug-related ('lupoid' drug reactions), and also have been observed by the authors in close temporal association with visceral malignancy. Thus, definitive diagnosis of SLE in these cases is contingent upon response to drug withdrawal, and evaluation for underlying diseases.

The dermatologic clinical features of SLE are pleomorphic. Erythema, scaling, crusting, depigmentation, and alopecia may be seen. Ulcers may eventuate from bullae in the skin, mucocutaneous junctions, and mucous membranes. Generalized exfoliative dermatitis, ulcers of the pawpads, panniculitis, and lesions closely mimicking discoid lupus erythematosus have been noted. The face, ears, and distal extremities are common sites of involvement. Partial symmetry, especially facial, is an important diagnostic clue. Photo-aggravation may be seen. Lymphadenopathy is common. A rare variant characterized by widespread, polycyclic, psoriasiform, and ulcerative lesions similar to subacute or chronic cutaneous lupus erythematosus in humans, has been seen in the dog by one author (P.J.I.).

A single dog (Bichon Frise) has been reported with bullous ulcerative skin disease that met the criteria for the SLE subgroup in humans designated 'bullous systemic lupus erythematosus' (Olivry et al., 1999). Immunologic findings mirrored those of epidermolysis bullosa acquisita, with IgG autoantibodies directed against the non-collagenous amino terminus (NC1 domain) of type VII collagen (see Chapter 2). Erosions and ulcers affected mucocutaneous junctions, pawpads, and areas of friction (Olivry et al., 1999).

The Spitz, Collie, Shetland Sheepdog, German Shepherd Dog, and Poodle are at increased risk. Purebred cats in general, and Siamese, Persian and Himalayan cats specifically, may be over-represented (Scott et al., 2001). Age or sex predilection has not been reported in the dog or cat.

Clinical differential diagnoses are legion based on the protean nature of the disease. Multisystemic disease in conjunction with widespread erythematous exfoliative dermatitis should increase suspicion for SLE. Discoid lupus erythematosus, bullous autoimmune diseases, cornification disorders, vasculitis, and idiopathic sterile nodular panniculitis probably are the most important differential diagnoses. Lupoid drug reactions may mimic the cutaneous signs of SLE such that only response to drug termination allows the diagnosis. Bullous SLE must be differentiated from epidermolysis bullosa acquisita and other autoimmune diseases that cause ulceration at frictional sites (Olivry et al., 1999).

Biopsy site selection

Care should be taken to avoid ulcers or erosions, since an intact epidermis is necessary to substantiate the diagnosis. Erythematous areas adjacent to ulcers may yield diagnostic results. Oral specimens rarely are beneficial, since ulcers, which are inherently not diagnostic, are common in this location. In addition, the mucosa may be disrupted easily from the submucosa in apparently intact lesions.

Histopathology (Figure 3.11)

The histopathologic findings of SLE may be variable, a dilemma which also is encountered in human medicine. Those cases may elude histopathologic diagnosis and require clinical and immunologic confirmation. Ideally, basal cell vacuolation and apoptosis of basal cells occur, leading to dermal–epidermal separation and ulceration. Superficial hair follicles to the level of the isthmus may be similarly affected. Direct immunofluorescence of skin biopsies in a large series of dogs with SLE revealed granular deposits of IgG in 74.5% of cases (Fournel et al., 1992). Vasculitis may occur (Scott et al., 2001).

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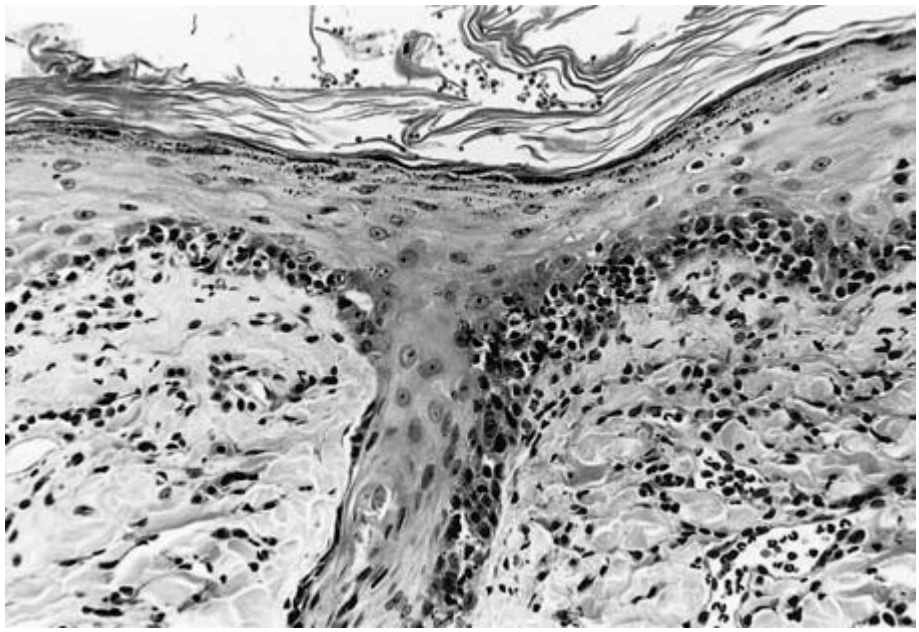


Fig. 3.11 Systemic lupus erythematosus in a cat demonstrating degeneration of the basal cell layer. Note severe apoptosis of basal cells and interface dermatitis. (Case material courtesy W.S. Rosenkrantz.)

Bullous SLE has been described in a dog (Olivry et al., 1999). Interface dermatitis was lacking; instead there were subepidermal vesicles that were variably filled with neutrophils and histiocytic cells. There was a mixed dermal infiltrate and secondary ulceration. Direct and indirect immunofluorescence detected IgG targeting the basement membrane zone.

Other forms of lupus erythematosus and erythema multiforme are the principal differential diagnoses for SLE. Lupoid drug reactions of essentially identical appearance to the classical interface reactions of lupus erythematosus have been observed, particularly secondary to topical otic medications. Clinical differentiation may be required. If the breed is not known, differentiation of cutaneous lesions of SLE from vesicular cutaneous lupus erythematosus of the Shetland Sheepdog and Collie, and exfoliative cutaneous lupus erythematosus of the German Shorthaired Pointer may be problematic, as all may be characterized by significant basal cell damage. Discoid lupus erythematosus may have a more intense, band-like dermal infiltrate, and less severe basal cell degeneration than SLE; however, these two diseases can be indistinguishable histologically, and clinical differentiation may be required. Erythema multiforme shows prominent individual keratinocyte necrosis at all levels of the epidermis, in addition to basal cell degeneration. Dermatomyositis (ischemic dermatopathy) of Collies in particular may be profoundly interface and thus histopathologically resemble SLE; the ischemic dermal and follicular changes may not permit differentiation, as SLE may be potentially vasculopathic. Clinical differentiation may be required.

Type I bullous SLE may be histologically and immunologically identical to epidermolysis bullosa acquisita (see Chapter 2). Identification of criteria compatible with SLE is required for differentiation.

PEMPHIGUS ERYTHEMATOSUS

Clinical features (Figures 3.12 and 3.13)

See Chapter 1.

Biopsy site selection

See Pemphigus foliaceus, Chapter 1.

Histopathology (Figure 3.14)

The epidermal lesions of pustulation with acantholysis are essentially those of pemphigus foliaceus, and have been described (see Chapter 1). Dermal lesions consist of a superficial infiltrate composed of lymphocytes, histiocytes, and plasma cells. Inflammation usually obscures the dermal–epidermal interface, and resembles that of discoid and systemic lupus erythematosus. Pigmentary incontinence is mild to moderate.

The histopathologic changes of facial lesions of pemphigus foliaceus are similar to those of pemphigus erythematosus. Pemphigus erythematosus (PE) has an interface component, as would be expected with pemphigus–lupus crossover disease, rather than simple lichenoid inflammation, as in facial pemphigus foliaceus (see Chapter 11). Without confirmatory immunologic find-

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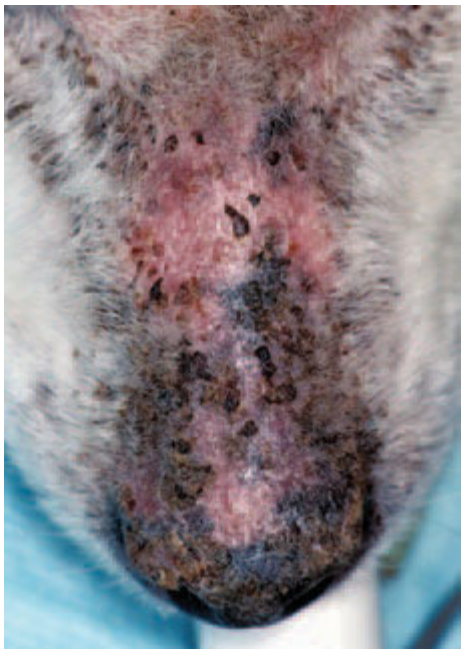


Fig. 3.12 Pemphigus erythematosus in a Spitz-crossbreed. Adherent, thick crusts symmetrically cover the dorsal muzzle and planum nasale.

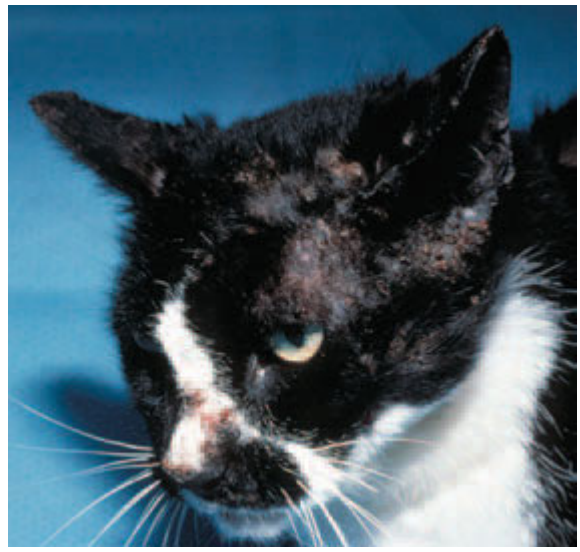


Fig. 3.13 Pemphigus erythematosus in a cat. Partially bilaterally symmetric vesicopustules, accompanied by later stage erosions, and ulcerations with adherent crusts affect the planum nasale, dorsal muzzle, ears, and temporal region. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

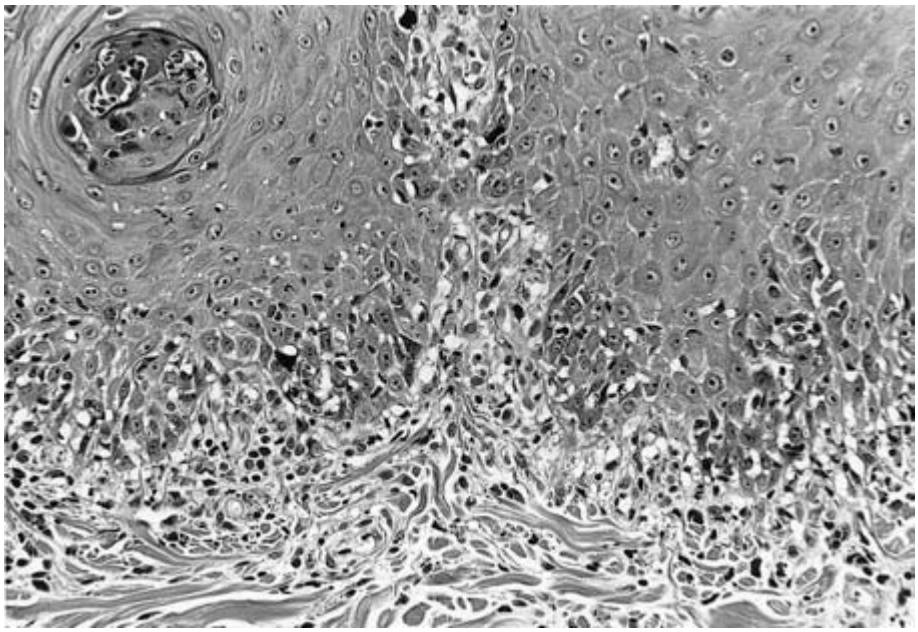


Fig. 3.14 Pemphigus erythematosus in a dog. Interface dermatitis is accompanied by a small intraepidermal pustule containing free keratinocytes.

ings, assignment of a diagnosis of PE may be impossible. Adherence to the immunologic criteria of PE requires that the diagnosis be made only when immunohistochemical or immunofluorescence testing is compatible, and when other clinical testing is supportive, particularly a positive antinuclear antibody (ANA) test. The principal microscopic method of differentiating these two diseases is through immunofluorescence or immunohistochemical techniques; PE exhibits deposition of immunoglobulin along the basement membrane in addition to the typical intercellular deposition of pemphigus foliaceus.

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Fig. 3.15 Exfoliative cutaneous lupus erythematosus of the German Shorthaired Pointer. Adherent scale and crusting are present on the muzzle and pinna.

EXFOLIATIVE CUTANEOUS LUPUS ERYTHEMATOSUS OF THE GERMAN SHORTHAIRED POINTER

(Synonym: lupoid dermatosis of the German Shorthaired Pointer)

Clinical features (Figures 3.15 and 3.16)

The term hereditary lupoid dermatosis of the German Shorthaired Pointer was initially used to characterize a unique scaling, exfoliative skin disease seen in the German Shorthaired Pointer (Gross & Ihrke, 1992; Vroom et al., 1995; White & Gross, 1995). Recognition of this syndrome to date exclusively in this breed suggests a strong hereditary component. A case in which three of ten siblings, as well as one half-sibling, were reputedly affected has been observed (White, S.D., personal communication, 1990). Recent work suggests that this syndrome resembles an exfoliative form of cutaneous lupus erythematosus seen in humans (Olivry et al., 1999). Humoral and cell-mediated immune responses directed against basal epithelial cells putatively are involved in the pathogenesis, thus supporting the use of the new name, 'exfoliative cutaneous lupus erythematosus' (Olivry et al., 1999).

Adherent scale and crusting are the most prominent clinical features. Fronds of keratin may surround and entrap hair shafts (White & Gross, 1995). Thickening of the skin may be evident. Lesions commonly begin on the head and back, but usually generalize. The muzzle and ear pinna may be markedly affected. In dogs with generalized disease, the hocks, other pressure points and scrotum may be severely involved. Pruritus and pain are variable. Secondary pyoderma and *Malassezia* dermatitis may be present. Pyrexia, lethargy and peripheral lymphadenopathy may be observed. Severity may wax and wane.



Fig. 3.16 Exfoliative cutaneous lupus erythematosus of the German Shorthaired Pointer. Note scaling involving the caudal lower leg. (Photograph courtesy S.D. White.)

The syndrome has been seen only in the German Shorthaired Pointer. Age of onset is between 5 and 7 months. Sex predilection has not been noted, but few cases have been observed.

Clinical differential diagnoses should include primary cornification disorders such as primary seborrhea and ichthyosis, as well as sebaceous adenitis. The young age of onset is considered atypical for sebaceous adenitis. Occurrence to date is exclusively in the German Shorthaired Pointer, and the distinct histopathologic appearance will allow differentiation from primary cornification disorders.

Biopsy site selection

Multiple specimens should be selected from lesions of varying stages. If early lesions can be identified, these may more reliably reveal typical basal cell damage.

Histopathology (Figures 3.17 and 3.18)

The most characteristic lesions are severe vacuolar degeneration of the basal cell layer of the epidermis, accompa-

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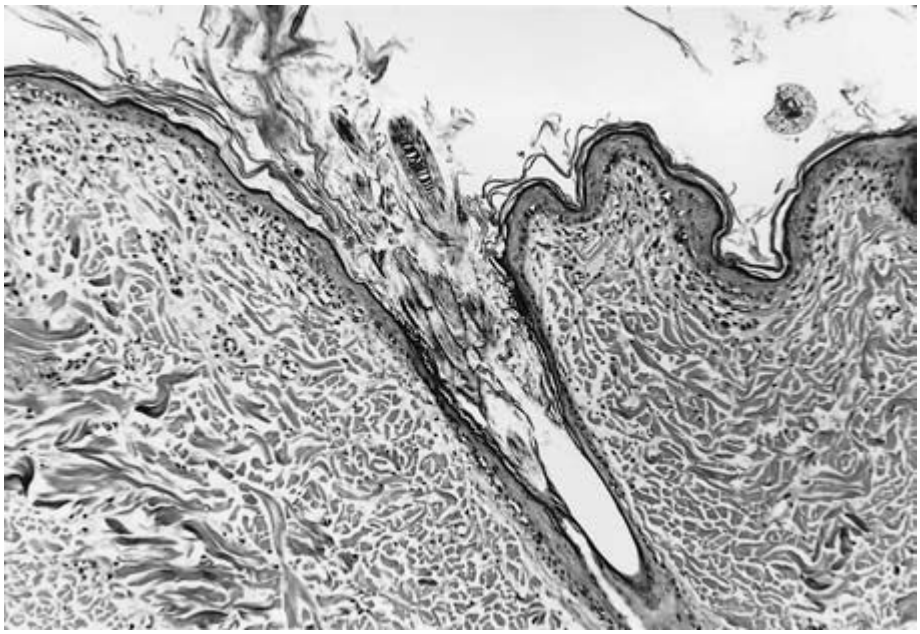


Fig. 3.17 Mild interface dermatitis in exfoliative cutaneous lupus erythematosus of the German Shorthaired Pointer. Note follicular hyperkeratosis.

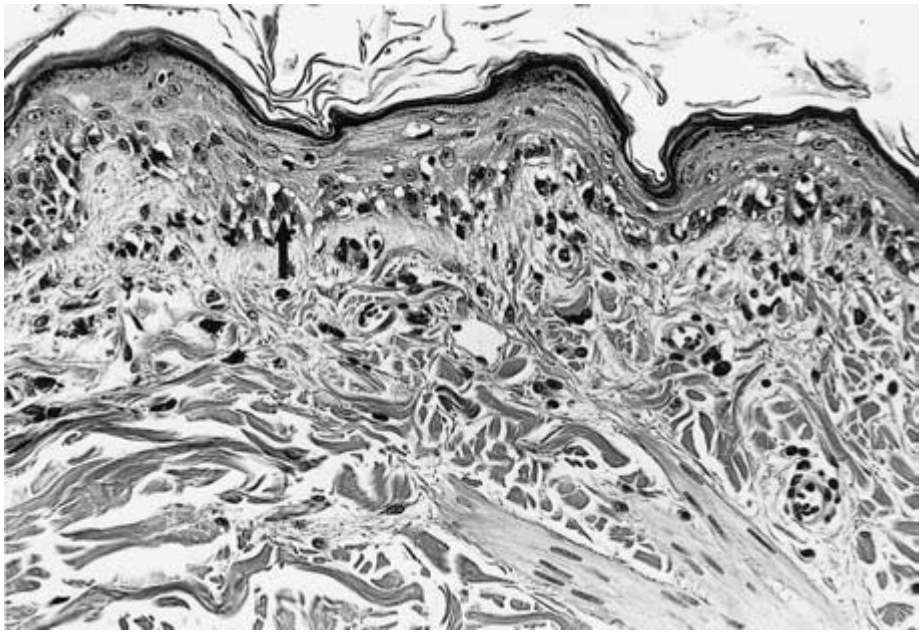


Fig. 3.18 High magnification of exfoliative cutaneous lupus erythematosus. Note prominent basal cell vacuolation and occasional apoptosis (arrow).

nied by apoptosis. Mild dermal–epidermal separation is present, and is often seen at the margins of specimens as useable artifact (see ischemic dermatopathy, p. 49). Apoptotic cells are shrunken and rounded or angular; nuclei are pyknotic. Occasionally, apoptosis may extend throughout the epidermis, and in rare cases becomes focally confluent, resulting in superficial epidermal necrosis. Frank ulceration may occur. The epidermis is mildly to moderately acanthotic, and may have multifocal parakeratosis and serocellular crusting. There is moderate hyperkeratosis.

Similar vacuolar and necrotic lesions also affect the superficial hair follicles to the level of the adnexal glands. There may be marked accompanying follicular and sebaceous gland atrophy. Progressive sebaceous atrophy was identified in a dog over a 3-month period in a previous study (Olivry et al., 1999). Sebaceous gland atrophy may explain the presence of hyperkeratosis, as seen in sebaceous adenitis (see Chapter 8).

Pigmentary incontinence is often prominent in the superficial dermis, and is the result of basal cell damage. Lymphocytes, macrophages, neutrophils, and plasma cells

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accumulate in mild or moderate numbers around superficial vessels, and form a thin discontinuous or continuous band (lichenoid pattern) in close proximity to the epidermis and superficial hair follicles. Mononuclear cells infiltrate the lower epidermis, the wall of superficial hair follicles to the isthmus, and occasionally are grouped in nodules in lopsided orientation at the site of putative sebaceous glands.

A previous study identified the epitheliotropic lymphocytes as CD8+ T cells. In that study, IgG, IgA, IgM, and C3 were detected at the basement membrane zone in 97%, 3%, 18%, and 13% of cases, respectively (Olivry et al., 1999).

Histopathologic differential diagnoses include sebaceous adenitis (due to the sebaceous atrophy observed in some cases), other forms of lupus erythematosus, and erythema multiforme. Sebaceous adenitis is not characterized by interface dermatitis. Lupus-like (lupoid) drug reactions of similar appearance have been observed, particularly secondary to topical otic medications. Knowledge of breed affected and young age of onset may be most helpful in differentiating exfoliative cutaneous lupus erythematosus from other forms of lupus erythematosus as well as drug reactions. Discoid lupus erythematosus may have a more intense, band-like dermal infiltrate. Erythema multiforme will closely mimic those cases of exfoliative cutaneous lupus erythematosus dermatosis in which apoptosis is seen at all levels of the epidermis. Clinical differentiation may be required, specifically the characteristic breed affected. Further, erythema multiforme usually does not occur in dogs less than 1 year of age.

VESICULAR CUTANEOUS LUPUS ERYTHEMATOSUS OF THE SHETLAND SHEEPDOG AND COLLIE

(Synonym: ulcerative dermatosis of the Shetland Sheepdog and Collie)

Clinical features (Figures 3.19 and 3.20)

Ulcerative dermatosis of the Shetland Sheepdog and Collie was the name initially given to a poorly understood syndrome postulated to represent a subgroup of canine familial dermatomyositis (Gross & Ihrke, 1992; Ihrke & Gross, 1995). Recent work now suggests that this syndrome resembles a photosensitive vesicular form of subacute cutaneous lupus as seen in humans (Jackson & Olivry, 2001; Jackson, 2004). IgG autoantibodies directed against nuclear antigens were noted in sera from 9 of 11 affected dogs using immunoblotting and enzyme-linked immunosorbent assay (ELISA), but indirect immunofluorescence testing was consistently negative (Berget et al., 2002). Demonstration of autoantibodies that target nuclear antigens supports the hypothesis that this syndrome is a unique variant of cutaneous lupus erythematosus featuring lymphocyte-mediated toxicity that targets basal epidermal keratinocytes (Berget et al., 2002). Routine antinuclear antibody (ANA) testing has been consistently negative in this syndrome.

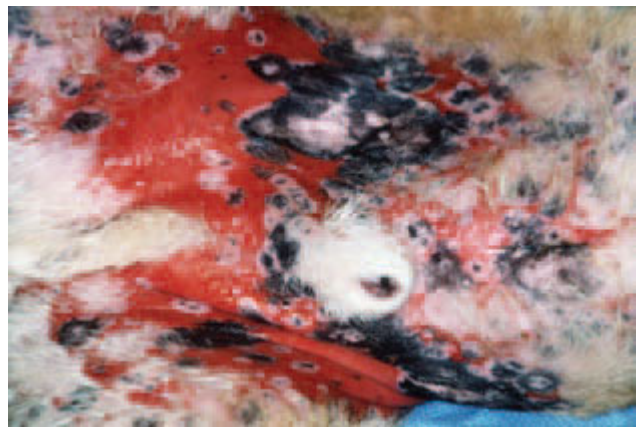


Fig. 3.19 Vesicular cutaneous lupus erythematosus of the Shetland Sheepdog and Collie. Extensive ulcers on the ventral abdomen exhibit undulating, serpiginous borders.

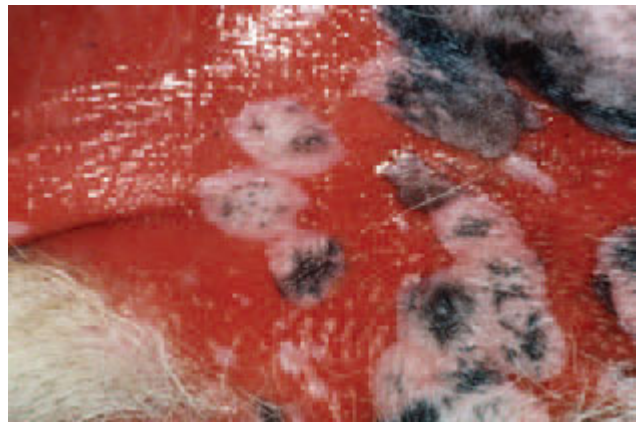


Fig. 3.20 Closer view of the dog in Fig. 3.19. Coalescing ulcers with well-demarcated, undulating serpiginous borders are present.

Transient vesicobullous eruptions develop in areas of figurate erythema and lead to coalescing ulcers with well-demarcated, undulating serpiginous borders. The intertriginous areas of the groin and axillae are most often affected. Lesions may involve the mucocutaneous junctions of the eyes, mouth, external genitalia, and anus. Partial bilateral symmetry may be seen. Solar exposure may exacerbate the disease. Pain may be evident if ulceration is widespread or secondary pyoderma is present. A concomitant myositis has been documented by electromyography in several affected dogs.

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This syndrome has been recognized only in the adult Shetland Sheepdog, Rough Collie, and their crossbreeds. Middle-aged and older dogs are affected. Sex predilection has not been noted.

In the past, this syndrome probably was misdiagnosed as bullous pemphigoid or 'hidradenitis suppurativa'. Other clinical differential diagnoses should include severe erythema multiforme, systemic lupus erythematosus, and pemphigus vulgaris. Histopathology, the specific breeds affected, and immunologic studies should aid in differentiation.

Biopsy site selection

Foci of erythema at the margins of crusting or ulcerated lesions are preferred sites for the demonstration of characteristic histopathologic lesions. Due to the fragility of the dermal–epidermal junction in lesions of ulcerative dermatosis, wedge biopsy is recommended for sampling.

Histopathology (Figures 3.21 and 3.22)

Interface vacuolation and basal cell apoptosis are present and are often severe. Subepidermal vesiculation is common and leads to severe ulceration and exudation. Damage to basal cells also allows weakening of the dermal–epidermal junction, and the 'usable artifact' of dermal–epidermal separation may be seen at the margins of specimens (see ischemic dermatopathy, p. 49). Apoptosis and vacuolation affect the outer cells of superficial hair follicles to the level of the isthmus. Apoptosis may also be seen suprabasally, predominantly within the lower stratum spinosum. Apoptotic cells in these areas may be surrounded by lymphocytes (satellitosis).

The superficial dermis contains a mixed mononuclear infiltrate that is closely applied to the dermal–epidermal interface, sometimes in a band or lichenoid configuration; in combination with the interface damage this results in a lichenoid–interface pattern. Lymphocytes migrate into the overlying basal cell layer and obscure the dermal–epidermal junction. Superficial dermal edema and congestion may be intense. Neutrophils are prominent in ulcerated lesions and may also collect in subepidermal vesicles. Superficial dermal fibrosis follows ulceration and may be severe. Direct immunofluorescence testing with IgG may demonstrate staining of basal cells, as well as variable basement membrane staining.

The principal differential diagnoses include erythema multiforme, and other forms of lupus erythematosus. Dermatomyositis (ischemic dermatopathy) of Collies may feature striking basal cell degeneration, but also demonstrates variable ischemic alteration of the dermis and follicles, in contrast to vesicular cutaneous lupus erythematosus. Lupus-like (lupoid) drug reactions of essentially identical appearance have been observed, particularly secondary to topical otic medications. Knowledge of signalment may be critical in the differentiation of these diseases. Erythema multiforme may be very similar, but tends to feature apoptosis in a more transepidermal pattern, rather than predominantly in the basal or suprabasal regions. Discoid lupus erythematosus will most often have a more intense, band-like dermal infiltrate than vesicular cutaneous lupus erythematosus, as well as less severe basal cell degeneration. Vesicular cuta-



Fig. 3.21 Vesicular cutaneous lupus erythematosus in a Shetland Sheepdog. An ulcer is covered by a serocellular crust. The intact epidermis shows basilar vacuolation; note interface inflammation.

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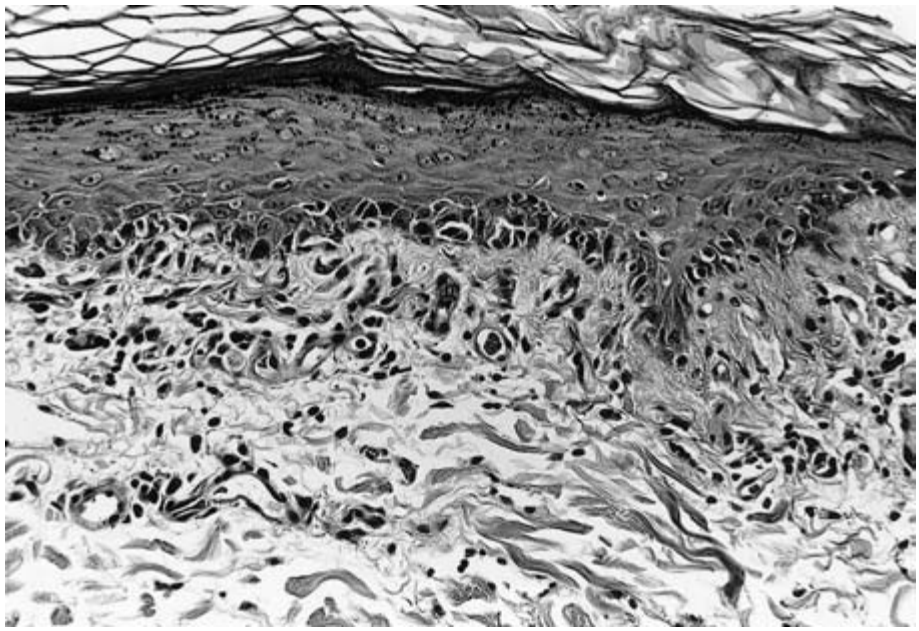


Fig. 3.22 Higher magnification of vesicular cutaneous lupus erythematosus in a Shetland Sheepdog. Basal cells are apoptotic.

neous lupus erythematosus does not feature sebaceous or follicular atrophy, as seen in exfoliative cutaneous lupus erythematosus.

ERYTHEMA AB IGNE

(Synonyms: chronic moderate heat dermatitis, chronic radiant heat dermatitis)

Clinical features (Figure 3.23)

The term 'erythema ab igne' is used in human medicine to describe a skin disease initiated by repetitive and prolonged exposure to chronic radiant or conductive heat. This syndrome is characterized by erythema and mottled pigmentary changes. Commonly reported radiant and conductive heat sources include open fires (stoves), heating pads, steam radiators, and hot water bottles. Venous stasis and aging are thought to be predisposing factors. After many years, precancerous thermal keratoses and, eventually, thermal carcinomas may arise in humans (Schwartz & Stoll, 1999).

Lesions similar to erythema ab igne have been seen in dogs and cats, and most often result from exposure to conductive heat sources; thus the term 'chronic moderate heat dermatitis' is used (Walder, 1994; Declercq & Vanstapel 1998; Walder & Hargis, 2002). Reported heat sources in the dog and cat include heating pads, heated kennel mats, electric blankets, plant warmers, metal heat register covers, infrared lamps and sun-heated driveways (Walder & Hargis, 2002). One author (T.L.G.) has seen this syndrome in cats secondary to sleeping on cable television boxes, and the informal designation of 'cable box kitty syndrome' has been applied to those cases. Other electronic devices that commonly are left turned on and radiate or conduct moderate heat also could initiate the condition.

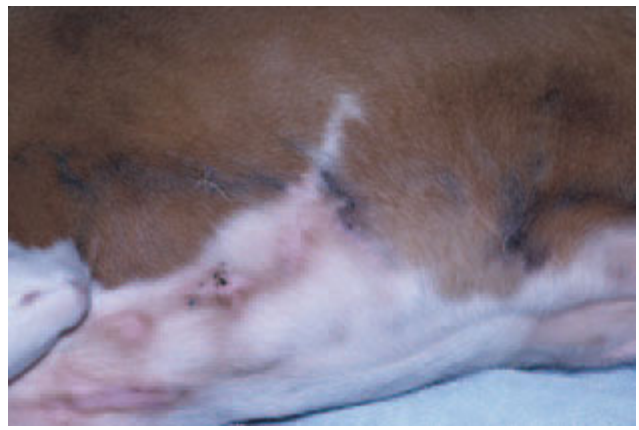


Fig. 3.23 Erythema ab igne affecting the lateral and ventral trunk of a dog. Note the strikingly linear and intersecting lattice-like alopecia with hyperpigmentation.

The clinical presentation is variable and reflects the type and site of chronic thermal damage. Alopecia is the most frequent clinical feature. Mottled erythematous scaly or crusted macules and plaques give rise to hyperpigmentation with chronicity. Strikingly linear and intersecting lattice-like hyperpigmentation with alopecia, when present, is a highly characteristic feature (Walder & Hargis, 2002). Lesions acquired during recumbency occur

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on the ventral or lateral chest, abdomen, and flank and neck (Walder & Hargis, 2002). Other sites may be involved, contingent on the site exposed to the chronic radiant heat source.

Breed, age or sex predilections have not been reported. Differential diagnosis may be problematic, as areas of macular pigmentary alteration and alopecia are not clinically distinctive. The site affected and a history of chronic moderate heat exposure are the most helpful aids to diagnosis. Skin biopsy is usually confirmatory; however, subtle microscopic lesions may be difficult to discern. A high index of clinical suspicion is therefore of benefit.

Biopsy site selection

Areas of maximum alopecia with different ranges of pigmentary change should be sampled. If present, plaque-like as well as macular regions should be sampled.

Histopathology (Figures 3.24 and 3.25)

Erythema ab igne features a cell poor interface reaction that features mild apoptosis of basal cells. Viable basal cells may be mildly dysplastic, characterized by enlarged and more deeply staining nuclei (karyomegaly). Apoptosis and karyomegaly may extend suprabasally, and may affect superficial hair follicles. Subepidermal bubbling vacuolation just beneath the basement membrane is an occasional finding. Subepidermal vesiculation may be observed. Damage to basal cells also allows weakening of the dermal–epidermal junction, and the 'usable artifact' of dermal–epidermal separation may be seen at the margins of specimens (see ischemic dermatopathy, p. 49).

A characteristic but variably subtle feature is the presence of eosinophilic, wavy elastin fibrils in the superficial dermis ('red spaghetti of Walder'). These fibers may stand out against a background of edema or mucin, and are accentuated with Verhoeff–van Gieson stain for elastin (Walder & Hargis, 2002). These fibers appear fine, irregular, and grayish black with this staining method. The superficial dermis has variable laminar fibrosis (scarring). Dermal collagen may also appear faded or smudged. Superficial to deep dermal edema is observed, and mucin has been reported (Walder & Hargis, 2002). Increased acid mucopolysaccharide in the superficial dermis was demonstrated in affected dogs with alcian blue stain (pH not stated) (Declercq & Vanstapel, 1998). There is subtle vasculopathy characterized principally by loss of endothelial cells; affected vessels may have slightly thickened or smudged walls. Hair follicles are atrophic, and appear telogenized or, in some cases, more severely atrophic or 'faded'. Association of follicular and adnexal atrophy with heat-related vascular damage (ischemic dermatopathy) has been postulated (Walder & Hargis, 2002). In fact, the blood vessels of erythema ab igne resemble the cell poor vasculitis of ischemic dermatopathy (see Chapter 10). Further, the faded collagen is typical for that entity.

There is moderate acanthosis with hyperkeratosis (basket weave and compact), and variable serocellular parakeratotic crusting. Epidermal thinning is reported as a rare feature of erythema ab igne (Walder & Hargis, 2002). Concurrent thermal burns, characterized by focal ulceration, crusting, and necrosis of the epidermis or adnexal glands, were reported in three of nine animals in a recent review (Walder & Hargis, 2002). There is pigmentary incontinence, likely secondary to basal cell damage, which is accompanied by usually mild infiltra-

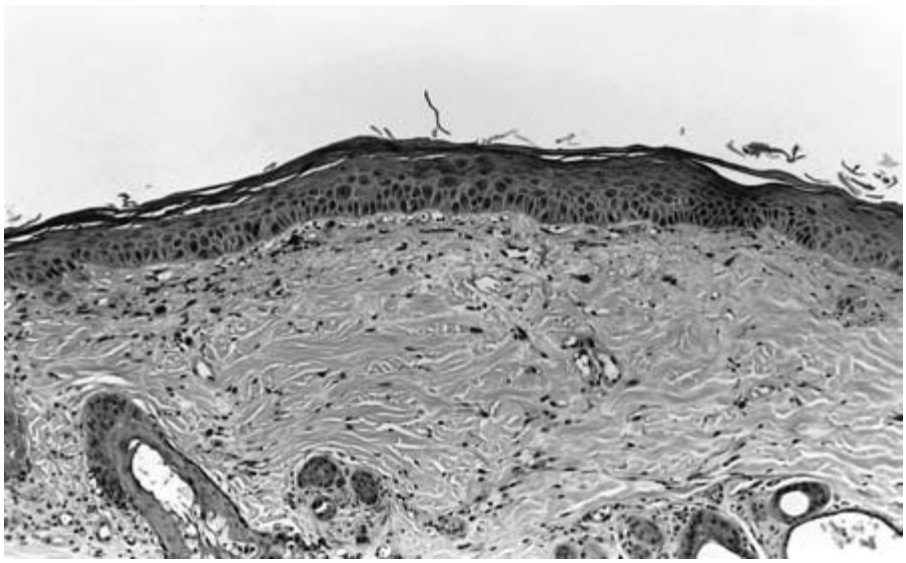


Fig. 3.24 Erythema ab igne in a dog. Cell poor interface dermatitis is accompanied by subepidermal bubbling vacuolation and smudging of dermal collagen.

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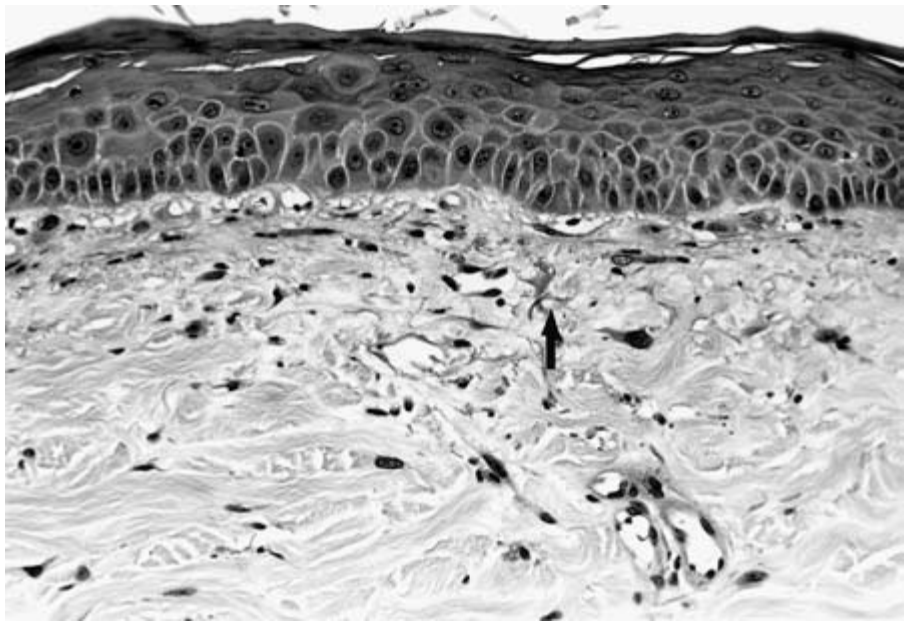


Fig. 3.25 Higher magnification of Fig. 3.24. Note 'red spaghetti' of Walder (arrow) and mild karyomegaly of keratinocytes.

tions of lymphocytes, macrophages, and plasma cells. Macrophages often contain hemosiderin and/or melanin pigment, reflecting both basal cell and endothelial cell damage. Neutrophils or eosinophils are rare.

Erythema ab igne is differentiated from other cell poor interface dermatoses by the presence of dysplastic keratinocytes with karyomegaly, or the presence of eosinophilic elastic fibers ('red spaghetti'). If these are lacking, the lesions may resemble ischemic dermatopathy of dogs or feline thymoma-associated exfoliative dermatitis of cats. Ischemic dermatopathy features more prominent and consistent ischemic collagen (faded, pale staining, or smudged), as well as more obvious cell poor vasculitis (see Chapter 10). Feline thymoma-associated dermatitis has a more pronounced interface cellular infiltrate. Clinical differentiation is often of prime importance; lesions of erythema ab igne are typically asymmetrical and limited in distribution, suggesting thermal exposure.

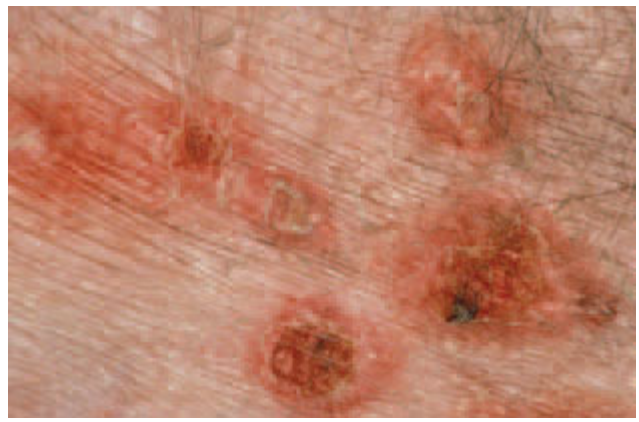


Fig. 3.26 Erythema multiforme in a dog caused by a drug reaction to trimethoprim-sulfa. Coalescing erythematous target lesions are present on the ventral abdomen.

ERYTHEMA MULTIFORME

Clinical features (Figures 3.26 and 3.27)

The varied use of the term 'erythema multiforme' (EM) has lead to considerable confusion in both veterinary and human dermatology. This confusion stems from the fact that the term is used by clinicians to connote clinically distinctive targetoid lesions characterized by concentric circular zones of varying color and textural change. Conversely, pathologists tend to use the term whenever implosive keratinocyte death (apoptosis) occurs with lymphocyte satellitosis. Clinicians and pathologists both agree that EM is a cutaneous reaction pattern of multifactorial etiology that is seen uncommonly in the dog and rarely in the cat. Erythema multiforme is believed to be a host-specific T cell-mediated hypersensitivity phenomenon in which the cellular immune response is directed against various keratinocyte-associated antigens, including those associated with drug administration, infection, neoplasia, and connective tissue disease. Lymphocytes bind to the antigenically altered keratinocytes and trigger cell death via apoptosis (Affolter et al., 1998).

The subcategorization of EM adopted by veterinarians from the human literature also is confusing and contro-

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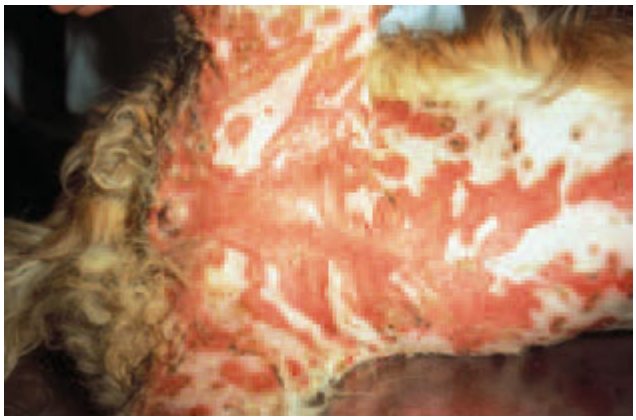


Fig. 3.27 Severe erythema multiforme in a dog caused by a drug reaction to ampicillin. Widespread coalescing erosions and ulcers with serpiginous borders involve most of the ventral abdomen and inner thighs. (From Ihrke, P.J. (1980) Dermatologic therapy. Part I, Topical therapy. *Comp Contin Edu Prac Vet* **1**, 28–36. Reprinted with permission.)

versial. In 1993, an attempt was made to standardize nomenclature in human dermatology (Bastuji-Garin et al., 1993). Recently, this nomenclature was adapted for veterinary dermatology (Hinn et al., 1998). The terms, 'erythema multiforme minor' (EM minor) and 'erythema multiforme major' (EM major) formerly have been used to describe syndromes with substantial variations in percentage of body involvement and severity. Using this nomenclature, EM minor is reserved for patients with target lesions, no more than one mucosal surface affected, and less than 10% of body surface affected; EM major refers to a clinically similar syndrome but with more than one mucosal surface affected, between 10% and 50% of body surface affected, and with less than 10% epithelial detachment. The eponym Stevens–Johnson syndrome (SJS) should be reserved for those patients with severe EM that exhibit greater than 50% body surface affected, and epithelial detachment varying from 10% to 30%. Toxic epidermal necrolysis (TEN), considered by the authors to be a separate syndrome, is reserved for patients with generalized disease and more than 30% epithelial detachment (see Chapter 4). An SJS–TEN overlap syndrome is diagnosed in patients with clinical features of both syndromes but with between 10% and 30% epithelial detachment (Bastuji-Garin et al., 1993; Hinn et al., 1998). The clinical usefulness of this new classification scheme in veterinary medicine has yet to be determined.

Categorization of the most common induction triggers of EM also is controversial. In contrast to current thoughts on the pathogenesis of EM in humans, popular belief still holds that most documented cases of EM in small animals are associated with drug hypersensitivity. Neoplasia and infection are viewed as considerably less common initiators. Most links to underlying neoplasia are anecdotal. Confirmed association between EM and neoplasia in humans is rare. One author (T.L.G.) has seen localized oral EM overlying a deeper squamous cell carcinoma.

Scott and Miller (1999) reported that 26 of 44 (59%) cases in dogs probably were drug-induced while six of six cases in cats were drug-induced. Trimethoprim-potentiated sulfonamides, penicillins, and cephalosporins have been the drugs incriminated most commonly (Ihrke, 1996; Scott & Miller, 1999). Rarely, dyes, preservatives and stabilizers in pet foods may act as drugs and induce EM. Data utilizing the newer classification described above indicated that causative drug exposure was likely in only 19% of dogs with EM minor and major, but dogs with SJS, SJS–TEN overlap syndrome, or TEN were likely to have been drug-induced in 92% of cases (Hinn et al., 1998).

Herpesvirus is a common trigger for EM in humans (Fritz & Ruiz-Maldonado, 2003). It has been hypothesized that epitheliotropic viruses may be a more common initiator of EM minor in dogs also (Olivry, T., personal communication, 2001). The only well-substantiated case of viral induced EM in a dog was triggered by canine parvovirus-2 (Favrot et al., 2000). Recently a series of five puppies with skin lesions reportedly characterized by apoptosis and satellitosis had positive immunohistochemistry and polymerase chain reaction (PCR) testing for canine distemper virus, canine parvovirus, and canine herpesvirus (Hubert et al., 2002). Drugs (especially the same three antibiotics as listed for dogs above), and herpesvirus infection have been implicated in feline EM (Scott et al., 2001).

A subgroup of chronic and persistent, idiopathic EM is seen in older dogs ('old dog EM') without a history compatible with known triggers. Lesions are more exudative and proliferative, and often predominantly involve the face and ears. The authors have identified occult leukemia, and *Pneumocystis* pneumonia (probably indicating immune dysfunction) in two dogs with this syndrome; however, often investigation for systemic disease is fruitless.

Erythema multiforme is characterized clinically by a remarkably pleomorphic eruption considering the commonality of the histopathologic changes. In dogs, typically there is an acute onset of erythematous annular macules, elevated circular plaques, and papules that develop rapidly in partially symmetrical patterns. Early lesions may appear urticarial. As lesions evolve, crusting becomes more noticeable. Some lesions become strikingly and distinctively targetoid with multiple concentric circular zones of erythema, blanching, and exfoliation. Adjacent lesions may coalesce to form distinctive arciform and serpiginous patterns. Epidermal collarettes may be

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present. In subgroups of severity beyond EM minor, lesions are more severe and ulceration may be substantial. Mucosal lesions may begin as vesicles and bullae and eventuate in widespread ulceration. Severely affected animals may be febrile, depressed and anorectic. Pain is associated with more severe disease.

Although lesions may be seen anywhere, truncal lesions are more frequent and especially involve the glabrous skin of the groin and axillae. Other common sites of involvement include the mucocutaneous junctions, oral mucosa, ears, and axillae. The ventrum, mucocutaneous junctions, oral cavity, pinnae, and pawpads were reported as the four most common sites in order of diminished frequency (Scott & Miller, 1999). Clawbed and perianal lesions have been seen less commonly.

Feline EM is reported to exhibit predominantly vesicular, bullous, and ulcerative lesions involving the trunk and mucocutaneous junctions (Scott & Miller, 1999). Generalized exfoliative dermatitis with alopecia also has been seen.

German Shepherd Dogs and Pembroke Welsh Corgis were reported to be at increased risk in one study (Scott & Miller, 1999). Other signalment predilections have not been reported for the dog or cat.

Clinical differential diagnoses are legion due to the pleomorphic nature of EM. Milder cases (EM minor) may resemble urticaria, urticarial allergic eruption, superficial spreading pyoderma, bacterial folliculitis, dermatophytosis, demodicosis and early lesions of bullous autoimmune skin diseases. Cases that feature prominent erythema with plaques may resemble canine sterile neutrophilic dermatosis (Sweet's syndrome; see Chapter 14). Erythema multiforme major and SJS must be differentiated from necrotizing syndromes such as TEN, burns, systemic lupus erythematosus, vasculitis, toxic pustular erythroderma of Miniature Schnauzers, or other causes of ischemic necrosis. Superficial necrolytic dermatitis, zinc-responsive dermatosis, and generic dog food-associated dermatosis are additional differential diagnoses for chronic EM of older dogs due to the proliferative and exudative nature of these lesions. Histopathology usually will allow differentiation of EM from the aforementioned diseases.

Biopsy site selection

Areas of erythema without crusting or ulceration are ideal sites for skin biopsy. An intact epidermis or mucosa is crucial for the diagnosis of EM.

Histopathology (Figure 3.28)

Although apoptosis with lymphocyte satellitosis is the most characteristic feature of EM (see Chapter 4), an interface dermatitis is invariably present. Lesions extend to superficial hair follicles. A few cases of EM predominantly affecting the hair follicles have been observed (see Chapter 4). Lymphocytes and macrophages are grouped along the dermal–epidermal junction, and partially obscure it. Inflammation is usually mild, but can approach a band-like, or lichenoid configuration occasionally. Neutrophils, eosinophils, and plasma cells may be present, particularly if there is ulceration. Pigmentary incontinence is variable. There is vacuolation of the base-

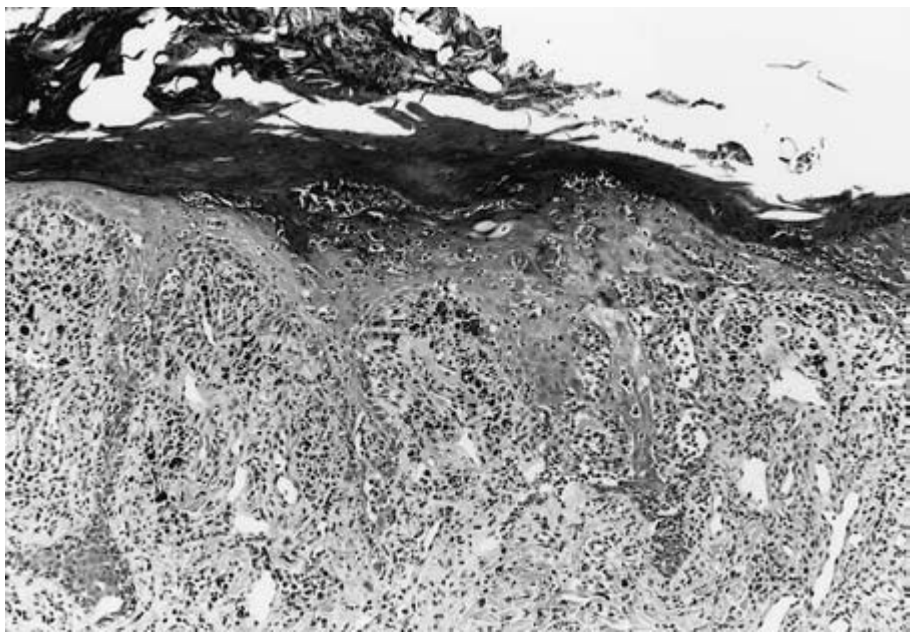


Fig. 3.28 Interface inflammation of canine erythema multiforme. Note prominent pigmentary incontinence and apoptosis of keratinocytes in overlying epidermis.

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ment membrane zone, often in a bubbling pattern, and individual basal cell apoptosis may be present.

Differentiation of the interface lesions of EM from all forms of lupus erythematosus is required, as all may show apoptosis of basal cells and an interface dermal inflammatory infiltrate. In EM, apoptosis is more prominent and is seen at all levels of the epidermis. Lupus erythematosus has apoptosis that is principally confined to the basal cell layer. Feline thymoma-associated dermatitis features interface dermatitis, but has milder transepidermal apoptosis than typical EM. Differentiation is probably artificial as feline thymoma-associated dermatitis may represent a variant of graft-versus-host disease or EM; these diseases differ principally in the source of the antiepithelial T cells (see below).

FELINE THYMOMA-ASSOCIATED EXFOLIATIVE DERMATITIS

(Synonym: paraneoplastic exfoliative dermatitis)

Clinical features (Figures 3.29 and 3.30)

Feline thymoma-associated exfoliative dermatitis is a rare paraneoplastic syndrome seen in the cat (Scott et al., 1995). Exfoliative skin disease often precedes the development of any systemic signs. Many paraneoplastic syndromes of putative immunologic basis are seen in conjunction with thymomas in humans. The paraneoplastic nature of feline thymoma-associated exfoliative dermatitis has been proven by the regression of clinical signs after surgical removal of the neoplasm (Forster-Van Hijfte et al., 1997; Rivierre & Olivry, 1999; Rottenberg et al., 2004).

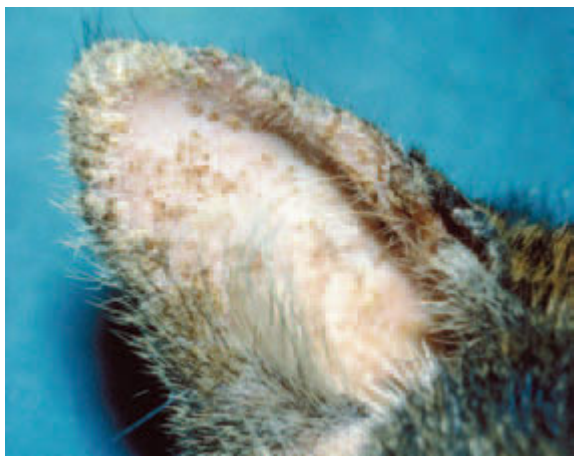


Fig. 3.29 Feline thymoma-associated exfoliative dermatitis. Adherent keratinous debris is present on the pinna. (Photograph courtesy T. Olivry.)



Fig. 3.30 Feline thymoma-associated exfoliative dermatitis. Large sheets of exfoliated stratum corneum are entrapped in the hair coat. (Photograph courtesy T. Olivry.)

In humans, it has been shown that thymomas generate new and possibly aberrant populations of autoantigen-responsive, CD4+ T cells (Nenninger et al., 1998). In paraneoplastic myasthenia gravis, for example, naïve T cells are produced and exported from the neoplastic thymic milieu; this is uncommon in thymoma patients without myasthenia gravis (Strobel et al., 2002). Diverse pathogenic mechanisms involving cytotoxic T cell attack on keratinocytes are central to the pathogenesis of graft-versus-host disease and erythema multiforme (Affolter et al., 1998). Similar development of autoreactive T cell populations may be involved in the pathogenesis of feline thymoma-associated exfoliative dermatitis, as the histopathology of these three syndromes shares marked similarity (Rivierre & Olivry, 1999; Walder & Kornet, 1999; Heripret, 2000). Differentially, the source of the antiepithelial T cells is exogenous in graft-versus-host disease, pre-existing in erythema multiforme, and newly generated in thymoma-associated exfoliative dermatitis. One author (T.L.G.) has observed two cases with skin lesions that were histologically identical, but had no underlying evidence of neoplasia or other internal disease upon postmortem examination. This further supports the contention that this disease is a reaction pattern indicative of T cell-driven immunity and is not specific for thymoma. The syndrome may be most common with thymoma as this may be the most likely setting for induction of autoreactive T cells in the cat.

Regions of erythema and exfoliation develop with gradually increasing severity. Alopecia is noted secondary to exfoliative erythroderma. The head, neck, and pinnae commonly are affected first before the syndrome generalizes. As the syndrome progresses, large visually striking sheets of exfoliated stratum corneum develop, often greater than 1 cm in diameter, and may become entrapped

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in the remaining haircoat. Keratosebaceous debris may accumulate in claw folds and interdigital regions (Scott et al., 1995). Pruritus usually is absent, unless secondary yeast or bacterial infection is present. Secondary *Malassezia* dermatitis may markedly exacerbate the skin lesions (Forster-Van Hijfte et al., 1997). Frequently, skin lesions are the only manifestation. Coughing and dyspnea may occur as systemic signs; less diagnostic systemic signs of anorexia and lethargy may be present in advanced cases.

Feline thymoma-associated exfoliative dermatitis primarily affects middle-aged to older cats. Breed or sex predilections have not been reported.

Clinical differential diagnoses include other feline exfoliative dermatoses such as epitheliotropic T cell lymphoma (mycosis fungoides), pemphigus foliaceus, systemic lupus erythematosus, erythema multiforme, dermatophytosis, superficial demodicosis, or underlying diseases such as hyperglucocorticoidism or diabetes mellitus with secondary bacterial or dermatophyte infection. Thoracic radiographs, ultrasonography, and fine needle aspirates of thymic masses, along with skin biopsy, will support the diagnosis.

Biopsy site selection

Multiple regions of exfoliation and erythroderma should be sampled. Care should be taken to include exfoliative material.

Histopathology (Figures 3.31 and 3.32)

Mild transepidermal and follicular apoptosis and hyperkeratosis are consistent features of feline thymoma-associated dermatitis (see Chapter 4), but may be subtle in some cases. Interface dermatitis is invariably present, and extends to superficial hair follicles to the level of the isthmus. Follicular interface inflammation with scattered basal cell apoptosis is striking, and sebaceous glands are often absent. Their absence may contribute to hyperkeratosis (Rivierre & Olivry, 1999); as also seen in sebaceous adenitis (see Chapter 8). Vacuolation occurs along the dermal–epidermal interface as well, and there may be scattered basal cell and spinous layer apoptosis. Lymphocytes and macrophages predominate and there is pigmentary incontinence. *Malassezia* colonization has been reported (Forster-Van Hijfte et al., 1997; Mauldin et al., 2002).

The diagnosis of feline thymoma-associated dermatitis is centered upon identification of a thymic mass. However, two cases have been observed by one author (T.L.G.) that did not have underlying thymoma; this suggests that this is not a disease exclusive to thymoma association but instead is an immunologic reaction pattern that is most common in that context.

Feline thymoma-associated dermatitis has milder transepidermal apoptosis than typical erythema multiforme, but is similar in other respects, particularly to the hyperkeratotic form. Differentiation is probably artificial as feline thymoma-associated dermatitis may represent a

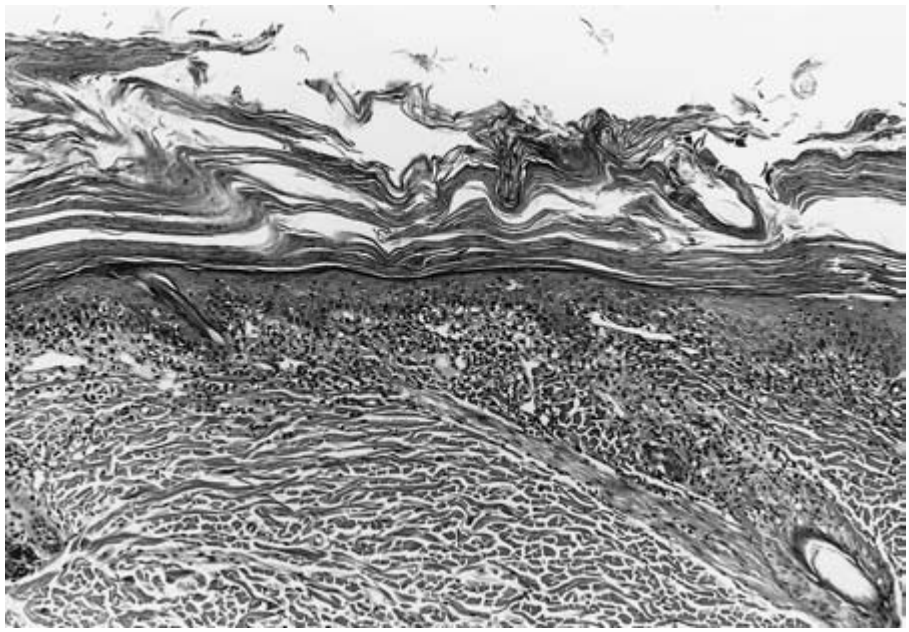


Fig. 3.31 Feline thymoma-associated dermatitis demonstrating interface inflammation and hyperkeratosis.

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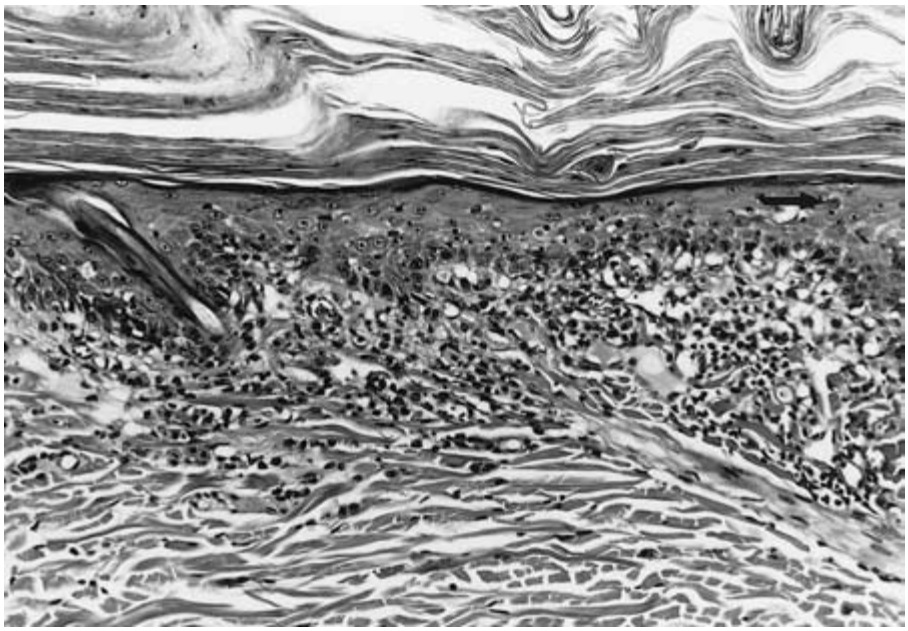


Fig. 3.32 Higher magnification of Fig. 3.32. Note interface inflammation and occasional apoptosis (arrow).

variant of graft-versus-host disease or erythema multiforme; these diseases differ principally in the source of the antiepithelial T cells (see above). Erythema multiforme and graft-versus-host disease are histologically indistinguishable and have a similar cell mediated pathogenesis (Affolter et al., 1998).

The interface lesions of feline thymoma-associated dermatitis resemble all forms of lupus erythematosus. As apoptosis in feline thymoma-associated dermatitis is often mild, differentiation from lupus erythematosus may be difficult based on histopathology alone; clinical differentiation is required. Feline sebaceous adenitis might be considered for cases in which sebaceous glands are absent; however, the inflammation of sebaceous adenitis is confined more exclusively to the follicular isthmus, and apoptosis is not a feature of that dermatosis.

LUPOID ONYCHITIS

(Synonym: symmetrical lupoid onychodystrophy)

Clinical features (Figures 3.33 and 3.34)

Lupoid onychitis is a canine syndrome of probable multifactorial etiology. Lupoid onychitis is characterized by separation of the claw from the clawbed, sloughing of claws, and the regrowth of misshapen, dry, brittle, short claws. Usually, all claws are affected on all feet. The term 'symmetrical lupoid onychodystrophy' has been used (Scott et al., 1995). The authors prefer the term 'lupoid onychitis' because it emphasizes that the changes in the claw are due to underlying inflammation of the clawbed.



Fig. 3.33 Lupoid onychitis in a Rhodesian Ridgeback. Affected claws are dry, brittle, and crumbling. One claw has avulsed. (Photograph courtesy T.E. Bonenberger; case material University of California, Davis.)

Most cases of this syndrome are idiopathic, but adverse reaction to food and drug administration are reported (Mueller et al., 2000; Scott et al., 2001). One textbook lists this syndrome as an immune-mediated disease (Scott et al., 2001). A similar clinical presentation with similar histopathology has been associated with canine leishmaniasis (Koutinas et al., 2002).

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Initially, claw abnormalities develop simultaneously on several digits of multiple paws. Within 3 months, all claws on all four paws usually are affected. Claws separate from the underlying clawbed, and more severely affected claws slough. Hemorrhage is an inconsistent feature of claw sloughing. Regrowth of markedly abnormal claws is characterized by dryness, brittleness and crumbling. Wide variability occurs in the changes seen in individual dogs. Pain and resultant lameness varies from minimal to severe, with approximately one half of the dogs exhibiting some lameness and pain (Scott et al., 2001). Secondary bacterial infection is common, and may be due to either *Staphylococcus* or *Staphylococcus* plus Gram-negative organisms.

Large breed dogs, such as German Shepherd Dogs, Rottweilers, and possibly Giant Schnauzers and Standard Schnauzers may be at increased risk (Scott et al., 1995, 2001; Bergvall, 1998). However, this syndrome has been seen in a wide variety of breeds. Affected dogs commonly are young adults to middle-aged.

There are few known diseases that affect only the claws of all four paws. While diseases such as vasculitis, systemic lupus erythematosus, pemphigus vulgaris, or bullous pemphigoid can affect the clawbeds, the authors have not seen these diseases limited to this site.



Fig. 3.34 Lupoid onychitis in a Rottweiler. All claws are dry, brittle, and cracked.

Biopsy site selection

Biopsy of the clawbed is not easily accomplished. Traditionally, biopsy has been via the amputation of a third phalanx (P3). If present and affected, a dewclaw may be sacrificed. Specimens must include the clawbed to establish a diagnosis. A new punch biopsy technique allowing onychobiopsy without onychectomy was published recently (Mueller & Olivry, 1999). However, the authors prefer the specimen procured by the amputation of P3 as it delivers a less disrupted specimen. Further, partial removal of the clawbed epithelium may result in a permanently disfigured claw.

Histopathology (Figures 3.35 and 3.36)

Interface inflammation obscuring the junction between clawbed epithelium and adjacent dermis is the hallmark



Fig. 3.35 Clawbed of dog with lupoid onychitis demonstrating variable interface inflammation.

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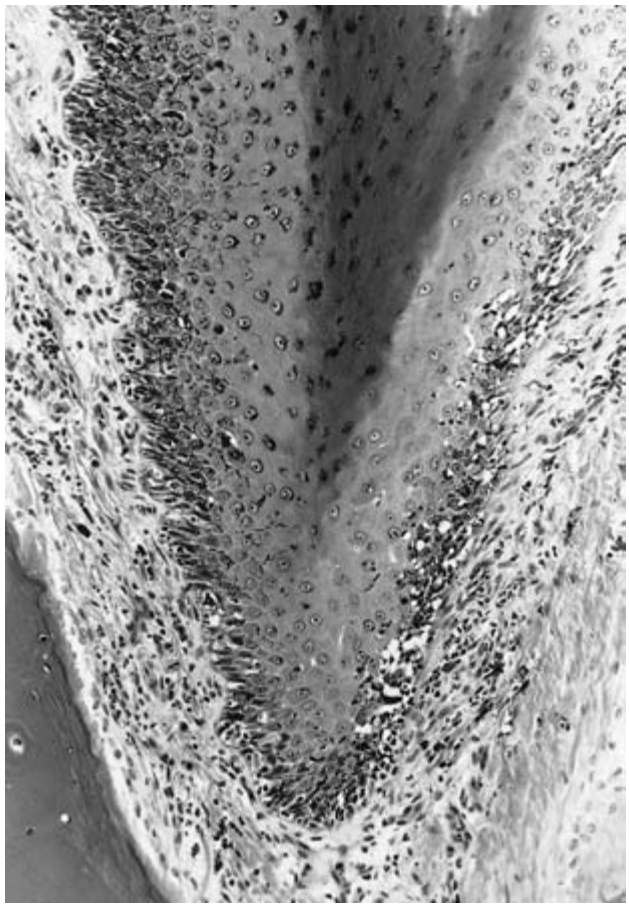


Fig. 3.36 Higher magnification of interface dermatitis in clawbed of dog with lupoid onychitis; P3 is at lower left.

feature of lupoid onychitis. In rare cases, inflammation may be severe and more band-like, or lichenoid. There is pigmentary incontinence. Inflammation consists of lymphocytes and macrophages intermingled with fewer neutrophils and plasma cells. Plasma cells may predominate in chronic lesions.

Apoptosis and vacuolation of basal cells are common. Suprabasilar apoptosis may occur. Mild basilar vacuolation only is not diagnostic, as this is a normal finding in the canine clawbed (Mueller et al., 1993). There is frequently subepithelial vesiculation. Damage to basal cells allows weakening of the dermal–epidermal junction, and thus 'usable artifact' of dermal–epidermal separation may occur during processing (see ischemic dermatopathy, p. 49).

Congestion and hemorrhage of the corium may accompany separation. Secondary ulceration of the clawbed epithelium is common and is accompanied by suppurative exudation. Laminar areas of fibrosis beneath the clawbed epithelium are not uncommon and are relatively uninflamed; inflammation may subtend these areas of fibrosis. Inflammation and fibrosis may spread to surrounding tissue after the claw is lost and osteomyelitis of the distal phalangeal bone may develop. Reactive new bone proliferation may be observed. The adjacent skin of the claw bed may have superficial perivascular dermatitis of similar inflammatory cell composition, accompanied by acanthosis.

There are no significant differential diagnoses for lupoid onychitis as the lesions of the affected tissue are characteristic. However, it should be kept in mind that this diagnosis is not specific; lupoid onychitis is a reaction pattern and is likely multifactorial in etiology. For example, lichenoid mononuclear inflammation without basal cell apoptosis (lichenoid but not interface onychitis) characterized dogs with leishmaniasis that had concurrent clawbed disease (Koutinas et al., 2002). Erythema multiforme of the clawbed has been observed, but although the interface dermatitis is similar between these two entities, erythema multiforme features transepithelial apoptosis and lymphocytic satellitosis, not found in lupoid onychitis. The chronic and diffuse fibrosing inflammation, with osteomyelitis of P3, is nonspecific, and also can occur as a sequel to onychitis of infectious or traumatic origin.

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See Chapter 1.

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Chapter 4

Necrotizing diseases of the epidermis

Necrotizing diseases of the epidermis are characterized by keratinocyte cell death. Death of the cell may be due to necrosis or apoptosis. While these are separate processes, there may be biochemical overlap (Zeiss, 2003). Although apoptosis and necrosis are distinct, it is conventional (and convenient) to group diseases demonstrating either form of cell death as 'necrotizing' until a new broader term is designated. It may not always be possible for the pathologist to recognize morphologic differences between necrosis and apoptosis at the light microscopic level. However, single cell death is often the result of apoptosis (Fadok, V.A., personal communication, 2004). In diseases of this chapter for which the underlying mechanism of keratinocyte cell death is not yet known, the authors will assign 'apoptosis' to lesions that initiate with individual death of keratinocytes (accompanied by other features described for apoptosis; see below), and 'necrosis' to processes dominated by severe and confluent death and disintegration of keratinocytes.

Apoptosis is generally the result of a genetically driven cellular signal that induces a preprogrammed pathway to cell death (Noli et al., 1998). Apoptosis is triggered by Fas/Fas ligand interaction (Puviani et al., 2003). Stimuli to apoptosis may be viral, drug-induced, or autoimmune in origin, among others. An apoptotic keratinocyte is brightly eosinophilic and shrunken due to condensation, and has a rounded or angular contour; apoptotic cells do not rupture. Necrosis is associated with cellular swelling and rupture (also termed 'oncosis'); coagulation and caseation necrosis falls in this category. External stimuli, such as trauma or infection, will induce this type of necrosis.

Necrolysis has been used occasionally as a synonym for necrosis. Technically, necrolysis is defined as disintegration, separation, or exfoliation occurring secondary to cell death.

Diseases involving death of the keratinocyte may be diffuse, or affect individual keratinocytes throughout the epidermis or superficial hair follicles; the latter is most often the result of apoptosis. There may be surface or follicular hyperkeratosis as apoptotic keratinocytes accumulate. Necrotizing diseases may have prominent ulceration as devitalized keratinocytes are sloughed.

ERYTHEMA MULTIFORME

Clinical features (Figures 4.1 and 4.2)

See Chapter 3.

Biopsy site selection

See Chapter 3.

Histopathology (Figures 4.3 through 4.6)

Apoptosis of keratinocytes is the most characteristic histologic lesion of erythema multiforme (EM). Solitary or grouped, brightly eosinophilic and shrunken apoptotic keratinocytes are present at all levels of the epidermis. Apoptosis extends throughout superficial hair follicles to the level of the isthmus. Lymphocytes, which have induced apoptosis, surround the affected keratinocytes ('satellitosis').

The authors have seen cases of EM featuring large histiocytic round cells (putative Langerhans cells) in clusters within the epidermis. These lesions may mimic epitheliotropic lymphoma with apoptosis. The presence of intraepithelial aggregates of Langerhans cells has been referred to by some authors as 'pseudo-Pautrier abscesses' (Candiago et al., 2000; Burkert et al., 2002).

Secondary neutrophilic infiltration and exudative crusting are observed, particularly if there is ulceration. There may be superficial pustulation as well. Interface dermatitis, which also extends to superficial follicles, is invariably present (see Chapter 3).

Progressive keratinocyte apoptosis may lead to ulceration or hyperkeratosis; the latter morphology has been informally termed 'hyperkeratotic EM'. Which secondary lesion occurs (ulceration versus hyperkeratosis) may depend upon the rapidity, location, and severity of apoptosis. Severe transepidermal apoptosis often becomes

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Fig. 4.1 Erythema multiforme due to a drug reaction to trimethoprim-sulfa in a dog. Note well-demarcated, erythematous, coalescing target lesions with erythematous borders surrounding central crusts.

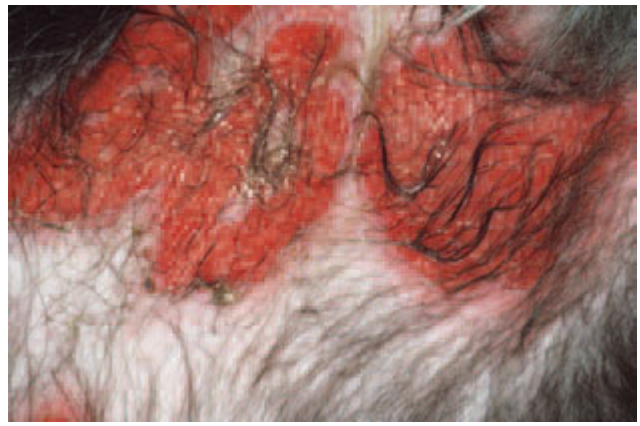


Fig. 4.2 Erythema multiforme in the same dog as in Fig. 4.1 photographed 6 hours later. Note that the magnitude of ulceration has intensified.

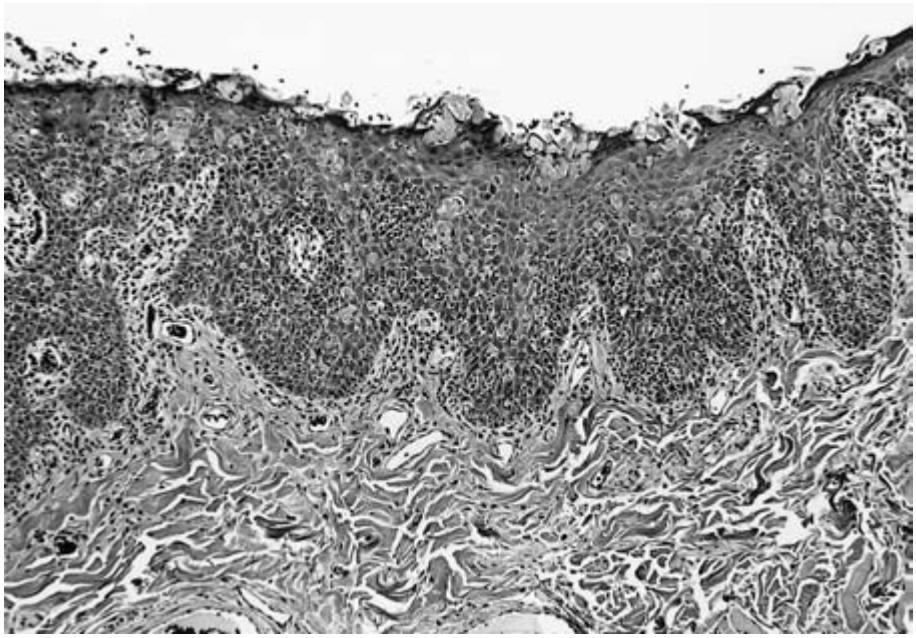


Fig. 4.3 Erythema multiforme in a dog demonstrating widespread individual keratinocyte apoptosis; confluence of apoptotic cells is apparent.

confluent, and is more likely to progress to ulceration. Hyperkeratosis, which usually occurs with milder and persistent apoptosis, is orthokeratotic and parakeratotic; however, parakeratosis usually is more prominent. Keratin is increased both epidermally and within superficial follicles. Hyperkeratotic EM may be more common in cats.

Isolated cases of EM involving predominantly the hair follicles have been observed in both dogs and cats. Severe interface folliculitis and striking apoptosis result in follicular destruction and/or moderate to severe atrophy. Hair follicles may become severely attenuated as lesions advance. Perifollicular and follicular inflammation is lymphohistiocytic, and includes a prominent component of neutrophils. A nodular pattern of inflammation with granuloma formation may be observed in severe lesions, resembling granulomatous mural folliculitis (see Chapter 18). Sebaceous glands may be degenerate or absent and there is concurrent follicular keratosis, as seen in sebaceous adenitis (see Chapter 8). In a case of EM due to *E. coli* otitis media, massive isthmus follicular necrosis and degeneration were accompanied by severe vacuolar degeneration of sebaceous glands. Sebocytes were replaced by round vacuoles of variable size. This vacuolar glandular change has been observed in other cases of EM in which severe follicular damage has occurred.

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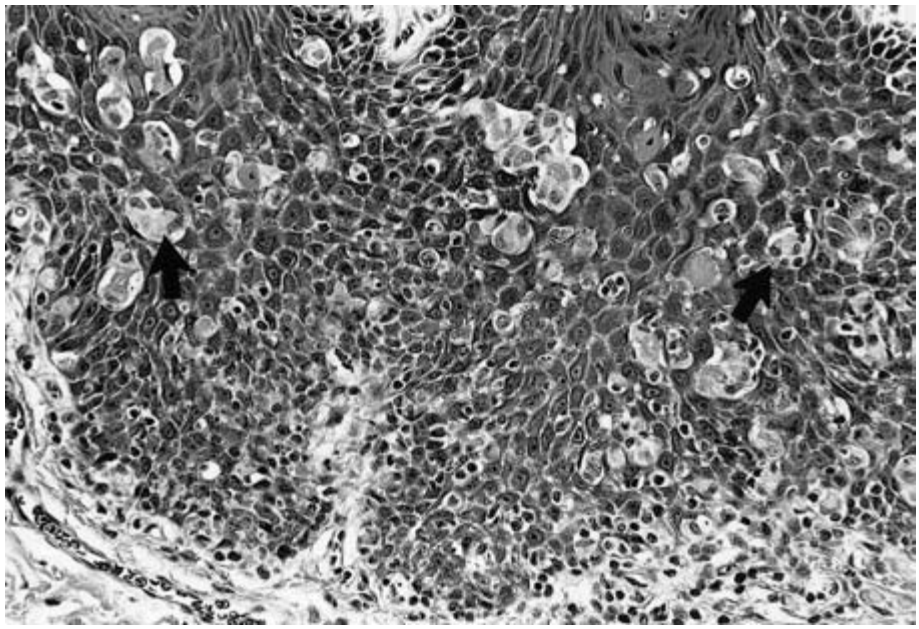


Fig. 4.4 Erythema multiforme in a dog. Note pale apoptotic keratinocytes and occasional lymphocytic satellitosis (arrows).



Fig. 4.5 Follicular erythema multiforme in a dog secondary to *Escherichia coli* otitis media. There is extensive destruction of the follicular wall; residual sebaceous glands are inflamed and vacuolated.

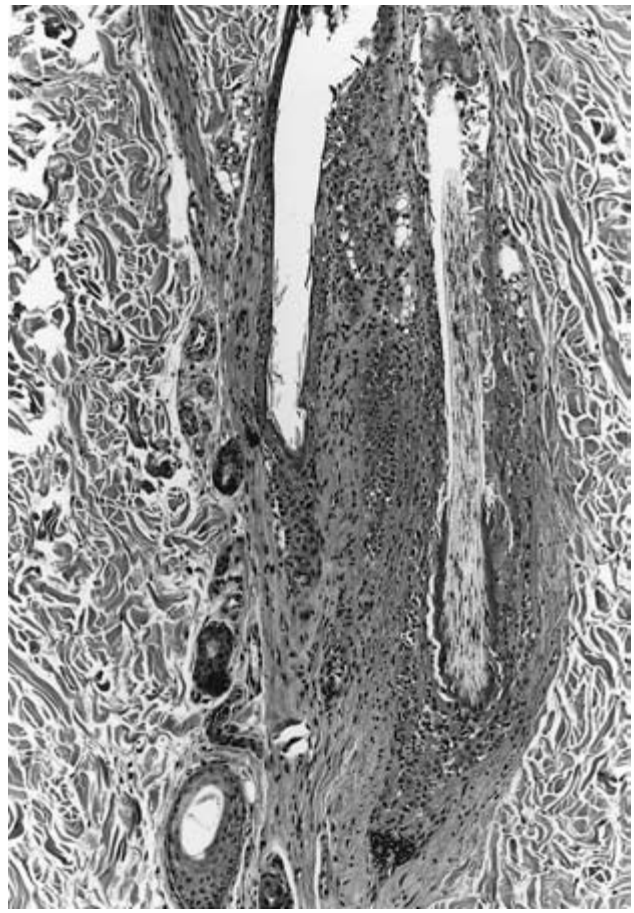


Fig. 4.6 Higher magnification of follicular erythema multiforme in the dog of Fig. 4.5. Partially destroyed sebaceous glands are severely vacuolated; the inner portion of the subjacent primary follicle is degenerated.

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Confluent areas of cell death in lesions of EM may resemble toxic epidermal necrolysis (see p. 80). Although the two diseases may be etiopathogenically related, severe EM is clinically and histopathologically distinct from toxic epidermal necrolysis. Confluent cell death in EM always is associated with dermal and often epidermal inflammation; lesions of toxic epidermal necrolysis consist of diffuse epidermal necrosis without obvious associated inflammation, at least in the earliest lesions.

Other differential diagnoses include the various syndromes of lupus erythematosus, feline thymoma-associated dermatitis, and some forms of epitheliotropic lymphoma that feature prominent apoptosis (see Chapter 37). Lupus erythematosus may feature suprabasilar apoptosis (see Chapter 3). In most cases, transepidermal apoptosis is more severe in EM. Feline thymoma-associated dermatitis has interface dermatitis and mild transepidermal apoptosis with often striking hyperkeratosis. Differentiation from EM is probably artificial, as feline thymoma-associated dermatitis may represent a variant of graft-versus-host disease or EM; these three diseases differ principally in the source of the antiepithelial T cells (see thymoma-associated exfoliative dermatitis, Chapter 3). Erythema multiforme and graft-versus-host disease are histologically indistinguishable and have a similar cell mediated pathogenesis (Affolter et al., 1998). Erythema multiforme that features accumulations of large intraepidermal histiocytic cells (resembling T cells but likely representing Langerhans cells) may be particularly difficult to distinguish from epitheliotropic lymphoma with apoptosis. Lymphocytic infiltration of apocrine sweat glands is a highly diagnostic feature of epitheliotropic lymphoma but is not a prominent feature of EM. Clinical as well as immunohistochemical differentiation may be required for problematic cases (see Chapter 37).

FELINE THYMOMA-ASSOCIATED EXFOLIATIVE DERMATITIS

(Synonym: paraneoplastic exfoliative dermatitis)

Clinical features

See Chapter 3.

Biopsy site selection

See Chapter 3.

Histopathology (Figure 4.7)

Mild transepidermal and superficial follicular apoptosis, and mild to severe hyperkeratosis are present. In some cases apoptosis may be difficult to identify and interface dermatitis may predominate (see Chapter 3). The keratin layer may be lifting or flaking from the surface of the skin, resulting in actual decrease in the thickness of the normal keratin layer in some areas. Although apoptosis may be mild and sporadic, its presence in the context of hyperkeratosis is highly characteristic. Lymphocytes may closely surround the apoptotic keratinocytes ('satellitosis'). Increased keratin is of ortho- and parakeratotic

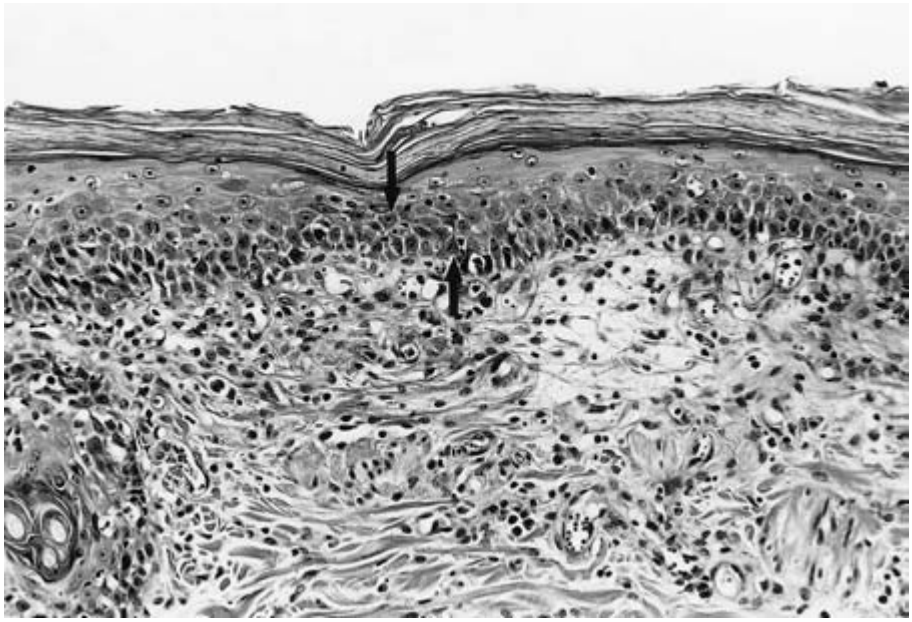


Fig. 4.7 Feline thymoma-associated exfoliative dermatitis. Scattered basilar and suprabasilar apoptosis (arrows) is accompanied by hyperkeratosis.

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types, and there may be neutrophilic pustules and crusts. *Malassezia* colonization has been reported (Forster-Van Hijfte et al., 1997; Mauldin et al., 2002).

The diagnosis of feline thymoma-associated dermatitis is centered upon identification of a thymic mass. However, two cases have been observed by one author (T.L.G.) that did not have underlying thymoma; this suggests that this is not a disease exclusive to thymoma association, but instead is an immunologic reaction pattern that is most common in that context.

Feline thymoma-associated dermatitis has milder transepidermal apoptosis than typical erythema multiforme, but is similar in other respects, particularly to the hyperkeratotic form. Differentiation is probably artificial as feline thymoma-associated dermatitis is similar immunologically to graft-versus-host disease or erythema multiforme; these diseases differ principally in the source of the antiepithelial T cells (see thymoma-associated exfoliative dermatitis, Chapter 3). Erythema multiforme and graft-versus-host disease are histologically indistinguishable and have a similar cell mediated pathogenesis (Affolter et al., 1998).

Cutaneous lesions of lupus erythematosus may feature suprabasilar apoptosis, as well as interface dermatitis, and should be differentiated from feline thymoma-associated dermatitis. As apoptosis in feline thymoma-associated dermatitis is often mild, differentiation from lupus erythematosus may be difficult based on histopathology alone. A positive lupus band test may be of benefit, but is not consistently present in randomly selected biopsies of cats with lupus erythematosus. Clinical differentiation may be required.

PROLIFERATIVE NECROTIZING OTITIS OF KITTENS

Clinical features (Figure 4.8)

Proliferative necrotizing otitis of kittens is a rare, highly characteristic syndrome of uncertain etiology. As the name implies, the syndrome is seen only in cats less than 1 year of age. Since the syndrome bears some resemblance histopathologically to hyperkeratotic erythema multiforme, an immunologic basis is suspected. Currently, there is no evidence to link this syndrome to any infectious viral diseases. Polymerase chain reaction (PCR) testing for feline herpesvirus 1 using primers for thymidine kinase and polymerase glycoprotein has been negative in five cats (Foley, J.E., personal communication, 2002). Papillomavirus immunohistochemistry has also been negative.

Well-demarcated erythematous plaques with adherent, thick keratinous debris are present on the medial aspect of the pinnae, the entrance to the auditory canal, and in some cats, the preauricular region of the face. Lesions develop very rapidly and coalesce, sometimes creating annular or serpiginous borders. Adherent crusts are trapped in the hair coat. As the lesions progress, erosion and ulceration occur. Most affected cats appear indifferent to the lesions. Mild pruritus or discomfort may be noted when ulceration is present.



Fig. 4.8 Proliferative necrotizing otitis of kittens. Severe, proliferative inflammation is present on the pinna. Note well demarcated plaques with adherent keratinous debris. (Photograph courtesy T.E. Bonenberger; case material University of California, Davis.)

Lesions develop in kittens between 2 months and 6 months of age and regress, apparently spontaneously, by 12 to 24 months. Although other signalment data are not available, most cases have occurred in domestic shorthaired cats.

Proliferative necrotizing otitis of kittens is visually distinctive. The authors have not seen lesions with these clinical characteristics in the context of other diseases. Diagnosis is confirmed by skin biopsy.

Biopsy site selection

Erythematous plaques should be sampled, taking care that adherent keratinous crusts are obtained. If lesions are present in the preauricular zone, sampling from this region is less difficult than biopsy of the medial surface of the pinnae or the entrance to the auditory canal.

Histopathology (Figures 4.9 through 4.11)

The raised plaques are often sharply demarcated from adjacent normal skin. Scattered apoptotic-appearing keratinocytes are present within severely hyperplastic epidermis and superficial follicular epithelium. There is striking parakeratotic hyperkeratosis with intermingled neutrophilic crusts, often in layers. The process extends

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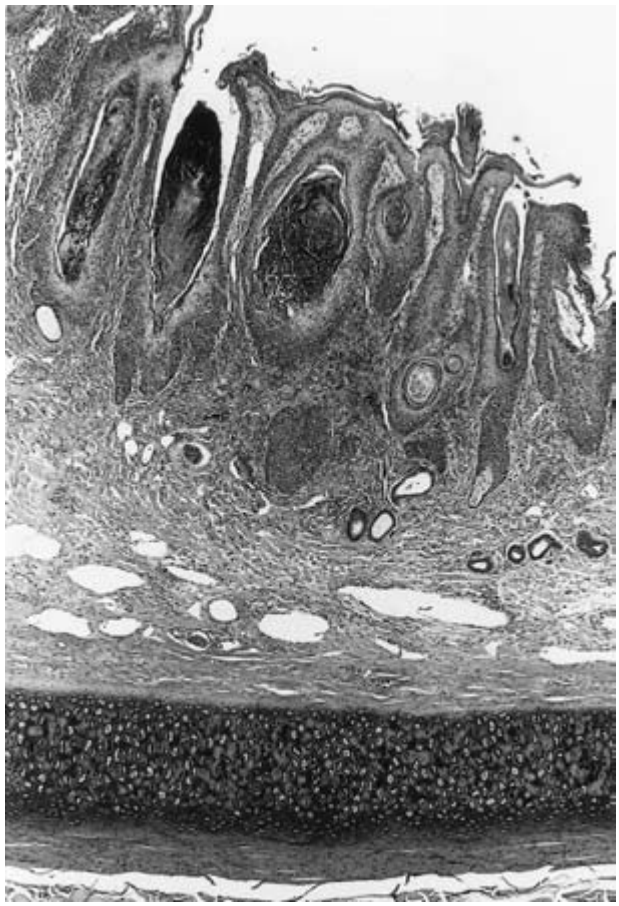


Fig. 4.9 Proliferative necrotizing otitis of kittens. The inflammatory plaque is characterized by massive follicular plugging with inflammatory debris; there is laminar pallor of the epidermis and follicular infundibulum. Aural cartilage is at bottom.



Fig. 4.10 High magnification of proliferative necrotizing otitis in the kitten of Fig. 4.9. Note surface and follicular infundibular neutrophilic parakeratosis and intense superficial dermatitis.

to superficial hair follicles, which are dilated, sometimes massively, with keratin and neutrophils. Active superficial and luminal follicular pustulation may be present. Neutrophils, eosinophils, and lymphocytes migrate through mildly spongiotic epidermis and superficial hair follicles. There may be somewhat laminar epidermal and follicular infundibular pallor adjacent to the parakeratotic accumulations. Lymphocytes or eosinophils may lie adjacent to apoptotic-appearing cells, but true satellitosis (lymphocytes encircling affected keratinocytes) is not seen. The superficial and perifollicular dermis is moderately to severely inflamed. Eosinophils and neutrophils are numerous and are intermingled with lymphocytes, macrophages, and plasma cells.

Affected keratinocytes, which are brightly eosinophilic and shrunken, may be in diffuse distribution, but often are present adjacent to areas of increased keratin, i.e. just beneath the epidermal keratin layer or surrounding the follicular lumen. The pattern and proximity of these cells may indicate a dyskeratotic rather than apoptotic process; these two processes are indistinguishable morphologically and must be analyzed in the context in which they are found. At this time, it is unclear whether these abnormal keratinocytes result from dyskeratosis or apoptosis; the severity of associated inflammation suggests the latter.

Differential diagnoses are few as the condition is striking histopathologically as well as clinically. Hyperkeratotic erythema multiforme may be similar, but generally does not feature the same degree of neutrophilic crusting and parakeratosis, the prominent eosinophil infiltrates, nor the degree of hyperplasia observed with proliferative necrotizing otitis.

TOXIC EPIDERMAL NECROLYSIS

Clinical features (Figures 4.12 and 4.13)

Toxic epidermal necrolysis (TEN) is a very rare, severe, life-threatening syndrome. The word 'necrolysis' denotes

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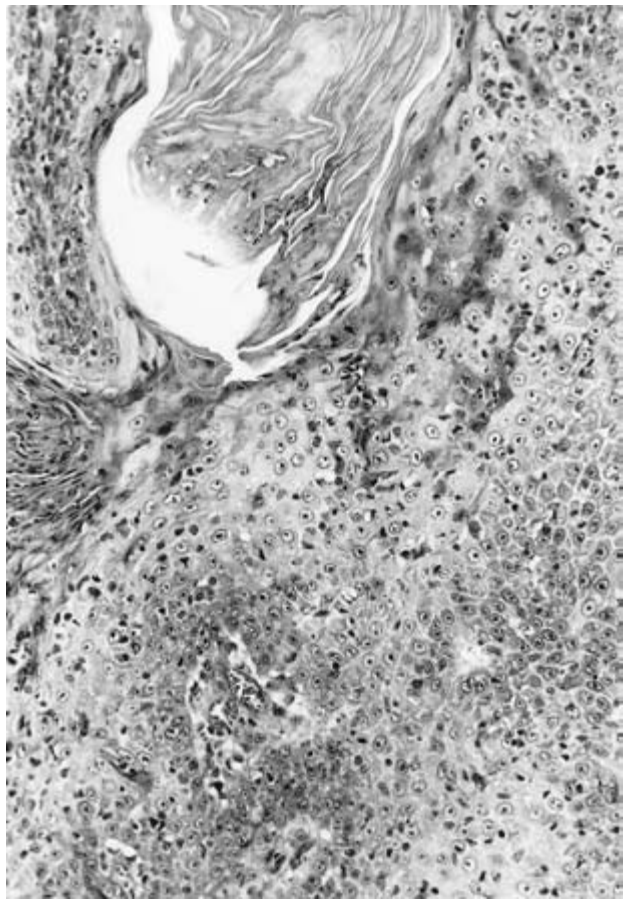


Fig. 4.11 High magnification of proliferative necrotizing otitis in a kitten. Darkly staining keratinocytes, clustered at the right, are apoptotic.



Fig. 4.12 Toxic epidermal necrolysis in a Collie associated with a splenic fibrosarcoma. Note the confluent ulcers covering most of the face. (Case material courtesy R.E.W. Halliwell.)



Fig. 4.13 Toxic epidermal necrolysis in a cat due to a repositol injection of penicillin. Confluent ulcers are present on the head. (Photograph courtesy G.A. Kunkle.)

separation or exfoliation of tissue due to necrosis. Bullous detachment of the epithelium rapidly progresses to widespread ulceration, resembling scalding burns. Toxic epidermal necrolysis is recognized in the dog and cat.

Toxic epidermal necrolysis is a highly controversial syndrome in both veterinary and human medicine (Bastuji-Garin et al., 1993; Ihrke, 1996; Garcia-Duval et al., 2000; Scott et al., 2001). Difficulties with nomenclature abound, as some authors (these authors included) view TEN as clinically and histopathologically distinct from erythema multiforme. Controversy still exists as to whether TEN represents a pathophysiologically similar, but more severe and fulminating, form of erythema multiforme. Irrespective of this controversy, it is of clinical importance to separate erythema multiforme and TEN, as the biological behavior of these two disorders is dissimilar. The rapid spread and dramatic severity of TEN aid in differentiating this syndrome from severe erythema multiforme. Toxic epidermal necrolysis is always a potentially life-threatening disease, while erythema multiforme most often follows a relatively benign, although occasionally chronic, course. Some authors consider TEN to be the most severe manifestation of a continuum that stretches from mild cases of erythema multiforme (EM minor) through severe forms of erythema multiforme (EM major and Stevens–Johnson syndrome [SJS]), to SJS–TEN overlap syndrome, and TEN (Bastuji-Garin et al., 1993; Fritsch & Ruiz-Maldonado, 2003).

Although TEN is a polyetiologic reaction pattern, over 80% of TEN seen in humans is associated with an adverse drug reaction (Fritsch & Ruiz-Maldonado, 1999). Similar findings have been reported for the dog (Hinn et al.,

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1998). Toxic epidermal necrolysis also may be seen secondary to infection, vaccination, as a sequela to graft-versus-host disease, or accompanying diseases of enhanced immune activation such as collagen vascular diseases and neoplasia. Sulfonamides, anticonvulsives, and nonsteroidal anti-inflammatory drugs are the prime initiators in humans (Fritsch & Ruiz-Maldonado, 2003). Most data for cases of TEN in animals indicate the likelihood of drug induction; visceral neoplasia has been noted in a small number of cases.

While the exact pathomechanisms initiating TEN are not yet known, recent sources agree that TEN likely represents induction of an overwhelming apoptosis of keratinocytes, mediated by cytotoxic T cells and mononuclear cells (Fritsch & Sideroff, 2000). Although cytotoxic lymphocytes have been conclusively documented in TEN, their numbers are sparse in comparison to erythema multiforme (Fritsch & Ruiz-Maldonado, 1999). Currently, many authorities believe that lesions result in part from a drastic overexpression of toxic cytokines such as tumor necrosis factor alpha (TNF-α). The source of the TNF-α may be both macrophages and keratinocytes (Paquet et al., 1994; Fritsch & Ruiz-Maldonado, 1999).

Initially, widespread macular erythema progresses to confluent erythema. The animal may be tender to palpation. Full thickness confluent epidermal death results in ulceration as the epidermis is shed (necrolysis). A positive Nikolsky sign usually is present. The epithelium may be lost in translucent sheets resembling moist tissue paper. Sloughing may result from even gentle contact during handling. Facial skin, mucocutaneous junctions, and footpads commonly are involved, but lesions may be widespread. The pharynx, esophagus, trachea, and mainstem bronchus may be affected. Concurrent hemorrhagic diarrhea in some cases suggests that gastrointestinal mucosa also may be targeted. Toxic epidermal necrolysis always is a life-threatening syndrome.

In humans, TEN almost always is preceded by systemic prodromal signs including 'fever, malaise, headache, rhinitis, cough, sore throat, chest pain, vomiting, diarrhea, myalgia and arthralgia' (Fritsch & Ruiz-Maldonado, 2003). Many of these clinical features (such as headache, sore throat, chest pain and myalgia) may be difficult to determine in domestic animals. Fever and malaise have been noted as prodromal signs in the dog.

In humans, an increased incidence of drug-induced TEN observed in certain major histocompatibility complex (MHC) antigen groups has led to the suggestion that these groups may have an impaired capacity to break down reactive intermediate drug metabolites (Friedmann et al., 1994). The paucity of published cases of TEN in domestic animals has not allowed any statistical analyses for incidence. Age, breed, or sex predilections have not been noted with drug-associated TEN. Toxic epidermal necrolysis secondary to visceral neoplasia would be expected to occur more frequently in older animals.

Major clinical differential diagnoses include thermal burns, severe erythema multiforme, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, epidermolysis bullosa acquisita, toxic shock syndrome, sterile pustular erythroderma of Miniature Schnauzers, and vasculitis or other causes of ischemic necrosis. The rapid spread and dramatic severity of TEN aid in differentiating this syndrome from severe erythema multiforme; differentiation is important due to the life-threatening nature of TEN. On rare occasion, dogs may present with erythema multiforme that progresses to TEN, or with erythema multiforme and TEN simultaneously (SJS–TEN overlap). Biopsy is required to diagnose TEN.

Biopsy site selection

Areas of erythema without evidence of ulceration should be selected. Intact epidermis is vital to the histopathologic diagnosis of this syndrome.

Histopathology (Figures 4.14 and 4.15)

Toxic epidermal necrolysis is characterized by diffuse devitalization of the epidermis in the setting of sparse inflammation. Superficial hair follicles may be involved. The nuclei of affected keratinocytes lose detail and are pale or hyperchromatic; the cytoplasm is hypereosinophilic. In early lesions, keratinocytes retain their normal configuration and inter-relationship, and the overall architecture of the epidermis is intact. In older lesions, the devitalized epidermis separates from the subjacent dermis in large sheets, forming flaccid bullae. Necrolysis refers to this separation of tissue due to confluent cell death. Bullae rupture, which results in ulceration. After separation from the dermis, the epidermis may lose all architectural detail and severe ballooning degeneration may occur.

Superficial dermal inflammation is scant in preulcerative lesions, and includes lymphocytes and macrophages. Ulceration provokes severe secondary dermatitis that includes prominent neutrophils. Because of the potentially fatal nature of this disease, it is vital that the pathologist immediately alerts the clinician to the likelihood of TEN so that any potentially causative drugs may be stopped and aggressive therapy instituted.

Toxic epidermal necrolysis and severe erythema multiforme are distinct histopathologically; however, erythema multiforme may progress to confluent epidermal death similar to that seen in TEN. Toxic epidermal necrolysis may also follow or accompany erythema multiforme, con-

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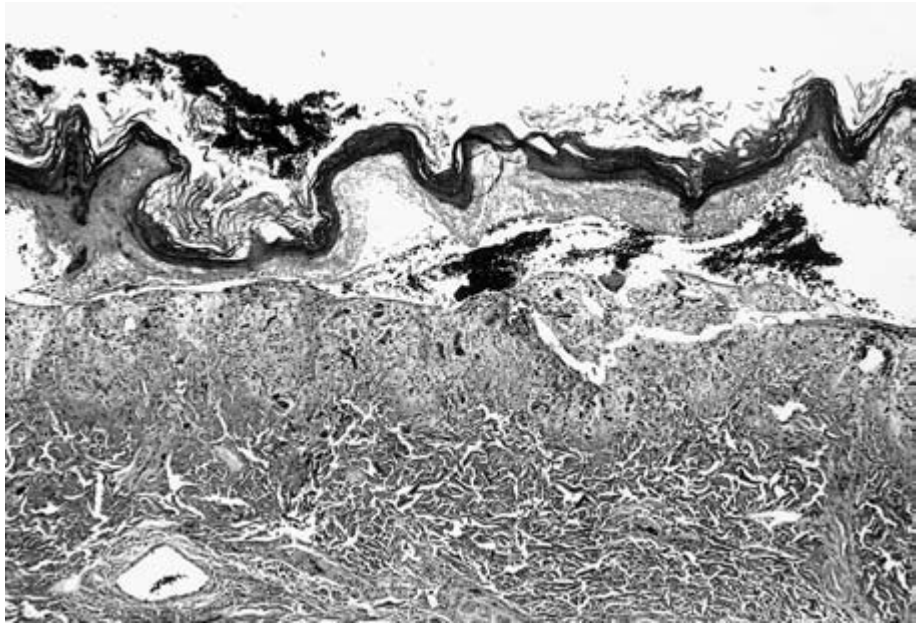


Fig. 4.14 Toxic epidermal necrolysis in a dog. Diffusely necrotic epidermis is separating from the underlying dermis to form a large bulla.



Fig. 4.15 Toxic epidermal necrolysis in a dog. Diffuse necrosis and early separation from the adjacent dermis extend to the hair follicles.

fusing the morphologic picture. Apoptosis is the underlying mechanism of cell death in TEN in humans (Fritsch & Sideroff, 2000), as it is in erythema multiforme (see p. 75). Interestingly, a recent study in animals identified apoptotic cells using immunohistochemistry for the detection of free 3′ DNA ends (resulting from endonuclease activity in apoptosis) in lesions of erythema multiforme but not in TEN (Noli et al., 1998); these results suggest the pathogenetic mechanisms may be different in some clinical contexts. Toxic epidermal necrolysis may represent an immunologic milieu in which toxic cytokines, such as TNF-α (Paquet et al., 1994), or drug metabolites (Friedmann et al., 1994) predominate. The confluent cell death of end stage erythema multiforme, in contrast, may be dominated by progressive cytotoxic cell-mediated destruction of keratinocytes. Although the two diseases may be etiopathogenically related, severe erythema multiforme is histopathologically distinct from TEN. Confluent necrosis in erythema multiforme always is associated with dermal and often epidermal inflammation; lesions of TEN consist of diffuse epidermal necrosis without obvious associated inflammation, at least in the earliest lesions.

Toxic epidermal necrolysis may appear similar to first-degree burn, which is manifested by coagulation necrosis of the epidermis and follicles. Clinical differentiation, specifically knowledge of lesion distribution, which tends to be patchy, asymmetric, or localized in thermal trauma, may be required. Burns may feature deep vasculitis, which is absent in TEN. Late stage toxic shock syndrome may feature massive necrosis of the epidermis with separation from the dermis, as in TEN. However, neutrophils should

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be prominent within the devitalized epidermis of toxic shock syndrome, in contrast to TEN.

TOXIC SHOCK SYNDROME OF DOGS

Clinical features

Toxic shock syndrome (TSS) of dogs is a very rare skin disease with marked clinical and cutaneous histopathologic similarities to staphylococcal TSS in people. Staphylococcal TSS in people is a life-threatening multisystemic disease caused by the staphylococcal exotoxin, toxic shock syndrome toxin-1 (TSST-1), enterotoxin B, enterotoxin C, or TSST-1 combined with enterotoxin C (Lee et al., 2003). This syndrome is distinct from staphylococcal scalded skin syndrome (SSSS), a syndrome seen in infants and children that is characterized by severe exfoliation resulting from a different staphylococcal exotoxin. Definitive diagnosis of TSS in people requires fever, diffuse macular erythroderma, desquamation, hypotension, and evidence of the involvement of three or more visceral organ systems including the muscular system (myalgia and rhabdomyolysis), central nervous system (toxic encephalopathy), kidney (azotemia), liver (elevated aspartate transaminase and serum bilirubin), or hematologic system (thrombocytopenia) (Feldman, 1993; Lee et al., 1999, 2003). Causes in humans include the use of superabsorbent tampons in menstruating women, staphylococcal wound infections, abscesses, mastitis, osteomyelitis, burns, and visceral infections. Cutaneous lesions in people are characterized by blanching, confluent, macular erythema without pruritus (Feldman, 1993). Dogs with putative TSS have exhibited remarkably similar cutaneous and constitutional signs, and some have responded to broad-spectrum systemic antibiotics (cephalexin). However, neither the primary sites of infection nor the presence of staphylococcal exotoxin production have yet been documented.

Toxic shock syndrome in humans appears to be caused by both the direct action of the exotoxin plus cytokine induction coupled with as yet undetermined host factors (Feldman, 1993; Lee et al., 1999). Staphylococcal toxins stimulate the release of tumor necrosis factor alpha (TNF-α) and shock correlates with the synergistic action of TNF-α and interleukin-1 (Lee et al., 2003). T cell-dependent cytokine release may be crucial in the production of mucocutaneous lesions (Kamel et al., 2002).

Toxic shock syndrome of dogs is distinct from the reported syndromes of streptococcal toxic shock syndrome in dogs and streptococcal necrotizing fasciitis (Miller et al., 1996; Yager et al., 1997), as well as cellulitis and toxic shock in a dog due to *Staphylococcus intermedius* (Girard & Higgins, 1999), even though pathomechanisms may be similar. In these other reported syndromes, localized severe infection releases bacterial toxins that produce severe secondary systemic toxic reactions including disseminated intravascular coagulation, but without specifically targeting the skin.

Toxic shock syndrome, confirmed by histopathology, has been observed by the authors in ten dogs. Clinical lesions are generalized macular erythema of the trunk and legs, often accompanied by marked edema, particularly of the legs. Vesicles and ulcers are sometimes observed; ulcers are generally seen in advanced lesions. There is variable crusting. Presenting constitutional signs include fever, severe malaise, and anorexia. Hypoalbuminemia was found in all six dogs for which hematologic evaluation was performed; leukocytosis was present in three dogs. One dog had severe cellulitis and deep pyoderma of one rear leg and foot, which may have represented the primary site of infection. Skin culture in an additional dog recovered *Pseudomonas aeruginosa* and a hemolytic coagulase negative *Staphylococcus* sp. The role of these organisms in the generation of the skin lesions is not known; secondary infection may have been present, as this dog developed severe ulceration. The remaining dogs did not have a primary source of infection discovered.

Five dogs succumbed to TSS; postmortem examination was available in three dogs only. Disseminated intravascular coagulopathy (DIC) was a consistent finding and affected various organ systems, including the liver, lung, and kidneys.

Too few cases of TSS in dogs have been seen to assess signalment predilections clearly; however, three of ten dogs were Pugs. Also, all dogs but one were 6 years of age or younger; five dogs, including all of the Pugs, were 3 years or younger.

Clinical differential diagnoses include generalized vasculitis, canine sterile neutrophilic dermatoses (see Chapter 14), toxic epidermal necrolysis, and erythema multiforme. The primary source of infection and putative toxin production should be sought, but may be elusive. Evaluation should include hematology, as well as radiographs and ultrasound evaluation in an attempt to discern clinically occult infection.

Biopsy site selection

Regions of macular erythema should be obtained. Suspected primary sites of infection should be sampled as well. An intact epidermis is important for the histopathologic diagnosis of this syndrome.

Histopathology (Figures 4.16 through 4.19)

Toxic shock syndrome is histopathologically identical to the human condition that is associated with toxin production by *Staphylococcus aureus* (Hurwitz & Ackerman,

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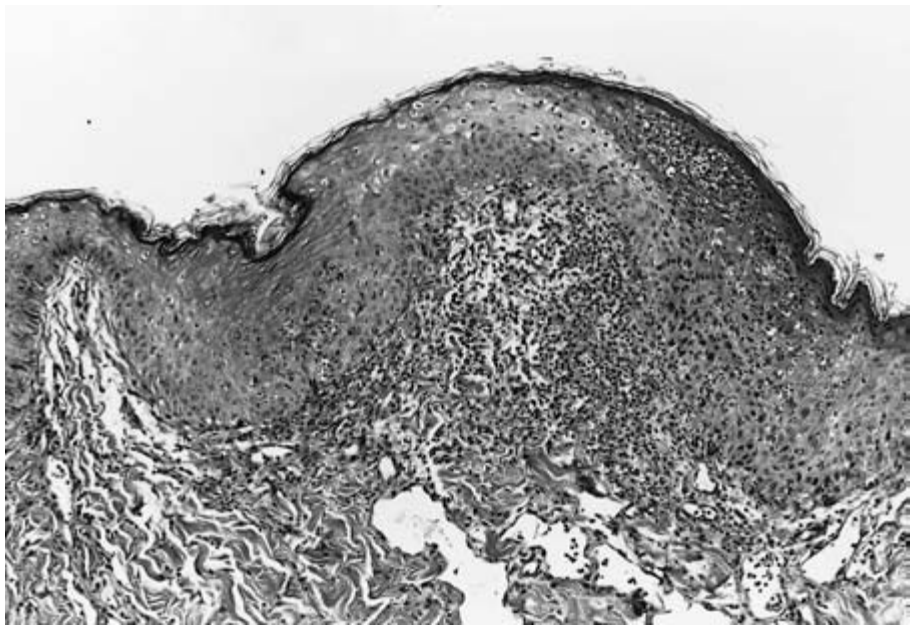


Fig. 4.16 Toxic shock syndrome in a dog. Neutrophils are migrating through the epidermis to form a surface crust. Note superficial dermal inflammation.

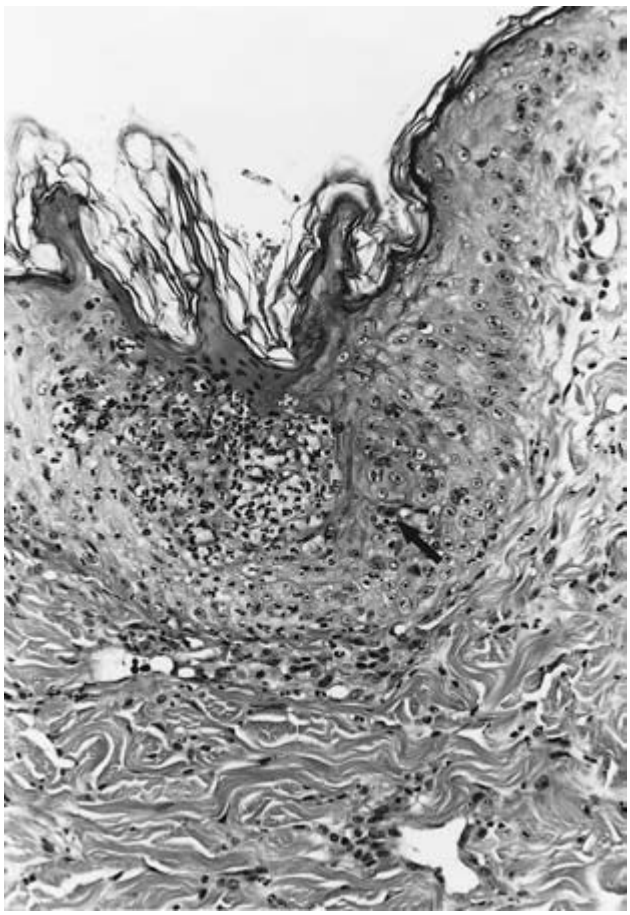


Fig. 4.17 Higher magnification of toxic shock syndrome in a dog. A focal pustule is surrounded by apoptotic keratinocytes (arrow).

1985; Vuzevski et al., 1989). In early lesions, there is mild spongiosis. Presumptive apoptosis of keratinocytes of the epidermis and superficial hair follicles is associated with migration of neutrophils and occasional eosinophils, which may lie adjacent to devitalized cells. Apoptotic cells and neutrophils may occur in random clusters, resembling a 'scatter-shot' pattern. Neutrophils may form small epidermal pustules that progress to surface crusts. As lesions progress, apoptosis becomes confluent, resulting in lifting of the devitalized and inflamed epidermis to form large ulcers. Devitalized epidermal tissue is riddled with degenerating neutrophils.

The superficial to middle dermis is moderately edematous. Blood vessels are dilated and have swollen endothelia. Extravasation of red blood cells may be observed. Mild to moderate numbers of neutrophils and fewer eosinophils surround blood vessels, and are loosely distributed interstitially. Inflammation is often prominent, surrounding middle hair follicles where blood vessels are concentrated. Lymphocytes and macrophages are intermingled in smaller numbers. Dermal inflammation is more intense in advanced necrotic lesions.

Early epidermal lesions of TSS resemble erythema multiforme, except that inflammatory cells surrounding the apoptotic epithelial cells are neutrophils rather than lymphocytes, and the apoptotic cells in TSS tend to cluster rather than being more diffusely distributed. Late stage TSS may feature massive devitalization of the epidermis with separation from the dermis, as in toxic epidermal necrolysis. However, neutrophils should be prominent within the devitalized epidermis of TSS, in contrast to toxic epidermal necrolysis.

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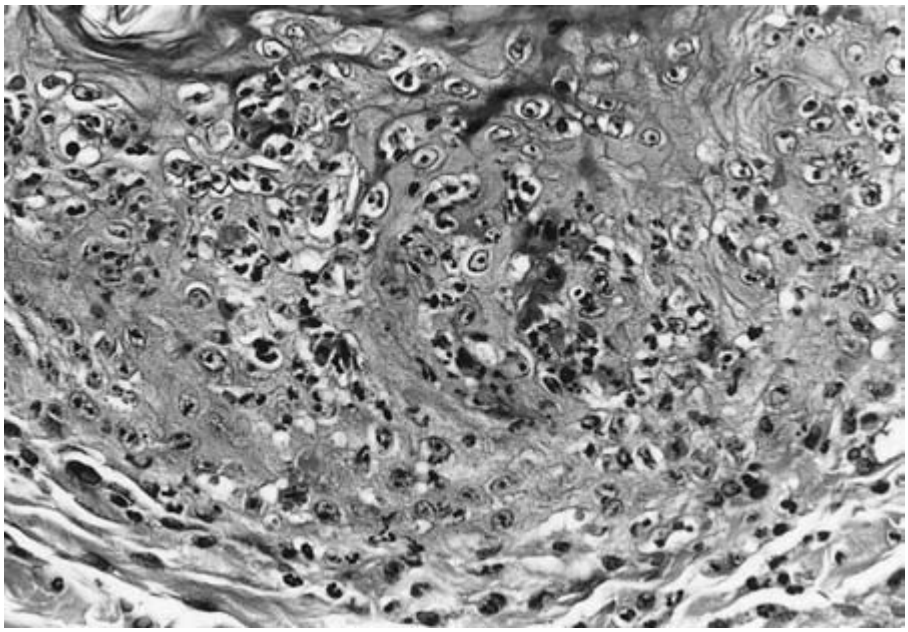


Fig. 4.18 High magnification of toxic shock syndrome demonstrating neutrophils amidst darkly staining apoptotic keratinocytes.

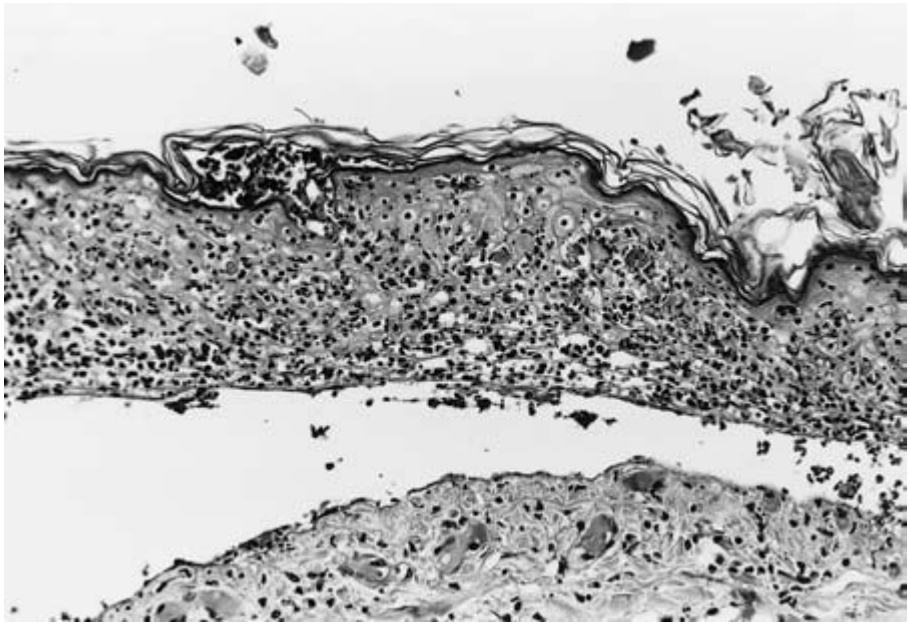


Fig. 4.19 Confluent epidermal necrosis of late lesion of toxic shock syndrome. The devitalized epidermis is riddled with neutrophils.

SUPERFICIAL NECROLYTIC DERMATITIS

(Synonyms: metabolic epidermal necrosis, hepatocutaneous syndrome, necrolytic migratory erythema)

Clinical features (Figures 4.20 through 4.22)

Superficial necrolytic dermatitis (SND) is an uncommon, necrotizing skin disorder of dogs associated with incompletely characterized metabolic hepatic disease (Gross et al., 1993; Byrne, 1999). Superficial necrolytic dermatitis is very rare in the cat; only four cases have been reported to date (Patel et al., 1996; Day, 1997; Mauldin et al., 2002; Kimmel et al., 2003).

The unifying feature of most of the reported canine cases appears to be underlying metabolic hepatic dysfunction driving cutaneous nutritional deprivation, which results in necrotizing skin disease. When serum amino acids are measured, profound hypoaminoacidemia is a consistent feature. Plasma amino acid profiles reveal up

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Fig. 4.20 Superficial necrolytic dermatitis in an aged mixed breed dog. Perioral and mucocutaneous erosions, ulcers, and crusts are present. (Photograph courtesy I.J. Ameti.)



Fig. 4.21 Superficial necrolytic dermatitis in an aged mixed breed dog. The pads of all four paws are heavily crusted. Fissures with exudation are evident on and at the margins of the pads.



Fig. 4.22 Superficial necrolytic dermatitis in an aged Poodle. Secondary suppurative crusting is evident on the fissured carpal pad and at the periphery of the pads.

to 80% reduction in several amino acids (Gross et al., 1993). A recent large study in 36 dogs showed that mean plasma amino acid values were significantly lower than values from dogs with either acute or chronic hepatitis. The authors hypothesized that the causative defect is a metabolic hepatopathy that increases hepatic catabolism of amino acids (Outerbridge et al., 2002). A recent report of SND in dogs receiving phenobarbital suggested that drug induction of hepatic microsomal enzymes may result in excessive utilization of amino acids by the liver, leading to deficiency (March et al., 2004).

It is tempting to consider glucagon derangement as the trigger for this metabolic disease because of the striking similarities to necrolytic migrating erythema in humans (hypoaminoacidemia, diabetes mellitus, and histologically identical skin lesions) which often results from glucagonoma syndrome. This syndrome most commonly is associated with a pancreatic endocrine tumor that secretes high levels of glucagon. However, elevated glucagon levels in conjunction with glucagon-producing pancreatic endocrine tumors are seen in only a minority of canine cases of SND (Bond et al., 1995; Torres et al., 1997; Allenspach et al., 2000).

Superficial necrolytic dermatitis in dogs is most often associated with severe vacuolar hepatopathy with or without accompanying diabetes mellitus (hepatopathic SND). Identical cutaneous lesions have been seen rarely secondary to glucagon-producing pancreatic endocrine tumors (pancreatic SND) (Gross et al., 1990; Bond et al., 1995; Cerundolo et al., 1999); this suggests that cutaneous pathogenic mechanisms probably are similar in these two forms of SND. Severe hepatopathy is absent in pancreatic SND, suggesting a different metabolic subtype (Gross et al., 1990; Bond et al., 1995). Although most cases of vacuolar hepatopathy occurring in SND are idiopathic, SND has been seen in conjunction with the ingestion of a mycotoxin (Little et al., 1991), long-term anticonvulsant therapy with phenobarbital and phenytoin (Bloom et al., 1992; March et al., 2004), and other metabolic liver disease (Taboada & Merchant, 1997). Regardless of the initiating mechanism, the histologic pattern of epidermal damage is similar. Resolution of the cutaneous signs of canine SND was reported to follow excision of a glucagon-secreting pancreatic tumor (Torres et al., 1997).

Superficial necrolytic dermatitis in cats has been reported in conjunction with pancreatic carcinoma, probably of endocrine origin (Patel et al., 1996), thymic amyloidosis (Day, 1997), pancreatic carcinoma, hepatopathy, and intestinal lymphoma (Mauldin et al., 2002), and hepatopathy and probable unrelated squamous cell carcinoma *in situ* (Kimmel et al., 2003). Two additional feline cases observed by the authors have been hepatopathic in origin.

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In dogs, erosions and ulcers, with exudation, alopecia, and thick adherent crusts are seen on and surrounding the pawpads, and around the mucocutaneous junctions of the lips, eyes, clawbeds, and anus. Similar lesions also may occur on the pinnae, pressure points including the elbows and hocks, ventral thorax, and the scrotum and vulva. Adherent crusts without underlying erosion may be seen in very early lesions. Facial and pedal lesions may exhibit striking bilateral symmetry. Skin lesions may be more severe in regions of pressure trauma or self-trauma, as these sites are prone to the increased cutaneous fragility that results from loss of epithelial integrity. Secondary infection with dermatophytes or bacteria, or colonization by *Malassezia* is common. Pruritus and pain frequently are evident.

Considerably less information is available for the clinical features of feline SND. Scaling and alopecia of the trunk and limbs were the only cutaneous features noted in two cats (Patel et al., 1996, Mauldin et al., 2002). Pruritus was noted in two cats, but may not have been associated with SND (Mauldin et al., 2002; Kimmel et al., 2003). Bilateral ventral truncal alopecia progressing down the medial thighs, ulceration and crusting of the oral mucocutaneous junction and interdigital regions was reported recently in a well-documented case (Kimmel et al., 2003). Secondary *Malassezia* dermatitis has been reported in conjunction with feline SND (Mauldin et al., 2002) and also has been noted by the authors.

Canine SND is seen primarily in older dogs. In one large study, both the mean and median age of affected dogs was 10 years (Outerbridge et al., 2002). Although population-corrected data on breed predilections are not available, the authors suspect that small breed dogs are over-represented. In one recent study, 61% (22/36) of the dogs were of only six breeds: West Highland White Terriers (6), Shetland Sheepdogs (5), Cocker Spaniels (4), Scottish Terriers (3), Lhasa Apsos (2) and Border Collies (2) (Outerbridge et al., 2002). Retrospective data indicates that males may be over-represented (Byrne, 1999). In a recent study, 75% (27/36) of the dogs were male (Outerbridge et al., 2002). Too few cats have been seen with SND to determine signalment predilections.

Clinical differential diagnoses for canine SND include chronic erythema multiforme of older dogs, drug eruption, pemphigus foliaceus, systemic lupus erythematosus, zinc-responsive dermatosis, and generic dog food-associated dermatosis. Histopathology is useful in the differentiation of most of these diseases. Generic dog food dermatosis, which is histologically very similar to SND, is seen most often in younger animals. The morphologic similarity may be due to a partially common pathogenesis for SND and generic dog food dermatosis, possibly via depression of serum amino acids or other nutrients. Elevation of serum hepatic enzymes (especially serum alkaline phosphatase and alanine aminotransferase) is supportive of SND (Byrne, 1999). If other criteria are met, ultrasonographic evaluation of the liver should be performed to assess for the presence of the unique and pathognomonic 'honeycomb' pattern seen with SND (Nyland et al., 1996), as well as to rule out the possibility of underlying pancreatic neoplasia.

Clinical differential diagnosis of feline SND is more problematic based on small case sampling. Prime differential diagnoses should include exfoliative feline skin diseases such as erythema multiforme, thymoma-associated exfoliative dermatitis, and cutaneous epitheliotropic lymphoma. The presence of elevated serum hepatic enzymes in an older cat should enhance suspicion for SND. Abdominal ultrasonographic evaluation and skin biopsy are needed for diagnosis.

Biopsy site selection

Erythematous plaques with mild to moderate adherent crusts are ideal sites. Care should be taken not to disturb the crusts when taking the biopsy. Pawpad margins should be sampled as these specimens create less lameness and are still likely to yield a definitive diagnosis. Ulcers should be avoided. Multiple biopsy specimens are recommended, as characteristic lesions may not be present in every specimen.

Histopathology (Figures 4.23 through 4.26)

On low power, the distinctive epidermal feature of SND is the pink, white and blue layering, referred to by some as the 'French flag'. Parakeratosis and neutrophilic crusting comprise the top eosinophilic layer, striking pallor of keratinocytes creates the pale middle layer, and hyperplastic basal and suprabasal keratinocytes compose the deepest basophilic layer. In some chronic lesions, the pale middle layer is absent or minimal, and parakeratosis with crusting predominates. The parakeratotic cells may have plump rather than the traditionally markedly flattened nuclei, mimicking diseases of abnormal cornification (see Chapter 8). Superficial pustulation may be seen. Bacteria, dermatophytes, or yeast may be present within crusts, often abundantly. Cells of the middle pale layer lack discrete borders, and pallor is due to diffuse intracellular and intercellular edema. Secondary splitting through this devitalized layer may be observed; this combination of changes is consistent with true 'necrolysis'. Epidermal splitting may be accompanied by pustular inflammation within the cleft; erosion and ulceration may follow. The subjacent epidermis is hyperplastic, and is basophilic due to an increased nuclear to cytoplasmic ratio and cyto-

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Fig. 4.23 Superficial necrolytic dermatitis in a dog. Note layering of superficial parakeratotic crust, edema, and hyperplastic keratinocytes.

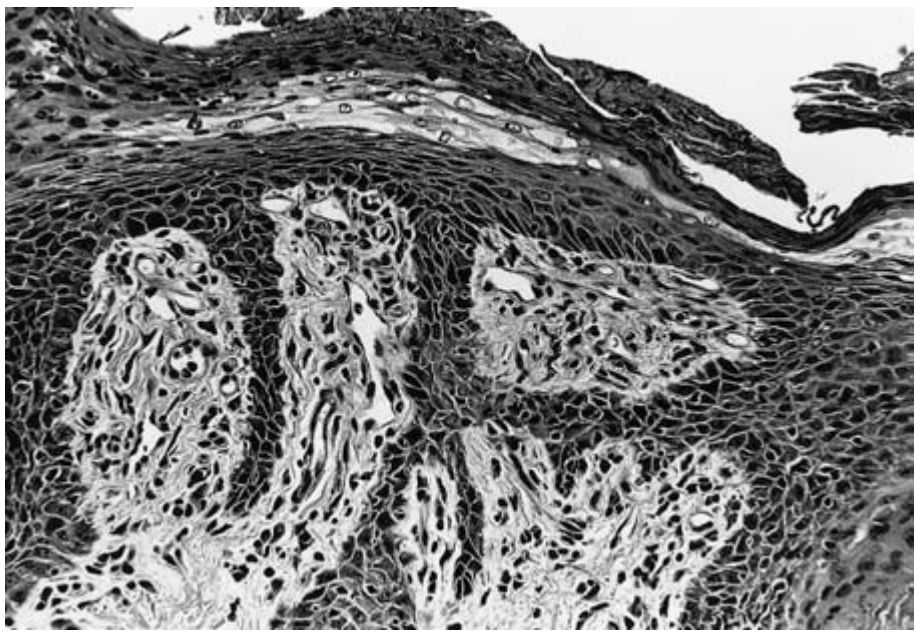


Fig. 4.24 Higher magnification of Fig. 4.23. The middle layer of the epidermis shows the prominent laminar pallor of swollen keratinocytes.

plasmic immaturity. Changes mildly affect the superficial hair follicle, but generally do not extend beyond the superficial infundibulum.

In some cases, there may be mild to severe individual cell death, suggesting apoptosis. Apoptosis may be accompanied by lymphocytic satellitosis, resembling erythema multiforme (see p. 75). It is not known whether these latter cases represent erythema multiforme superimposed upon SND. Alternatively, one author (E.J.W.) has proposed that the hyperkeratotic form of erythema multiforme in old dogs may be due to protein deficiency/imbalance and thus could be very similar pathogenetically to SND.

Dermal inflammation is mixed and is generally superficial and perivascular to interstitial. Neutrophils may be prominent, depending on the degree and stage of overlying epidermal degeneration. Macrophages, lymphocytes, plasma cells, eosinophils, and mast cells may be observed. Lymphocytes and neutrophils may migrate into the overlying epidermis.

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Fig. 4.25 Secondary splitting or 'necrolysis' of the epidermis in superficial necrolytic dermatitis in a dog. Note loose pustular inflammation within the split.



Fig. 4.26 Apoptosis in superficial necrolytic dermatitis in a dog. Note typical parakeratotic layer at top.

Hepatic lesions in dogs with hepatopathic SND consist of severe metabolic vacuolar hepatopathy. Hepatocytes are severely ballooned in a pattern of both water and lipid accumulation, and progress to frank degeneration. Areas of severe parenchymal collapse result in a condensation of the reticulin fiber network. Foci of nodular hepatocellular regeneration are prominent. This combination of parenchymal collapse, condensation of reticulin, and nodular regeneration has been confused with hepatic cirrhosis by many authors. An increase in collagen deposition may occur in some cases of anticonvulsant-associated SND in which portal inflammation and accompanying portal fibrosis are identified (chronic-active or chronic-persistent hepatitis). Severe vacuolar hepatopathy is not present in dogs with pancreatic SND.

Superficial necrolytic dermatitis is identical histopathologically in cats. Two reported cases had associated pancreatic carcinoma (Patel et al., 1996; Mauldin et al., 2002). In the former report a pancreatic endocrine tumor was found; glucagon staining was inconclusive. The liver was minimally affected, which is similar to the absence of hepatopathy in dogs with SND and pancreatic endocrine tumors. In the latter report there was also follicular atrophy typical of paraneoplastic alopecia (see Chapter 19). The pancreatic tumor of that report was not described as exocrine or endocrine; acute hepatocellular swelling and necrosis were described, and were similar to the hepatopathy of canine SND. This second feline case may have had concurrent hepatopathic SND and paraneoplastic alopecia due to a pancreatic exocrine carcinoma, and not SND due to a pancreatic endocrine tumor. A third reported feline case had typical hepatopathy as

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Fig. 4.27 Generic dog food dermatosis in an adult Chesapeake Bay Retriever. Crusting, scaling, and alopecia are present around the mouth and eye. (From Sousa, C.A. et al. (1988) Dermatosis associated with feeding generic dog food: 13 cases (1981–1982). *J Am Vet Med Assoc* 192, 676–80. Reprinted with permission.)



Fig. 4.28 Closer view of Fig. 4.27. Thick, adherent crusts entrap the remaining hair near the mucocutaneous junction of the upper lip.

well as concurrent multifocal bowenoid *in situ* carcinoma of the skin, or Bowen's disease (Kimmel et al., 2003). The authors have seen two cases of SND in cats with associated hepatopathy; one of these had severe *Malassezia* colonization. *Malassezia* colonization also has been reported in one case of feline SND (Mauldin et al., 2002).

The reaction pattern of SND is unique in cats and not shared by other recognized entities to the authors' knowledge. Superficial necrolytic dermatitis in cats should prompt a search for secondary *Malassezia* colonization, and vice versa. Differential diagnoses in dogs include zinc-responsive dermatosis and generic dog food dermatosis. Zinc-responsive dermatosis is differentiated from SND by the lack of laminar epidermal edema and degeneration; chronic lesions of SND without laminar epidermal degeneration may require clinical differentiation. Clinical differentiation between generic dog food dermatosis and SND also may be needed, as both diseases are characterized by laminar epidermal edema and degeneration, in addition to parakeratosis. This similarity suggests that there may be a partially common pathogenesis for SND and generic dog food dermatosis, possibly via depression of serum amino acids or other nutrients. Finally, some pinnal irritant reactions to plastics may be similar to SND. Clinical differentiation is required (see p. 98).

GENERIC DOG FOOD DERMATOSIS

Clinical features (Figures 4.27 and 4.28)

Generic dog food dermatosis is an uncommon to rare syndrome seen in association with the exclusive feeding of poor quality (generic) dog food (Sousa et al., 1988). An outbreak was seen in North America during the mid and late 1980s. To the authors' knowledge, this syndrome has not been reported in North America since then. Reformulation of generic dog foods probably was responsible for the dramatic decrease in cases. Nutritional skin diseases are uncommon in geographical locales where dogs are fed either good quality dog food or balanced human diets.

In circumstances where rations are deficient in nutrients, vitamins, or trace minerals, this dermatosis probably is more common. The systemic signs of fever, depression, dependent edema, and lymphadenopathy (coupled with histopathologic findings beyond those seen with zinc-responsive dermatosis) lead to speculation that a deficiency of multiple trace minerals, vitamins, or amino acids may be occurring. Since both copper and zinc are required for proper cornification, conceivably this syndrome could be associated with a combined zinc and copper deficiency. Also, since all bivalent cations compete for common binding sites in the intestine, any severe imbalance could be problematic.

Clinical signs closely parallel those of dogs that exhibit the more severe manifestations of zinc-responsive dermatosis, syndrome II (see Chapter 8). Eroded and ulcerated, fissured, well-demarcated annular plaques with thick, adherent crusts and erythematous borders are noted. Lesions are seen most commonly on the muzzle, mucocutaneous junctions, pressure points, flexure surfaces, and distal extremities. Pain is evident. Lymphadenopathy is common.

Most affected dogs are young, rapidly growing, and less than 1 year of age. Adult dogs also have been seen occasionally with this syndrome. In some cases all dogs in a multiple-dog household being fed the same ration have developed generic dog food dermatosis; in other cases,

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only some dogs of a group sharing identical environment and diet have been affected. Breed or sex predilections have not been noted.

Clinical differential diagnoses should include zinc-responsive dermatosis, superficial necrolytic dermatitis, demodicosis, dermatophytosis, and pyoderma, as well as autoimmune skin diseases such as pemphigus foliaceus. Generic dog food dermatosis usually is seen in puppies during their rapid growth phase. Differentiation may require skin scrapings, chemistry screening profiles, fungal culture, and histopathology.

Biopsy site selection

Skin biopsy specimens should be obtained from annular, crusted plaques. Areas of erosion and ulceration should be avoided since an intact epidermis is necessary to establish the diagnosis.

Histopathology (Figures 4.29 and 4.30)

The epidermis is moderately to severely acanthotic. Parakeratosis is moderate and may be interspersed with layers of hyperkeratosis and crusting. In some cases, there is abrupt transition of the superficial epidermis to a uniform, eosinophilic layer of compact parakeratosis; hypogranulosis is evident in these areas. Prominent laminar edema, and keratinocyte swelling and degeneration, as seen in superficial necrolytic dermatitis (see p. 86) affect the superficial epidermis. The epidermis also may appear slightly dysplastic, characterized by loss of normal stratification and uneven size of keratinocyte nuclei. There may be individual cell death of keratinocytes suggesting apoptosis. Mild to moderate deep spongiosis may be accompanied by exocytosis of lymphocytes, macrophages, and neutrophils. Epidermal lesions often extend to superficial hair follicles. Intraluminal accumulation of degenerating neutrophils and frank pustular folliculitis are seen. The superficial dermis contains plasma cells, lymphocytes, neutrophils, mast cells, macrophages, and melanophages.

The major histopathologic differential diagnoses are superficial necrolytic dermatitis and zinc-responsive dermatosis. Lesions most closely resemble superficial necrolytic dermatitis, suggesting at least a partially common pathogenesis for the development of the epidermal lesions, possibly via depression in serum amino acids or other nutrients. Zinc-responsive dermatosis does not show epidermal laminar edema and degeneration, and apoptosis is rare.

SPLIT PAWPAD DISEASE

Clinical features (Figures 4.31 and 4.32)

Split pawpad disease is a highly characteristic syndrome of unknown etiology. It is seen very rarely in the dog, and was observed by one author (T.L.G.) in a cat. Both clinical and histologic features are suggestive of an anatomic defect in the cornification of the pawpads. It is possible that a primary degenerative process leads to the characteristic splitting and peeling of the pawpad keratin layer.

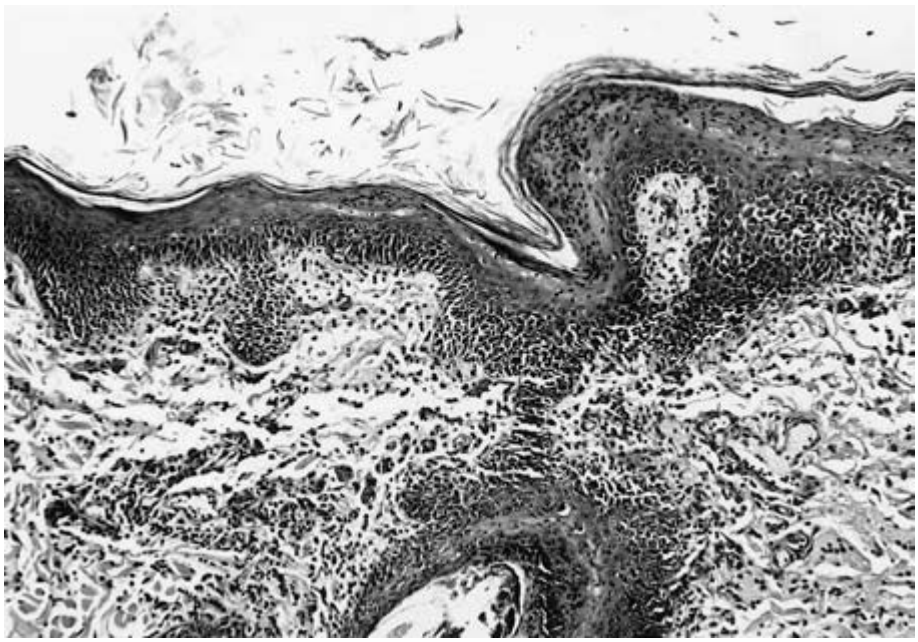


Fig. 4.29 Generic dog food dermatosis in a dog demonstrating superficial parakeratosis with neutrophilic crusting, subjacent epidermal pallor and degeneration, and deep spongiosis.

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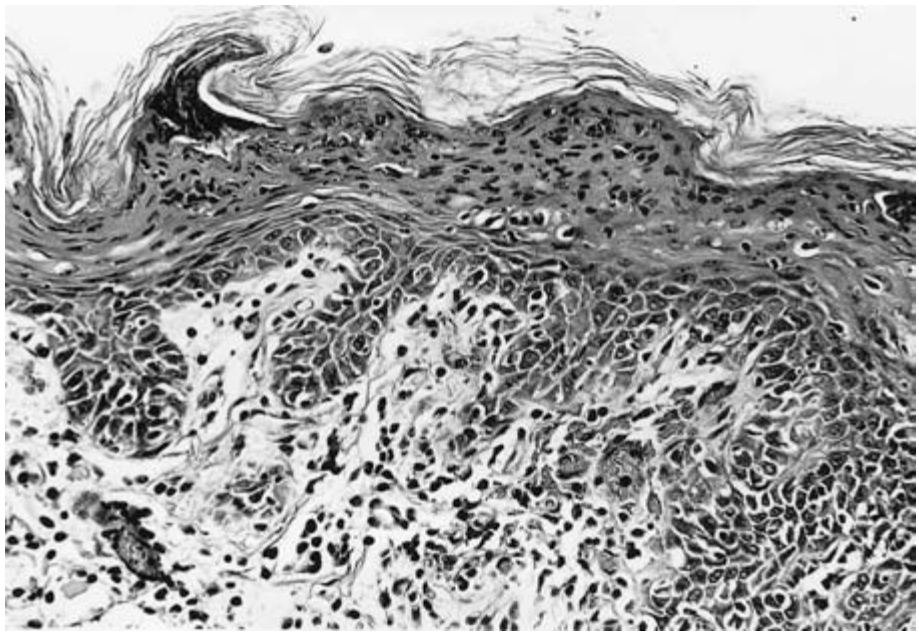


Fig. 4.30 Higher magnification of generic dog food dermatosis. Superficial parakeratosis and crusting overlie laminar edema and ballooning degeneration of keratinocytes. Deep spongiosis is prominent.



Fig. 4.31 Split pawpad disease in a dog. Splitting of the pawpad has occurred in an axis parallel to the contact surface. (Photograph courtesy A.G. Cannon.)

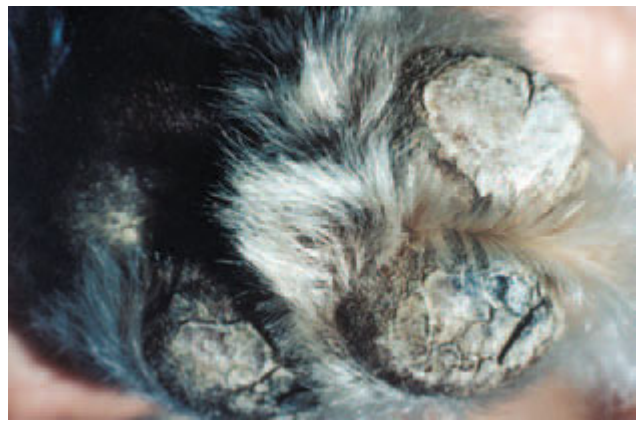


Fig. 4.32 Split pawpad disease in a dog. Chronic thickening with cracking is affecting multiple pawpads. (Photograph courtesy A.G. Cannon.)

Qualitative cytokeratin studies were performed on one case; none of the expected cytokeratins were missing (Cannon, A., personal communication, 2002). The syndrome bears some resemblance clinically, but not histopathologically, to epidermolytic palmoplantar keratoderma and other devastating heritable defects of cornification that occur on the skin of the soles and palms in humans. However, current data do not suggest that this syndrome is an analog to any of the described human pedal syndromes. Several owners have believed that exposure to moisture (rain, mud) may precipitate individual events.

The initial clinical feature of this syndrome in the dog is splitting of the pawpad followed by loss of superficial layers in an axis parallel to the contact surface. Areas of seemingly normally cornified pawpads split and peel. Adjacent haired skin is not affected. The syndrome is greatly aggravated by self-trauma. Pain or pruritus may provoke the dog to rip off the torn fragments of the pawpads with its teeth. In severe cases, aggressive self-trauma can lead to almost complete denuding of cornified tissue. Curiously, dogs can appear normal between episodes of splitting and peeling. Lameness is variable but may be moderate. Dogs with repeated episodes may display irregular pad cornification with lumpy keratinous proliferations and chronic inflammation. However, initial lesions do not exhibit obvious inflammation. Affected animals are otherwise healthy.

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Initially, only one pawpad may be affected, followed by development of similar lesions in other pads. Usually, all pawpads eventually are involved.

The lesions seen in a cat by one author (T.L.G.) mirror those seen in the dog. The affected cat was lame and had difficulty using the litterbox. Grossly, there was lifting of dry epidermal tissue from underlying pink tissue (Wedemeyer, S.M., personal communication, 2003). All pads were affected. There was no history of trauma.

Young adult dogs are affected. Other signalment data are not available. The affected cat was 4 years of age at disease onset.

Clinical differential diagnoses are few as the syndrome is highly characteristic. Somewhat similar clinical lesions can be seen with early cases of canine pemphigus foliaceus restricted to the pawpads. Chronic lesions also can resemble those seen with zinc-responsive dermatosis, generic dog food dermatosis, and superficial necrolytic dermatitis. However, the lesions seen with all of these diseases should not be confined to the pawpads. Histopathology is required for definitive diagnosis.

Biopsy site selection

Tissue from the advancing margin of a split should be sampled. Punch biopsy of affected tissue along the margin of a pad may be most easily accomplished.

Histopathology (Figures 4.33 and 4.34)

The superficial epidermis of the pawpad has a brightly eosinophilic, coagulated or 'cooked' appearance that extends through the keratin layer to the underlying superficial viable layer. The lesions resemble severe coagulation necrosis of a burn. The deep edge of abnormal keratin may extend into the underlying epidermis in ragged distribution, with varying depth of penetration. Retention of nuclei in the coagulated layer is variable and is sometimes prominent. The surface is disrupted and infiltrated by degenerating neutrophils to form crusts. There is often a visible separation between the deep viable epidermis and the abnormal necrotic layer, which may be pronounced in some lesions. Splitting leads to erosions and occasionally ulcers that are accompanied by suppurative exudation. Marginal areas or chronic lesions are parakeratotic and crusted. The superficial dermis has variable inflammation consisting of lymphocytes, macrophages, plasma cells, neutrophils, and eosinophils.

Differential diagnosis is uncomplicated due to the characteristic histopathologic changes of this dermatosis. Lesions resemble those of severe thermal trauma, but the location is atypical for thermal burns. If parakeratosis predominates and separation is not observed, as in chronic lesions, consideration of superficial necrolytic dermatitis might be made. Clinical differentiation may be required.



Fig. 4.33 Split pawpad disease in a dog. A massive split has occurred through the devitalized superficial epidermis.

BURNS

Clinical features (Figures 4.35 through 4.39)

Thermal and chemical burns are relatively common injuries in the dog and cat. Burns may be due to either thermal injury or the direct toxic action of a noxious substance on the skin or mucous membranes. Thermal burns are seen more frequently than chemical burns, and often cause deeper injury. Partial-thickness thermal and chemical burns may be clinically indistinguishable unless residue of the chemical agent is present on the haircoat or underlying skin. Less commonly, electrical current or microwave radiation can cause lesions that are clinically and histopathologically indistinguishable.

Boiling liquids, electric heating pads, animal-drying cages, fires, and heated metal (automobile mufflers and wood stoves) are the most common causes of thermal

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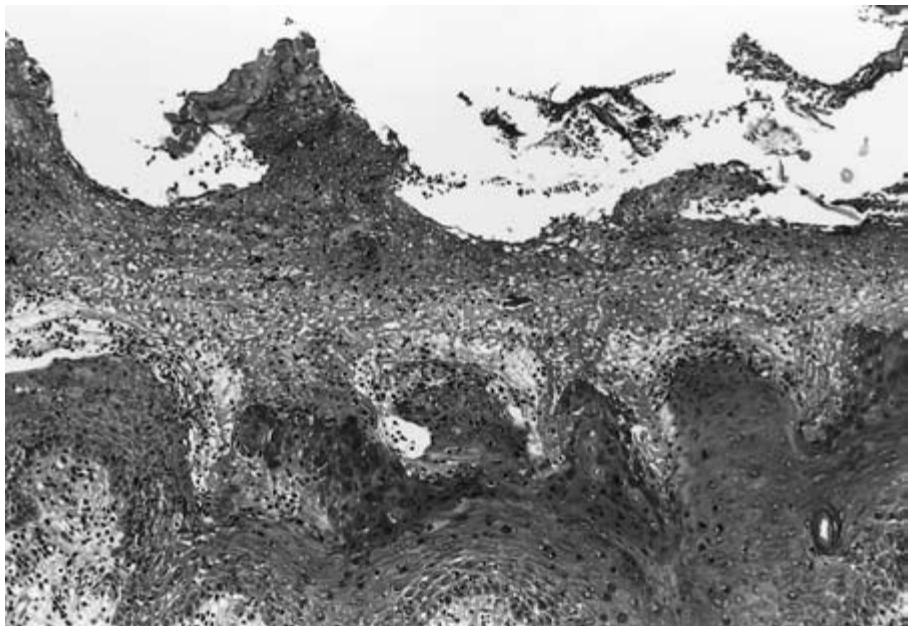


Fig. 4.34 Higher magnification of Fig. 4.33 showing severe coagulative necrosis of the superficial epidermis.



Fig. 4.35 Partially healed thermal burn in a Doberman Pinscher puppy. Islands of less affected tissue are surrounded by ulceration.

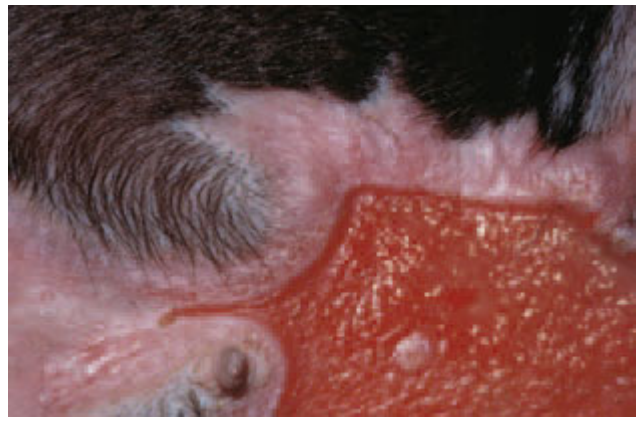


Fig. 4.36 Closer view of Fig. 4.35, demonstrating wound contraction at the margins of the ulcer.

burns (Scott et al., 2001). Electric heating pads remain the least predictable source of thermal burn (Swaim et al., 1989). The critical determinants in the severity of a burn are the temperature of the heat source and the length of exposure. One author (T.L.G.) has seen seemingly identical skin lesions in conjunction with heat exhaustion and a markedly elevated core body temperature of 107°F (41.7°C).

In human medicine, combinations of pressure, sheering forces, ischemia, diminished perfusion due to underlying disease, and heat may closely mimic the lesions of what are traditionally called 'burns' (Stewart, 1998). Pressure/ischemia/thermal complex injury is seen in veterinary medicine, often unexpectedly in the setting of anesthesia and prolonged recumbency in conjunction with normally functioning circulating water heating pads.

Under unusual circumstances, even intense sunlight may cause thermal injury in black-haired dorsal skin (Hargis & Lewis, 1999). This syndrome has been termed 'dorsal thermal necrosis' by the authors, and is seen in dogs with short, dark hair coats exposed to outdoor, high intensity summer sun and heat. In one instance, an entire litter of dark haired puppies that could not ambulate well to avoid excessive sun exposure were affected (Vandenabeele, S.C., personal communication, 2003). The authors have seen similar lesions in a dark brown Shar Pei, a Rottweiler, and a black and tan Dachshund, and have heard anecdotal reports of similar cases from

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Fig. 4.37 Chemical burn in a German Shepherd Dog due to the application of a nondiluted flea and tick dip. Punctate areas of ulceration are present on the swollen, erythematous affected area. The haircoat has been clipped from the lesion.



Fig. 4.38 Dorsal thermal necrosis in a chocolate Labrador Retriever puppy. This puppy and its littermates could not escape California midsummer sunlight. Photographs were taken several weeks after the insult. (Photograph courtesy S.C. Vandenabeele.)

others. Presumably, the dark, short hair coats of these dogs provide a heat sink that concentrates the effects of solar and/or thermal radiation. Typically, irregular, well-demarcated lesions develop dorsally, and otherwise resemble other thermal burns (see below).

Burns in domestic animals are categorized as partial-thickness or full-thickness, based on depth of involvement. The full extent of tissue damage following a burn may not be readily assessable for 4 to 5 days, as progression may be insidious. Burns may be more obvious in nonhaired areas. In haired regions, the overlying haircoat may conceal the severity and extent of damage for as long as a week before the owner notices thick adherent crusts embedded in the hair coat or the odor of necrosis. Well-demarcated erythema, if noted, is the earliest clinical sign.



Fig. 4.39 Closer view of Fig. 4.38 with the affected area clipped. The scar is contracting. (Photograph courtesy S.C. Vandenabeele.)

Erosion and ulceration vary depending on the depth of injury. In full-thickness burns, the damaged skin becomes firm and dry due to avascular necrosis and eventually may slough. Secondary bacterial infection due to necrosis of tissue and impairment of local defense mechanisms is common. Life-threatening sepsis may be seen, especially if large body surfaces are involved. Pain may be the initial presenting complaint. As expected, age, breed, or sex predilections are not noted.

Clinical differential diagnoses include toxic epidermal necrolysis, severe erythema multiforme, pemphigus vulgaris and other bullous autoimmune diseases, vasculitis, and other causes of ischemic or pressure necrosis. Lack of progression of lesions after the initial 5 days is an important differentiating feature of burns, unless the insult is repetitive. Biologically abnormal patterns such as straight or angular borders, 'drip' configurations, or unusual symmetry may increase the index of suspicion of a burn.

Biopsy site selection

Areas of erythema without ulceration are preferred sites for skin biopsy. Chronic or severe lesions comprising ulcers, deeply necrotic tissue, severe secondary inflammation, and scarring may not yield a definitive diagnosis.

Histopathology (Figures 4.40 through 4.43)

Coagulation necrosis of the epidermis is present. In most thermal burns, necrosis typically extends through the epidermis to hair follicles, sometimes including the bulb, and may affect adnexal glands (second degree burn). Dermal collagen may be affected, but usually is comparatively less

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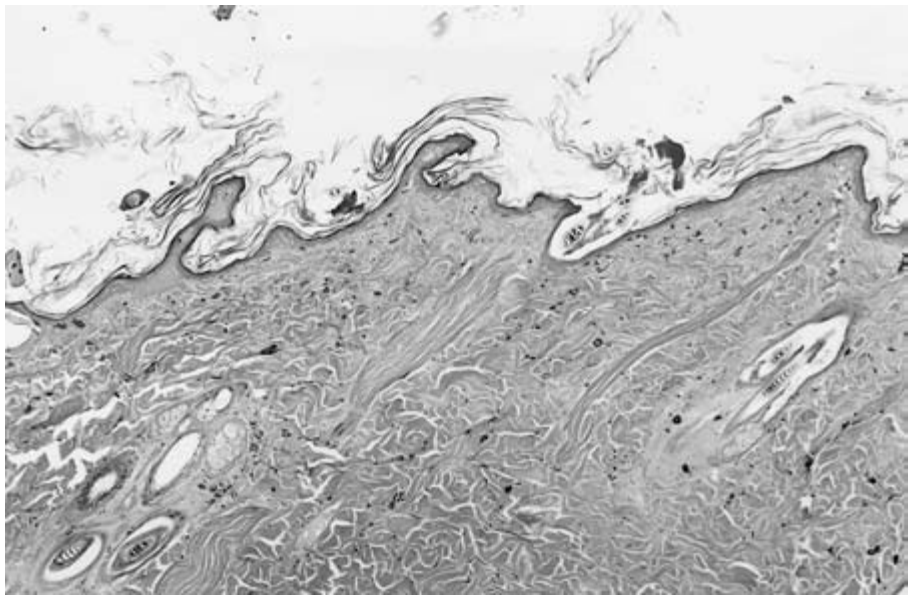


Fig. 4.40 Diffuse coagulation necrosis of skin in thermal burn of a cat, characterized by generalized pallor of the tissue.

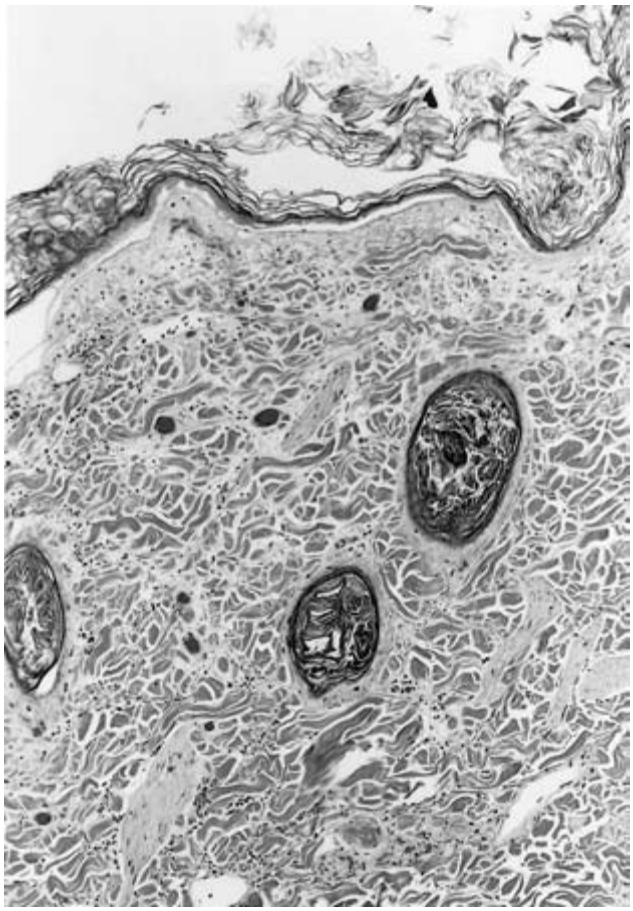


Fig. 4.41 High magnification of thermal burn from the cat of Fig. 4.40. Devitalized epidermis is lifting from the dermis; note extreme pallor of follicular walls.

necrotic than epithelial structures in all cases save the most severe and deep thermal burns. The exception is dorsal thermal necrosis, which often is characterized by more intense superficial necrosis to include all tissue.

In contrast, most chemical burns (as well as milder thermal burns) may be of partial epidermal thickness (first degree burn), particularly in areas of thick epidermis, and may not penetrate follicular epithelium beyond the depth to which the adjacent dermis is affected. Chemical burns may be bordered by zones of parakeratosis, indicative of a milder and chronic response to a superficial irritant (see p. 98). This may result from dilution of the offending chemical in the peripheral areas of exposure.

Both chemical and thermal burns may be full-thickness, resulting in severe obliterative acellular necrosis of all dermal structures. This necrosis may extend to the panniculus or even the deeper subcutis (third degree burn).

Dermal–epidermal separation occurs, as cohesion is lost between nonviable and viable tissue. In deep second or third degree burns, separation can occur within the dermis; condensation and desiccation of the devitalized zone results in a thick eschar. Erosion and ulceration are common in advanced lesions, and are accompanied by crusts composed of exuded serum and neutrophils. Severe dermal inflammation, including large numbers of neutrophils, is the result of ulceration and secondary bacterial infection. Full thickness third degree burns often result in massive neutrophilic inflammation, and are accompanied by marked fibrosis of subjacent viable tissue. Neutrophilic panniculitis with vasculitis and thrombosis may be a sequel of both chemical and thermal burn trauma (see Chapter 21). Accompanying granulomatous panniculitis is more suggestive of thermal injury.

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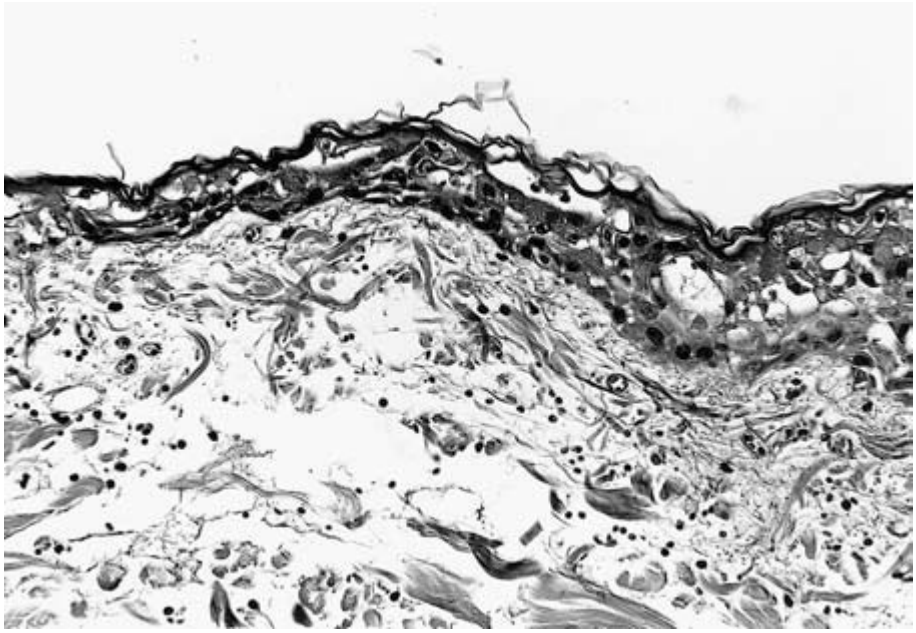


Fig. 4.42 Thermal burn from a dog demonstrating diffuse necrosis and ballooning degeneration of the epidermis.



Fig. 4.43 Dorsal thermal necrosis in a brown Shar Pei left in direct sun in an unshaded outdoor pen. Extensive necrosis has resulted in a thick eschar of necrotic tissue.

Toxic epidermal necrolysis is an important differential diagnosis for superficial burns; knowledge of clinical distribution may be important as most burns are asymmetrically distributed or localized. Toxic epidermal necrolysis, in contrast, affects large portions of the skin in a relatively symmetrical pattern. Primary vasculitis is a differential diagnosis for thermal burns that have secondary vascular inflammation of the panniculus. Historical and clinical information may be required to differentiate vasculitis from thermal burns. Vascular damage from vasculitis sufficient to create tissue damage resembling a burn (infarction) usually is associated with severe systemic illness. Dogs with thermal burns are usually remarkably well.

IRRITANT CONTACT DERMATITIS

Clinical features (Figures 4.44 and 4.45)

Irritant contact dermatitis (ICD) is a rare to uncommon inflammatory skin disease seen in dogs and cats that is caused by direct contact with an irritating concentration of an offending substance. Immune mechanisms are not involved. The irritating substance damages the skin by direct toxic action causing cellular damage. Irritant contact dermatitis can be viewed as a milder version of chemical burn, discussed above. Causes include corrosive substances such as strong acids and alkalis, as well as less potent irritants such as soaps, detergents, solvents, and various other chemicals. One author (T.L.G.) has seen two cases of pinnal contact reaction to plastics (dog door and lawn chair); lesions regressed when access to plastic was

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Fig. 4.44 Irritant contact dermatitis on the pawpad of a cat. The pads are diffusely swollen, focally eroded, and necrotic.

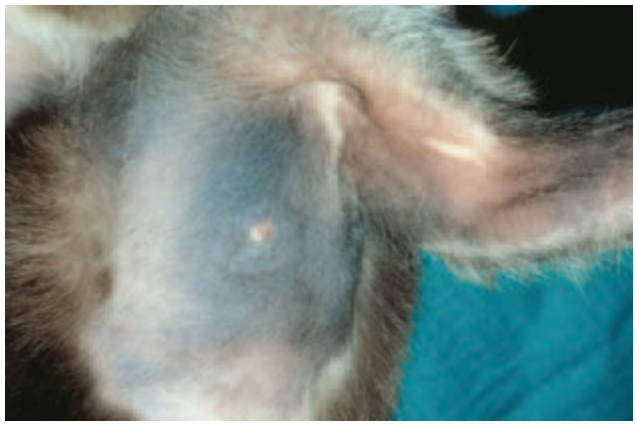


Fig. 4.45 Irritant contact dermatitis in a Siamese cat 3 weeks after accidental emersion in motor oil. The cat was cleansed immediately after emersion. The affected axilla is alopecic, hyperpigmented, and lichenified.

prevented. Moisture, which decreases the normal skin barrier function and increases the effective contact area by allowing diffusion of the irritant, predisposes to irritant-induced skin damage. Tissue maceration resulting from prolonged shampooing may facilitate ICD to a shampoo ingredient. As seen in human medicine, previously existing inflammatory skin diseases may increase susceptibility to ICD. Contact time, concentration, and the total dose of the agent are additional determinative factors.

Previously, differentiation between irritant and allergic contact dermatitis was not considered problematic in human or veterinary medicine. Differentiation hinged on allergic contact dermatitis requiring induction prior to elicitation, as well as the concept of 'uniqueness of allergens involved in allergic contact dermatitis' versus the 'universality of irritant reactions' (Rietschel, 1997). It is now known that potent contact allergens can initiate induction and elicitation simultaneously, thus mimicking ICD. Consequently, differentiation currently is considered to be predominantly conceptual (Rietschel, 1997). The authors believe that much of the clinical veterinary literature describing ICD should be viewed with skepticism. Others share this view (Scott et al., 2001).

Erythema and papules are the most common initial lesions. Exudation, scaling and crusting follow. Generalized erythroderma with variable exfoliation may be seen with irritant contact reactions to substances such as shampoos or rinses that are dispersed over an entire animal. Lichenification, hyperpigmentation, alopecia, and gradual expansion of the lesions result from chronic exposure.

The hair coat normally is protective against most contactants. Thus, most environmental irritants that initiate ICD are more likely to affect glabrous skin or areas where the hair coat is either naturally thin or missing due to skin disease or clipping (Scott et al., 2001). Lesions may be strikingly well demarcated at the margins of nonhaired and haired skin. The abdomen, perianal region, external genitalia (especially in the male dog), axillae, medial surface of the pinnae, ventral surface of the tail, pawpads, and interdigital space are affected most commonly. The plastic reactions in two dogs were limited to the inner pinnae. Liquid contactants can cause lesions with either splash or drip configurations or a more generalized distribution. Reactions to topical medications commonly are restricted to the sites of application. Pruritus is variable in intensity but usually is present. Irritant contact dermatitis may be less likely than allergic contact dermatitis to become chronic, since identification and elimination of the offending substance may be more readily accomplished. Breed, age, or sex predilections have not been noted and would not be expected.

Allergic contact dermatitis is the primary clinical differential diagnosis. In most circumstances, the lesions of ICD are clinically indistinguishable from allergic contact dermatitis. Single episodes may be more common with ICD, since the cause may be more readily determined than in allergic contact dermatitis. Clinical signs compatible with contact dermatitis in multiple animals in the same environment favor irritant rather than allergic contact dermatitis. Chronic contact dermatitis can mimic many other chronic inflammatory dermatoses, since the grossly visible chronic reaction patterns of the skin are limited. However, clear limitation of lesions to glabrous or relatively hairless skin is suggestive of a contact etiology.

Biopsy site selection

Erythematous macules or papules represent early stages of contact dermatitis and, if present, should be sampled

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Fig. 4.46 Irritant contact dermatitis in a dog secondary to bathing and dipping. Parakeratosis is accompanied by mild intraepidermal inflammation and serum accumulation.



Fig. 4.47 Higher magnification of Fig. 4.46 demonstrating parakeratosis, neutrophilic inflammation, and serum accumulation.

for biopsy. Newer lesions should be chosen over chronic lesions, as lesions characterized by hyperpigmentation and lichenification are less likely to provide useful diagnostic information. Self-traumatized lesions also should be avoided.

Histopathology (Figures 4.46 through 4.49)

Irritant and allergic contact reactions have been reportedly difficult to definitively distinguish histologically, based on patch test analysis in dogs with spontaneous allergic contact dermatitis (Thomsen & Thomsen, 1989). Recent evidence indicates much immunologic overlap between the two contact reactions in humans (Rietschel, 1997). Thus there may be expected variation in contact reactions as they are presented to the pathologist, particularly in the setting of a patch test biopsy (see allergic contact dermatitis, Chapter 5). Ideally, irritant reactions can be considered as those inflicting direct cellular damage to the keratinocyte, and thus should generally demonstrate some degree of epidermal degeneration histopathologically.

Acute ICD usually is transient in the natural setting, and consequently lesions of chronic ICD are more com-

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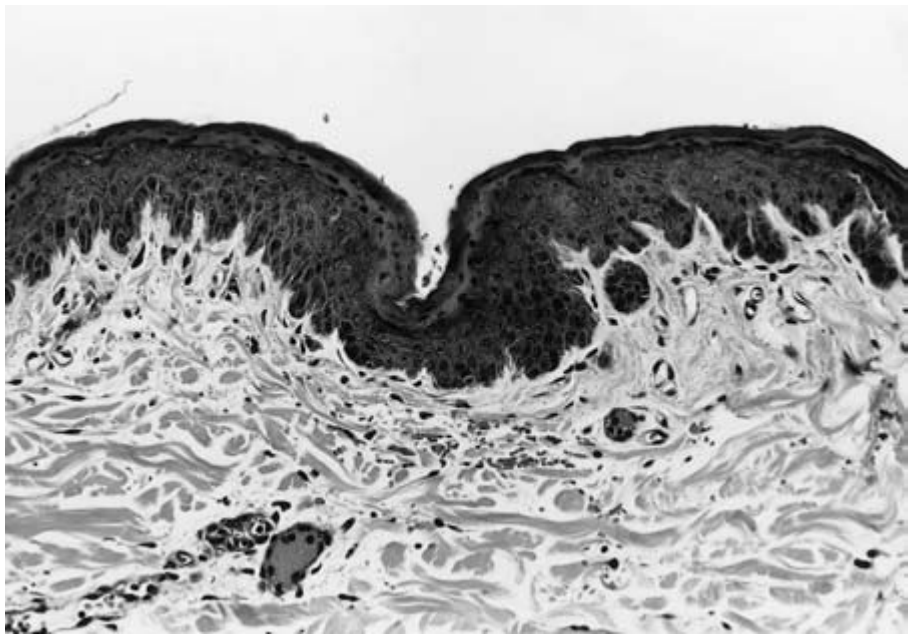


Fig. 4.48 Chronic irritant contact dermatitis in a dog. Note acanthosis and dense parakeratosis.

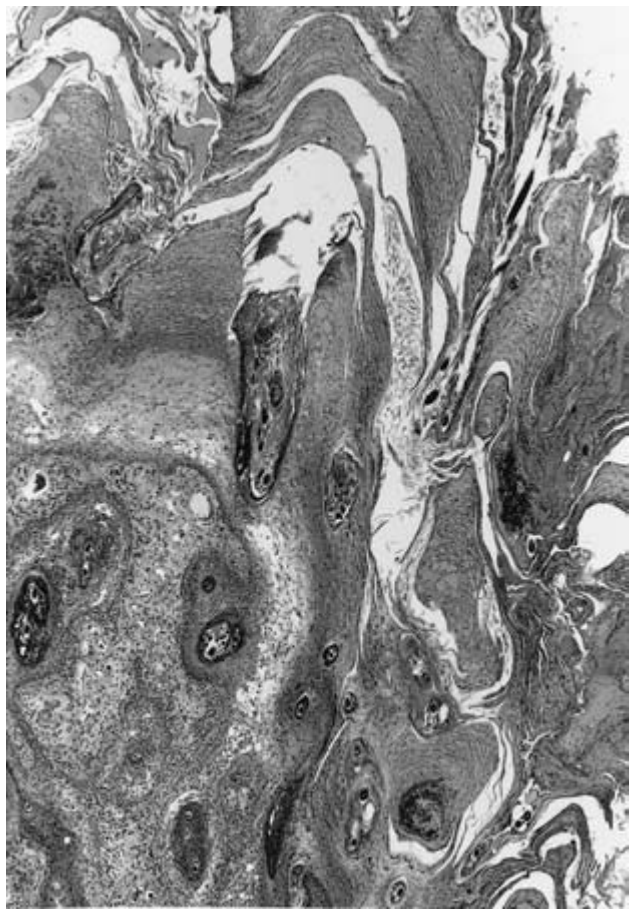


Fig. 4.49 Irritant contact reaction to a plastic lawn chair. Note massive parakeratosis and intraepidermal edema and degeneration resembling superficial necrolytic dermatitis.

monly presented to the pathologist. Experimental ICD in dogs was characterized by epidermal necrosis with subepidermal separation and neutrophilic dermatitis (Krawiec & Gaafar, 1975; Walder & Conroy, 1994). Changes extended to hair follicles in severe lesions (Krawiec & Gaafar, 1975). Earliest lesions were epidermal spongiosis and spongiotic vesicles containing neutrophils (Walder & Conroy, 1994).

Chronic lesions are not considered diagnostic of an irritant reaction, as self-traumatic lesions predominate. A confluent layer of parakeratosis is suspicious for an irritant reaction, particularly if it occurs in glabrous skin. In this context, parakeratosis likely reflects hastened epidermal maturation secondary to direct keratinocyte injury. Parakeratosis also characterizes the reaction to some irritants in humans (Rietschel, 1997). Parakeratosis is accompanied by variable acanthosis, and there may be accompanying serous and neutrophilic inflammation, leading to crusts. Severe ulceration and exudation of glabrous skin may be suspicious for severe irritant-induced epidermal necrosis. Variable superficial perivascular infiltrations of lymphocytes, neutrophils, and macrophages are present; inflammation is more severe and suppurative if there is ulceration.

Rare cases of pinnal disease due to plastic exposure (plastic dog doors and plastic lawn chairs) have been observed in dogs, and may represent an exaggerated irritant contact reaction. Marked laminar epidermal edema and degeneration are accompanied by severe parakeratosis and variable crusting, resembling superficial necrolytic dermatitis (see p. 86); the reason for this striking resemblance is not known. Severe epidermal vesiculation may

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be present, and there may be small accumulations of serum throughout the parakeratotic layer. There may be individual cell death of epidermal and follicular keratinocytes resembling apoptosis. Spongiosis may be pronounced in the lower intact layers of the epidermis or outer hair follicles. Perivascular accumulations of lymphocytes, macrophages, plasma cells, and neutrophils are mild to severe.

Chronic putative ICD was observed in a cat with a history of thrice weekly shampooing. Compact orthokeratotic hyperkeratosis, mimicking ichthyosis (see Chapter 8) was found. The lesions were presumed to be a hyperkeratotic reaction to chronic and persistent low-level irritant exposure, but may also represent a reaction to the mechanical removal of lipids and other surface components of the epidermis.

Acute irritant reactions may resemble superficial chemical burns if they are severe. In fact, chemical burns are considered to fall at the most severe end of the spectrum of irritant contact dermatitis (Walder & Conroy, 1994). It may be difficult (and unimportant) histopathologically to separate a superficial chemical burn from an irritant reaction, since both imply a noxious contactant that must be removed. Chronic ICD resembles chronic superficial dermatitis of any cause. The diffuse parakeratosis seen in some cases of ICD is suggestive of zinc-responsive dermatosis, but is clinically distinct. Pinnal irritant reactions to plastics may be similar to the lesions of superficial necrolytic dermatitis, and clinical differentiation may be required in these cases. In cases of orthokeratotic hyperkeratosis resembling ichthyosis (see Chapter 8), but occurring in an atypical clinical setting, ruling out a reaction to persistent mechanical and/or chemical irritation may be required.

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Chapter 5

Spongiotic and vesicular diseases of the epidermis

Spongiotic dermatitis is characterized by edema of the intercellular spaces of the epidermis and superficial follicular wall. Severe spongiosis may lead to breakdown in the integrity of the architecture, resulting in vesiculation. Generally, inflammatory cell influx accompanies spongiotic change. Spongiotic foci usually eventuate in focal parakeratosis due to reactive increased epidermal turnover and incomplete keratinocyte differentiation. Parakeratosis may intermingle with inflammatory exudate; the term 'parakeratotic scale-crust' signifies this combined event.

Many diseases, not described in this chapter, are characterized by mild spongiosis. Allergic skin diseases, for example, produce multifocal spongiosis. The diseases included in this chapter are those in which spongiosis is characteristically a significant and predominant diagnostic feature. Not all stages of these diseases will show spongiosis; obtaining the earliest lesions possible is critical to the diagnosis.

ALLERGIC CONTACT DERMATITIS

Clinical features (Figures 5.1 and 5.2)

Allergic contact dermatitis (ACD) is a rare inflammatory skin disease of dogs and cats caused by an adverse immunologic reaction to a nonirritating concentration of the offending substance. Classically, ACD is believed to be a type IV or delayed hypersensitivity reaction mediated by lymphocytes that occurs in previously sensitized individuals. Previously, differentiation between irritant contact dermatitis and ACD was not considered problematic in human or veterinary medicine. Differentiation hinged on ACD requiring induction prior to elicitation, as well as the concept of 'uniqueness of allergens involved in ACD' versus the 'universality of irritant reactions' (Rietschel, 1997). It is now known that potent allergens can initiate induction and elicitation simultaneously, thus mimicking irritant contact dermatitis. Consequently, differentiation currently is considered to be predominantly conceptual (Rietschel, 1997). The authors believe that much of the clinical veterinary literature describing ACD should be viewed with skepticism. Others share this view (Scott et al., 2001).

Previously, lymphocytes were viewed as the predominant cell type in ACD, which supported the view of ACD as a 'pure' type IV hypersensitivity reaction. However, more recent data indicate that type I hypersensitivity involving eosinophils may play a role in ACD, especially in dogs with concomitant atopic dermatitis (Walder & Conroy, 1994). This participation of eosinophils in ACD speaks against a 'pure' type IV hypersensitivity (Marcella et al., 1997). Eosinophils have been reported as playing a role in canine atopic dermatitis along with percutaneous penetration of allergens (Olivry et al., 1997), thus blurring the distinction between ACD and atopic dermatitis. Currently, the sequence of events leading to the development of ACD is thought to involve the binding of a hapten to a protein to form a complete antigen. According to the classical view of the pathogenesis, interaction of the hapten–protein conjugate with epidermal Langerhans cells leads to T lymphocyte activation and the release of multiple cytokines, especially tumor necrosis factor alpha (TNF-α). The role of eosinophils in ACD is as yet unexplained.

Most well-documented cases of ACD reported in domestic animals are reactions to sensitizing plants such as wandering Jew plant (*Tradescantia fluminensis* and other *Tradescantia* species), spreading dayflower (*Commelina diffusa*), doveweed (*Eremocarpus setigerus*), and dandelion (*Taraxacum officinale*) (Scott et al., 2001). Topical medications (especially otic products) also may produce reactions. Danish studies have confirmed a wide variety of offending chemicals by patch testing (Thomsen & Kristensen, 1986; Thomsen & Thomsen, 1989). The review of McGovern & Barkley (1998) gives an excellent overview of the plants and plant products that can initiate both immunologic and nonimmunologic reactions in humans. One author (P.J.I.) has observed cedar chips and the aminoglycoside component of topical medications as among the most common inducers of ACD. Offending contactants may be in the environment for as short a

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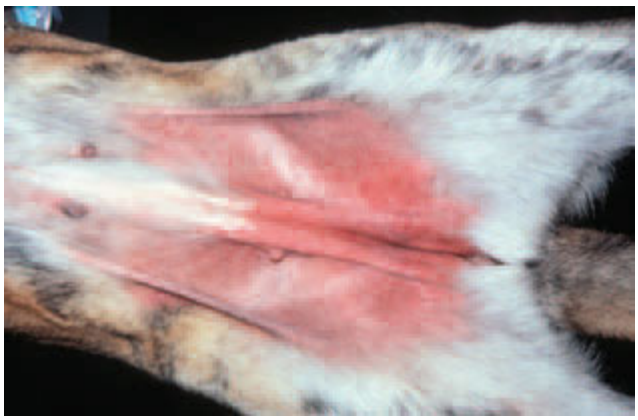


Fig. 5.1 Allergic contact dermatitis in a mixed breed dog due to cedar chip bedding. The nonhaired area of the ventral abdomen is diffusely erythematous. Lesions do not extend into haired areas.



Fig. 5.2 Closer view of Fig. 5.1. Small papules are seen against a background of diffusely erythematous, exudative skin.

time as 1 month to as long as 2 years before initiating disease.

The clinical signs and affected sites of ACD are virtually identical to those of irritant contact dermatitis (see Chapter 4). Allergic contact dermatitis may be more likely than irritant contact dermatitis to become chronic, since identification and elimination of the offending substance may be more difficult to accomplish. Macular erythema and papules are the most common initial lesions. Rarely, vesicles may be seen. Exudation leads to crusting. Lichenification, hyperpigmentation, alopecia, and gradual expansion result from chronic exposure. Since the normal haircoat usually is protective, lesions may be strikingly well-demarcated at the margins of nonhaired and haired skin. The abdomen, perianal region, external genitalia (especially in the male dog), axillae, ventral surface of the tail, and interdigital space are affected most commonly. Reactions to topical medications generally are restricted to the sites of application. Cats are more likely than dogs to spread contactants by grooming. Licking can result in extension of lesions to the oral mucosa. Pruritus is variable in intensity but usually present. Positive patch tests may be more papular and vesicular than typical clinical lesions, since very early lesions are rarely seen in clinical cases.

Signalment predilections are controversial since older data may not reflect true ACD. Allergic contact dermatitis usually is seen in adult animals. A Danish study reported the German Shepherd Dog to be at increased risk (Thomsen & Kristensen, 1986). Wirehaired Fox Terriers, Scottish Terriers, West Highland White Terriers, French Poodles and Golden Retrievers may be at increased risk (Olivry et al., 1990). Sex predilection has not been noted.

Irritant contact dermatitis is the primary clinical differential diagnosis. In most circumstances, the lesions of irritant contact dermatitis are clinically indistinguishable from ACD. Clinical signs compatible with contact dermatitis in a single animal within a multiple animal household favor ACD over irritant contact dermatitis. Allergic contact dermatitis may be more papular than irritant contact dermatitis and is more likely to be chronic. Atopic dermatitis and food allergy also may resemble ACD clinically. Lesions of contact dermatitis in glabrous skin may subside strikingly at the junction with haired skin, in contrast to other allergic diseases. Chronic ACD can mimic many other chronic inflammatory dermatoses, since reaction patterns of the skin are limited. Closed patch testing may be the best diagnostic test for ACD, but currently rarely is performed.

Biopsy site selection

Erythematous macules or papules represent early stages of contact dermatitis and, if present, should be sampled for biopsy. Newer lesions should be chosen, as lesions characterized by hyperpigmentation and lichenification are less likely to provide useful diagnostic information. Self-traumatized lesions also should be avoided. The most diagnostic specimens may be obtained from positive patch tests at 24 to 48 hours.

Histopathology (Figures 5.3 through 5.6)

Allergic contact dermatitis does not always conform to the classical type IV delayed hypersensitivity reaction in which lymphocytes predominate, and a component of type I hypersensitivity may play a role, particularly in atopic dogs (Walder & Conroy, 1994). Histopathologic changes of naturally occurring 'allergic' contact dermatitis are inconsistent; a range of lesions, even in patch test sites, may reflect a variable immunologic basis and cytokine milieu, as well as immunologic differences in the

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Fig. 5.3 Allergic contact dermatitis in a dog (positive patch test at 48 hours). Locally extensive spongiosis is accompanied by exocytosis of mononuclear cells.



Fig. 5.4 Higher magnification of Fig. 5.3. Severe spongiosis is progressing to vesiculation. Note exocytosis of mononuclear cells.

host (atopic versus nonatopic patient). For example, patch test reactions to known contactants such as *Tradescantia fluminensis* can vary among individual dogs (see below).

Lesions of ACD may be best exemplified by biopsy of clinically positive patch tests at 24 to 48 hours. Multifocal epidermal and superficial follicular spongiosis may progress to vesiculation, but spongiosis may be mild in some clinically positive sites. Some patch test reactions demonstrate lymphocytic migration into epidermal and follicular spongiotic foci, including patch test reactions to plants such as *Tradescantia fluminensis*. In others, including some to *Tradescantia fluminensis*, spongiosis is mild and an edematous dermal inflammatory reaction predominates, resembling urticarial allergic eruption (see Chapter 9). Previous reports of positive patch test reactions in dogs with naturally occurring ACD have described eosinophilic epidermal pustules or eosinophilic spongiosis in patch test sites (Merchant et al., 1993; Marsella et al., 1997). Epidermal necrosis with neutrophilic inflammation, similar to irritant contact reactions (see Chapter 4), also has been reported in patch test sites of dogs with ACD (Thomsen & Thomsen, 1989); this has not been observed by the authors to date, and putatively might have been due to too high a concentration of the test substance, resulting in a true irritant reaction. In dogs with experimentally induced ACD to 0.1% 2,4-dinitrochlorobenzene, patch test sites revealed

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Fig. 5.5 Eosinophilic allergic contact dermatitis to wool in a dog demonstrating inflammation and spongiosis of the epidermis.

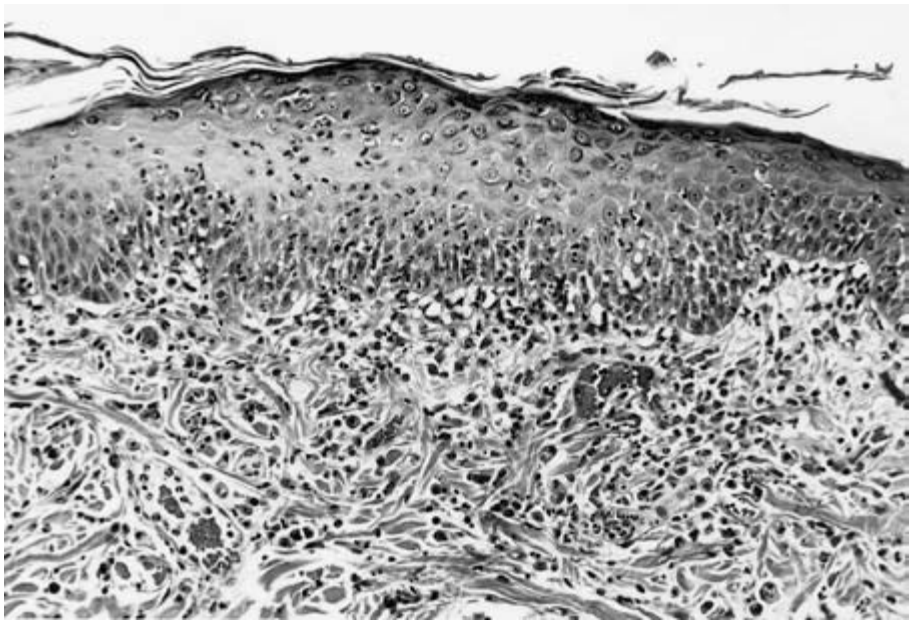


Fig. 5.6 Higher magnification of a dog with allergic contact dermatitis due to wool. Note exocytosis of eosinophils.

a mononuclear dermatitis with edema and marked mural folliculitis (see Chapter 18). This variation may be due to the technique of induction used that may have targeted deeper follicular epithelium primarily (Krawiec & Gaafar, 1975).

In random biopsies from nonpatch-tested skin of dogs with patch test-confirmed ACD, there is often eosinophilic and/or neutrophilic migration into epidermal and superficial follicular spongiotic foci (eosinophilic or neutrophilic spongiosis). Eosinophilic or neutrophilic intraepidermal pustules may be observed. Lymphocytes may migrate into spongiotic foci, but this is a sparse feature in most cases. Spongiosis and intraepidermal inflammation evolve to superficial crusts with focal parakeratosis. Most biopsy specimens are obtained from chronic lesions. In those cases the epidermis is acanthotic and there may be ulceration and exudation due to severe self-trauma attending pruritus.

Dermal inflammation is variable and mixed both in natural lesions and in patch test reactions (see Chapter 9). Edema may be prominent particularly in patch test reactions.

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Fig. 5.7 Feline eosinophilic plaques on the hindleg of a cat. Individual plaques are raised, well-demarcated, alopecic, eroded, and intensely erythematous. Larger plaques show the partial contours of lesions that have coalesced.

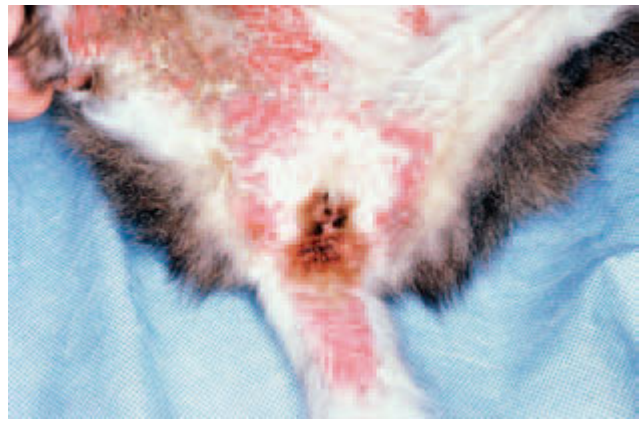


Fig. 5.8 Multiple brightly erythematous eosinophilic plaques on the ventral abdomen, perianal region, and ventral tail of a cat. (Photograph courtesy B.A. Atlee; case material University of California, Davis.)

Allergic contact dermatitis mimics allergic dermatitis of any cause; thus, histopathology alone often does not allow definitive diagnosis of ACD. In fortuitous cases, lymphocytic exocytosis and spongiosis may be prominent features of ACD, especially in early lesions. Eosinophilic intraepidermal pustulation or eosinophilic spongiosis also may be suggestive if the clinical presentation is appropriate. Intraepidermal eosinophilic pustules also have been reported in a small percentage of atopic dogs in one study (see Chapter 9); since percutaneous penetration of allergens also is involved in atopic dermatitis, its distinction from ACD may be impossible in some clinical settings. Differentiation between irritant and allergic contact dermatitis may be requested by the clinician due to the similar clinical distribution of these conditions. Necrosis of the epidermis usually is not a feature of ACD, but may be found in irritant contact dermatitis. Diffuse parakeratosis is characteristic of some irritant contact reactions (see Chapter 4) but not ACD.

FELINE EOSINOPHILIC PLAQUE

Clinical features (Figures 5.7 and 5.8)

Feline eosinophilic plaque is a common, highly pruritic, and localized skin disorder of cats. The highly abrasive, firm papillae present on the tongue of the cat probably play an integral part in the progression of the syndrome. An underlying allergic hypersensitivity is suspected frequently, but is less commonly definitively documented. Evidence that a heat-stabile cytophilic antibody is involved in the pathogenesis lends further credence to an allergic etiology (Roosje & Willemse, 1995). Flea allergy dermatitis, atopic dermatitis, and food allergy all may manifest as feline allergic miliary dermatitis, and have all been recognized as occurring in conjunction with eosinophilic plaques. Further, feline eosinophilic plaques are reported to have responded to flea control, allergen specific immunotherapy, and elimination diets. The authors view flea allergy dermatitis as the prime initiator of feline eosinophilic plaque in regions of the world where fleas are present. Feline eosinophilic plaques commonly have been grouped as part of the 'eosinophilic granuloma complex' (Mason & Burton, 2000; Scott et al., 2001). The authors prefer the term 'feline eosinophilic skin diseases' as some of the conditions are not granulomatous and also do not seem to form a cohesive disease complex when etiologic factors are considered (Power & Ihrke, 1995).

Well demarcated, circular to oval, intensely erythematous, eroded or ulcerated, oozing, alopecic plaques are noted most commonly on the abdomen and medial thighs, but can occur in almost any location that the cat can self-traumatize. Lesions may have steep margins similar to wheals. Plaques vary between 0.5 and 5 cm in diameter, and may be single or multiple. They may coalesce, leading to polycyclic shapes. Rarely, dozens of coalescing plaques may be present. Constant licking of the affected area is a common feature and is indicative of the severity of pruritus. Regional lymphadenopathy usually is present.

Age or breed predilections have not been reported. Females may be at increased risk (Scott et al., 2001).

Clinical differential diagnoses should include neoplasms such as lymphoma, mast cell tumor, metastatic mammary adenocarcinoma, and squamous cell carcinoma. The finding of eosinophils on impression smears supports the diagnosis of eosinophilic plaque. Since malignant tumors occasionally may closely mimic

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eosinophilic plaques visually, skin biopsy is indicated if lesions are not typical or initial response to therapy is not as expected.

Biopsy site selection

Erythematous plaques with minimal erosive or exudative changes are ideal specimens for biopsy. Ulcers and severely crusted lesions should be avoided. If multiple lesions are present, the clinician should select a site that will be less readily self-traumatized after surgery.

Histopathology (Figures 5.9 and 5.10)

Epidermal changes consist of severe acanthosis and generally moderate to severe spongiosis with eosinophilic exocytosis. Spongiosis may be mild in some otherwise typical lesions. Spongiosis is diffuse in distribution, and often involves follicular infundibula. Epidermal and follicular mucinosis is common and may be severe. Spaces between epidermal and follicular epithelial cells become widened by deposition of pale gray or gray-blue mucin, often to the point of vesiculation. Mucin may extend

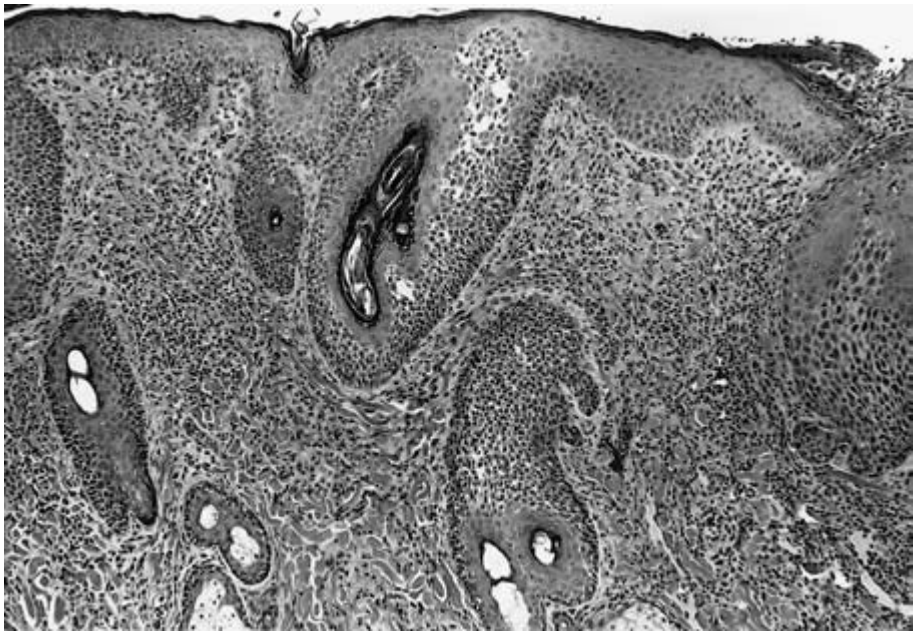


Fig. 5.9 Feline eosinophilic plaque. Marked acanthosis is accompanied by spongiosis; superficial hair follicles also are affected.

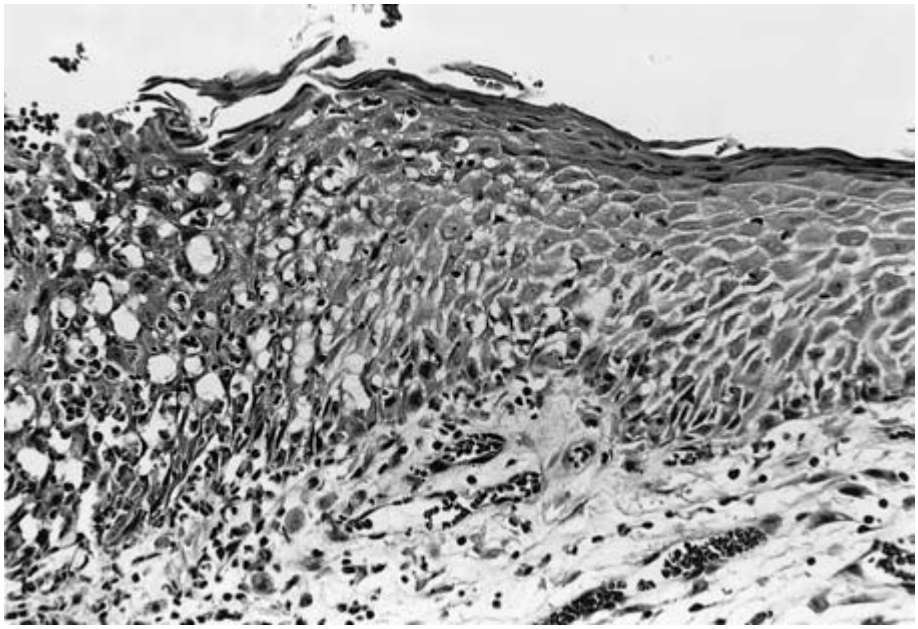


Fig. 5.10 Higher magnification of feline eosinophilic plaque. Note prominent spongiosis and exocytosis of eosinophils.

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around follicles in severe cases. There usually is severe secondary erosion or ulceration in advanced lesions (see Chapter 6).

Dermal inflammation consists of variably intense, usually diffuse infiltrations of eosinophils. These extend to the middle (follicular) dermis, but also commonly reach the superficial panniculus (see Chapter 14). Mast cells, lymphocytes, histiocytes and neutrophils are identified in smaller numbers, particularly in resolving or ulcerated lesions.

Histopathologically, the profound spongiotic and mucinotic lesions of typical eosinophilic plaque are unique. Eosinophilic plaque is qualitatively similar to allergic miliary dermatitis, but is more dramatically spongiotic, mucinotic, inflamed, and ulcerated, and involves a larger expanse of skin (Gross et al., 1986). Since eosinophilic plaque and miliary dermatitis both may be manifestations of allergic skin disease in the cat (and can exist concurrently), histopathologic separation of severe lesions of miliary dermatitis from lesions of eosinophilic plaque may not be critical diagnostically.

PSORIASIFORM DERMATITIS OF THE PAWPADS

Clinical features (Figure 5.11)

Psoriasiform dermatitis of the pawpads is a syndrome or reaction pattern of uncertain etiology that has been seen in the dog. Some of the histologic features of these lesions suggest a hypersensitivity reaction pattern targeting the pawpads. It is tempting to hypothesize that percutaneous penetration of environmental allergens or contactants may initiate this syndrome. Psoriasiform dermatitis of the pawpads may be an additional manifestation of canine atopic dermatitis in which percutaneous penetration of allergens is considered central to the etiopathogenesis (see Chapter 9).

Affected dogs have proliferative, fissured central, carpal, and tarsal pawpads. Smaller digital pawpads are affected less frequently. Self-trauma to the pads and the pad margins may exacerbate lesions, as the syndrome is pruritic. Some affected dogs may have coexistent self-trauma in other sites suggestive of allergic skin disease such as atopic dermatitis. Breed, age or sex predilections have not been noted.

Clinical differential diagnoses may include pemphigus foliaceus restricted to the pawpads, early cases of superficial necrolytic dermatitis, zinc-responsive dermatosis, split pawpad disease, and irritant contact dermatitis. Affected dogs should be evaluated for allergic skin disease and skin biopsy should be performed.



Fig. 5.11 Psoriasiform dermatitis of the pawpads in a dog. Affected pawpads are thickened and fissured. (Photograph courtesy C.B. Vitale.)

Biopsy site selection

Pawpad biopsy is best accomplished using a punch to sample an active area of disease near the margin of a pad. Best used on pawpads are 6 mm and 4 mm biopsy punches as the defects created with 8 mm punches may cause difficulties with hemostasis and healing.

Histopathology (Figures 5.12 through 5.14)

Psoriasiform dermatitis of the pawpads is characterized by prominent conical peaks, or 'church spires' of parakeratosis interlayered with serum. These are subtended by epidermal foci of often subtle spongiosis. Cytoplasmic swelling of keratinocytes can be seen, and fortuitous foci of mild vesiculation may be observed. In active lesions, the dermis at the base of conical projections has dilated superficial blood vessels and variable edema. Mixed inflammatory cells (neutrophils, eosinophils, and/or lymphocytes) migrate from these 'dermal papillae' through the overlying epidermis to eventuate in small crusts within the peaked keratin layer. In some cases the parakeratotic layer is more diffuse and dense. Intact neutrophils, or occasionally eosinophils, are entrapped in the parakeratotic layer, often sparingly. Rarely, an intracorneal pustule is observed. Erosion with more intense exudative crusting may occur. Adjacent haired skin is similarly affected, but less severely.

The dermis has a perivascular to diffuse, mild to moderate, mixed infiltrate of lymphocytes, macrophages, neutrophils, and eosinophils. Eosinophils may be prominent.

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Fig. 5.12 Psoriasiform dermatitis of the pawpads. Large parakeratotic peaks or spires overlie an inflamed dermis.

Inflammation may be superficial, or may extend around subjacent eccrine glands or adnexal appendages in haired skin.

Psoriasiform dermatitis of the pawpads featuring peaked parakeratosis is unique. In cases with diffuse parakeratosis, differentiation from chronic superficial necrolytic dermatitis or zinc-responsive dermatosis may be necessary. Superficial necrolytic dermatitis usually features laminar epidermal pallor due to ballooning degeneration of keratinocytes. Clinical differentiation from zinc-responsive dermatosis may be required.

FACIAL DERMATITIS OF PERSIAN AND HIMALAYAN CATS

Clinical features (Figures 5.15 and 5.16)

An uncommon, progressive, idiopathic facial dermatitis of presumed hereditary origin has been reported in young Persian cats (Bond et al., 2000). An apparently identical syndrome has been noted in Himalayan cats (Power, 1998). The adherent debris is presumed to be a sebaceous gland product (Bond et al., 2000).

Darkly colored, greasy or waxy, tightly adherent debris that mats the facial hair is the first abnormality noted. As the syndrome becomes chronic, erythema and exudation occur. Although lesions may be more severe in the facial folds, they also are present in nonintertriginous locations. A bilaterally symmetric ceruminous otitis externa was seen in seven of 13 affected Persian cats (Bond et al., 2000). The muzzle, periorbital regions, and chin are

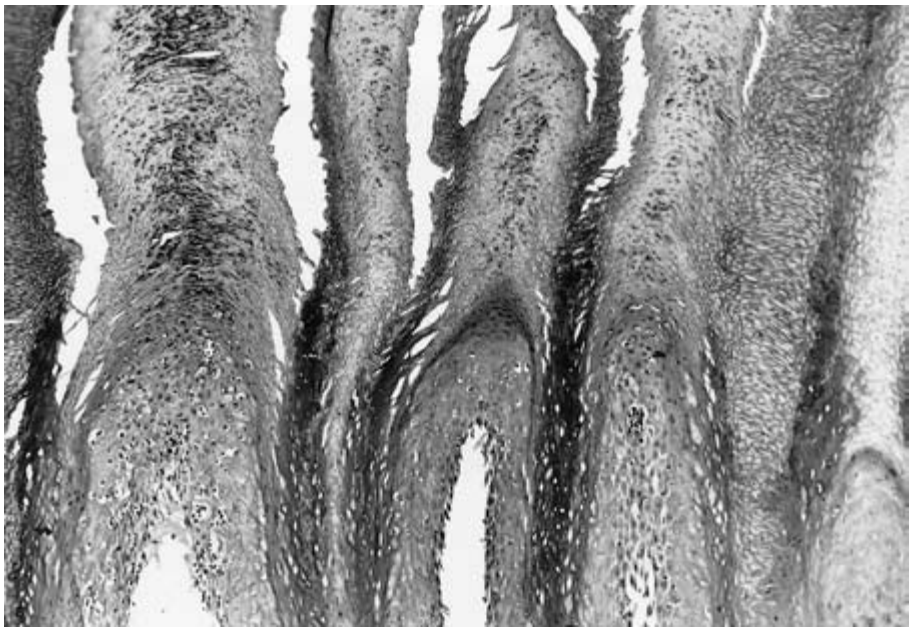


Fig. 5.13 Higher magnification of psoriasiform dermatitis of the pawpads. Parakeratotic spires contain degenerating inflammatory cells; note leukocytic exocytosis.

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Fig. 5.14 High magnification of parakeratotic spire in psoriasiform dermatitis of the pawpads. Note vascular dilatation and edema of 'dermal papilla'.



Fig. 5.15 Facial dermatitis of Persian cats. Dark, waxy adherent debris mats the facial hair. Inflammation is relatively moderate, despite copious debris. (Photograph courtesy L.P. Schmeitzel.)



Fig. 5.16 Facial dermatitis of Persian cats. Less adherent debris is present than in the cat in Fig. 5.15. Traumatic excoriations and alopecia are present, indicating pruritus. (Photograph courtesy J. Fontaine.)

affected most commonly. Less severe lesions less commonly affect body regions beyond the head. Secondary pyoderma or secondary *Malassezia* dermatitis may enhance the severity of clinical signs. Although pruritus may not be a feature of early disease, pruritus commonly becomes intense with chronicity. Submandibular lymphadenopathy was noted in five of 13 Persian cats (Bond et al., 2000).

Affected Persian cats are generally between 10 months and 6 years of age (median 2.5 years) at first presentation (Bond et al., 2000). Eight males and five female Persian cats were reported (Bond et al., 2000). The authors are aware of multiple other Persian and Himalayan cats seen with this syndrome by various dermatologists on a worldwide basis.

Facial dermatitis of Persian and Himalayan cats is visually distinctive. Clinical differential diagnoses are few. Adherent dark facial debris occasionally is seen with severe feline acne. A primary seborrhea of Persian cats has been reported, but other body regions beyond the face frequently are affected (Paradis & Scott, 1990).

Biopsy site selection

Representative specimens should be obtained from the muzzle. The adherent debris should be left attached to the hairs.

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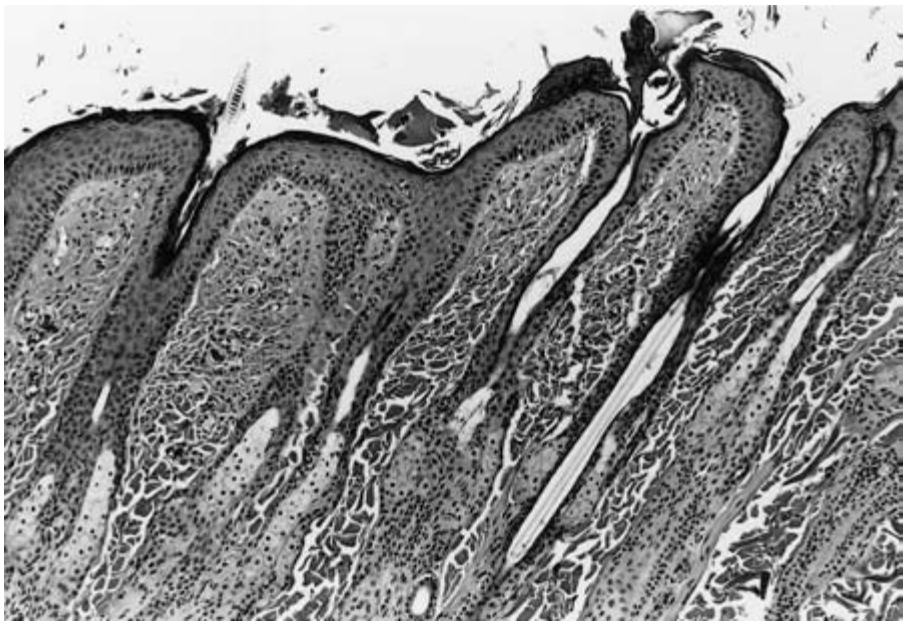


Fig. 5.17 Facial dermatitis in a Persian cat featuring acanthosis and serocellular crusting.

Histopathology (Figures 5.17 through 5.19)

The epidermis and follicular infundibula usually are severely acanthotic and moderately, often diffusely, spongiotic. Neutrophils and eosinophils migrate into the epithelium, sometimes heavily, and occasionally form small pustules. Luminal folliculitis has been reported (Bond et al., 2000). There is often mild to severe superficial parakeratotic and neutrophilic scale/crusting, often with serum exudation and bacterial colonization. Erosion may be seen. *Malassezia* have been identified cytologically (Bond et al., 2000), and thus should be theoretically present in tissue section in some cases.

Individual degeneration of keratinocytes resembling apoptosis occurs throughout the epidermis and superficial follicular epithelium, and is a characteristic but usually sparse feature of facial dermatitis. Occasional pustules may incorporate apoptotic cells.

Vacuolation of basal cells may represent, at least in part, regional spongiotic change. Although there may be scattered basal cell apoptosis, true interface dermatitis is not observed. The superficial and middle dermis contains a moderate infiltrate of varying proportions of neutrophils, macrophages, eosinophils, lymphocytes, plasma cells, and often numerous mast cells. Melanophages are often abundant. Sebaceous glands are large, but sebaceous glands may be prominent in facial skin of normal cats.

The histopathologic features of facial dermatitis of Persian and Himalayan cats are not highly specific, and diagnosis generally requires consideration of the clinical context. A spongiotic allergic reaction may appear similar; most of these do not feature apoptosis, however.



Fig. 5.18 Higher magnification of facial dermatitis in a Persian cat. Note extensive crusting and exocytosis of granulocytes.

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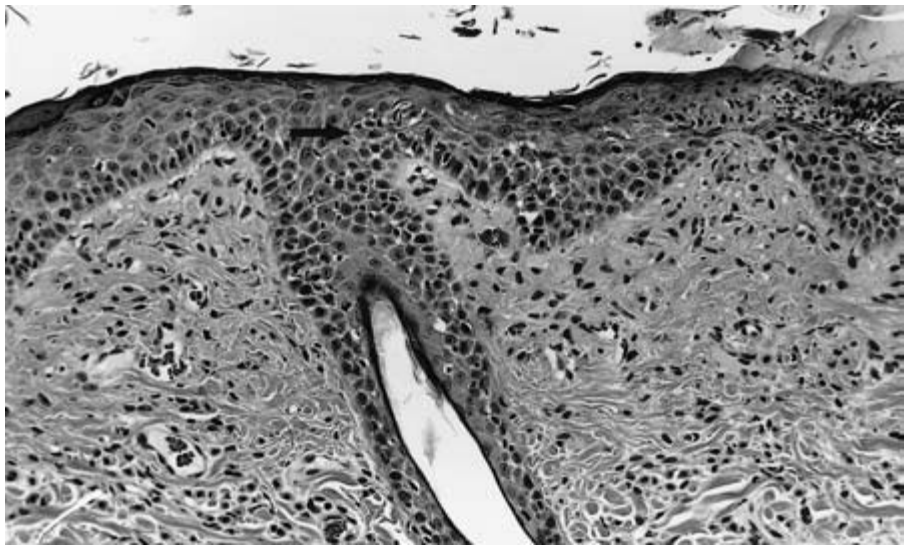


Fig. 5.19 Higher magnification of facial dermatitis in a Persian cat. Note spongiosis, exocytosis, serocellular crust (right), and single apoptotic keratinocyte (arrow). Lesions extend to the follicle.

The absence of lymphocytic satellitosis of apoptotic keratinocytes differentiates facial dermatitis from feline thymoma-associated exfoliative dermatitis, in which apoptosis may also be mild. Spongiosis also is not a prominent feature of feline thymoma-associated exfoliative dermatitis.

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Chapter 6

Ulcerative and crusting diseases of the epidermis

Ulcerative dermatitis is a primary feature of skin diseases characterized by prominent self-trauma, such as pyotraumatic dermatitis. Ulceration may also be a key characteristic of diseases in which there is marked inflammation and necrosis, such as some viral infections. Crusting or exudative dermatitis is characterized by the accumulation of inflammatory cells on the surface of the epidermis, leading to the formation of crusts. Ulcerative diseases also are crusting; self-trauma or other tissue injury leads to erosion or ulceration, which induces subsequent surface migration of inflammatory cells, usually neutrophils. Crusting also may be primary, as in nontraumatized lesions of miliary dermatitis in which allergy-induced transepithelial migration of neutrophils and eosinophils results in their accumulation and degeneration on the epidermal surface.

Many skin diseases are characterized by some crusting and epidermal damage, particularly allergic skin diseases that may produce erosion and crusting secondary to intense inflammation and through self-trauma from pruritus. Any disease characterized by surface pustulation, such as superficial pyoderma or pemphigus foliaceus, also can lead to crusting as pustules degenerate. The diseases in this chapter include those for which ulceration and exudation are the predominant pathologic processes occurring in the skin.

PYOTRAUMATIC DERMATITIS

(Synonyms: acute moist dermatitis, 'hot spot')

Clinical features (Figures 6.1 and 6.2)

Pyotraumatic dermatitis is a self-induced traumatic skin disease seen commonly in the dog and rarely in the cat. It is believed to be initiated by a vicious itch–scratch cycle secondary to underlying pruritic (especially allergic) skin disease. The characteristic lesions appear to result from licking, chewing, and scratching. The sharply demarcated nature of this disease is unexplained. Confusingly, extreme self-trauma in some dogs will not initiate pyotraumatic dermatitis, while surprisingly minimal self-trauma will create lesions in others. Most canine pyotraumatic dermatitis is seen secondary to flea allergy dermatitis. In cats, pyotraumatic lesions, clinically and histopathologically resembling those of dogs, have been seen secondary to flea allergy dermatitis, especially in the dorsal lumbosacral region. Other allergic skin diseases, otitis externa, and anal sacculitis occasionally have been implicated in dogs. Pyotraumatic furunculosis, which is pyotraumatic dermatitis overlying deep bacterial folliculitis and furunculosis, occurs in some breeds (Reinke et al., 1987) (see Chapter 17).

The clinically characteristic lesion of pyotraumatic dermatitis is a rapidly developing, self-traumatized, erythematous, exudative, alopecic, sharply-demarcated and slightly elevated plaque. Erosion and ulceration occur, and viscid proteinaceous debris adheres to the surface and mats the surrounding hair. Lesions are rapidly progressive and may coalesce. Pyotraumatic furunculosis may also feature smaller satellite lesions characterized by intense erythema, exudation and patches of erect hairs.

Since the lesions of pyotraumatic dermatitis usually are associated with flea allergy dermatitis, most lesions are seen primarily in the dorsal lumbosacral region and on the lateral thighs. Lesions also may be seen near the ears or anal sacs. Pyotraumatic furunculosis occurs most commonly on the face ventral to the ear and on the neck. Pain or pruritus is a consistent feature.

Canine breed predilections have been noted for large, dense-coated breeds such as the German Shepherd Dog, Golden Retriever, Labrador Retriever, Collie, and the Saint Bernard. Pyotraumatic dermatitis also is seen overlying focal deep pyoderma in breeds such as the Golden Retriever and the Saint Bernard. Age or sex predilections have not been noted. A marked seasonality is recognized; pyotraumatic dermatitis is seen most frequently in warm, humid weather.

Pyotraumatic dermatitis is visually distinctive and differential diagnoses are few. Occasionally, ulcerated neoplasms (apocrine gland carcinomas), or focal deep bacterial infections may resemble or initiate pyotraumatic

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Fig. 6.1 Pyotraumatic dermatitis in a German Shepherd Dog secondary to flea allergy dermatitis. The well-demarcated lesion is erythematous, swollen, and alopecic.



Fig. 6.2 Pyotraumatic dermatitis on the ventral neck of a German Shepherd Dog. Hair from the periphery is matted in the dried exudate.

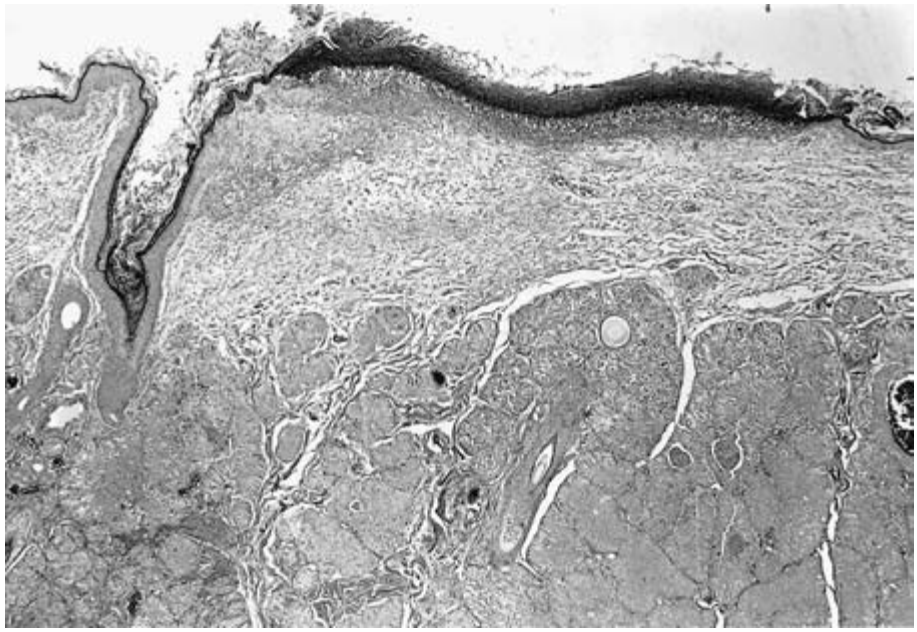


Fig. 6.3 Pyotraumatic dermatitis in perianal skin of a dog. A large discrete ulcer is covered by a prominent serocellular crust. Note subjacent large perianal glands.

dermatitis. The pain and self-trauma that are consistent features of pyotraumatic dermatitis aid in differentiation.

Biopsy site selection

Skin biopsy commonly is not employed to obtain a diagnosis. However, skin biopsy should be performed in recurrent or chronic cases, or in circumstances where neoplasia or underlying deep pyoderma is suspected. Newer erythematous lesions should be sampled in these cases. If deep pyoderma is suspected then peripheral, small, exudative lesions are most likely to yield diagnostic results.

Histopathology (Figures 6.3 and 6.4)

Epidermal lesions predominate and consist of severe erosion to ulceration and exudation. Superficial crusts contain degenerating neutrophils and serum, in addition

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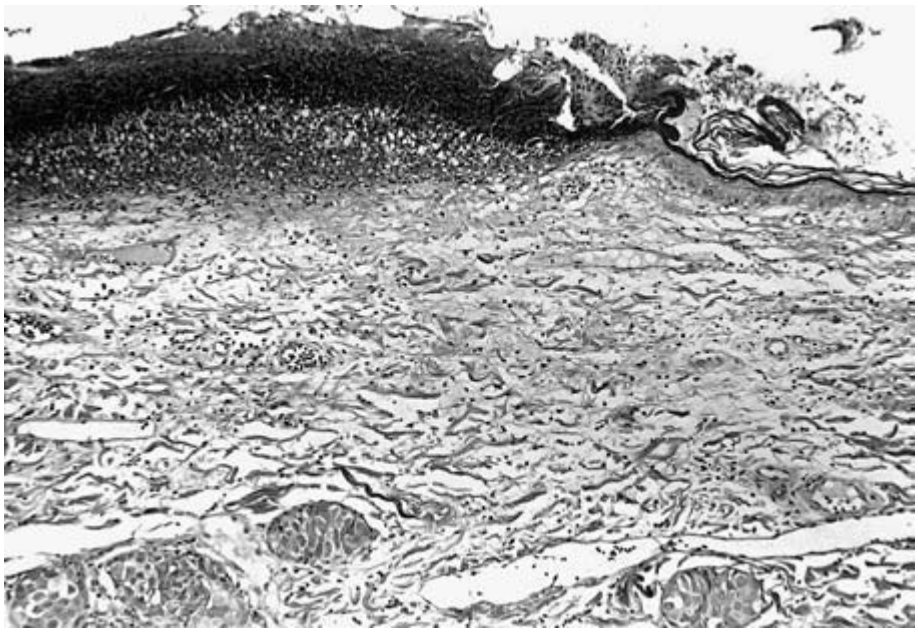


Fig. 6.4 Higher magnification of Fig. 6.3. Note sharp line of demarcation of the ulcer from the intact epidermis.

to necrotic epidermal debris. Colonization of crusts by Gram-positive staphylococci is common. Lesions are usually sharply demarcated from the adjacent epidermis, which may be spongiotic. Epidermal borders may have mild to moderate acanthosis in chronic lesions.

Necrosis may extend into the superficial dermis in severe cases. The dermis often contains mild to moderate neutrophilic and lymphohistiocytic inflammation, confined to the base of the erosion or ulcer. There may be edema or early fibroplasia. Eosinophils may be found at the intact skin margins.

Differential diagnoses are few, as lesions are distinctive. In cats, idiopathic ulcerative dermatosis and the neutrophilic form of indolent ulcer may appear similar histopathologically (see pp. 128, 130); clinical differentiation may be required. Pyotraumatic dermatitis with deep pyoderma is a distinct diagnostic entity, and is differentiated by the presence of deep folliculitis and furunculosis (see Chapter 17).



Fig. 6.5 Feline allergic miliary dermatitis featuring grouped, erythematous, crusted papules on the back of the neck.

FELINE ALLERGIC MILIARY DERMATITIS

Clinical features (Figures 6.5 and 6.6)

Feline allergic miliary dermatitis is a multifactorial cutaneous reaction pattern seen in cats. The older, looser term 'miliary dermatitis' was used previously to describe clinically similar lesions initiated by a wide variety of skin diseases. Histopathology readily differentiates allergic miliary dermatitis from other feline crusting skin diseases.

Feline allergic miliary dermatitis may be due to hypersensitivity to ectoparasites (especially fleas), atopic dermatitis, food products, and drugs. Evidence that a heat-stable cytophilic antibody is involved in the pathogenesis also is supportive of an allergic etiology (Roosje & Willemse, 1995). In locales where fleas are common, miliary dermatitis should be considered the result of hypersensitivity to fleas until proven otherwise. Other parasitic infestations capable of inducing allergic miliary dermatitis include cheyletiellosis, otodectic acariasis, trombiculiasis, pediculosis, and superficial demodicosis due to *Demodex gatoi*.

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Feline allergic miliary dermatitis is more often palpable rather than visible in cats with intact haircoats. Multiple, discrete, erythematous papules with adherent red-brown crusts are present. The crusted papule seen in feline allergic miliary dermatitis is a primary lesion and not the result of self-trauma. Pruritus is variable but usually present. Pruritus with attendant self-trauma leads to excoriation, and increased erythema and crusting. Self-traumatic alopecia is seen in severe cases, and results in increased visibility of miliary lesions. Somewhat bilaterally symmetric localization of lesions to the neck, dorsum, or tail base is noted in cats with flea allergy dermatitis. Lesions may be generalized in severe cases. Allergic miliary dermatitis affecting predominantly the face and neck may be the initial or only sign of food hypersensitivity in cats.



Fig. 6.6 Severe feline allergic miliary dermatitis. Hair has been clipped from the dorsal lumbosacral area to show confluent, erythematous, crusted papules.

Breed, age, or sex predilections have not been noted. However, predilections may match those of the initiating underlying allergic skin disease. Clinical differential diagnoses include the rare, nonallergic causes of similar miliary lesions such as dermatophytosis, and bacterial impetigo or superficial folliculitis. Impression smears demonstrating eosinophils support a tentative diagnosis of feline allergic miliary dermatitis.

Biopsy site selection

Nontraumatized, recently erupted, crusted papules are ideal for biopsy. If pruritus is extreme, special care should be taken to avoid traumatized lesions. The region of the dorsum of the neck between the shoulder blades is not recommended as a biopsy site, as any manipulation or the creation of inflammation in this region may lead to the development of feline idiopathic ulcerative dermatosis (see p. 130).

Histopathology (Figures 6.7 through 6.9)

Primary epidermal lesions consist of discrete foci of superficial serocellular crusting, accompanied by a variable



Fig. 6.7 Feline allergic miliary dermatitis. The moderately acanthotic epidermis is covered by discrete serocellular crusts.

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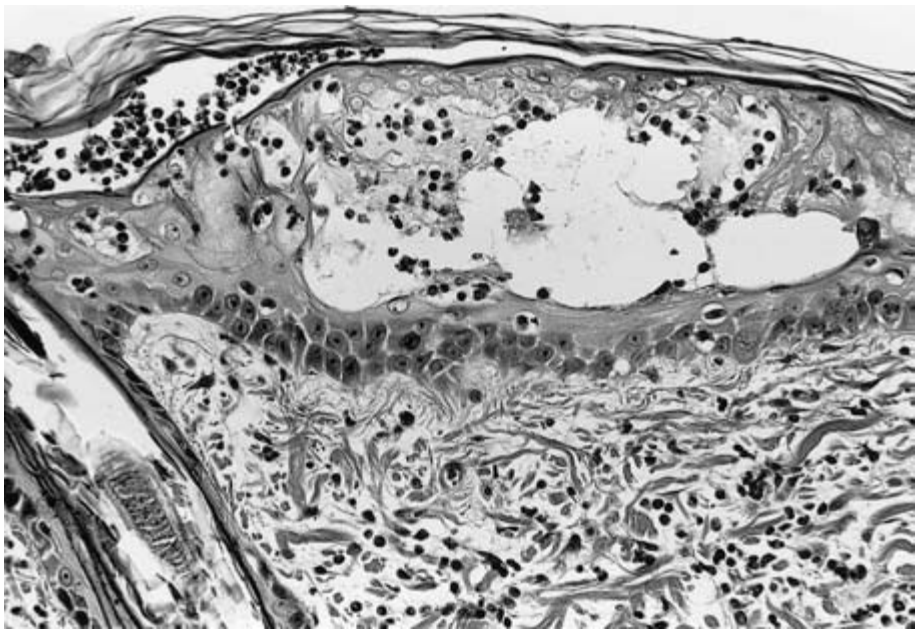


Fig. 6.8 Higher magnification of feline allergic miliary dermatitis featuring an eosinophilic vesicopustule.



Fig. 6.9 Extensive ulceration and surface exudative crusting in feline allergic miliary dermatitis.

degree of spongiosis of the subjacent epidermis and superficial hair follicles. Serum may be abundant within the crusts. There is accompanying erosion to focal ulceration. The epidermis may be focally necrotic beneath the crust and have a brightly eosinophilic, coagulated appearance. Small numbers of intact neutrophils and eosinophils accumulate within the subjacent or adjacent intact epidermis or in superficial follicular epithelium. Occasionally, there is marked epidermal vesiculation with eosinophilic exocytosis (eosinophilic vesicopustulation). Mild to moderate acanthosis, and mild spongiosis of the adjacent epidermis and hair follicles may be present. More severe lesions exhibit extensive spongiosis and broader foci of erosion and ulceration. Dermal inflammation is superficial to mid-dermal, perivascular to interstitial, and consists predominantly of eosinophils and mast cells (see Chapter 9).

The epidermal lesions of allergic miliary dermatitis are fairly characteristic; however, the diagnosis of allergic miliary dermatitis is not etiologically specific as many allergic causes can produce this pattern. Severely spongiotic and eroded or ulcerated lesions of allergic miliary dermatitis may resemble those of eosinophilic plaque. Since eosinophilic plaque and allergic miliary dermatitis both may be manifestations of allergic skin disease in the cat (and can exist concurrently), histopathologic separation of severe lesions of miliary dermatitis from lesions of eosinophilic plaque may not be critical diagnostically. Eosinophilic plaque may have striking epidermal and follicular mucinosis, which is generally not a feature of miliary dermatitis. Superficial pustular pyoderma (impetigo) is rare in cats, but crusts formed from chronic

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pustules may be reminiscent of miliary dermatitis. Miliary dermatitis features dermal eosinophilic inflammation more prominently than most cases of impetigo, and also can exhibit transepithelial migration of eosinophils, a rare occurrence in pyoderma.

FELINE EOSINOPHILIC PLAQUE

Clinical features (Figures 6.10 and 6.11)

See Chapter 5.

Biopsy site selection

See Chapter 5.

Histopathology (Figure 6.12)

Severe erosion or ulceration usually is seen in advanced lesions of eosinophilic plaque. The ulcer bed is covered by a crust that is brightly eosinophilic, due to the presence of degenerating eosinophils. There is severe acanthosis. Mild to severe spongiosis and/or mucinosis with eosinophilic exocytosis also extends to the superficial follicular epithelium (see Chapter 5).

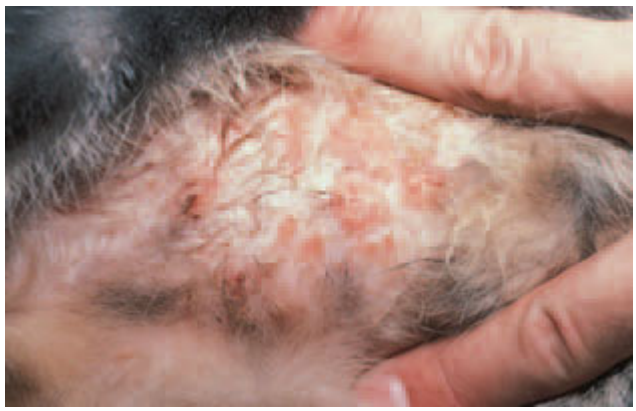


Fig. 6.10 Early feline eosinophilic plaque characterized by multifocal erythematous, erosive, alopecic plaques in a cat with allergic miliary dermatitis. (Photograph courtesy A.H. Werner; case material University of California, Davis.)



Fig. 6.11 Severe feline eosinophilic plaque. Multiple, well-demarcated, ulcerated, erythematous plaques are present on the ventral abdomen of a cat with allergic miliary dermatitis.

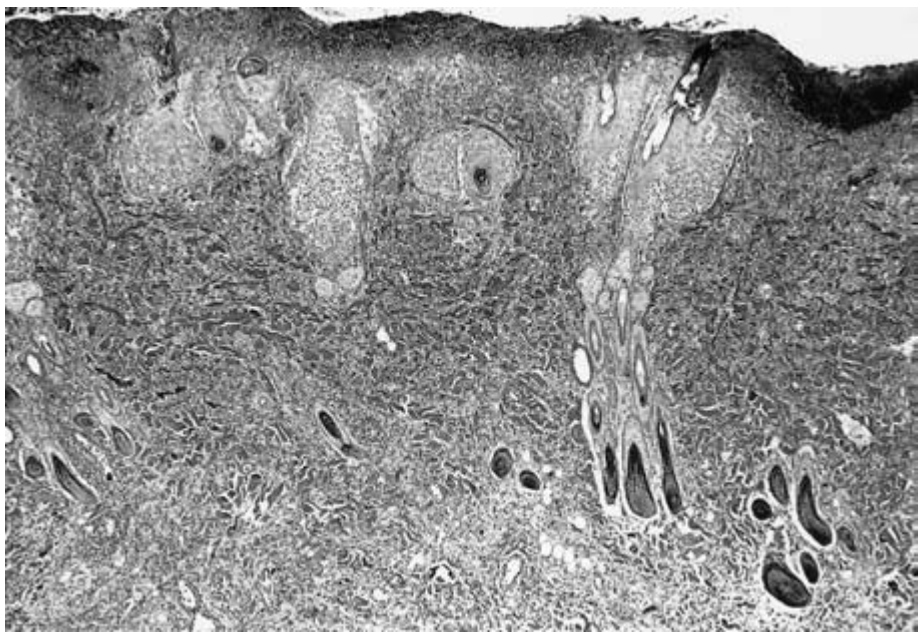


Fig. 6.12 Feline eosinophilic plaque. Diffuse severe dermal inflammation lies beneath extensive ulceration and exudation. Pallor of the remaining superficial follicular epithelium is due to spongiosis and mucinosis.

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Fig. 6.13 Feline mosquito bite hypersensitivity. A striking, well-demarcated, erythematous lesion with swelling, alopecia, erosion, ulceration, and exudation has developed rapidly on the dorsal muzzle. Note that the planum nasale is affected.



Fig. 6.14 Acute feline mosquito bite hypersensitivity demonstrating focal swelling, erosion, and ulceration of the dorsal muzzle and planum nasale accompanied by alopecia.

Dermal inflammation consists of variably intense, usually diffuse infiltrations of eosinophils, which extend to the middle (follicular) dermis, but also commonly reach the superficial panniculus (see Chapter 14).

The severe ulceration and depth of eosinophilic inflammation of some eosinophilic plaques may resemble feline mosquito bite hypersensitivity, feline indolent ulcer (eosinophilic type), and feline herpesvirus ulcerative dermatitis (eosinophilic type). The diffuse prominent spongiosis and mucinosis of typical eosinophilic plaque are not observed in these other conditions. Eosinophilic degranulation, or flame figure formation, is not observed in eosinophilic plaque, as in the other diseases (see Chapter 14).

Eosinophilic plaque is qualitatively similar to allergic miliary dermatitis, but is more dramatically spongiotic, mucinotic, inflamed, and ulcerated, and involves a larger expanse of skin. Since eosinophilic plaque and miliary dermatitis both may be manifestations of allergic skin disease in the cat (and can exist concurrently), histopathologic separation may not be critical diagnostically

FELINE MOSQUITO BITE HYPERSENSITIVITY

(Synonym: feline insect bite hypersensitivity)

Clinical features (Figures 6.13 and 6.14)

Feline mosquito bite hypersensitivity is a visually distinctive, relatively uncommon, predominantly facial, allergic skin disease associated with mosquito bites. Lesions have been documented to occur at the exact site of previous mosquito bites (Mason & Evans, 1991). It is not known if the same reaction pattern can be seen with the bite of other flying insects. The clinical and histologic features of this syndrome were described before the etiology was known (Wilkinson & Bates, 1982).

Similar to mosquito bite allergy in humans, allergy in cats likely involves both immediate and delayed hypersensitivity. Intradermal testing and Prausnitz–Kustner (PK) testing (injecting serum from a putatively allergic animal intradermally into a test animal and then performing intradermal skin testing at that specific site) have confirmed immediate hypersensitivity in affected cats (Nagata & Ishida, 1997). Concomitant delayed hypersensitivity has been inferred by the clinical reaction pattern (Nagata & Ishida, 1997).

The syndrome follows the classic seasonal pattern of mosquito bite hypersensitivity in humans, characterized by development of lesions in the summer and regression during autumn (Wilson & King, 1999). Further, the syndrome has been seen predominantly in cats allowed outdoors, and lesions resolve when strict indoor confinement is instituted (Mason & Evans, 1991). Diagnosis of feline mosquito bite hypersensitivity is highly regional; frequency of occurrence varies from uncommon in most areas to endemic in some locales. Highly variable frequency of occurrence among different geographic regions that support mosquito populations suggests that only some species of mosquito may induce hypersensitivity.

In humans, mosquitoes display preference for darker skin over lighter skin, younger over older skin, warmer over cooler skin, and scented over unscented victims (Wilson & King, 1999). Similarly, preference for darker hair coat or skin color occurs in cats (Nagata & Ishida,

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1997). This color preference may determine site predilections. In one study in Japan, many more cats displayed darker coat coloring on the pinnae than the muzzle; the pinnae were affected more frequently (Nagata & Ishida, 1997). The affected body regions also are relatively less haired and thus presumably are attractive targets for flying insects.

The most common clinical feature of feline mosquito bite hypersensitivity may be miliary dermatitis affecting both pinnae (Nagata & Ishida, 1997). However, this clinical presentation is less visually distinctive, and clinicians are less likely to biopsy pinnae. A partially symmetrical, erythematous facial eruption with papules and crusting may precede the more severe and characteristic lesions of rapidly progressive, strikingly well-demarcated, bilaterally symmetric facial swelling, alopecia, erosion, ulceration, and exudation (Ihrke & Gross, 1995). Fistulation may develop. Hyperpigmentation or hypopigmentation may be sequela to active disease, and firm, hyperpigmented nodules may be present in chronic cases. The planum nasale, periorbital region, and pinnae may be affected. Disease may be more widespread, and may affect the flexor surfaces of the carpi and the junction of pawpads and adjacent skin (Power & Ihrke, 1995). Bilateral symmetry is marked.

Regional lymphadenopathy is common. Pruritus usually is moderate, but may be severe. Occurrence of the disease coincides with the mosquito season of the region, and lesions may increase in severity over subsequent years of exposure.

Short-coated, free-roaming cats seem to be predisposed, which probably correlates with increased opportunity for exposure and easier mosquito access to the skin of short-haired animals (Nagata & Ishida, 1997). Age or sex predilections have not been noted.

Clinical differential diagnoses for the milder papular and crusting form of pinnal and facially-oriented dermatitis mirror those of feline allergic miliary dermatitis (see p. 118). More severe, classical mosquito bite hypersensitivity affecting the muzzle and pinnae is visually highly distinctive. The major clinical differential diagnosis is feline herpesvirus ulcerative dermatitis (see p. 124). Some cases may resemble pemphigus foliaceus or squamous cell carcinoma. Histopathology will often suggest the diagnosis, but definitive diagnosis is based on the resolution of clinical signs following elimination of exposure to mosquitoes.

Biopsy site selection

Multiple specimens should be taken from affected areas. Because lesions are mostly confined to sparsely haired, highly vascular facial areas that bleed easily and readily show scars, small specimens should be procured carefully. Four millimeter biopsy punches are cosmetically advantageous for the muzzle or pinnae of cats. Care should be taken not to damage underlying cartilage if the pinna is sampled. Periorbital lesions should not be sampled to avoid scarring at the lid margins.

Histopathology (Figure 6.15)

There is moderate acanthosis with variable erosion, ulceration, and exudation. Serum exudation and crusting may be severe. The intact epidermis and superficial hair follicles are acanthotic and mildly spongiotic. Epidermal and follicular mucinosis rarely is observed. The dermis has severe eosinophilic inflammation; eosinophils often degranulate to form flame figures, sometimes within follicular walls, or rarely, lumens (see Chapter 14).

Differential diagnoses for the ulcerative lesions of feline mosquito bite hypersensitivity, occurring in the context of eosinophilic dermatitis, include eosinophilic plaque, eosinophilic indolent ulcer, and feline herpesvirus ulcerative dermatitis (eosinophilic type). Eosinophilic plaque features more profound spongiosis and mucinosis of intact epidermis and superficial hair follicles; indolent



Fig. 6.15 Feline mosquito bite hypersensitivity demonstrating severe ulceration and exudation above intense dermal inflammation.

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Fig. 6.16 Feline herpesvirus ulcerative dermatitis. Ulcers covered by an adherent thick crust are present on the dorsal muzzle. Note that the planum nasale is affected. (Photograph courtesy C.A. Outerbridge; case material University of California, Davis.)



Fig. 6.17 View of the cat in Fig. 6.16 with adherent crust removed. (Photograph courtesy C.A. Outerbridge; case material University of California, Davis.)

ulcer often has eosinophilic degranulation in or just beneath the ulcer bed. Herpesvirus ulcerative dermatitis may be indistinguishable from mosquito bite hypersensitivity if inclusion bodies cannot be identified. These cases may require clinical differentiation or immunohistochemical or polymerase chain reaction (PCR) detection of viral infection.

FELINE HERPESVIRUS ULCERATIVE DERMATITIS

Clinical features (Figures 6.16 and 6.17)

Feline herpesvirus ulcerative dermatosis is an uncommon, predominantly facial feline skin disease caused by herpesvirus infection. Testing by polymerase chain reaction (PCR) and DNA sequencing recently showed that the virus recovered from cats with this facial skin disease was indistinguishable from feline herpesvirus 1 (Hargis et al., 1999). Feline herpesvirus 1 is known to cause upper respiratory tract disease, including rhinotracheitis and conjunctivitis. Similar to other species, feline herpesvirus 1 is believed to establish latency in the trigeminal ganglia (Hargis et al., 1999). Affected cats may have a history of upper respiratory disease and/or show chronic signs such as sneezing or excess tearing. Both stress and immunosuppression commonly have been implicated as triggers for herpesvirus infection. Associations with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infection were not noted, although preceding glucocorticoid therapy and environmental stresses were hypothesized as possible triggers in eight of ten cats evaluated (Hargis et al., 1999). Although skin disease associated with herpesvirus infection has been reported previously, this syndrome is distinct in that lesions are focal, seen predominantly on the face, and are usually characterized by marked tissue eosinophilia (Hargis et al., 1999).

Clinical lesions are striking, but vary greatly in severity. The disease is most commonly characterized by erosion and ulceration of the face. Erythema, swelling, exudation, and erosion or ulceration occur to variable degrees. Adherent crusts may mat the haircoat. Vesicles have been reported (Hargis & Ginn, 1999). The dorsal and lateral muzzle, and the periorbital regions most commonly are involved. The planum nasale may be affected. A small percentage of cats may exhibit bilaterally symmetric facial lesions mimicking autoimmune skin disease. Although most cats have lesions confined to the face, other body regions including the distal extremities and the trunk may be affected in some cases. Lesions on the distal forelegs may reflect direct contact during grooming of the face.

Regional lymphadenopathy may be seen. Lesions may be painful or pruritic. One of ten cats initially reported exhibited coexistent proliferative and ulcerative stomatitis (Hargis et al., 1999).

The age range of cats reported is between 4 months and 16 years, with an average age of 4.5 years. Sex or breed predilections were not noted (Hargis et al., 1999).

Clinical differential diagnoses include mosquito bite hypersensitivity, food allergy with facial predominance,

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pemphigus foliaceus, and neoplasia such as squamous cell carcinoma. Previously, cats with feline herpesvirus ulcerative dermatitis may have been misdiagnosed as having mosquito bite hypersensitivity or other eosinophilic feline skin diseases. Exacerbation of lesions following glucocorticoid therapy due to erroneous diagnosis may, in fact, be an important clue as to the true etiology.

Biopsy site selection

Both nonulcerated erythematous lesions and ulcers should be sampled. Four millimeter biopsy punches are cosmetically advantageous for the muzzle of cats. Periorbital lesions should not be sampled to avoid scarring at the lid margins.

Histopathology (Figures 6.18 through 6.20)

Severe necrosis and ulceration of the epidermis with extension of necrosis into the underlying dermis typifies feline herpesvirus ulcerative dermatitis. There is generally massive exudation to form large superficial crusts. The epidermis adjacent to the ulcer is acanthotic. There may be severe spongiosis, and occasionally superficial



Fig. 6.18 Feline herpesvirus ulcerative dermatitis featuring a large, deep ulcer with extensive crusting.

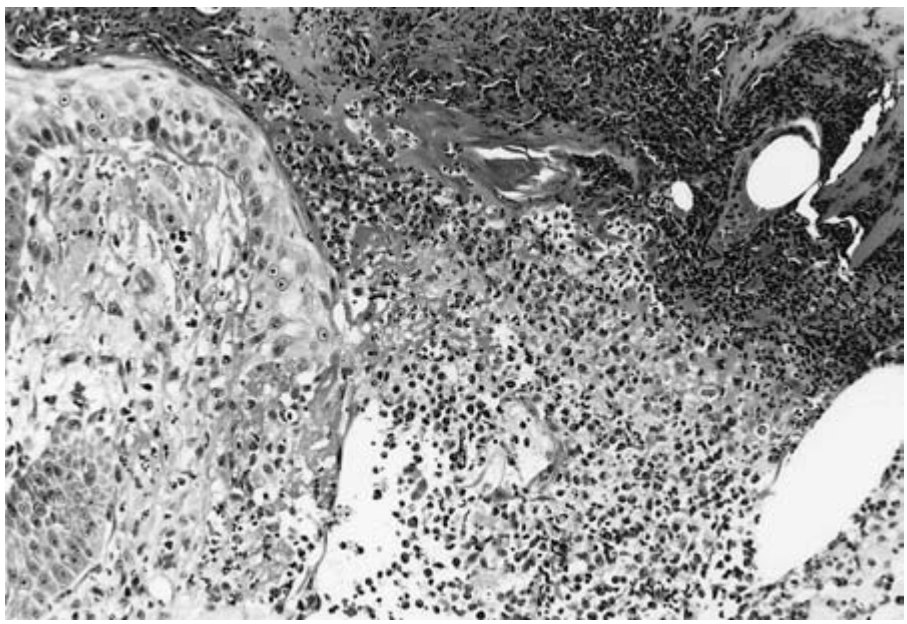


Fig. 6.19 Higher magnification of feline herpesvirus ulcerative dermatitis. Eosinophils are abundant within the ulcer bed; note necrosis and degeneration of marginal epithelium.

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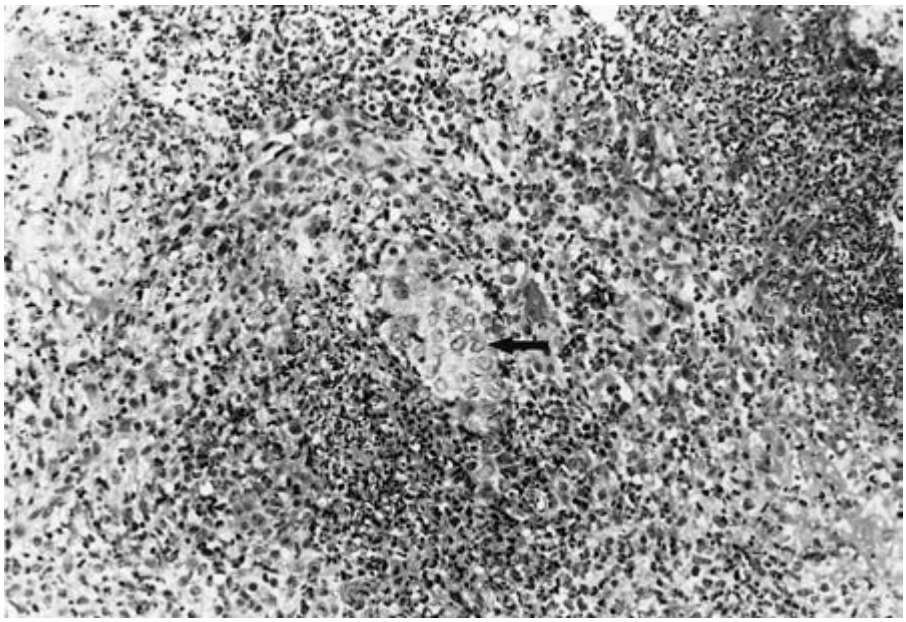


Fig. 6.20 Higher magnification of feline herpesvirus ulcerative dermatitis. Note intranuclear inclusions (arrow) within epithelial island in sea of necrosis.

vesiculation is seen. Necrosis and spongiosis extend into superficial follicles, often to the level of the isthmus. Intact follicular infundibular epithelium is hyperplastic. Necrotic epithelium is brightly eosinophilic and coagulated. Eosinophils often migrate into necrotic epithelium of the follicular wall and degranulate there. This may result in linear follicular 'casts' surrounding central hairs.

Intranuclear inclusion bodies may not be present in all cases. These are best identified in intact epithelium immediately adjacent to foci of necrosis, including within superficial hair follicles. In foci of deeper necrosis, inclusions may be striking within sebaceous glands. Inclusions in these glands are easy to identify as they are brought into relief by the highly contrasting, pale cytoplasm of the affected sebocytes. Islands of intact, inclusion-bearing adnexal epithelial cells within a sea of necrosis may be observed. Inclusions are lightly basophilic to amphophilic and have a smudged or homogenous appearance. There is margination of nuclear chromatin. Electron microscopic examination revealed virions compatible with herpesvirus within inclusions (Hargis et al., 1999).

Since herpesvirus inclusion bodies may be difficult to identify with routine histopathology, testing by PCR may be useful (Hargis et al., 1999; Suchy et al., 2000); however, access to this test may be limited in some areas. Polymerase chain reaction testing targeting the thymidine kinase gene is positive for feline herpesvirus 1 in fortuitous samples. DNA sequencing indicated a polymerase gene identical to feline herpesvirus 1 (Hargis et al., 1999). Immunohistochemistry for feline herpesvirus is also commercially available, but is not as sensitive as PCR.

The dermis is intensely and diffusely inflamed, usually with eosinophils. Occasionally, neutrophils predominate. There may be foci of eosinophilic degranulation (flame figures) within the dermis (see Chapter 14).

Differential diagnoses for the ulcerative lesions of eosinophilic feline herpesvirus dermatitis in which inclusion bodies are not recognized include eosinophilic plaque, mosquito bite hypersensitivity, and eosinophilic indolent ulcer. Eosinophilic plaque features more profound spongiosis and mucinosis of intact epidermis and superficial hair follicles. Indolent ulcer often has eosinophilic degranulation in or just beneath the ulcer bed, a feature not found in herpesvirus ulcerative dermatitis. Herpesvirus ulcerative dermatitis may be indistinguishable from mosquito bite hypersensitivity if inclusion bodies cannot be identified. These cases may require clinical differentiation or immunohistochemical or PCR detection of viral infection.

Differential diagnoses for neutrophilic herpesvirus ulcerative dermatitis are few. The inflammatory pattern could be indicative of chronic bacterial infection or trauma with infection. Inclusion bodies allow definitive diagnosis; if these are absent, correlation with clinical findings, immunostaining, or testing by PCR may be required. The lesions of feline cowpox virus infection are superficially similar to those of neutrophilic herpesvirus ulcerative dermatitis, particularly on low power examination. The presence of typical inclusion bodies of poxvirus infection are diagnostic.

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Fig. 6.21 Feline cowpox virus infection. Ulcers are visible on the face, tip of the pinna, and in the groin. (Photograph courtesy J. Declercq.)



Fig. 6.22 Closer view of the cat in Fig. 6.21. Ulcerated plaques affect the dorsal muzzle, planum nasale, philtrum, and tip of the pinna. (Photograph courtesy J. Declercq.)



Fig. 6.23 Closer view of the cat in Fig. 6.21. Disseminated ulcerated plaques affect the groin and ventral abdomen. (Photograph courtesy J. Declercq.)

FELINE COWPOX VIRUS INFECTION

Clinical features (Figures 6.21 through 6.23)

Feline cowpox virus infection is an uncommon to rare regional viral dermatosis caused by the cowpox poxvirus (Bennett et al., 1998). This disease is diagnosed most commonly in the United Kingdom, but has been reported in The Netherlands, Belgium, Austria, Germany, Italy, and France (Guaguère & Declercq, 2000). The disease is very rare in North America. Reservoir hosts in Europe include voles, wood mice, ground squirrels, and gerbils (Bennett et al., 1998). Consequently, feline cowpox virus infection is seen predominantly in rural outdoor cats that hunt rodents and presumably receive bite wounds (Bennett et al., 1998). Summer and autumn seasonal occurrence is especially marked in the United Kingdom (Guaguère & Declercq, 2000). Cowpox is a rare zoonosis that can cause severe systemic illness including death (Bennett et al., 1998).

Cutaneous clinical signs in the cat include an initial primary lesion, usually an ulcerating, erythematous, crusted macule or plaque that occurs most frequently on the head, neck or forelegs. Secondary lesions develop within 10 days following viremia, and include disseminated macules, papules, and nodules (Guaguère & Declercq, 2000). Ulcers of the mouth and tongue develop in a minority of cats (Guaguère & Declercq, 2000). Secondary bacterial infection may occur. Systemic signs can include pyrexia, inappetence, and depression (Bennett et al., 1998). Breed, age, or sex predilections have not been reported (Bennett et al., 1998).

Clinical differential diagnoses include bacterial and fungal infections, and neoplasia such as mast cell tumors, lymphoma, or feline progressive dendritic cell histiocytosis (see Chapter 35). Impression smears of ulcerated lesions may reveal intracytoplasmic eosinophilic inclusion bodies (Guaguère & Declercq, 2000); histopathology is generally diagnostic. Viral isolation may be performed on dried crusts, but this test is available only in specialized laboratories. Electron microscopy also may be confirmative.

Biopsy site selection

Biopsy specimens should be obtained from within the margins of recent lesions (Guaguère & Declercq, 2000). Early, intact lesions are more likely to yield a definitive diagnosis.

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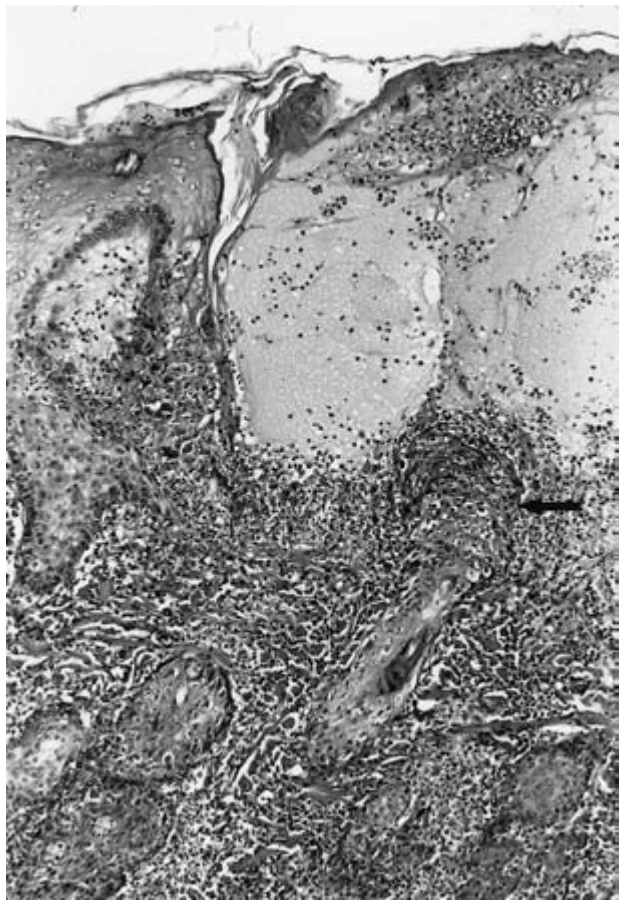


Fig. 6.24 Severe ulceration and serocellular exudation of feline cowpox virus infection. Inclusion bodies are in a hair follicle at the base of the ulcer (arrow). (Case material courtesy J. Declercq.)

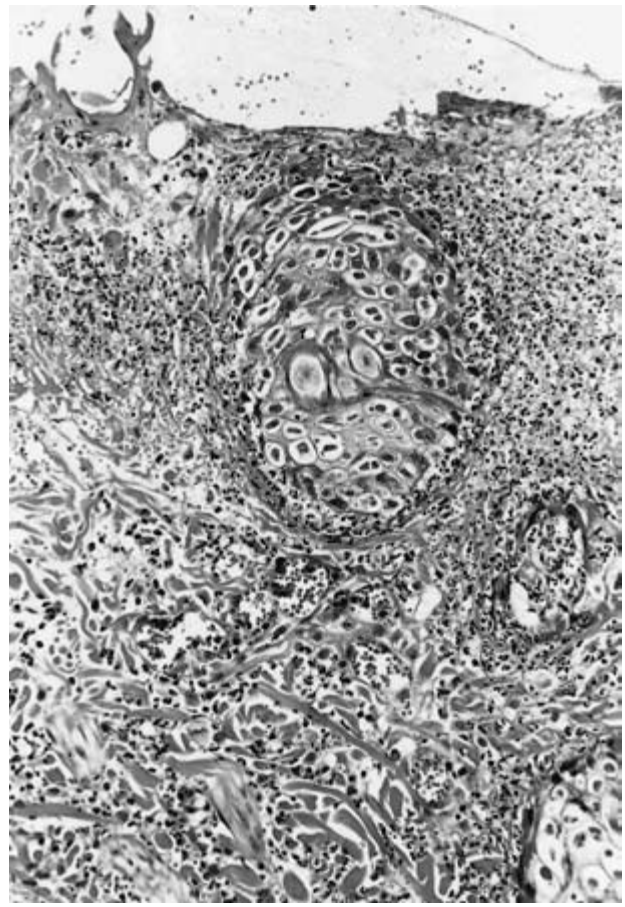


Fig. 6.25 Higher magnification of feline cowpox virus infection. Note large inclusion bodies within ballooned keratinocytes of hair follicle at center. (Case material courtesy J. Declercq.)

Histopathology (Figures 6.24 and 6.25)

Feline cowpox infection is characterized by severe ulceration. There is moderate to severe serocellular crusting. Ballooning degeneration of keratinocytes affects the adjacent intact epidermis and superficial hair follicles. There are usually numerous, large intracytoplasmic, brightly eosinophilic inclusions of variable size (type A inclusion bodies). These vary from round to elongated and even angular, and have a somewhat refractile staining quality. Ballooning leads to frank necrosis of epidermal and superficial follicular epithelium accompanied by infiltration of neutrophils. Necrotic tissue, including within surface exudate, may contain ghosts of inclusion bodies.

The dermis has neutrophilic inflammation, accompanied by macrophages, lymphocytes and scattered eosinophils. Inflammation extends to the deep dermis, and in severely ulcerated lesions, to the panniculus.

The lesions of feline cowpox virus infection are superficially similar to those of feline herpesvirus ulcerative dermatitis, particularly on lower magnification. The presence of typical inclusion bodies of poxvirus infection is diagnostic.

FELINE INDOLENT ULCER

(Synonyms: feline eosinophilic ulcer, rodent ulcer)

Clinical features (Figures 6.26 and 6.27)

Feline indolent ulcer is a common feline syndrome or reaction pattern of uncertain etiology. An underlying allergic hypersensitivity is suspected frequently, but is less commonly documented. Flea allergy dermatitis, atopic dermatitis, and food allergy have been linked to the development of feline indolent ulcer. Further, feline indolent ulcers have responded to flea control, allergen specific immunotherapy, and elimination diets. Five of eight cats with experimentally-induced flea allergy dermatitis devel-

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Fig. 6.26 Feline indolent ulcer. A well-demarcated, dish-like ulcer with an elevated margin is present at the mucocutaneous junction of the upper lip just lateral to the philtrum.



Fig. 6.27 Severe feline indolent ulcer. Bilateral ulcers have become confluent to involve most of the upper lip.

oped feline indolent ulcers of the lip in one recent study (Colombini et al., 2001). Feline indolent ulcers were shown to commonly coexist with feline eosinophilic granuloma in a closed, inbred colony of cats (Power & Ihrke, 1995). Those cats had not had exposure to fleas or other ectoparasites, and could not be documented with either atopic dermatitis or food allergy by intradermal skin testing and elimination diets.

Well-demarcated, concave ulcers with an elevated margin develop from focal areas of intense erythema. The elevated margins are firm and have an unusual orange-tan color, while the central ulcerated area is granular and colored whitish-yellow or salmon. Lesions vary in size from 2 mm to 5 cm. The most common site is the juncture of the skin and mucous membrane of the upper lip apposing the lower canine tooth, just lateral to the philtrum. Lesions usually are solitary and unilateral, but may be bilateral. They occasionally become confluent to involve most of the upper lip. Rarely, similar lesions may develop at other sites, especially the hard palate. Palatine lesions may cause tissue destruction with arteriole damage leading to hemorrhage (Mason & Burton, 2000). One author (T.L.G.) has seen histologically identical interdigital lesions of one foot, occurring concurrently with classical lip ulceration.

Indolent ulcers usually are asymptomatic, although regional lymphadenopathy may be present. Malignant transformation to squamous cell carcinoma has been noted (Scott et al., 2001), but the authors have not observed this phenomenon. Breed or age predilections have not been reported. Females may be at increased risk (Scott et al., 2001).

Although indolent ulcers are usually visually distinctive, clinical differential diagnoses should include neoplasms such as squamous cell carcinoma or mast cell tumor, as well as ulcers associated with underlying fungal granulomas. Since malignant tumors or fungal granulomas may mimic indolent ulcers, skin biopsy is indicated for clinically atypical lesions.

Biopsy site selection

Deep punch biopsy is recommended in order to include deep tissue beneath the ulcer. General anesthesia usually is advisable since hemostasis may be problematic in this location.

Histopathology (Figure 6.28)

Sequential sampling of feline indolent ulcers from a related group of specific pathogen-free cats showed variation in the histopathologic appearance over time, as subsequently reported (Power & Ihrke, 1995). Acute lesions (48 to 96 hours) are moderately to severely ulcerated with minimal underlying necrosis. Chronic lesions exhibit severe ulceration of the epidermis or mucosa with underlying necrosis and eosinophilic degranulation. The intact epidermis is hyperplastic at all stages, and is variably spongiotic. Dermal inflammation is deep and eosinophil-rich (see Chapter 14).

Random specimens from cats affected with classical upper lip ulcers are similar to those of the specific

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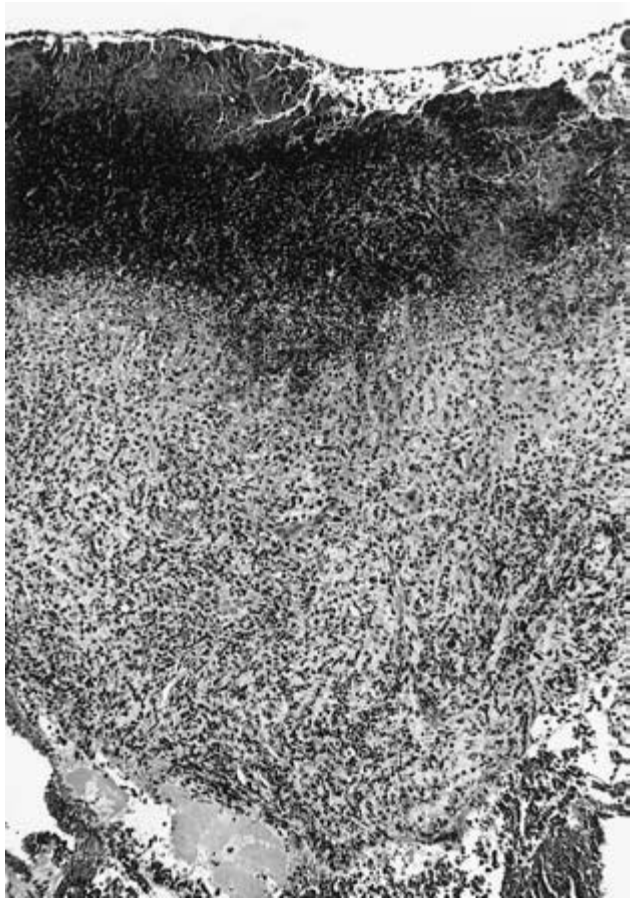


Fig. 6.28 Feline indolent ulcer. Severe exudation, ulceration, and necrosis overlie deep inflammation.

pathogen-free cats observed. Field cases demonstrate similar severe ulceration and exudation as well as deep and severe eosinophilic inflammation (see Chapter 14). Superficial eosinophilic degranulation may occur, creating a brightly eosinophilic band in the ulcer bed. Neutrophilic inflammation reportedly may predominate (Colombini et al., 2001); however, this variation is extremely rare in the authors' experience; only a single case has been observed.

Differential diagnoses for eosinophilic indolent ulcers include herpesvirus ulcerative dermatitis (eosinophilic type), mosquito bite hypersensitivity, or severely ulcerated eosinophilic plaque. Eosinophilic plaque features prominent epidermal and follicular spongiosis and mucinosis that are absent in indolent ulcers. Indolent ulcers generally exhibit eosinophilic degranulation within or beneath ulcer beds, rather than the deeper, often folliculocentric degranulation observed with mosquito bite hypersensitivity or herpesvirus ulcerative dermatitis (see Chapter 14); herpesvirus inclusions also may allow differentiation. Neutrophilic indolent ulcers resemble idiopathic ulcerative dermatosis or pyotraumatic dermatitis, the latter being very rare in cats. Idiopathic ulcerative dermatosis is much less inflamed than indolent ulcer.



Fig. 6.29 Feline idiopathic ulcerative dermatosis in a kitten. An oval, well demarcated ulcer developed rapidly between the shoulder blades.

FELINE IDIOPATHIC ULCERATIVE DERMATOSIS

(Synonym: chronic ulcerative dermatitis with linear subepidermal fibrosis)

Clinical features (Figures 6.29 and 6.30)

Feline idiopathic ulcerative dermatosis is an uncommon syndrome of unknown etiology. A hypersensitivity reaction to subcutaneously injected medication or vaccine has been proposed because of site predilection for the region between the scapulae and adjacent dorsal neck, which are popular injection sites in cats (Mason & Rosser, 1990). However, the syndrome has been seen in cats that apparently have never received injections in these locations. The dorsal neck of cats is a region with unusually dense aggregations of sensory nerves. It is tempting to speculate that overstimulation of these nerve endings due to multiple and various causes may initiate this syndrome. A behavioral component may be present.

The prime clinical feature is a focal area of alopecia containing a well-demarcated ulcer with adherent necrotic debris. Peripheral swelling and erythema may be present. Chronic lesions exhibit a firm elevated border.

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Lesions usually are solitary and range from 2 to 5 cm in diameter. The site is highly characteristic; the lesions are seen almost exclusively on the dorsal thoracic midline between the scapulae, or on the dorsal neck.

The presence of pain or pruritus is variable and difficult to determine. Cats intermittently maniacally self-traumatize the lesion. Regional lymphadenopathy is noted occasionally, but systemic signs are not present. Age, breed, or sex predilections have not been noted.



Fig. 6.30 Closer view of Fig. 6.29. The ulcerated lesion is alopecic, erythematous, and crusted.

Clinical differential diagnoses are few as this syndrome is visually highly distinctive. A thermal or chemical burn or other physical trauma at this site might appear similar.

Biopsy site selection

Since surgical ablation may be curative, complete and deep resection always should be considered. Wedge biopsy is preferred over punch biopsy since wedge specimens obtained from the margins of ulcers will more easily include both the ulcer and adjacent skin. Subcutaneous tissue should be included since a reaction to vaccine or other subcutaneously injected medications has been hypothesized.

Histopathology (Figures 6.31 and 6.32)

The epidermis is extensively ulcerated, and necrosis extends to the superficial dermis. The intact epidermis at the borders of the ulcer is acanthotic. The necrotic dermis may have a coagulated appearance, and the ulcer bed often contains a layer of devitalized epidermal or superficial dermal tissue embedded with degenerating neutrophils. Characteristically, the adjacent and subjacent viable dermis is minimally inflamed. Low numbers of neutrophils and a few mixed mononuclear cells may be present. Eosinophils are rare.

There may be subepidermal superficial and laminar fibrosis in lesions of several months' duration. This fibrosis extends as a band beneath the adjacent acanthotic epidermis. Subepidermal laminar (linear) fibrosis was first reported as a consistent feature of idiopathic ulcerative

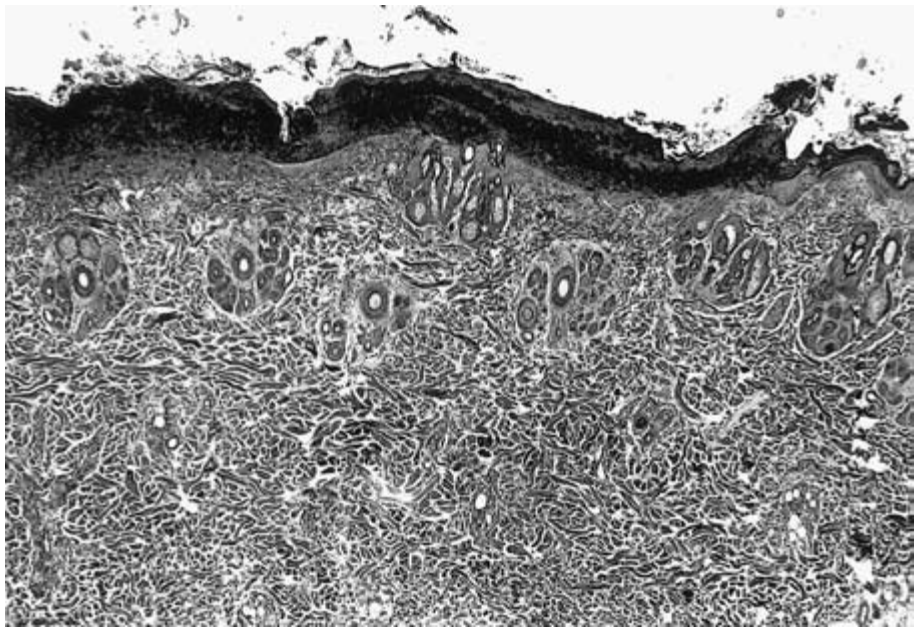


Fig. 6.31 Feline idiopathic ulcerative dermatosis. Extensive ulceration is accompanied by prominent exudative crusting.

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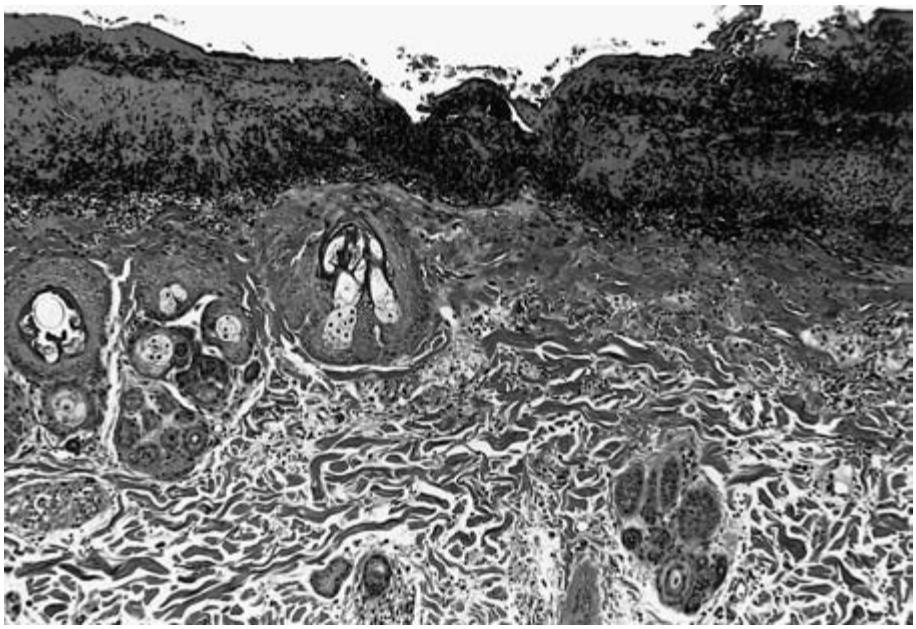


Fig. 6.32 Higher magnification of feline idiopathic ulcerative dermatosis. Note deep extension of necrosis to the level of the isthmus of hair follicles.

dermatosis (Scott, 1990), but those cats had longstanding lesions of 6 months to a year. Subepidermal laminar fibrosis has not been observed in earlier lesions.

Idiopathic ulcerative dermatosis should be differentiated from pyotraumatic dermatitis (very rare in cats), or the neutrophilic form of indolent ulcer. In general, the inflammation of idiopathic ulcerative dermatosis is milder that these. Clinical differentiation may be required.

CANINE PYODERMA GANGRENOSUM

Clinical features (Figures 6.33 and 6.34)

Canine pyoderma gangrenosum is a very rare, destructive, idiopathic sterile inflammatory disease that has been observed rarely in dogs. It is characterized by painful pustules or nodules that become necrotic, ulcerate, and drain. Highly similar clinical and histopathologic features, including association with underlying systemic disease, are shared between canine and human pyoderma gangrenosum.

The etiopathogenesis of pyoderma gangrenosum is unknown in both the dog and in humans. Growing evidence in human medicine suggests a disturbance of cellular immune function, including impaired neutrophil function (Wolff & Stingl, 2003). Response to a variety of immunomodulatory and immunosuppressive treatments lends credence to this theory. In humans, pyoderma gangrenosum may either be idiopathic and confined to the skin (50–60% of cases) or associated with underlying systemic disease such as Crohn's disease, ulcerative colitis, polyarthritis, monoclonal gammopathy, and myeloproliferative disorders (Wolff & Stingl, 2003; Crowson et al., 2003). More rarely, pyoderma gangrenosum in humans has been linked with laparotomy, other surgery, insect bites, and various drugs including potassium iodide (Wolff & Stingl, 2003). Canine pyoderma gangrenosum has been tentatively and putatively associated with ovariohysterectomy in an obese dog, myelogenous leukemia, and to presumptive emerging lymphoma. The cause has not been discovered in other cases.



Fig. 6.33 Canine pyoderma gangrenosum in a Boxer. Multifocal, moderately well-circumscribed ulcerated lesions are present on the trunk. (Photograph courtesy K. Fostvedt.)

Clinical features include multifocal, moderately well-circumscribed, large, dark, boggy subepidermal pustules and nodules that ulcerate, fistulate, and drain seropurulent exudate. Well-defined ulcers centralize on less distinct

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nodules. Lesions may be indolent or gradually progressive, and have been predominantly truncal in distribution. Affected dogs may be febrile and have malaise.

Signalment predilections have not been noted to date in the small number of cases seen. In humans, autosomal dominant inheritance has been described in some patients (Wolff & Stingl, 2003).

Clinical differential diagnoses include infectious ulcerative skin disease, such as deep bacterial folliculitis and furunculosis, deep fungal infection, and lesions caused by necrotoxins such as the venom of brown recluse spiders. Reactive histiocytosis may present with similar crateriform ulcers. Canine pyoderma gangrenosum is diagnosed

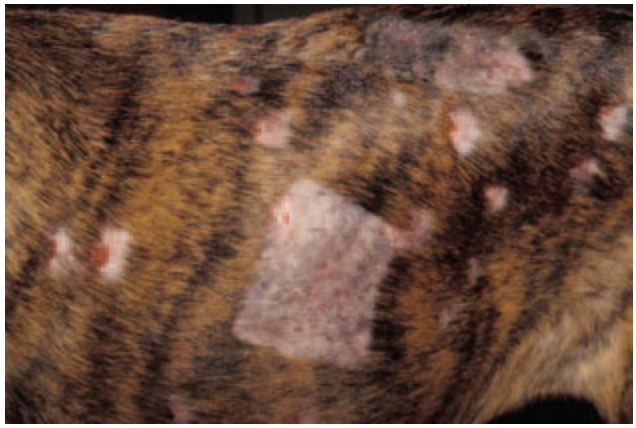


Fig. 6.34 Closer view of Fig. 6.33. Lesions ulcerate, fistulate, and drain seropurulent exudate. (Photograph courtesy K. Fostvedt.)

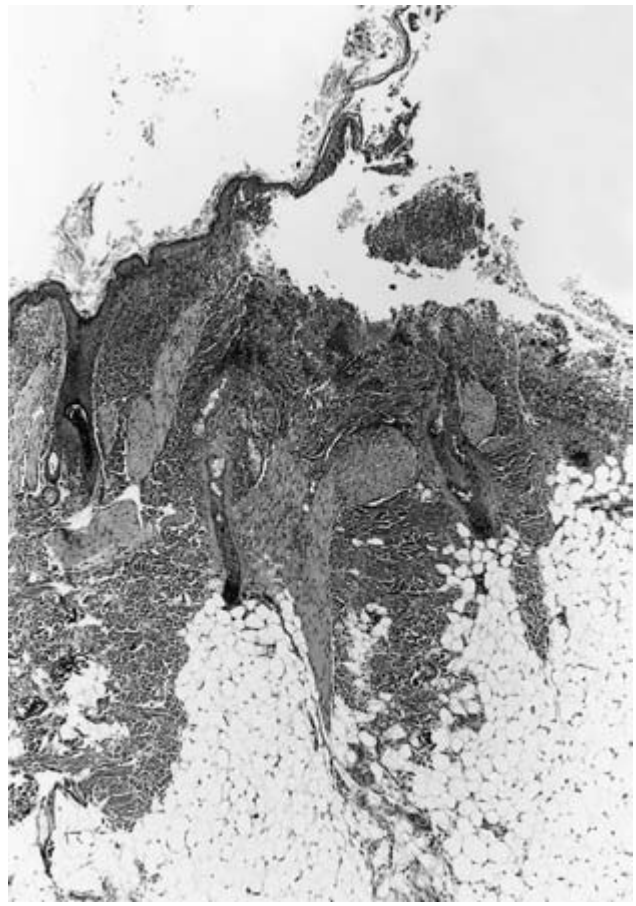


Fig. 6.35 Canine pyoderma gangrenosum demonstrating early rupture of a large dermal pustule to form an ulcer.



Fig. 6.36 Large crateriform ulcer ablating the dermis in an advanced lesion of canine pyoderma gangrenosum. Note inflamed fat of the panniculus in the ulcer bed.

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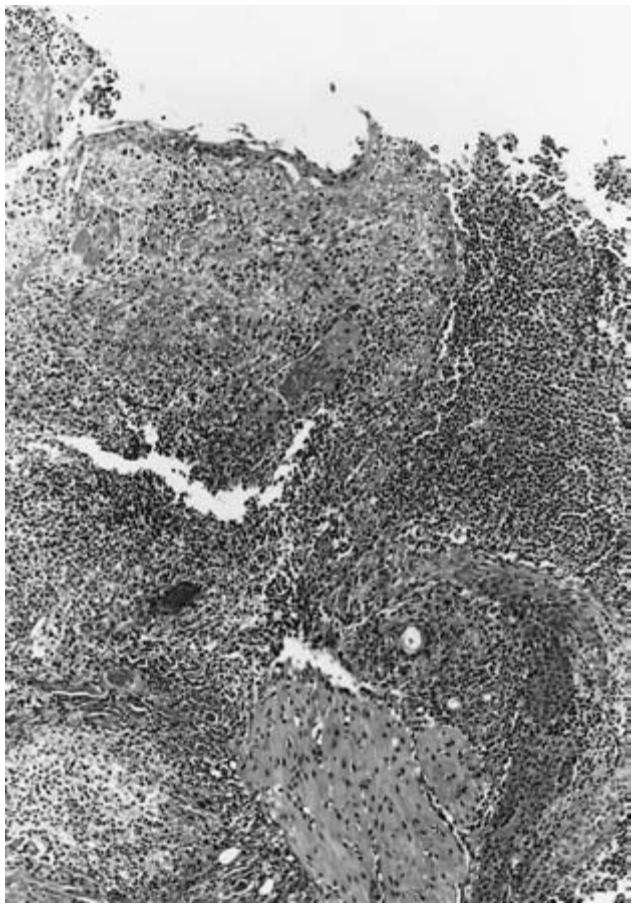


Fig. 6.37 Higher magnification of ulcer of canine pyoderma gangrenosum. Note intense neutrophilic inflammation and exudation.

by compatible clinical features, supportive histopathology, plus ruling out ulcerative disease of infectious etiology. Links to underlying systemic disease in the majority of dogs seen to date dictates a thorough medical evaluation in all suspected cases of pyoderma gangrenosum.

Biopsy site selection

Multiple biopsy specimens should be taken from ulcerated and intact nodules or pustules. Additionally, specimens should be obtained with sterile technique for aerobic and anaerobic bacterial culture and fungal culture.

Histopathology (Figures 6.35 through 6.37)

Microscopically, there are large crateriform ulcers that frequently penetrate to the deep dermis or panniculus. The ulcer bed may be covered with a crust of necrotic debris and neutrophils. Massive infiltrations of neutrophils are present throughout the remaining dermis beneath and adjacent to the ulcer, and extend into the subjacent panniculus frequently. A few eosinophils, lymphocytes, and macrophages are intermingled. There may be pronounced hemorrhage, edema, and fibrin exudation. The adjacent epidermis is acanthotic and may be spongiotic. Early lesions may be predominantly large, loosely organized dermal pustules with hemorrhage.

The crateriform ulcers of pyoderma gangrenosum are unique, and highly characteristic. Secondary deep ulceration and inflammation due to a spider bite might be considered as a differential diagnosis for pyoderma gangrenosum (see Chapter 14). Spider bite reactions are usually solitary, whereas lesions of pyoderma gangrenosum are multicentric in distribution. Early lesions may be very difficult to differentiate from bacterial pyoderma. Clinical differentiation may be important, including poor response to prolonged antibiotic therapy.

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Chapter 7

Hyperplastic diseases of the epidermis

Hyperplastic skin diseases are characterized by the proliferation of epidermal and follicular infundibular keratinocytes. Epithelial hyperplasia, or acanthosis, may be due to internal factors (metabolic, hereditary) or external injury (self-trauma). Changes in the keratin layer may occur, and in the case of chronic external trauma, it may undergo transition from a normal basketweave appearance to the denser laminated or compact patterns, with or without an increase in thickness (hyperkeratosis).

The diseases of this chapter are those in which hyperplasia is a primary and predominant pathologic feature. However, epidermal and follicular infundibular hyperplasia is a common and pervasive characteristic of chronic skin diseases of all causes. Thus, in general, its diagnostic specificity is limited. Differentiation among hyperplastic dermatoses requires the presence of other distinguishing features.

CHRONIC HYPERPLASTIC DERMATITIS

Clinical features (Figures 7.1 and 7.2)

Chronic hyperplastic dermatitis is seen primarily in the dog. Pruritus with attendant self-trauma is the unifying feature of many of the diseases characterized by chronic hyperplastic dermatitis histopathologically. Chronic allergy is the most common cause. The most beneficial reason for skin biopsy of suspected chronic hyperplastic dermatitis is to rule out other diseases with a more specific histopathologic appearance, such as occult neoplasia or endocrinopathy. Other chronic skin diseases such as pyoderma and cornification disorders, which frequently have pruritus as a component, may exhibit features of hyperplastic dermatitis.

Clinical changes in response to chronic self-trauma include alopecia, lichenification, and hyperpigmentation. Crusting is a common additional feature. Secondary surface bacterial overgrowth or *Malassezia* dermatitis may complicate chronic hyperplastic dermatitis. Breed and individual animal variation in the severity of lesions is considerable, as dramatically different degrees of lichenification and hyperpigmentation can be seen in response to similar amounts of self-trauma.

Clinical history and pattern of distribution often are helpful in differentiating amongst allergic skin diseases. Flea allergy dermatitis may be the most likely consideration if the dorsal lumbosacral area, groin, and caudal thighs are most severely affected. If chronic hyperplastic skin disease is most conspicuous on the head and distal extremities, underlying atopic dermatitis or food allergy should be suspected. Chronic allergic contact dermatitis, a rare disease, tends to involve the glabrous, exposed areas such as the muzzle, groin, axillae, ventral interdigital webs, and the perineum. The clinical differences between allergic skin diseases blur with chronicity, since the distribution pattern may become generalized.

Breed and age predilections may aid in the clinical differentiation of chronic hyperplastic dermatitis due to allergy. The reader is referred to the specific sections detailing allergic skin diseases (see Chapters 5 and 9).

Biopsy site selection

Biopsy site selection is not critical since clinical features of this histopathologic reaction pattern are uniform. Multiple specimens should be procured.

Histopathology (Figure 7.3)

Chronic hyperplastic dermatitis, sometimes referred to as the 'dermatitis reaction', is a very common histopathologic pattern in dermatopathology. Epidermal lesions of hyperplastic dermatitis include moderate to severe irregular acanthosis as well as thickening of the follicular infundibulum. Scalloping of the lower epidermal and outer follicular border may be present; in some cases this may signal accompanying *Malassezia* dermatitis (see p. 142). There is often transformation of normal basketweave keratin to compact keratin, and an overall increase in the keratin layer, or hyperkeratosis, may occur. In hyperplastic dermatitis due to allergy there may be patchy spongiosis and exocytosis of lymphocytes, neu-

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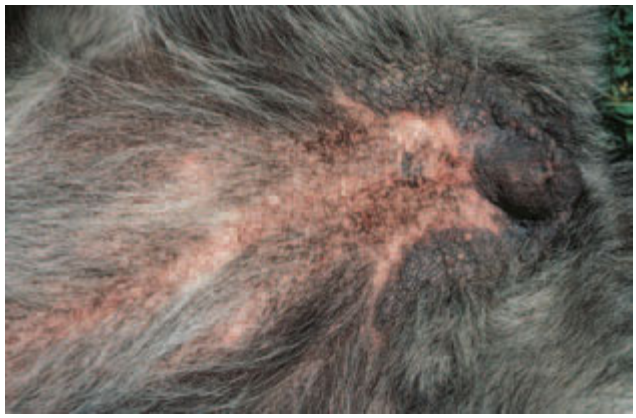


Fig. 7.1 Chronic hyperplastic dermatitis in a dog with flea allergy dermatitis. Lichenification, hyperpigmentation, and mottled erythema are present in the perivulvar region and the adjacent ventral abdomen. Note the cobblestone appearance of the lichenified, chronically traumatized lesions.



Fig. 7.2 Chronic hyperplastic dermatitis in the axillae of a dog with atopic dermatitis. Alopecia and lichenification alone are indicative of chronicity in a dog without the genetic propensity to hyperpigment.

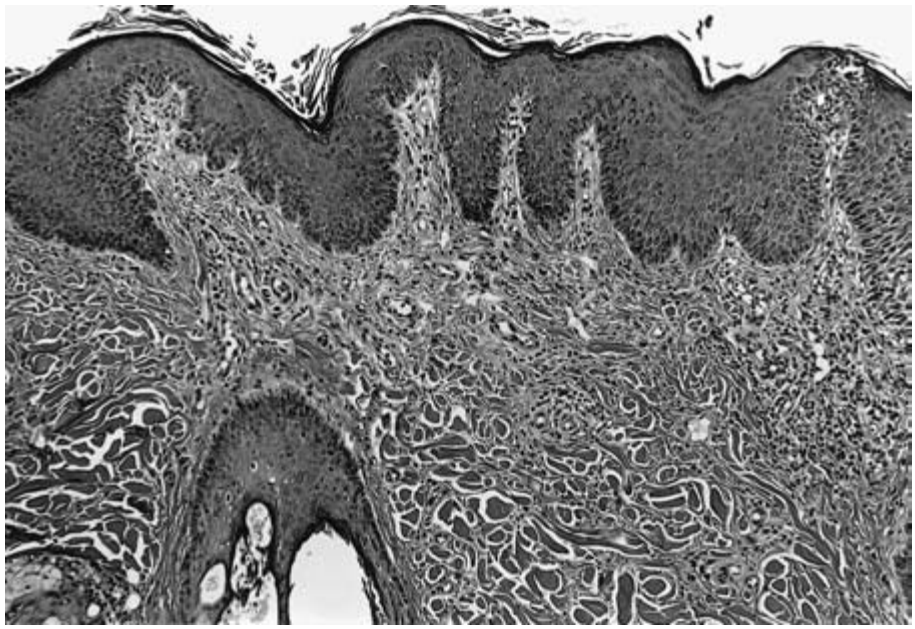


Fig. 7.3 Chronic hyperplastic dermatitis in a dog with flea allergy dermatitis. Irregular hyperplasia of the epidermis is accompanied by focal mild spongiosis at right.

trophils, or rarely eosinophils. This focal spongiosis and exocytosis may result in discrete parakeratotic scale with small, intermingled crusts of degenerated inflammatory cells (parakeratotic scale/crusts). Variable erosion, as well as discrete foci of superficial epidermal pustulation and crusting, also termed 'impetiginization', may be observed, and these lesions may be imbedded with colonies of staphylococci. *Malassezia* may colonize the keratin layer and are often best discovered within follicular ostia.

Dermal inflammation is perivascular to interstitial in most cases of chronic hyperplastic dermatitis. The inflammatory infiltrate is highly variable, both in cell type and severity. In chronic hyperplastic dermatitis of allergic origin, suggestion of the specific allergic disease can sometimes be made based on the predominant types of inflammatory cells observed (see Chapter 9). Hyperplastic lesions of self-trauma also feature sebaceous hyperplasia and apocrine dilatation. Enlarged and proliferative sebaceous glands may be diffusely distributed in the interfollicular dermis in severe cases. Squamous metaplasia of sebaceous gland epithelium, which may leave only small residual clusters of fully lipidized sebocytes in the centers of the lobules, is a frequent feature. Dilated apocrine

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Fig. 7.4 Multiple fibropruritic nodules in the dorsal lumbosacral area of a dog with chronic flea allergy dermatitis. The affected area is partially clipped to enhance the visibility of the lesions.



Fig. 7.5 Closer view of the dog in Fig. 7.4. Some of the nodules are hyperpigmented while others are nonpigmented. The largest nodule is ulcerated from self-trauma. The skin beneath the nodules is uniformly hyperpigmented and lichenified.

glands are generally filled with secretory material and may be lined by hyperplastic epithelium.

Many chronic dermatoses have some features of chronic hyperplastic dermatitis and thus this reaction pattern is not highly specific. Often, chronic hyperplastic dermatitis is a diagnosis of exclusion that is rendered when other diagnoses have been eliminated. The pathologist should not diminish this result by offering a diagnosis of 'chronic nonspecific dermatitis'. In fact, the elimination of other causes for the clinical lesions in question is a specific function and is diagnostically important in these cases.

FIBROPRURITIC NODULES

Clinical features (Figures 7.4 and 7.5)

Fibropruritic nodules are uncommon lesions seen in conjunction with chronic flea allergy dermatitis and self-trauma. These lesions appear to be specific for flea allergy dermatitis and have not been seen in conjunction with other allergic skin diseases of dogs.

The etiology of fibropruritic nodules is not known. It is tempting to speculate that hypersensitivity is the trigger for the initiation of these lesions, as eosinophils frequently are found in surface cytological preparations. In the experience of one author (P.J.I.), German Shepherd Dogs and Golden Retrievers (two breeds believed to be at increased risk for fibropruritic nodules) commonly present with atypically severe flea allergy dermatitis. In addition, German Shepherd Dogs as well as some retriever breeds may be predisposed to develop excessive fibroblastic responses to inflammation or trauma. Perhaps the development of fibropruritic nodules requires the combination of the propensity for severe flea allergy dermatitis plus the tendency to develop an exuberant fibroblastic response.

Solitary or multiple, firm, sessile or pedunculated, alopecic nodules develop, which vary in size from 0.5 to 2 cm in diameter. Individual nodules may be nonpigmented and erythematous, or hyperpigmented. Hyperpigmented nodules may be visually striking if the surrounding skin remains normally pigmented. Erosions and ulcers may affect larger lesions. As many as 50 nodules may be seen in long-standing cases. Smaller lesions may be subtle and may go unnoticed, especially if alopecia is not complete. Fibropruritic nodules are located predominately in the bilaterally symmetrical, alopecic wedge seen in the dorsal lumbosacral area of dogs with long-standing flea allergy dermatitis.

Fibropruritic nodules may be more common in German Shepherd Dogs, Labrador Retrievers, Golden Retrievers, and their related crossbreeds. An informal case population survey performed recently by one author (E.J.W.) indicated that eight of 12 affected dogs fitted into these

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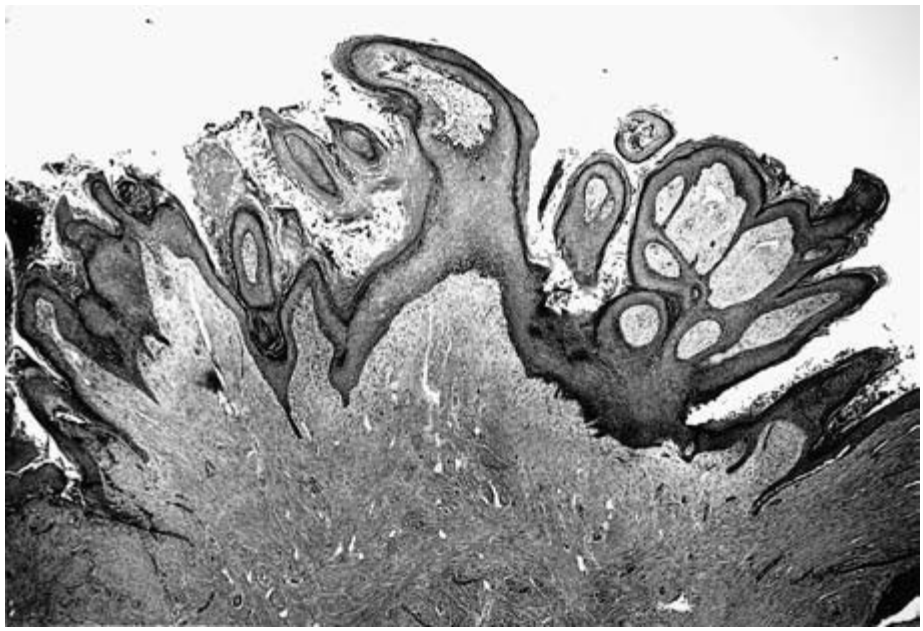


Fig. 7.6 Fibropruritic nodule in a dog with flea allergy dermatitis. Note irregular epidermal hyperplasia and subjacent fibrosis.

breed categories. Fibropruritic nodules are seen most commonly in dogs greater than 8 years of age. Sex predilections have not been noted.

Clinical differential diagnoses are few, since the lesions are visually characteristic. Cutaneous neoplasms should be considered, particularly in dogs of advancing age. Nodular sebaceous hyperplasia and sebaceous adenomas are the most likely differential diagnoses; melanocytic neoplasia is a consideration for pigmented fibropruritic nodules. Cytology performed on ulcerated lesions may reveal eosinophils, which increases the likelihood of a diagnosis of fibropruritic nodules. Skin biopsy is required to confirm the diagnosis.

Biopsy site selection

Sample selection is not critical as long as lesions are not severely ulcerated. Usually, wedge resection biopsy of an entire nodule is performed for cosmetic purposes.

Histopathology (Figures 7.6 and 7.7)

Fibropruritic nodules protrude in a tumor-like fashion above the surface of the skin. The epidermis is severely hyperplastic and may be papillomatous. The keratin layer is thickened and compact, as seen in other lesions of chronic, severe self-trauma; parakeratosis may be present. Ulceration and crusting may occur.

Dermal fibrosis is variable and may result in obliteration of adnexa. In general, coarse, thick bundles of collagen proliferate haphazardly in the dermis, creating a fibroma-like mass. A variation that is occasionally observed is characterized by prominent hyperplasia of

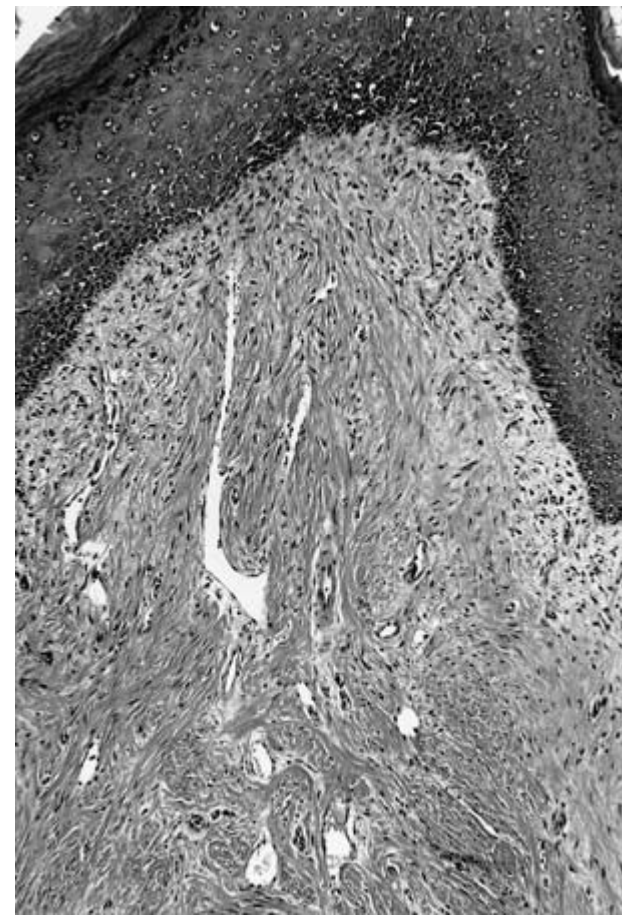


Fig. 7.7 Higher magnification of Fig. 7.6 demonstrating dense fibrosis beneath acanthosis.

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Fig. 7.8 Early acral lick dermatitis on the foreleg of a Doberman Pinscher. The lesion is well demarcated, alopecic, and focally ulcerated.



Fig. 7.9 Severe acral lick dermatitis on the foreleg of a Golden Retriever. The crateriform ulcer has peripheral hyperpigmentation and thickening. (Photograph courtesy H.T. Power; case material University of California, Davis.)

smooth muscle, presumably derived from arrector pili muscles, in addition to fibrosis. There may be moderate vascularization. Inflammation within the collagenous tissue is usually scant and mixed, but may include prominent neutrophils if there is ulceration. Mild accumulations of lymphocytes, macrophages, and plasma cells may be present just beneath the epidermis, and mild pigmentary incontinence may be evident. The adjacent intact (nonfibrotic) dermis has perivascular accumulations of eosinophils, mast cells, lymphocytes, and macrophages as seen in flea allergy dermatitis (see Chapter 9).

The principal differential diagnosis is a fibroma of the dermis (see Chapter 27). A fibropruritic nodule tends to be less discrete than a fibroma and the epidermis is generally more hyperplastic. Inflammation is not a feature of a nonulcerated fibroma but is typical for a fibropruritic nodule.

ACRAL LICK DERMATITIS

(Synonym: lick granuloma)

Clinical features (Figures 7.8 and 7.9)

Acral lick dermatitis is a relatively common syndrome in the dog that is characterized by self-trauma to a focal area, usually a dorsal distal extremity. This results in an alopecic, firm, oval plaque. A subgroup of deep bacterial folliculitis and furunculosis, termed 'traumatic furunculosis', is common in acral lick dermatitis (see Chapter 17). It is the opinion of the authors that secondary deep bacterial folliculitis and furunculosis in acral lick dermatitis is the direct result of self-trauma, which leads to follicular rupture and hair displacement into the deep dermis (traumatic furunculosis). Self-mutilation may be performed in private. The owner may be unaware of any self-traumatic component to the syndrome and may be resistant to this suggestion.

Both physical (organic) and psychogenic origins have been postulated; organic triggers have been emphasized during the past decade (Scott et al., 2001). It has been recommended that organic triggers such as allergy, bacterial or fungal disease, demodicosis, previous trauma, and underlying joint disease be ruled out before entertaining psychogenic causes as the initiator (Scott et al., 2001). The authors believe that most, if not all, cases of acral lick dermatitis have a strong psychogenic component, even if a putative organic trigger, acting as an inflammatory or psychic nidus, is identified. In essence, individual animals may be predisposed to develop stereotypic behavior in response to pruritus or pain. Boredom, separation anxiety, and obsessive–compulsive behavior all probably contribute to the genesis of a vicious itch–lick cycle. Chronic inflammation created by traumatic furunculosis probably also contributes to persistence. The success of endorphin blockers in the treatment of this syndrome indicates that endogenous opiate release may encourage habituation (White, 1990).

Typical lesions are well-circumscribed, firm, alopecic plaques. Lesions usually are solitary, oval, and vary in diameter from 2 to 6 cm. Adjacent lesions may merge to form larger foci with irregular outer contours. A central, irregular, crateriform ulcer with a scalloped, elevated border surrounded by a characteristic hyperpigmented halo is present in active lesions. Surface exudate rarely is seen, since licking removes debris. In light coat-colored dogs, peripheral salivary staining may be present. Secondary deep bacterial folliculitis and furunculosis is common, but may not be visually obvious. A hand lens is useful in identifying minute fistulous tracts indicative of secondary bacterial infection. The dorsal carpal and metacarpal areas are the most common sites. Other sites

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include the cranial radial, metatarsal, and tibial regions. Rarely, similar lesions may be created on the tail, stifle, or hip.

Large, active, attention-demanding breeds such as the Doberman Pinscher, Great Dane, German Shepherd Dog, Labrador Retriever, and Irish Setter are at increased risk. However, acral lick dermatitis may be seen in any breed or in mixed breed dogs. Adult dogs over 3 years of age are most commonly affected. Males are thought to be predisposed (Scott et al., 2001).

Clinical differential diagnoses include neoplasms, kerion dermatophytosis, focal bacterial furunculosis, and other infectious granulomas. Lesions affecting the hip or stifle may grossly resemble pressure calluses, but calluses should not be crateriform with distinctive hyperpigmented peripheral halos. Location of the lesion, breed, and history of persistent licking also assist in differentiation. Histopathology will aid in ruling out visually similar diseases and determining if secondary deep pyoderma is present.

Biopsy site selection

Punch biopsy specimens should be obtained from nonulcerated areas if possible. Care must be taken to obtain deep dermal tissue (to investigate the possibility of secondary pyoderma) without damaging delicate underlying structures of the distal extremities, such as flexor tendons, blood vessels, or nerves.

Histopathology (Figures 7.10 through 7.12)

Compact hyperkeratosis and multifocal parakeratosis accompany severe irregular acanthosis of epidermal and

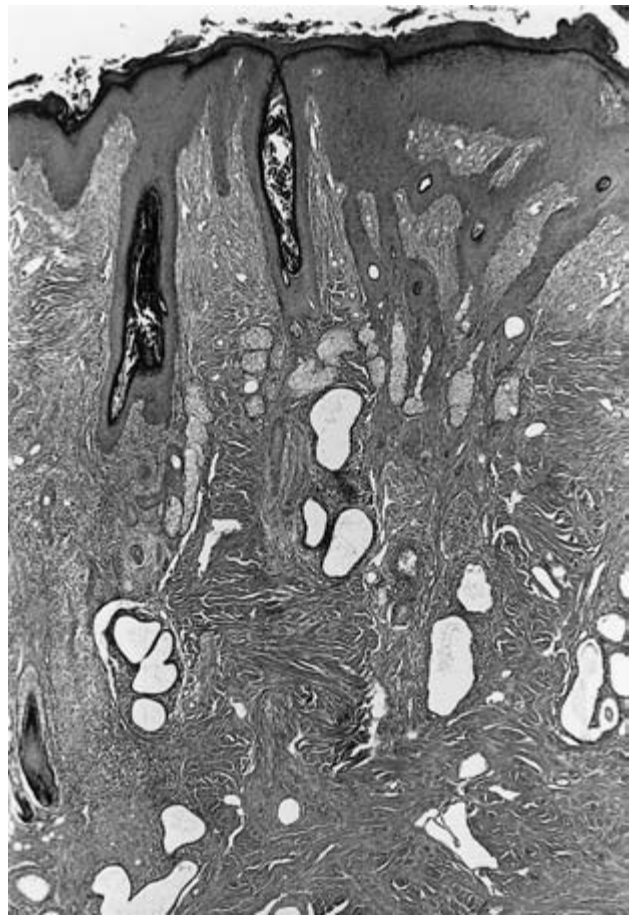


Fig. 7.10 Acral lick dermatitis in a dog. Irregular hyperplasia of the epidermis and follicular infundibula is accompanied by dilatation of apocrine sweat glands and periglandular inflammation; note compact hyperkeratosis.

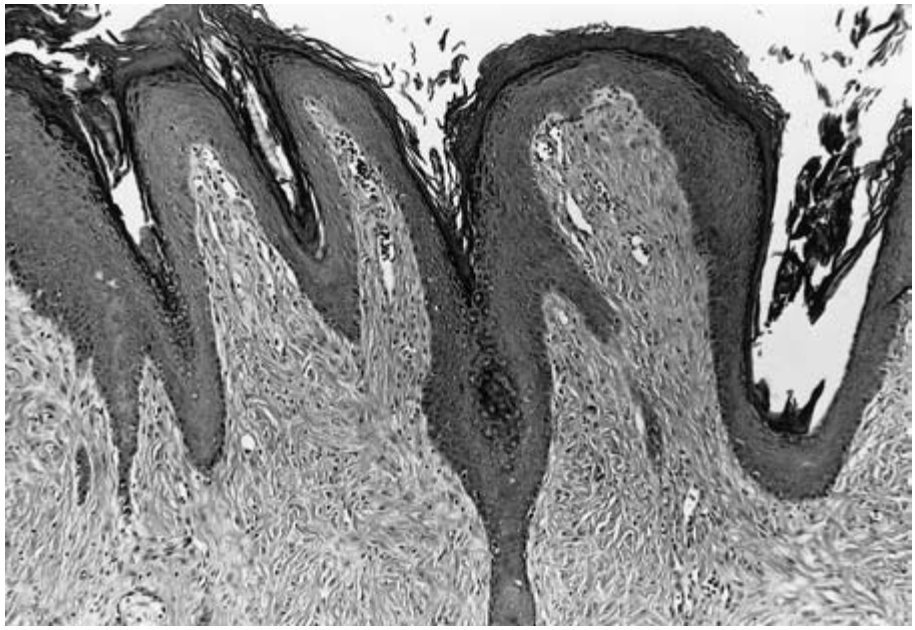


Fig. 7.11 Higher magnification of acral lick dermatitis demonstrating epidermal hyperplasia, compact hyperkeratosis, and vertical streaking fibrosis.

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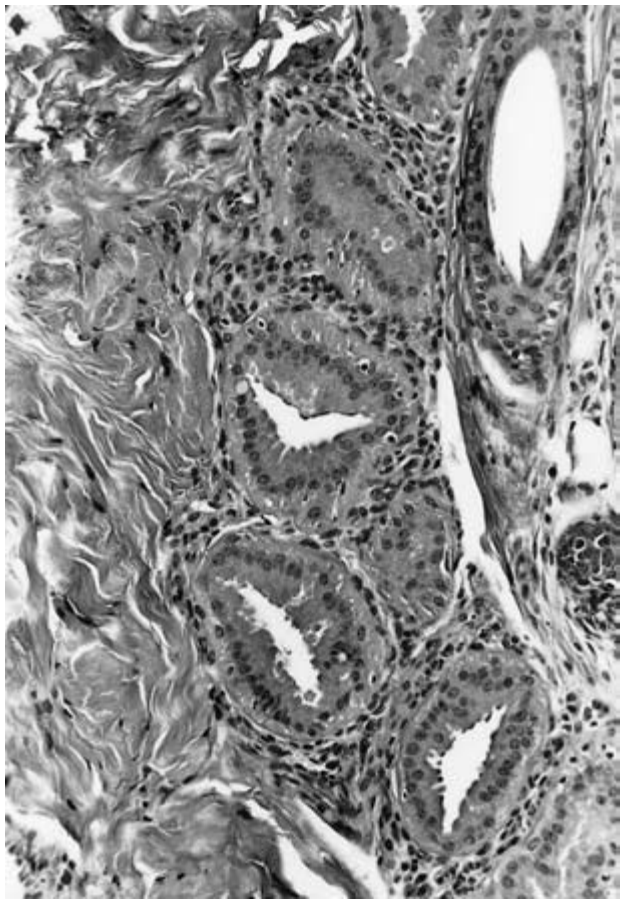


Fig. 7.12 Periglandular plasmacytic inflammation in acral lick dermatitis.



Fig. 7.13 *Malassezia* dermatitis secondary to atopic dermatitis affecting the skin folds of the axillae and ventral neck of a Cocker Spaniel. Acute inflammation is superimposed on the chronic changes of alopecia, lichenification, and hyperpigmentation.

superficial follicular epithelium. The skin surface may have a papillated or digitated configuration. Small neutrophilic serocellular crusts often are trapped in the keratin layer. Erosion or focal to extensive ulceration with exudation is often present.

Superficial dermal fibrosis, often in a 'vertical streaking' pattern, is seen between intact hair follicles. Hair follicles appear larger and are both thickened and elongated. Mixed dermal inflammation is perivascular, perifollicular, or diffuse, and includes lymphocytes, neutrophils, macrophages, and plasma cells. There is often prominent and distinctive plasmacytic inflammation around distended apocrine sweat glands (perihidradenitis). Rupture of hair follicles and displacement of hairs into the deep dermis or panniculus may accompany deep folliculitis and furunculosis. This displacement may be the direct result of licking which pushes a stiff hair shaft through the follicular wall (traumatic furunculosis).

Although the hyperplastic changes are nonspecific, acral lick dermatitis is distinctive if typical features of follicular elongation, plasmacytic periadnexal inflammation, and vertical streaking fibrosis are observed. Because the lesions are similar to those of persistently traumatized skin of any cause, knowledge of location of the lesion is often helpful in differentiation.

MALASSEZIA DERMATITIS

Clinical features (Figures 7.13 and 7.14)

Malassezia dermatitis is a very common canine and comparatively rare feline skin disease caused by the lipophilic, nonmycelial yeast *Malassezia pachydermatis* (*Pityrosporum pachydermatis*, *Pityrosporum canis*) or other *Malassezia* species. *Malassezia pachydermatis* has long been known as a ubiquitous commensal organism in the dog. Since the early 1990s, *Malassezia* has been recognized as an opportunistic secondary pathogen responsible for many cases of pruritic canine skin disease (Mason & Evans, 1991). *Pityrosporum ovale*, a related organism, is considered to be both a commensal and common opportunistic cutaneous pathogen in humans (Coffer et al., 1990). *Malassezia pachydermatis* of canine origin was reported as an opportunistic nosocomial pathogen in a human intensive care nursery (Chang et al., 1998).

The pathogenesis of *Malassezia* dermatitis remains controversial. It has been hypothesized that alterations in host defense mechanisms and skin surface microclimate allow the organism to become a facultative pathogen. Excessive sebum production, moisture accumulation, and disruption of normal barrier function may lead to yeast

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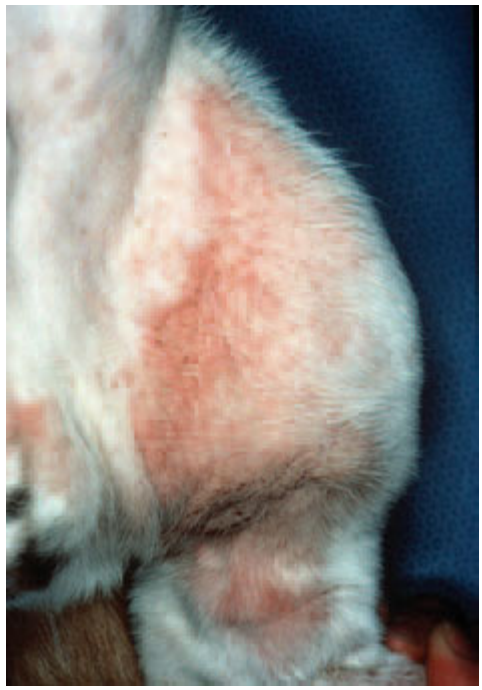


Fig. 7.14 *Malassezia* dermatitis secondary to allergic skin disease affecting the skin folds of the groin in a Basset Hound. Note that this breed does not hyperpigment in response to chronic inflammation. (Photograph courtesy A. Hargis & H.T. Power; case material University of California, Davis.)

proliferation, inflammation, and pruritus (Mason & Evans, 1991). Enzymes elaborated by the yeast induce host immune and inflammatory responses (Bond, 2002).

Recent work strongly supports the role of hypersensitivity in the pathogenesis of *Malassezia* dermatitis. Both immediate and delayed hypersensitivity reactions to *Malassezia* antigen, as evidenced by intradermal skin testing, have been noted in dogs with focal inflammatory skin disease (Nagata & Ishida, 1995). Atopic dogs with *Malassezia* dermatitis developed an IgE-mediated, type 1 hypersensitivity to intracellular protein extracts of *Malassezia pachydermatis* (Morris et al., 1998; Bond et al., 2002). Other recent work indicates that cell-mediated as well as humoral response to *Malassezia* probably contributes to the pathogenesis of atopic dermatitis (Morris et al., 2002). The number of organisms required to cause clinical disease is not defined. However, since clinical disease may be the result of hypersensitivity to *Malassezia* organisms, the density of organisms required may be highly variable.

Most cases of canine *Malassezia* dermatitis probably occur secondary to predisposing triggers such as underlying allergic skin disease (especially atopic dermatitis), diseases with abnormal cornification, and other chronic or recurrent inflammatory skin disease. Rarely, *Malassezia* dermatitis may be a primary event in the dog.

The finding of *Malassezia* in feline skin disease of sufficient severity to require skin biopsy may be a grave prognostic sign of underlying life-threatening disease (Mauldin et al., 2002). Feline skin diseases seen in conjunction with secondary *Malassezia* dermatitis include feline thymoma-associated exfoliative dermatitis (see Chapter 3), paraneoplastic alopecia (see Chapter 19), and superficial necrolytic dermatitis (see Chapter 4) (Forster-Van Hijfte et al., 1997; Godfrey, 1998; Mauldin et al., 2002).

The most common initial clinical signs of canine *Malassezia* dermatitis are erythema, either greasy or waxy adherent scales and crusts, and hair loss. Chronicity yields lichenification in most affected dogs. Breeds of dogs that are prone to hyperpigmentation (West Highland White Terriers, Cairn Terriers, Dachshunds, Newfoundlands, etc.) will dramatically hyperpigment. A 'musty' seborrheic odor commonly is noted. Lesions may be sharply and strikingly demarcated from adjacent normal skin and gradually increase in size via peripheral expansion (Ihrke, 2000). Concurrent colonization or infection with *Staphylococcus intermedius* may enhance the inflammation seen with *Malassezia*. The lesions of canine *Malassezia* dermatitis may be focal, multifocal, or generalized. Localized lesions may begin as macules, but become plaques with chronicity. Multifocal lesions coalesce to affect increasing body areas. Generalized disease can affect much of the body.

Site predilections include the ventral neck, ventral abdomen, axillae, face, pinnae, feet, forelegs, and skin folds including facial folds. Partial bilateral symmetry may be noted and commonly reflects the distribution pattern of the underlying and predisposing skin disease. Pruritus is a unifying clinical feature. Most cases are not visually distinctive as affected skin resembles chronic hyperplastic dermatitis of any cause, and lesional distribution reflects the underlying skin disease rather than inherent specificity of distribution of *Malassezia*.

Generalized feline *Malassezia* dermatitis exacerbates underlying skin disease. Diffuse erythema, greasy or waxy adherent scales and crusts, and alopecia are the most common clinical features. Locally more severe lesions may affect the chin, entrance to the ear canal, and clawbeds. Pruritus is variable, but commonly present. Cats diagnosed as having *Malassezia* dermatitis should be evaluated for underlying systemic diseases. Retrovirus status (feline immunodeficiency virus, FIV, and feline leukemia virus, FeLV) should be evaluated. Although, generalized feline *Malassezia* dermatitis may be a marker of grave, underlying disease, the authors have seen cats with generalized *Malassezia* dermatitis without

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identifiable underlying triggers. Also, localized feline *Malassezia* dermatitis in otherwise healthy cats may be seen occasionally.

Although *Malassezia* dermatitis may be seen in any breed of dog, reported predilections include the West Highland White Terrier, Basset Hound, German Shepherd Dog, American Cocker Spaniel, Shih Tzu, Silky Terrier, Maltese, Chihuahua, Poodle, Springer Spaniel, Shetland Sheepdog, and Dachshund. In the opinion of one author (P.J.I.) the Newfoundland has developed markedly increased risk over the past decade. Sex or age predilections have not been noted. Predilection information is not available for cats.

Clinical differential diagnosis is difficult, as *Malassezia* dermatitis can mimic most generalized chronic inflammatory skin diseases. Since canine *Malassezia* dermatitis commonly is secondary, it must be suspected in any dog exhibiting signs of allergic skin disease, diseases with abnormal cornification, and virtually all other chronic or recurrent inflammatory skin diseases. Other infectious skin diseases such as dermatophytosis and demodicosis are the prime differential diagnoses for the typical well demarcated and peripherally expansile lesions of *Malassezia* dermatitis. Skin cytology is the diagnostic procedure of choice. Usually, cytology has revealed *Malassezia* before skin biopsy is performed; in addition, skin biopsy is often falsely negative in canine *Malassezia* dermatitis (see below). Skin biopsy and complete systemic evaluation are required in cases of generalized feline *Malassezia* dermatitis to assess for the presence of underlying life-threatening disease.

Biopsy site selection

Multiple representative lesions should be sampled, taking care to retain scale and crusts during procurement. Ideally, the clinician should select both acute and chronic lesions, since histopathologic diagnosis may be difficult.

Histopathology (Figure 7.15 through 7.18)

Malassezia dermatitis of dogs features moderate to severe, irregular acanthosis and spongiosis, extending to the follicular infundibula. Prominent scalloping or festooning of the lower epidermal and outer follicular margin has been observed (Atlee's sign) and was previously reported in 61% of cases studied (Guaguère & Prélaud, 1996). Spongiotic intraepidermal neutrophilic pustules occur. Eosinophilic pustules have been reported in approximately 15% of cases in two studies (Guaguère & Prélaud, 1996; Mauldin et al., 1997). Mild compact or lamellar hyperkeratosis is interspersed with mounds or plaques of parakeratosis or parakeratotic crusts. There also may be diffuse parakeratosis; this pattern predominated in a report by Mauldin et al. (1997).

Budding oval or peanut-shaped yeasts are imbedded in keratin or crusts, but may be more easily visualized in keratin. *Malassezia pachydermatis* usually is not present diffusely in the stratum corneum, but may be seen in randomly distributed focal accumulations within superficial keratin, often in follicular ostia. Follicular yeasts may have more diagnostic specificity for clinical *Malassezia* infection than surface yeasts, at least in West Highland



Fig. 7.15 *Malassezia* dermatitis in a dog showing hyperkeratosis and a parakeratotic crust. Numerous yeasts are accumulating within the keratin (arrows).

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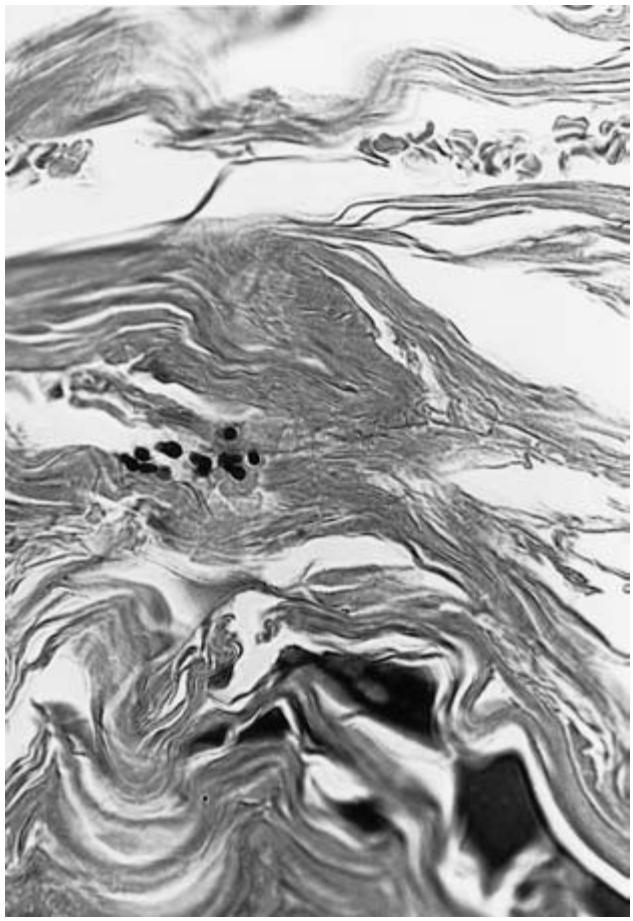


Fig. 7.16 *Malassezia* sp. within superficial keratin (periodic acid–Schiff).

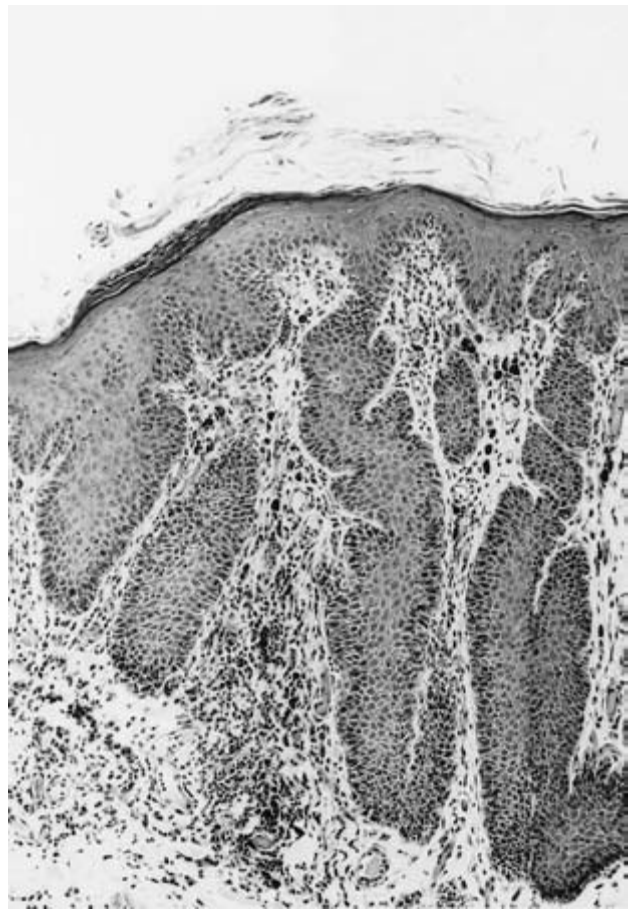


Fig. 7.17 *Malassezia* dermatitis in a dog demonstrating prominent scalloping of epidermis and follicles (Atlee sign). Note prominent spongiosis.

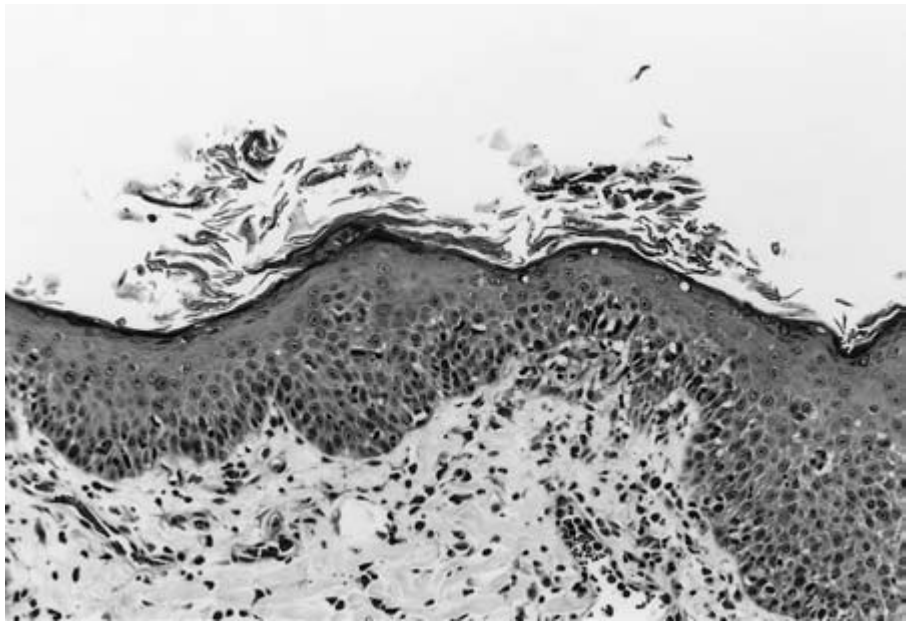


Fig. 7.18 *Malassezia* dermatitis in a cat. Organisms are numerous in the surface keratin; note mild epidermal scalloping and spongiosis.

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White Terriers with hyperplastic dermatosis (see below) (Scott, 1992a).

Previous canine studies indicated a false negative rate of approximately 30% using histopathology alone to identify these organisms (Guaguère & Prélaud, 1996; Mauldin et al., 1997). Yeasts are often more easily identified in follicular keratin where they are perhaps protected during routine processing for histopathology. Preparation of the skin prior to biopsy, or scratching, both of which would reduce the yeast-colonized keratin layer, as well as poor site selection, also have been suggested as causes for low numbers of yeasts in some canine cases of *Malassezia* dermatitis (Mauldin et al., 1997). A periodic acid–Schiff (PAS) stain will accentuate the presence of these organisms and allow easier assessment of their numbers.

Dermal inflammation usually is mild to moderate and is composed of a variable mixture of lymphocytes, eosinophils, neutrophils, sometimes prominent mast cells, and fewer plasma cells and macrophages. Linear subepidermal alignment of mast cells has been reported in dogs (Mauldin et al., 1997). Lymphocytic exocytosis is present, sometimes prominently. In the dog, the majority of epidermal lymphocytes were identified as T cells (Mauldin et al., 1997). Occasionally, there is mild inflammation around adnexa. Sebaceous glands may be hyperplastic, probably due to attendant self-trauma from pruritus.

Histologic findings in cats are similar to dogs; hyperkeratosis and parakeratosis are variable and may be mild to severe. Hyperkeratosis was the only histologic change common to all biopsy specimens in 15 cats with *Malassezia* dermatitis (Mauldin et al., 2002). Festooning or scalloping of epidermal and superficial follicular margins, as seen in dogs, has not been observed in cats. Spongiosis and lymphocytic exocytosis may be prominent, and neutrophils may also migrate through the epidermis, sometimes forming small superficial pustules. The dermis contains lymphocytes, mast cells, and neutrophils predominantly; eosinophils may be present. One author (T.L.G.) has seen a single feline case of *Malassezia* dermatitis characterized by diffuse severe superficial neutrophilic dermatitis and epidermal pustulation, accompanied by secondary epidermal degeneration, erosion, and parakeratosis. Staphylococcal colonization accompanied the yeasts and may have contributed to the marked pustular reaction observed (pyoderma).

The spongiotic and hyperplastic patterns of *Malassezia* dermatitis are not specifically diagnostic, and are as seen in chronic allergic dermatitis, at least in dogs. Festooning or scalloping of the epidermal and superficial follicular margins is suggestive for *Malassezia* dermatitis, but may be present in other hyperplastic conditions. Similarly, intraepidermal eosinophilic pustules may be evocative of *Malassezia* dermatitis in dogs (Guaguère & Prélaud, 1996; Mauldin et al., 1997); however, these pustules may occur in atopic dermatitis and parasitic dermatoses such as sarcoptic acariasis (see Chapter 9), as well as in allergic contact dermatitis (see Chapter 5). Diffuse lymphocytic exocytosis in a spongiotic and parakeratotic milieu has been proposed to be highly suggestive of *Malassezia* dermatitis in dogs, whether or not organisms are observed (Mauldin et al., 1997). Differential diagnosis is not problematic if large numbers of yeast are seen in association with correlative inflammatory changes. Note that in dogs and cats, yeasts may be seen in small numbers, not only in cases of clinically confirmed *Malassezia* dermatitis, but also in other clinical and histological contexts that may not relate etiologically to these organisms (Scott, 1992a, b). In cats with generalized skin disease and *Malassezia*, associated lesions of paraneoplastic alopecia, superficial necrolytic dermatitis, and feline thymoma-associated exfoliative dermatitis must be ruled out.

HYPERPLASTIC DERMATOSIS OF THE WEST HIGHLAND WHITE TERRIER

(Synonyms: epidermal dysplasia and *Malassezia pachydermatis* infection in West Highland White Terriers, 'armadillo Westie syndrome')

Clinical features (Figures 7.19 and 7.20)

Hyperplastic dermatosis of the West Highland White Terrier is an uncommon, severe, chronic hyperplastic skin disease with clinical features similar to primary seborrhea



Fig. 7.19 Hyperplastic dermatosis of the West Highland White Terrier. Partial alopecia of the ventral neck and a generally disheveled coat are present.

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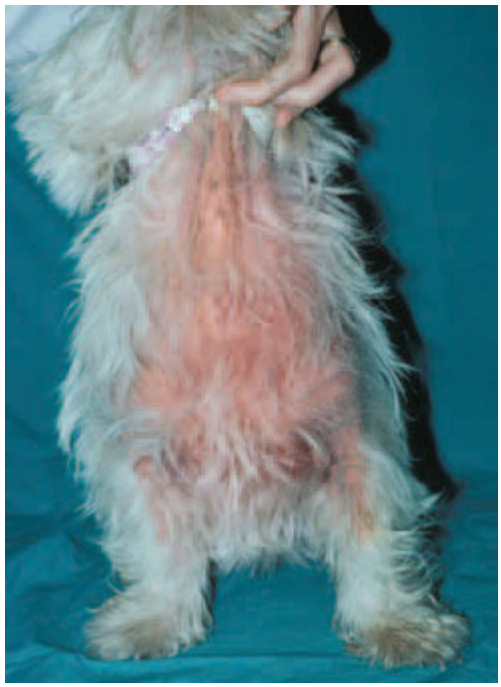


Fig. 7.20 Closer view of the dog in Fig. 7.19. Alopecia, erythema, lichenification, and hyperpigmentation are present on the ventral neck. Note the thickened skin folds.

and seborrheic dermatitis (see Chapter 8). The restriction of this syndrome to the West Highland White Terrier, coupled with evidence of familial involvement, indicates the probability of a hereditary disease.

Epidermal dysplasia with secondary *Malassezia pachydermatis* infection has been described in West Highland White Terriers (Scott & Miller, 1989; Scott et al., 2001). The authors have not noted histopathologic features compatible with epidermal dysplasia in the breed. Because of this difficulty, the term 'hyperplastic dermatosis' is preferred.

The authors believe this syndrome to be a breed-specific hyperproliferative reaction pattern initiated by various inflammatory stimuli and infectious agents (usually *Malassezia*). Recently a dramatic response of two sibling West Highland White Terriers with putative hyperplastic dermatosis to treatment for *Malassezia* dermatitis was reported; underlying atopic dermatitis potentially acted as a trigger for secondary infection and induction of the clinical signs (Nett et al., 2001).

Clinically, the distinction between this syndrome and all other chronic hyperplastic skin diseases affecting the breed is blurred. One author (P.J.I.) is reluctant to make this diagnosis unless all other causes are eliminated and biopsy results are compatible; thus, hyperplastic dermatosis of the West Highland White Terrier is a diagnosis of exclusion. This is complicated further by the probable frequent coexistence of allergic skin diseases such as flea allergy dermatitis, atopic dermatitis, and food allergy. Thus, differentiation of hyperplastic dermatosis of the West Highland White Terrier from chronic allergic dermatoses may be challenging, since the severely affected West Highland White Terrier often is the end product of multiple, coexistent skin diseases.

Affected dogs have generalized erythema with lichenification, hyperpigmentation, and alopecia. The skin is often malodorous with adherent, brownish-gray, greasy exfoliative debris. Alopecia may be extreme. Pruritus and accompanying self-trauma vary in intensity, but are consistent features. Thickened skin folds with intertrigo develop on the legs and on the trunk. *Malassezia* dermatitis and surface bacterial overgrowth or superficial pyoderma are common. Owners report that lesions often begin on the trunk but rapidly generalize. In advanced cases, lesions may involve virtually all haired or previously haired body surfaces plus the comparatively less well haired abdomen. There is often almost total alopecia, which sometimes spares the head, distal limbs, and distal tail. Regional or generalized lymphadenopathy is a consistent feature.

The syndrome, as described here, is seen only in West Highland White Terriers. Age of onset may be from less than 1 year to middle age. Clinical signs commonly commence at less than 1 year of age in severely affected dogs. Sex predilections have not been noted.

Clinical differential diagnoses include generalized demodicosis, sarcoptic acariasis, atopic dermatitis, food allergy, and flea allergy dermatitis; however, the documentation of any of these diseases should not preclude the coexistence of hyperplastic dermatosis of the West Highland White Terrier. Impression smears should be performed to determine if yeast infection or bacterial overgrowth is present.

Biopsy site selection

Multiple biopsy specimens should be taken from affected areas showing minimal self-trauma. Sites which have no evidence of secondary pyoderma are preferred.

Histopathology (Figures 7.21 and 7.22)

Epidermal features principally consist of severe acanthosis that also affects superficial hair follicles. Budding or scalloping of the lower border of the epidermis and outer border of hair follicles may be seen, as observed in *Malassezia* dermatitis (see p. 142). There may be slight crowding of basilar keratinocytes. These proliferative changes collectively do not indicate epithelial dysplasia, as considered conventionally by pathologists. The authors have not recognized typical indications of epithelial

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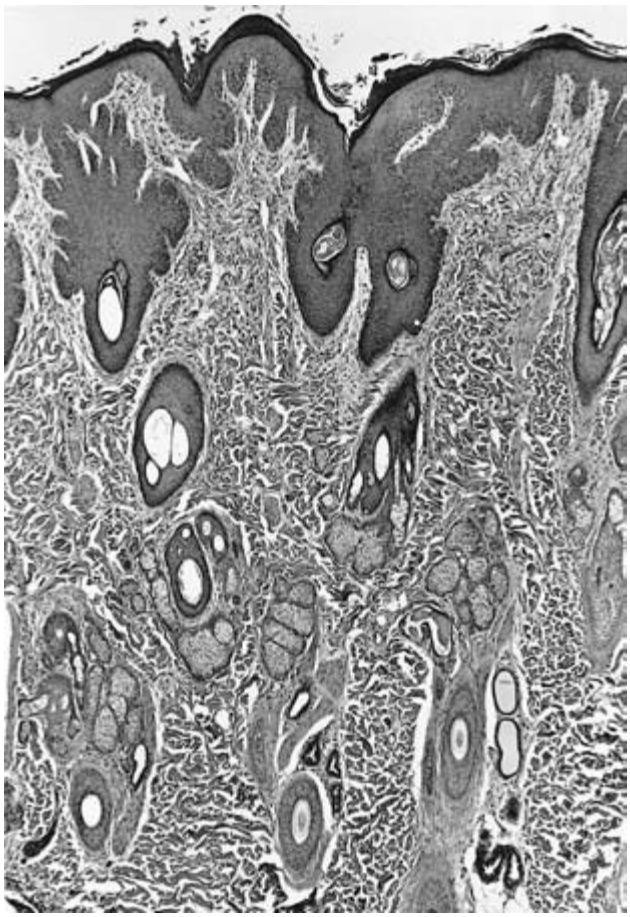


Fig. 7.21 Hyperplastic dermatosis of the West Highland White Terrier. Severe irregular hyperplasia of the epidermis and follicular infundibular epithelium is accompanied by prominent sebaceous glands.



Fig. 7.22 Higher magnification of hyperplastic dermatosis of the West Highland White Terrier, demonstrating irregular acanthosis, spongiosis, and mild superficial dermal inflammation.

dysplasia, such as uneven nuclear size, increased mitotic index, or premature keratinization. Affected dogs likely are predisposed to an abnormal hyperproliferative response to colonization by organisms such as staphylococci or *Malassezia*, as has also been suggested by Nett et al. (2001).

There is patchy or diffuse mild spongiosis with lymphocytic exocytosis. Parakeratosis often is present as multifocal mounds accompanied by serocellular crusting (parakeratotic scale/crusts). Colonization of the keratin layer by *Malassezia pachydermatis* may be observed; however, a negative result on biopsy does not exclude the etiologic importance of this yeast (see p. 142). Clinical assessment via cytology is superior for the quantification of these organisms.

Perivascular to interstitial inflammation is seen in the superficial dermis. Neutrophils, macrophages, plasma cells, and lymphocytes are present in varying proportions. Sebaceous glands are often markedly hyperplastic and may be distributed loosely throughout the middle dermis. Squamous metaplasia of sebaceous glands may be present. These glandular changes may be due to attendant self-trauma from pruritis.

Histopathologically, lesions of hyperplastic dermatosis of the West Highland White Terrier are not specific. They resemble chronic hyperplastic dermatitis due to allergy or other causes, and, if yeasts are present, chronic *Malassezia* dermatitis. Since these conditions may be concurrent in this breed, differentiation may be challenging.

ACTINIC KERATOSIS

(Synonyms: solar keratosis, squamous cell carcinoma *in situ*)

Clinical features (Figures 7.23 and 7.24)

Actinic keratoses are solar-induced hyperplastic and dysplastic epidermal lesions that occur in both the dog and

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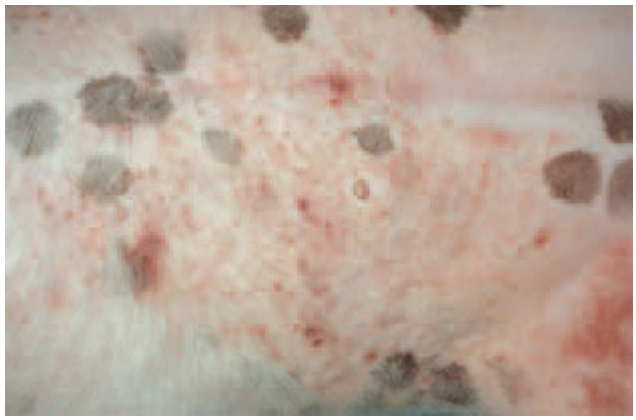


Fig. 7.23 Actinic keratoses on the relatively nonpigmented and hairless abdomen of a Bull Terrier. Note the multifocal erythema and crusted papules and plaques.

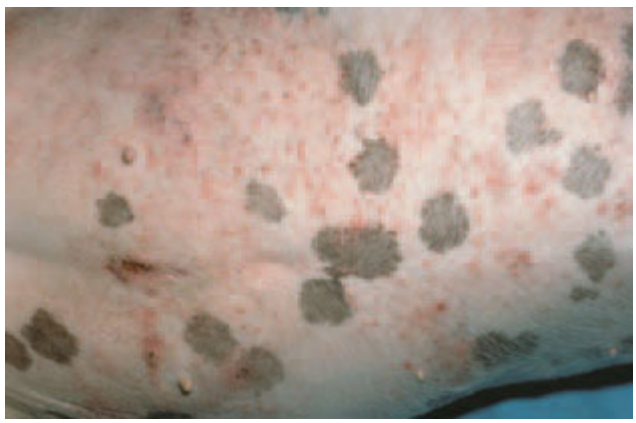


Fig. 7.24 Actinic keratoses on the sparsely pigmented abdomen of a Pit Bull Terrier. Actinic damage, characterized by blotchy erythema and irregular thickening, is confined to the nonpigmented areas. The skin in the darkly pigmented patches appears 'thin' in comparison to the irregularly thickened solar-affected nonpigmented areas. Diffuse pustules and crusted papules in predominantly nonpigmented areas indicate secondary pyoderma.

cat. Lesions develop in nonpigmented and lightly haired skin exposed repetitively to excessive ultraviolet light. Many affected dogs are known sunbathers. Multiple stages of malignant transformation may be present concurrently (Hargis et al., 1992). Actinic keratoses of both dogs and cats may progress to invasive squamous cell carcinoma (see Chapter 22). The reader is referred to Chapter 22 for a detailed discussion on the pathogenesis of actinic keratosis.

Clinical appearance in dogs is highly variable. Roughened, erythematous patches characterize early lesions. With chronicity, lesions range from focal erythema and crusting to scaly, red to red-brown, ill-defined exfoliating macules and papules, to darkly crusted, indurated, keratotic plaques and nodules. Erosions or ulcers have adherent hemorrhagic crusts. Palpation of visually normal skin may detect irregular firmness and thickening, suggesting that dysplastic change is more widespread than is visually apparent. Difference in skin thickness may be striking in dogs with colored spots; unaffected pigmented skin appears thinner than surrounding affected nonpigmented skin. Actinic comedones may be present (see Chapter 8). Larger, ulcerated, nodular, or infiltrative lesions are most suggestive of squamous cell carcinoma.

Canine lesions are restricted to sun-exposed, relatively nonpigmented skin in sparsely haired regions. The glabrous skin of the ventral and lateral abdomen, flank folds, and inner thighs is most frequently affected. One side of the abdomen and the opposite inner thigh may be more prominently affected, indicating favoring of one side during recumbency while sunbathing (Mason, 1987, 1999). The dorsal muzzle and periorbital regions also may be affected. Secondary pyoderma with follicular rupture (actinic furunculosis) is a common concurrent finding (see Chapter 17); actinic furuncles may generate from actinic comedones (see Chapter 8). Secondary pyoderma may make diagnosis more difficult by blurring classical lesions.

In cats, lesions consist of erosions, ulcers, or erythematous, slightly elevated plaques. Hemorrhagic crusts may overlie ulcers or erosions. Severe ulceration may be indicative of squamous cell carcinoma; however, ulceration cannot be used as a marker of occult squamous cell carcinoma since pruritus may initiate self-trauma in actinic keratoses. Actinic keratoses of cats are seen most commonly on the margins of the pinna, planum nasale, and face, especially in the comparatively less haired preauricular regions. Bilateral symmetry may be surprisingly prominent.

Lightly pigmented and sparsely haired animals are more likely to develop actinic lesions. Dalmatians, Whippets, Italian Greyhounds, Greyhounds, American Staffordshire Terriers, Bull Terriers, Beagles, and Basset Hounds are at increased risk for actinic lesions. Most feline actinic keratoses are seen in white haired areas of short-haired cats. Animals spending substantial time outdoors in areas of the world with increased solar exposure are at greater risk. Many affected dogs are reported to be sunbathers and spend long periods of time in dorsal or lateral recumbency in direct sunlight. Lesions occur most commonly in older animals, but have been seen in dogs as young as 2 years of age.

Early canine actinic keratoses must be differentiated from psoriasiform-lichenoid dermatosis and lichenoid keratosis by skin biopsy. Clinical differential diagnoses for severe, deep, and infiltrative lesions in the dog include deep bacterial folliculitis and furunculosis, and squamous cell carcinoma. In the cat, clinical differential diagnoses

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include bowenoid *in situ* carcinoma (see Chapter 22), squamous cell carcinoma, and severe facial autoimmune disease. Lesions of bowenoid *in situ* carcinoma are generally multifocal and also are located in nonsun-exposed sites. Since it is impossible clinically to differentiate actinic keratosis (an *in situ* carcinoma) from invasive solar-induced malignancies, biopsy of suspected actinic keratosis is mandatory.

Biopsy site selection

Specimens for biopsy should be obtained from different stages of the disease. If present, samples should include discolored macules, areas of erythema, crusted plaques, nodules, and margins of ulcers in order to reveal the full spectrum of disease present and to uncover possible neoplasia. If feasible, solitary lesions should be resected in their entirety to prevent progression to overt neoplasia. In dogs, it is highly advantageous to delay skin biopsy until the dog has received appropriate systemic antibiotics for at least 3 weeks so that secondary pyoderma will resolve.

Histopathology (Figure 7.25)

Epidermal changes of actinic keratosis vary in severity, depending on the stage of the disease. The principal diagnostic feature is epidermal hyperplasia with dysplasia. Hyperplasia and dysplasia without invasion through the basement membrane indicate actinic keratosis (carcinoma *in situ*); penetration into the dermis signifies squamous cell carcinoma, which may occur in advanced lesions. Lesions may be highly proliferative and have a papillomatous configuration. Parakeratosis in parallel layers, so-called 'stacked parakeratosis', is seen most commonly in the dog. See Chapter 22 for a more detailed description of the epidermal lesions of actinic keratosis.

In the dog, dermal inflammation is perivascular to band-like (lichenoid), and may be accompanied by solar elastosis and laminar fibrosis (see Chapter 15). When laminar fibrosis of the dermis is intense, inflammation may lie immediately below the fibrotic layer. Plasma cells and lymphocytes predominate and are accompanied by variable numbers of macrophages, neutrophils, and occasional eosinophils. Pigmentary incontinence may be present. Superficial dermal vessels may be proliferative and ectatic; frank solar vasculopathy may be seen (see Chapter 10). In some dogs with actinic keratosis there may be actinic comedones (see Chapter 8) or actinic furunculosis (see Chapter 17).

Lichenoid dermatitis generally is not present in actinic lesions of cats; inflammation is mild and perivascular. However, some feline cases of actinic keratosis have more intense dermal inflammation with fibrosis. Solar elastosis also is observed in the cat, but is often subtle (see Chapter 15).

As epidermal lesions are characteristic (see also Chapter 22), differential diagnoses are few. Lichenoid keratoses may have a similar low power appearance, but are not characterized by epidermal dysplasia. Some actinic keratoses may be identical histopathologically to lesions of bowenoid *in situ* carcinoma (multicentric squamous cell carcinoma *in situ*; see Chapter 22), and have been referred to as 'bowenoid' actinic keratoses. In fact, these probably represent bowenoid *in situ* carcinoma (caused by persist-

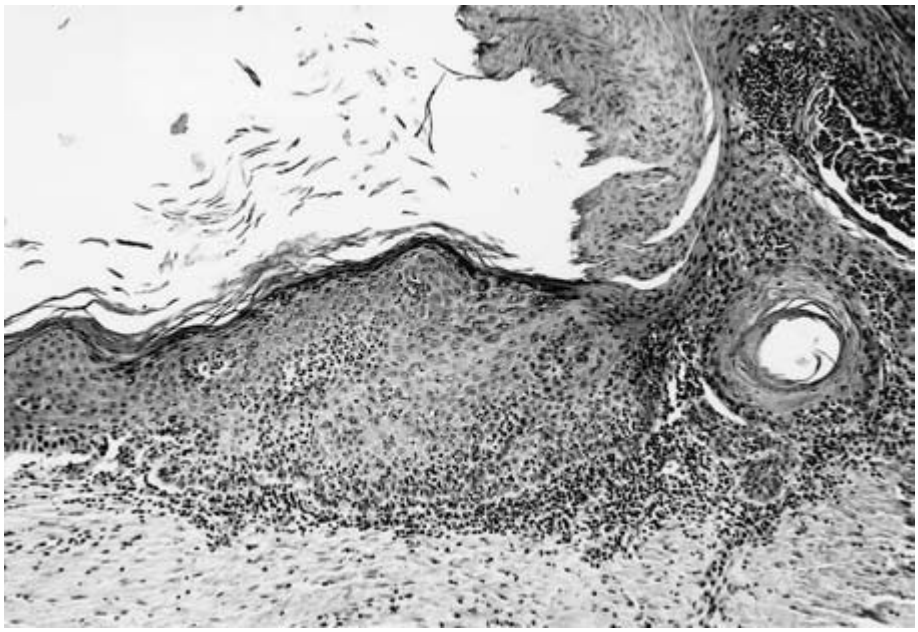


Fig. 7.25 Actinic keratosis in a dog demonstrating epidermal hyperplasia and early dysplasia with stacked parakeratosis. Note lichenoid inflammation and fibrosis.

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ent papillomavirus infection) arising in sun-exposed skin; ultraviolet radiation has a synergistic effect on the production of these lesions. The epidermis and superficial hair follicles of bowenoid lesions may have a more strikingly disorganized or 'windblown' appearance than typical actinic keratoses, and the dysplastic keratinocytes may be more vacuolated (see Chapter 22). Clinical differentiation may be of benefit.

ACANTHOSIS NIGRICANS OF DACHSHUNDS

Clinical features (Figures 7.26 and 7.27)

Acanthosis nigricans is, most specifically, a rare idiopathic primary genodermatosis seen exclusively in Dachshunds.



Fig. 7.26 Acanthosis nigricans in a Dachshund. The affected axillae and sternal region are alopecic, hyperpigmented, and lichenified. Primary lesions suggestive of other diseases mimicking acanthosis nigricans are absent.



Fig. 7.27 Acanthosis nigricans in a Dachshund. Lichenification and hyperpigmentation in the umbilical region were preceded by axillary lesions in this animal.

Symmetrical hyperpigmentation, lichenification, and alopecia characterize the disease. The cause is not known. Unfortunately, the term 'acanthosis nigricans' also has been used generically to describe a multifactorial, clinical cutaneous reaction pattern (secondary acanthosis nigricans), which is characterized by visually similar lesions and is seen in a variety of different breeds (Scott et al., 2001).

Acanthosis nigricans of Dachshunds begins with subtle, bilaterally symmetric axillary hyperpigmentation. Lesions progress slowly to lichenification and alopecia. Accumulation of greasy, odoriferous, keratinous debris is common in severely affected dogs. Many cases involve only the axillae and groin. In advanced cases, bilaterally symmetric lesions affect the abdomen, groin, perineum, hocks, chest, axillae, neck, forelegs, and periocular region. Secondary intertrigo (see mucocutaneous pyoderma, Chapter 11) with superficial pyoderma and/or *Malassezia* dermatitis are common sequelae. Pruritus is variable, and can be absent in early stages.

Acanthosis nigricans of Dachshunds commonly develops initially in dogs less than 2 years of age. Sex predilections have not been reported.

Even in the Dachshund, acanthosis nigricans should be a diagnosis of exclusion. Superficial bacterial folliculitis, superficial spreading pyoderma, *Malassezia* dermatitis, as well as the numerous other causes of axillary intertrigo and pruritus, including atopic dermatitis and food allergy, should be investigated and ruled out before the diagnosis of primary acanthosis nigricans of Dachshunds is made. Allergic skin diseases usually involve sites in addition to the axillae and groin, but chronic and severe cases of acanthosis nigricans have a similar appearance and distribution. Unlike pyoderma, true acanthosis nigricans should not have erythematous, exfoliative margins with papules or collarettes.

Biopsy site selection

Multiple samples should be taken from both hyperpigmented and lichenified central lesions, as well as from the advancing border. Marginal specimens are most useful in ruling out other visually similar diseases.

Histopathology (Figures 7.28 and 7.29)

In clinically typical cases of acanthosis nigricans, the epidermis is mildly to moderately and irregularly acanthotic. There may be mild to moderate hyperkeratosis, and focal parakeratosis often is observed. Follicular keratosis may be striking in some cases. Keratinocytes, especially those in the basal cell layer, are heavily pigmented.

The dermis has mild to moderate superficial perivascular to interstitial infiltrates of lymphocytes, macrophages,

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Fig. 7.28 Acanthosis nigricans in a Dachshund. Irregular acanthosis is accompanied by mild hyperkeratosis.

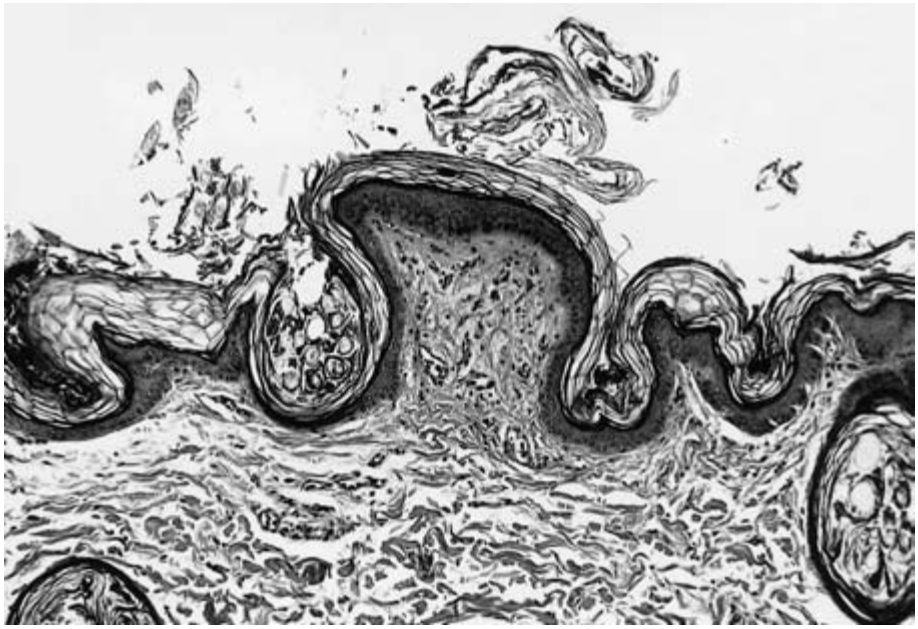


Fig. 7.29 Higher magnification of Fig. 7.28. Note sparse dermal inflammation.

and a few neutrophils or plasma cells. Pigmentary incontinence sometimes is prominent.

Histopathologically, the lesions of acanthosis nigricans are not specifically diagnostic, and do not permit definitive diagnosis of this entity. Acanthosis nigricans is similar to chronic hyperplastic dermatitis, particularly due to allergy, but may be less inflamed. Correlation with the breed affected and the clinical distribution of lesions, in addition to systematic clinical exclusion of other possible causes, is required for the definitive diagnosis of acanthosis nigricans.

PSORIASIFORM-LICHENOID DERMATOSIS

Clinical features (Figures 7.30 and 7.31)

Psoriasiform-lichenoid dermatosis is a distinctive, rare, asymptomatic skin disease seen most often in Springer Spaniels (Gross et al, 1986; Mason et al., 1986). The marked breed predilection suggests heritability. The etiology is not known. However, it has been proposed that this syndrome represents a genetically programmed and dis-

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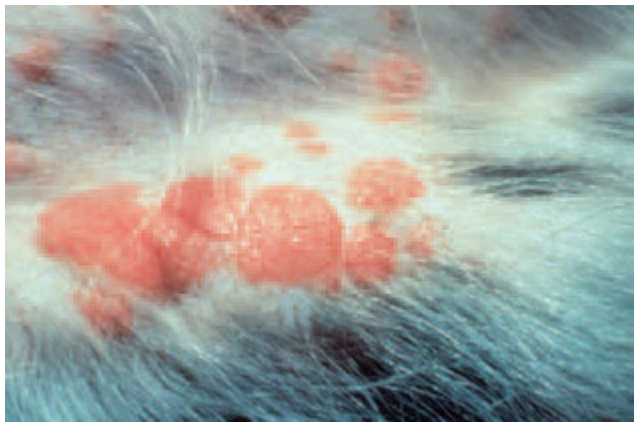


Fig. 7.30 Psoriasiform-lichenoid dermatosis in a Springer Spaniel. Erythematous papules and coalescing plaques are present on the ventral abdomen.

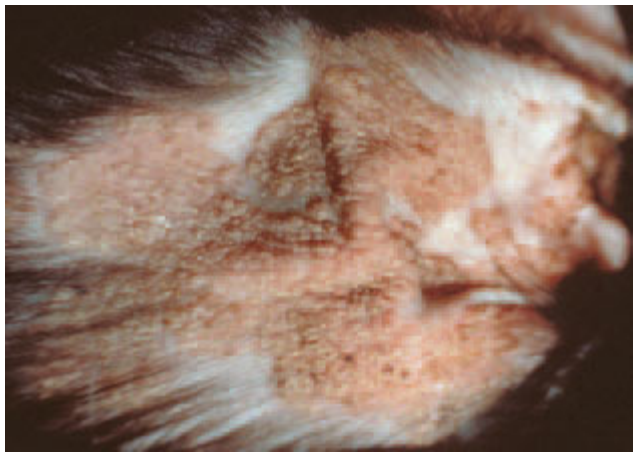


Fig. 7.31 Psoriasiform-lichenoid dermatosis in a Springer Spaniel. Waxy, crusted, erythematous, coalescing plaques and papules are seen on the medial surface of the pinna. (Photograph courtesy W. McDougal.)

tinctive reaction to superficial staphylococcal infection (Burrows & Mason, 1994).

Psoriasiform-lichenoid dermatosis is characterized clinically by erythematous to yellow, waxy, crusted papules that coalesce to form multiple well-demarcated lichenoid plaques. With chronicity, adherent keratinous debris covers the plaques. Advanced lesions may appear papillomatous (Scott et al., 2001). Lesions occur predominantly on the medial surface of the pinnae, external ear canal, ventral abdomen, prepuce, and perineal region. With time lesions may become more numerous in affected areas. Generalized scaling may be present but probably represents concurrent primary seborrhea (see Chapter 8). Pruritus is not noted. The clinical course is chronic but lesions may wax and wane.

Psoriasiform-lichenoid dermatosis occurs predominantly in the Springer Spaniel. The syndrome also has been seen in English Pointers, Irish Setters, Poodles, and a West Highland White Terrier. Initial lesions usually occur during the first $1\frac{1}{2}$ years of age. Sex predilections have not been noted.

Clinical differential diagnoses should include lichenoid keratosis (see p. 154) and possibly early actinic keratosis (see p. 148). Severe and more generalized cases may resemble primary seborrhea. Most cases of psoriasiform-lichenoid dermatosis are seen in Springer Spaniels and are multicentric. Lichenoid keratoses occur without breed predilection and are most often solitary. Actinic keratoses occur in sun-exposed, lightly pigmented, sparsely haired skin.

Biopsy site selection

Well-developed solitary plaques are preferred sites for biopsy. Multiple specimens from lesions in varying stages of development are ideal. If lesions are present both on the ventral abdomen and on the pinna, biopsy of abdominal lesions is more readily accomplished as pinnal biopsy may damage fragile underlying cartilage.

Histopathology (Figures 7.32 and 7.33)

The epidermis is irregularly acanthotic, often with deep projections into the dermis. This form of epidermal hyperplasia is similar to 'psoriasiform' hyperplasia, as described in humans with hyperplastic diseases that resemble psoriasis. Mild hyperkeratosis with focal parakeratosis is present. There may be hypergranulosis (increase in thickness of the granular layer). Characteristically, there are discrete, often round, intraepidermal pustules which contain eosinophils, neutrophils, or a mixture of both. Pustules progress to well-demarcated, mound-shaped parakeratotic crusts, which resemble 'Munro microabscesses', as described for psoriasis in humans. Necrosis of individual basal keratinocytes is seen rarely. Specimens from areas of generalized scaling may show hyperkeratosis and follicular keratosis, similar to primary seborrhea (see Chapter 8). Dermal inflammation is lichenoid and predominantly lymphocytic and plasmacytic (see Chapter 11).

The discrete intraepidermal pustules in the context of psoriasiform hyperplasia are diagnostic. Psoriasiform-lichenoid dermatosis may histopathologically parallel lichenoid keratosis. Differentiating clinical features are required for a definitive diagnosis; lichenoid keratoses are generally focal.

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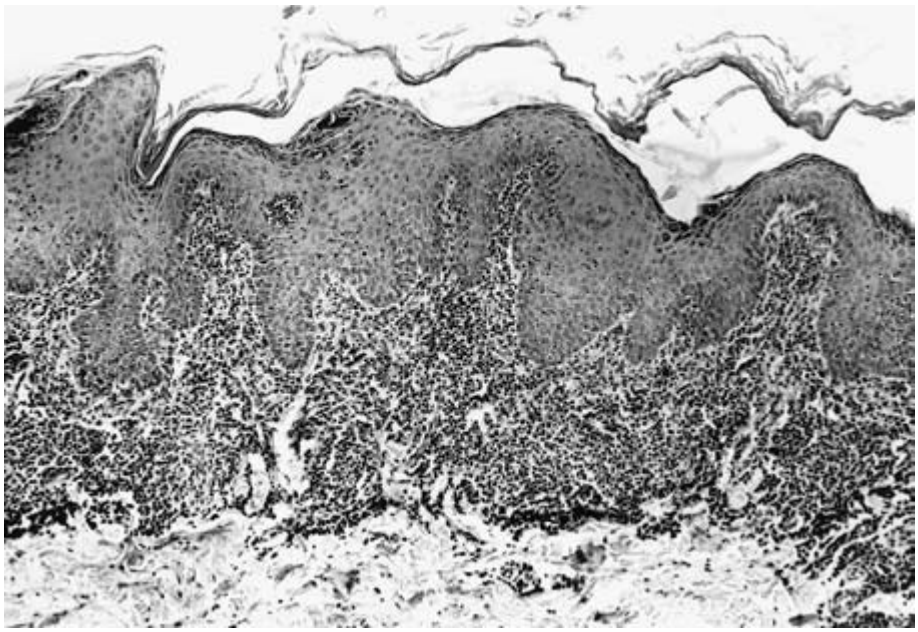


Fig. 7.32 Psoriasiform-lichenoid dermatosis in a Springer Spaniel. Irregular acanthosis is accompanied by discrete, round intraepidermal pustules. Note lichenoid dermatitis.

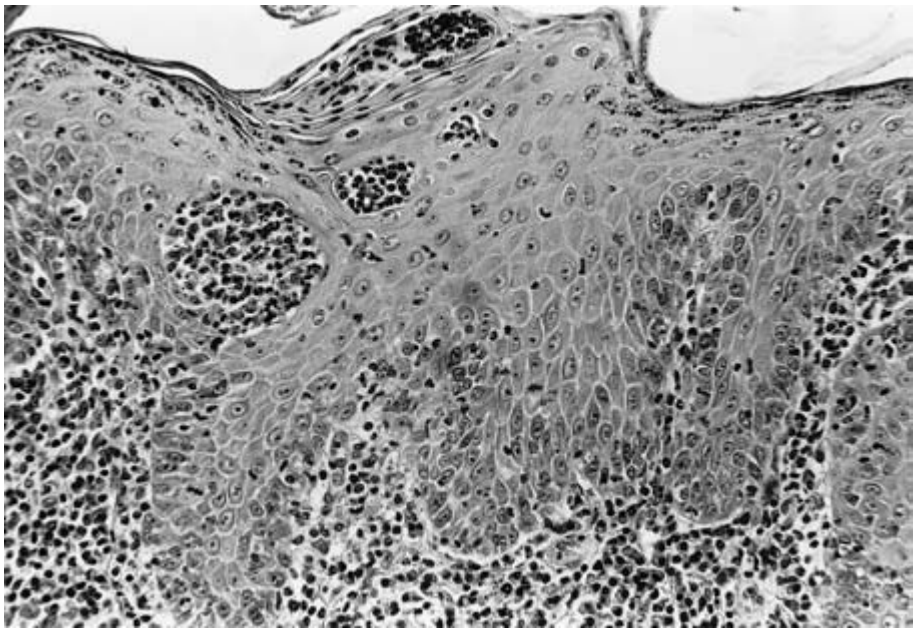


Fig. 7.33 Higher magnification of Fig. 7.32, demonstrating intraepidermal pustules. Mound-shaped superficial parakeratosis contains a degenerating pustule (Munro microabscess).

LICHENOID KERATOSIS

Clinical features (Figure 7.34)

Lichenoid keratosis is a rare canine skin disease characterized by usually solitary well-circumscribed plaques with adherent keratinous debris (Anderson et al., 1989; Gross & Ihrke, 1992). The etiology is unknown. Individual lesions closely resemble those seen in psoriasiform-lichenoid dermatosis (see p. 152). In humans, benign lichenoid keratoses are common solitary lesions of unknown etiology, resembling lichen planus, and are characterized by a T-cell-rich infiltration (Smith et al., 2002).

Lichenoid dermatoses are scaly or crusted plaques that may appear papillomatous. Erythema is variable, and hyperpigmentation may occur. Lesions usually are solitary and occur on the pinnae (Anderson et al., 1989). Less commonly, similar lesions may occur on the groin or elsewhere. Lichenoid keratoses are asymptomatic. Most lesions have been seen in adult dogs. Breed or sex predilections have not been noted.

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Lichenoid keratosis must be differentiated from psoriasiform-lichenoid dermatosis and actinic keratosis, as well as uncommon variants of viral warts (see Chapter 22). Psoriasiform-lichenoid dermatosis is the more probable diagnosis in the Springer Spaniel. Actinic keratoses usually are multicentric and occur only in sun-exposed, relatively nonpigmented skin in sparsely haired regions. Histopathology is required for the identification of viral warts.

Biopsy site selection

Excisional biopsy is recommended for solitary plaques. If lesions are present only on the pinnae, care should be taken not to damage fragile underlying cartilage.

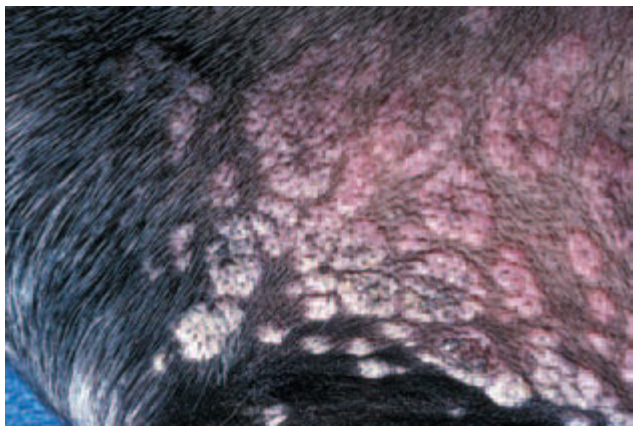


Fig. 7.34 Lichenoid keratosis in a German Shorthaired Pointer. Grouped scaly, crusted plaques are present. (Photograph courtesy T. Olivry; case material University of California, Davis.)

Histopathology (Figure 7.35)

The epidermis is irregularly acanthotic. In some cases there may be prominent psoriasiform hyperplasia, as in psoriasiform-lichenoid dermatosis (see p. 152). There is generally diffuse hyperkeratosis and multifocal, variably severe, parakeratosis. There may be hypergranulosis (increase in thickness of the granular layer). Serocellular crusting may be present. Intraepidermal pustules similar to those of psoriasiform-lichenoid dermatosis are less common but may be identified in some cases. Dermal inflammation is lichenoid and is predominantly lymphocytic and plasmacytic (see Chapter 11).

Histopathologic lesions may be strikingly similar to psoriasiform-lichenoid dermatosis, which is seen predominantly in Springer Spaniels. Clinical differences allow separation of these entities in dogs, as lichenoid keratoses are usually solitary and are found in many breeds.

INFLAMED LINEAR EPIDERMAL NEVUS

(Synonym: inflammatory linear verrucous epidermal nevus)

Clinical features (Figures 7.36 and 7.37)

The word 'nevus' refers to birthmarks or other localized defects of the skin presumed to be caused by an embryonic failure of normal development. Lesions are characterized by hyperplasia involving one or more components of the skin. 'Hamartoma' is a more inclusive term than nevus and is the preferred veterinary nomenclature for

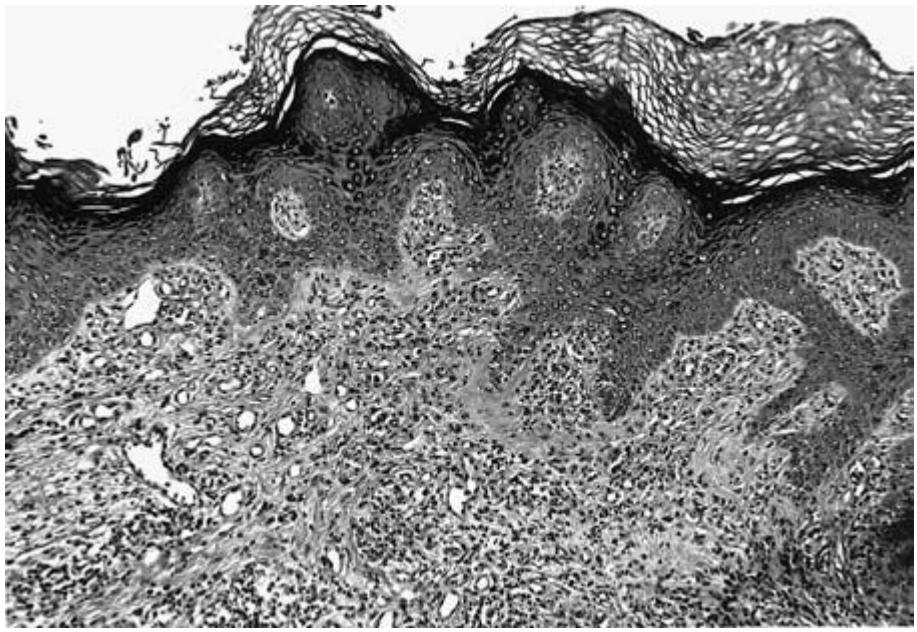


Fig. 7.35 Lichenoid keratosis in a dog demonstrating marked irregular acanthosis and hyperkeratosis. Note prominent hypergranulosis.

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Fig. 7.36 Inflamed linear epidermal nevus on the trunk of a Cocker Spaniel. Lesions follow the strikingly symmetric patterns of parallel often curved lines, termed Blaschko's lines. (Photograph courtesy S.D. White.)



Fig. 7.37 Closer view of an inflamed linear epidermal nevus from the dog in Fig. 7.36, showing an alopecic linear band of verrucous, hyperkeratotic, hyperpigmented, lichenified skin. (Photograph courtesy S.D. White.)

most lesions that are believed to be congenital or acquired malformations. However, 'nevus' is already established in the human and canine literature for this entity. The uninflamed linear malformation of the epidermis will remain 'linear epidermal hamartoma' (see Chapter 22).

Inflamed linear epidermal nevi are rare, apparently developmental, skin lesions reported in the dog (White et al., 1993). The syndrome bears striking resemblance to inflamed linear verrucous epidermal nevus (ILVEN) in humans. Epidermal nevi in humans (Bolognia et al., 1994) and in dogs tend to follow the strikingly symmetric patterns of parallel often curved lines, termed Blaschko's lines; thus, ILVEN can be considered a form of 'blaschkitis'. Interestingly, a recently recognized similar entity, inflamed linear pustular acantholytic dermatosis (Beningo & Scott, 2001), also appears to follow Blaschko's lines, and could conceivably be another form of blaschkitis in the dog.

Clinically, inflamed linear epidermal nevi are characterized by partially to completely alopecic linear bands of verrucous, hyperkeratotic, usually hyperpigmented, lichenified skin. The surface of the lesions may resemble papillomas. Keratin-plugged hair follicles may lead to enhanced susceptibility to secondary pyoderma. Lesions may be solitary or multiple. They have been seen most commonly on the lateral trunk, but also occur on the face, pinnae, and footpads (White et al., 1993). Lesions increase in size as the animal grows. Chronic lesions may be pruritic. Bacterial overgrowth and *Malassezia* dermatitis may exacerbate inflammation and cause additional pruritus.

Three of four dogs reported with this syndrome were related Cocker Spaniels (White et al., 1993). The authors have seen this syndrome in a variety of different breeds, including the Cocker Spaniel, Dachshund, and Miniature Schnauzer. While all four dogs reported by White et al. (1993) were female, it is not known if a sex predilection exists. All dogs of that report had lesions occurring before 6 months of age. Epidermal nevi should be present from birth, but may not be noted in well haired dogs until lesions increase in size.

Clinical differential diagnoses are few. Similar lesions can be seen with congenital follicular parakeratosis (see Chapter 8); however, affected dogs have more generalized disease in addition to linear lesions.

Biopsy site selection

Small lesions should be excised in their entirety. Multiple punch biopsy specimens can be taken from larger lesions.

Histopathology (Figures 7.38 and 7.39)

Inflamed linear epidermal nevus has severe irregular acanthosis accompanied by generally severe parakeratosis (see Chapter 8). The proliferative and parakeratotic changes extend to superficial follicles, which are often massively dilated. Frank neutrophilic pustules may be present superficially and within follicular infundibula. Acantholytic keratinocytes may be seen at the base of occasional pustules. Colonies of staphylococci are prominent within crusts. Surface colonization by *Malassezia* sp. has been reported (White et al., 1993). Idiopathic linear pustular acantholytic dermatosis also features epidermal and follicular epithelial hyperplasia and follicular pustules with acantholysis (Beningo & Scott, 2001), and may be a related phenomenon (blaschkitis).

Dermal inflammation is most prominent beneath areas of pustulation and crusting, and is minimal to mild in

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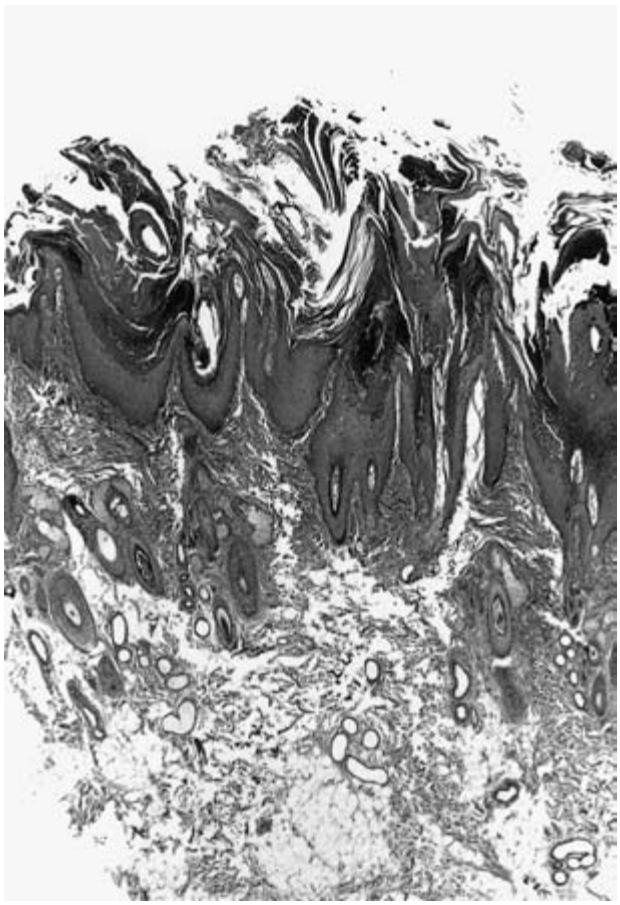


Fig. 7.38 Inflamed linear epidermal nevus demonstrating severe irregular acanthosis with massive parakeratosis and crusting. Note extension to hair follicles.



Fig. 7.39 Higher magnification of inflamed linear epidermal nevus. Note marked irregular acanthosis and parakeratosis.

other locations. Mild areas have lymphocytes and some macrophages, while more inflamed foci show neutrophils, plasma cells, and occasional eosinophils. Sebaceous glands may be hyperplastic.

The hyperplastic changes of inflamed linear epidermal nevi are relatively nonspecific. However, in the context of severe hyperplasia, the intense crusting and massive parakeratosis are highly suggestive. Clinical features are important in the ultimate diagnosis of these lesions.

GIANT CELL DERMATOSIS IN FeLV-POSITIVE CATS

Clinical features (Figures 7.40 and 7.41)

A variety of different cutaneous signs have been seen in conjunction with infection by the feline leukemia virus (FeLV), an immunosuppressive, oncogenic retrovirus. In the early 1990s, a rare, distinctive giant cell dermatosis was reported in FeLV-positive cats; FeLV antigen was detected in affected keratinocytes using immunohistochemistry (Gross et al., 1993). It was hypothesized that infection with FeLV may have initiated early neoplastic alteration of the keratinocytes through recombination with host oncogenes. Three of six cats in the study had previously received FeLV vaccination (Gross et al., 1993). The authors have seen only one additional confirmed case of this highly distinctive dermatosis since that report.

Clinical features include exfoliative dermatitis with adherent crusts and alopecia. Erythema and focal erosions are seen in more severely affected regions. Distribution is variable, but all reported cats had involvement of the muzzle or head (Gross et al., 1993). The more recently observed case had lesions of the pinnae that progressed to affect nasal and perioral sites, as well as the ventral neck, mammary region, and toes. Lips and perioral skin were involved in four of six reported cats. Other mucocutaneous junctions and the trunk were affected in some cats. Pruritus was present in five of six cats (Gross et al., 1993). Age, breed, or sex signalment predilections have not been noted.

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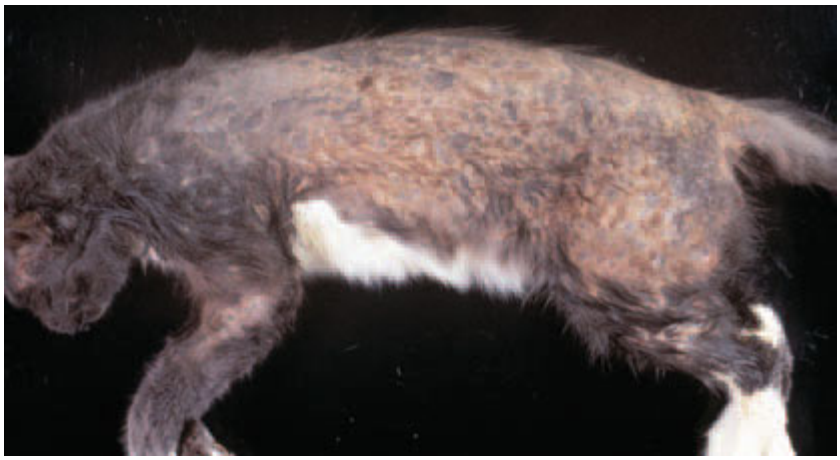


Fig. 7.40 Giant cell dermatosis in an FeLV-positive cat. The cat exhibited severe, generalized exfoliative dermatitis. (From Gross, T.L., Clark, E.G., Hargis, A.M., et al. (1993) Giant cell dermatosis in FeLV-positive cats. *Vet Dermatol* **4**, 117–22. Reprinted with permission.)

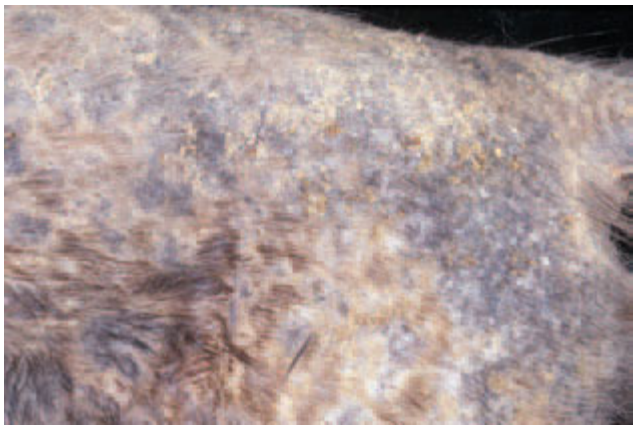


Fig. 7.41 Closer view of the cat shown in Fig. 7.40. Extensive alopecia with adherent crusts is present. (Photograph courtesy E.G. Clark.)

Clinical differential diagnoses should include any crusting, exfoliative skin disease including pemphigus foliaceus, generalized dermatophytosis, notoedric acariasis, feline thymoma-associated exfoliative dermatitis, epitheliotropic T cell lymphoma (mycosis fungoides), mural folliculitis, and erythema multiforme. Giant cell dermatosis in FeLV-positive cats is not visually distinctive; histopathology is required.

Biopsy site selection (Figures 7.42 through 7.44)

Areas of maximal exfoliative skin disease should be selected. Minimally eroded skin is more likely to display the histopathologic features necessary to make the diagnosis.



Fig. 7.42 Giant cell dermatosis in an FeLV-positive cat. Irregular acanthosis is accompanied by numerous, often darker-staining giant cells throughout the epidermis and hair follicles. (Case material courtesy E.G. Clark.)

Histopathology

There is moderate to severe irregular acanthosis accompanied by striking formation of giant cells. Syncytial giant

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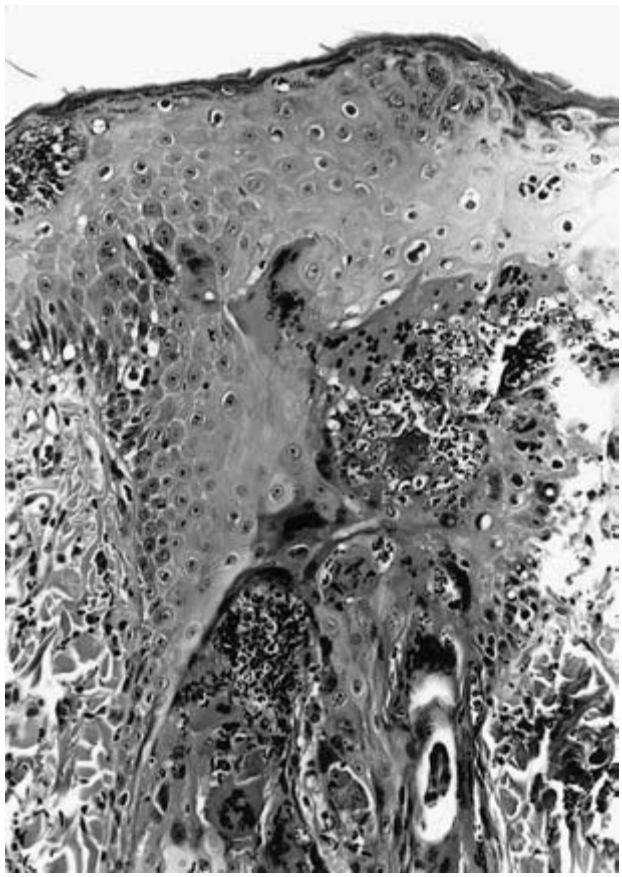


Fig. 7.43 Higher magnification of giant cell dermatosis in FeLV-positive cat showing massive multinucleated giant cells in the epidermis and follicular infundibulum. Note intraepithelial pustules.

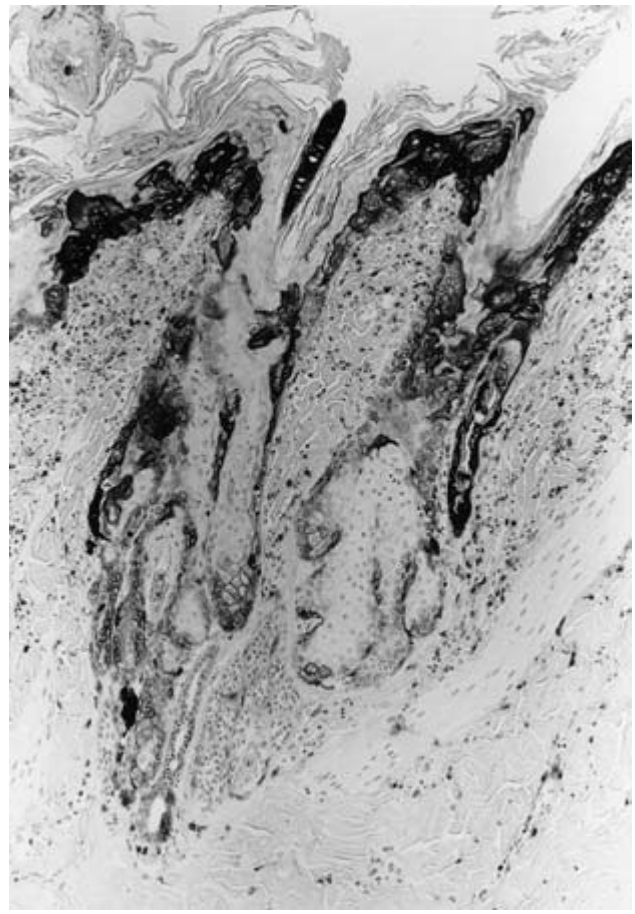


Fig. 7.44 Immunohistochemistry for FeLV gp70 antigen; FeLV-laden cells are darkly colored (chromogen diaminobenzidine [DAB]) (Case material courtesy E.G. Clark).

cells of keratinocytic origin contain up to 30 nuclei and are distributed throughout the epidermis and follicular infundibula. There is accompanying loss of orderly maturation of keratinocytes in areas of pronounced giant cell formation. Scattered keratinocytes are individually shrunken and degenerate, suggesting apoptosis. Feline leukemia virus gp70 antigen was demonstrated in numerous keratinocytes within areas of giant cell formation and in adjacent skin using immunohistochemistry (Gross et al., 1993), and in the recently observed case.

There may be hyperkeratosis and crusting with secondary colonization by staphylococci. Superficial pustulation of both the epidermis and hair follicles may be seen. The superficial and periadnexal dermis contains a mixed inflammatory cell population of lymphocytes, macrophages, neutrophils, eosinophils, and mast cells.

The histological findings of striking giant cell formation are diagnostically unique for this entity. Theoretically, other viral infections or drug reactions could produce giant cell formation of this type.

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Chapter 8

Diseases with abnormal cornification

The broad term 'cornification' encompasses all of the processes that lead to the formation of the horny layer of the epidermis. These include keratinization, which is a series of genetically programmed events by which keratinocytes in the epidermal basal cell layer mature and die, producing the stratum corneum. Cornification also includes the formation of all of the other constituent parts of the lipid-rich intercellular domain that provide the 'glue' that aids in binding terminally differentiated corneocytes to maintain a relatively impermeable barrier (Williams & Elias, 1993; Scott et al., 2001; Chu et al., 2003; Kimyai-Asadi et al., 2003). Thus, keratinization is but one part of the process of cornification; the terms are not synonymous.

Disorders of cornification may be subdivided into disorders of desquamation (retention hyperkeratosis) or hyperproliferative disorders (Williams & Elias, 1993). Hyperproliferative disorders can be further subdivided into diseases with a 'primary defect in the regulation of epidermal growth or, more commonly, secondary to a defect in barrier formation, resulting from one or more abnormal epidermal structural components' (Williams & Elias, 1993). Categorization of the defect leading to an abnormality of cornification requires molecular studies beyond clinical and routine histopathological evaluations. If molecular studies supporting a specific defect are not available, the broad term 'disorder of cornification' is preferred as the more narrow term; 'disorder of keratinization' connotes only a defect in keratinocyte differentiation. Most diseases of cornification have a hereditary, metabolic, or nutritional cause.

Diseases with abnormal cornification are usually characterized by the accumulation of abnormal keratin on the epidermal surface and within superficial hair follicles. The appearance of the keratin layer is not of the normal basketweave type and may be compact, lamellar (laminated), or parakeratotic. Basketweave keratin has regular layers with clear spaces, resembling scalloped lace. Lamellar or laminated keratin is condensed but still separates slightly into layers. Compact keratin is very dense and tends not to separate. Parakeratosis is persistence of keratinocyte nuclei within the stratum corneum. The granular layer, or stratum granulosum, may be thickened (hypergranulosis) or thinned (hypogranulosis).

Hyperkeratosis is defined as an increase in the cornified layer, and technically may be orthokeratotic (nuclei not retained) or parakeratotic. Conventionally, 'hyperkeratosis' is often used synonymously with 'orthokeratotic hyperkeratosis'. Diseases of cornification are not necessarily hyperkeratotic.

Other diseases not included in this group may have hyperkeratosis or parakeratosis. For example, as occurs prototypically in sebaceous adenitis, some infectious inflammatory diseases may destroy sebaceous glands (exfoliative cutaneous lupus erythematosus, demodicosis, leishmaniasis), which can lead to secondary hyperkeratosis. Diseases of abnormal follicular growth and differentiation, such as endocrine alopecia and follicular dysplasia, can result in follicular hyperkeratosis (follicular keratosis). Diffuse parakeratosis may be a feature of allergic conditions such as canine sarcoptic acariasis, irritant reactions, apoptotic necrosis as in erythema multiforme, or any disease with significant spongiosis. The diseases included in this chapter have abnormal development of the cornified layer as a predominant and primary pathologic feature.

PRIMARY SEBORRHEA AND SEBORRHEIC DERMATITIS

Clinical features (Figures 8.1 through 8.4)

Seborrhea is a confusing, nonspecific name that has been used to describe the clinical signs of excessive scaling, crusting, and greasiness. Seborrhea has connoted specific, heritable disorders of cornification as well as, more generically, the scaling and greasiness associated with a number of unrelated skin diseases such as hypothyroidism, demodicosis, sarcoptic acariasis, and flea allergy dermatitis (secondary seborrhea). A relationship between the term 'seborrhea' and sebaceous gland function has not

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Fig. 8.1 Primary seborrhea in a black Cocker Spaniel. The area has been clipped to allow better visualization of scales and crusts.



Fig. 8.2 Severe primary seborrhea in a blond Cocker Spaniel. Adherent keratinous deposits mat the hair remaining within the partially alopecic lesion.



Fig. 8.3 Seborrheic dermatitis on the ventrum of a blond Cocker Spaniel. Erythematous, well-demarcated, circular plaques with adherent keratinous debris are accompanied by lichenification and hyperpigmentation.



Fig. 8.4 Seborrheic dermatitis on the lateral thorax of a blond Cocker Spaniel. Candle wax-like keratinous deposits mat the haircoat.

been shown, despite 'seborrhea' meaning the excessive flow of sebum.

Primary seborrhea and seborrheic dermatitis are used more narrowly to describe inherited abnormalities characterized by exfoliation that are seen in specific breeds of dogs. Cornification is the entire process of the formation of the horny envelope, including keratinization plus the development of the lipid-rich interstitium (see p. 161). Defects in these complicated processes can lead to different exfoliative skin diseases with variable clinical expression. Epidermal hyperproliferation has been proven to be present in primary seborrhea (Kwochka & Rademakers, 1989). However, evidence is not conclusive as to whether primary seborrhea is caused by a true defect in cornification, such as occurs in ichthyosis (see p. 174). Primary seborrhea currently is separated from ichthyotic disorders. Clarification based on further molecular evidence awaits further studies. Secondary pyoderma or *Malassezia* dermatitis may be involved in the pathogenesis of seborrheic dermatitis.

The etiopathologic relationship between vitamin A-responsive dermatosis and primary seborrhea is not known. The similarity of affected breeds and histologic features suggests a final common pathway for the two entities. Further studies are needed.

The terms 'seborrhea sicca', 'seborrhea oleosa', and 'seborrheic dermatitis' have been used to describe dry and waxy, oily, and focal more inflamed lesions, respectively. These terms remain useful in the clinical characterization of primary seborrhea. Seborrheic dermatitis usually occurs focally in dogs with seborrhea oleosa.

Clinical signs commonly associated with primary seborrhea include variable scaling, crusting, dryness, waxiness, and oiliness of the skin and haircoat. A ceruminous or waxy otitis externa often is a concomitant feature. A

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rancid odor is a consistent finding in the oily forms of primary seborrhea. Erythema and alopecia are present in varying degrees. Lesions are most commonly located on the trunk. Focally severe lesions also may be present on the pinnae and preen gland (caudal gland). Pruritus is variable. Secondary pyoderma and *Malassezia* dermatitis are common. Regional or generalized lymphadenopathy may be present in more severe cases.

Seborrheic dermatitis is characterized by erythematous, well demarcated to coalescing, somewhat circular plaques. Adherent keratinous debris mats the surrounding hair and varies in color from yellow to brown, and in texture from greasy to candle wax-like. Alopecia, lichenification, and hyperpigmentation may be evident in older lesions. Lesions are located primarily on the thorax, especially ventrally.

An unexplained adult-onset phenomenon closely resembling primary seborrhea can occur occasionally, especially in Cocker Spaniels. Dogs without a prior history of primary seborrhea may develop visually and histopathologically identical skin disease, seemingly triggered by an acquired, severe inflammatory dermatosis. After successful management of the triggering disease, symptoms of primary seborrhea remain long-term. The mechanisms of how severe inflammatory skin disease can alter the long term course of cornification are not known; perhaps infectious agents or other inflammatory stimuli can trigger the epidermal hyperproliferation documented in this condition.

Breeds affected with primary seborrhea include the Cocker Spaniel, Springer Spaniel, Basset Hound, Chinese Shar Pei (usually seborrhea oleosa); and the Doberman Pinscher, Irish Setter, German Shepherd Dog, Miniature Schnauzer, and Dachshund (usually seborrhea sicca). Seborrhea oleosa is seen most frequently and most severely in the Cocker Spaniel. Although 'ichthyosis' has been reported in the Cavalier King Charles Spaniel (see p. 174), the histologic findings more closely resemble those of primary seborrhea of the Cocker Spaniel and other spaniel breeds; molecular studies are required to identify which classification is most appropriate for this condition. Clinically similar lesions are seen in hyperplastic dermatosis of the West Highland White Terrier; however, differences in the histopathology of this disease preclude its inclusion in the primary seborrhea group (see Chapter 7). Most dogs with primary seborrhea have a history of developing lesions during the first year of life; the syndrome increases in severity with age. Sex predilections have not been noted.

Clinical differential diagnoses for primary seborrhea are legion and include any disease that can initiate exfoliative dermatitis. Early age of onset is a clue in the diagnosis of primary seborrhea. Visually similar clinical signs are associated with endocrine abnormalities such as hypothyroidism, or less commonly, gonadal hormone aberrations. Rarely, clinically similar lesions may be associated with dietary fat deficiency, or malabsorption or maldigestion. Scaling and crusting ('secondary seborrhea') can be seen with many other dermatoses, including ectoparasitism, pyoderma, dermatophytosis, autoimmune disease, neoplasia, and environmental influences such as dry heat.

Biopsy site selection

Care should be taken to sample lesions with ample adherent scales and crusts. Uninflamed lesions should be preferentially sampled, as secondary inflammatory changes may obscure the diagnosis of primary seborrhea. If inflammation is severe, it may be helpful to delay biopsy until secondary pyoderma or *Malassezia* dermatitis is controlled.

Histopathology (Figures 8.5 through 8.7)

Difficulty in the histopathologic evaluation of primary seborrhea arises from the presence of secondary inflammation, or seborrheic dermatitis. Seborrheic dermatitis can mimic chronic dermatitis of varying etiology, particularly chronic allergic dermatitis or chronic superficial pyoderma. Since these diseases may be present concurrently in dogs with seborrhea, the histopathologic picture can be very confusing. Thus, the most convincing evidence of primary seborrhea is often best obtained from uninflamed skin lesions.

Hyperkeratosis is the principal feature of uninflamed primary seborrhea. Keratin is somewhat amorphous and loosely layered; the typical basketweave appearance of normal keratin is absent. In lesions typified by the disease in spaniels, there is often prominent keratin plugging of superficial follicles, which may result in distension of the infundibula. This creates a pseudopapillomatous or digitated configuration to the epithelial surface, as well as a predominantly vertical rather than horizontal distribution of keratin. The epidermis may be normal or slightly acanthotic in uninflamed lesions and dermal inflammation is minimal to absent.

Most cases of primary seborrhea also have concurrent lesions of seborrheic dermatitis. There is moderate to severe acanthosis and hyperkeratosis, accompanied by discrete, mound-shaped areas of parakeratosis and crusting. These parakeratotic caps or spikes form commonly at the openings ('shoulders') of follicular ostia, particularly in the Cocker Spaniel and other spaniel breeds, and have been termed 'follicular epaulettes'. The formation of follicular epaulettes may be the most distinctive histopathologic feature of seborrheic dermatitis, at least in these breeds. Follicular keratosis is often less

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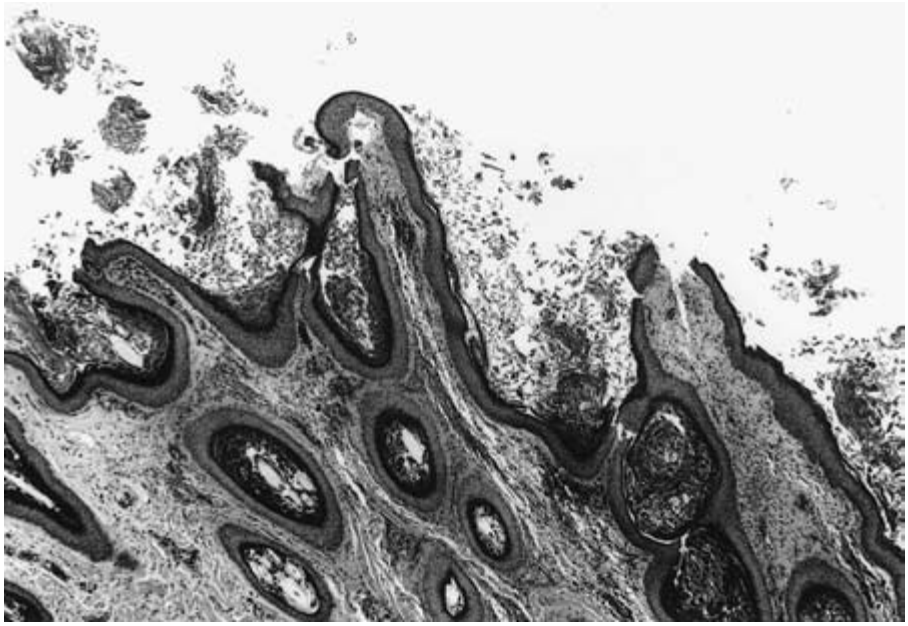


Fig. 8.5 Primary seborrhea in a Cocker Spaniel. Loosely organized keratin is distending follicular infundibula.



Fig. 8.6 Higher magnification of primary seborrhea in a Cocker Spaniel demonstrating fronds of keratin widening follicular ostia.

pronounced than in uninflamed primary seborrhea and may be accompanied by infundibular parakeratosis.

Dermal inflammation of seborrheic dermatitis is mixed and variable. Superficial perivascular to interstitial inflammation is composed of a mixed population of cells, including lymphocytes, plasma cells, macrophages, and variable neutrophils. Eosinophils and mast cells may also be found, particularly in cases further complicated by concurrent hypersensitivity disorders or *Malassezia* dermatitis. Inflammation often extends around adnexal appendages.

Uninflamed primary seborrhea resembles a reported form of ichthyosis in the Cavalier King Charles Spaniel (see p. 174). The mild keratinocyte vacuolation in conjunction with enlarged irregular keratohyalin granules, as seen in ichthyosis of the Cavalier King Charles Spaniel, is not present in primary seborrhea; however, the two conditions are otherwise identical. In severe lesions of primary seborrhea that have pronounced follicular keratosis, differentiation between primary seborrhea and vitamin A-responsive dermatosis may be difficult but is clinically unimportant. Histologic and clinical similarities

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Fig. 8.7 Seborrheic dermatitis in primary seborrhea. Note parakeratosis in a mound at the edge of a follicular ostium, acanthosis, and superficial dermal inflammation.

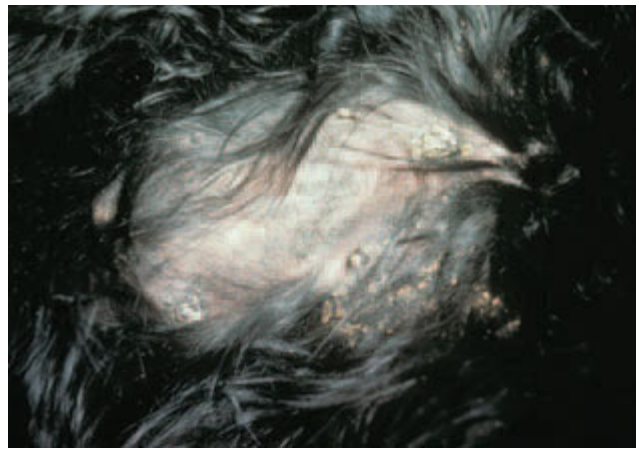


Fig. 8.8 Vitamin A-responsive dermatosis in a black Cocker Spaniel. Multifocal, well-demarcated, alopecic plaques are present on the ventral abdomen. Note severe frond-like accumulations of keratinous debris ('follicular fronds' or 'follicular casts'). (From Ihrke, P.J. & Goldschmidt, M.H. (1983) Vitamin A responsive dermatosis in the dog. *J Am Vet Med Assoc* **182**, 687–90. Reprinted with permission.)

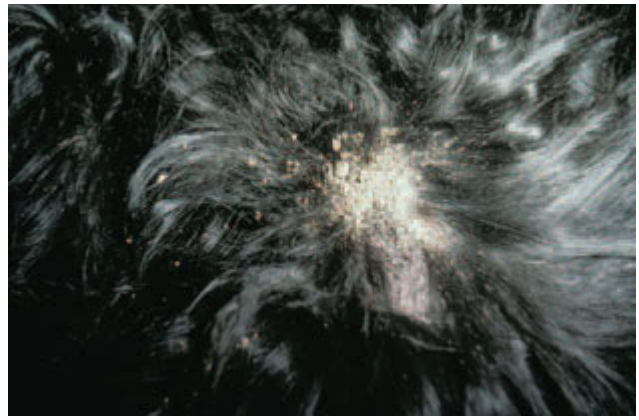


Fig. 8.9 Closer view of the dog in Fig. 8.8. Keratinous follicular fronds are emerging from dilated hair follicles. (From Ihrke, P.J. & Goldschmidt, M.H. (1983) Vitamin A responsive dermatosis in the dog. *J Am Vet Med Assoc* **182**, 687–90. Reprinted with permission.)

suggest etiopathogenic overlap of these two syndromes. Sebaceous adenitis with severe follicular keratosis (follicular fronds) may appear similar; however, sebaceous adenitis features a generalized absence of sebaceous glands. Ear margin seborrhea may be identical to primary seborrhea, but is confined to the ear margins.

The diagnosis of seborrheic dermatitis should not be difficult if concurrent lesions of primary seborrhea are found. If epidermal and follicular hyperkeratosis, as expected in primary seborrhea, is mild in the specimens available, it may be impossible to separate the lesions of seborrheic dermatitis from those of other chronic dermatitides, particularly chronic allergic dermatitis.

VITAMIN A-RESPONSIVE DERMATOSIS

Clinical features (Figures 8.8 and 8.9)

Vitamin A-responsive dermatosis is a rare abnormality of cornification that is seen predominantly in the Cocker Spaniel (Ihrke & Goldschmidt, 1983; Scott, 1986). Marked breed predilection and features in common with other primary cornification defects suggest a hereditary basis. Age of onset is a key feature in differentiating vitamin A-responsive dermatosis from primary seborrhea. Vitamin A-responsive dermatosis is an adult-onset disease, while primary seborrhea usually begins in young dogs, generally before 1 year of age. Vitamin A-responsive dermatosis in dogs bears resemblance to phrynoderma in humans, which is linked to vitamin A deficiency (Nieves & Goldsmith, 2003).

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The etiopathologic relationship between vitamin A-responsive dermatosis and primary seborrhea is not known. The similarity of affected breeds and histologic features suggests a final common pathway for the two entities. Further studies are needed.

Multifocal, alopecic, well-demarcated, erythematous plaques characterize vitamin A-responsive dermatosis. Severe follicular plugging with tenacious frond-like keratinous debris ('follicular fronds' or 'follicular casts') is a characteristic feature. Follicular papules with varying degrees of scaling, crusting, and alopecia are seen in the surrounding skin. Lesions are most prominent on the ventral and lateral chest and abdomen. Most affected dogs have a dry, dull, disheveled haircoat that may epilate easily. A concomitant ceruminous otitis with a rancid 'seborrheic' odor commonly is present.

This syndrome is seen almost exclusively in Cocker Spaniels. Similar lesions have been seen in several Miniature Schnauzers. Vitamin A-responsive dermatosis is an adult-onset disease. Sex predilections have not been noted.

The major clinical differential diagnosis is primary seborrhea with seborrheic dermatitis, as seen in Cocker Spaniels. Vitamin A-responsive dermatosis presents as a predominantly ventral, more focal disease, and has more prominent follicular keratinous deposits than does primary seborrhea. The adult onset of this syndrome aids in the differentiation from primary seborrhea, which is generally a juvenile-onset disease.

Biopsy site selection

A plaque with prominent follicular casting should be sampled. Care must be taken so that adherent keratinous debris is not dislodged from the specimen during biopsy.

Histopathology (Figures 8.10 and 8.11)

Severe follicular keratosis is the histopathologic hallmark of vitamin A-responsive dermatosis. Similar follicular lesions occur in vitamin A deficiency in humans (phrynoderma). Distention of follicular ostia and protrusion of massive plugs of keratin (follicular fronds) are seen. Contiguous dilated follicular infundibula may be mistaken for an uneven or papillated epidermal surface. Dilated follicles may rupture, leading to pustular follicular and perifollicular inflammation (furunculosis).

Epidermal hyperkeratosis accompanies the follicular changes. The epidermis is mildly to moderately acanthotic. Dermal inflammation varies from minimal to moderate and may resemble the dermal component of seborrheic dermatitis (see p. 161).

Differential diagnosis is relatively uncomplicated due to the severity of follicular keratosis observed in this syndrome. Follicular plugging is seen in primary seborrhea and late stage sebaceous adenitis, as well as ear margin seborrhea. Ear margin seborrhea is confined to pinnal edges. Sebaceous glands are predominantly or diffusely absent in sebaceous adenitis. Keratin accumulation in

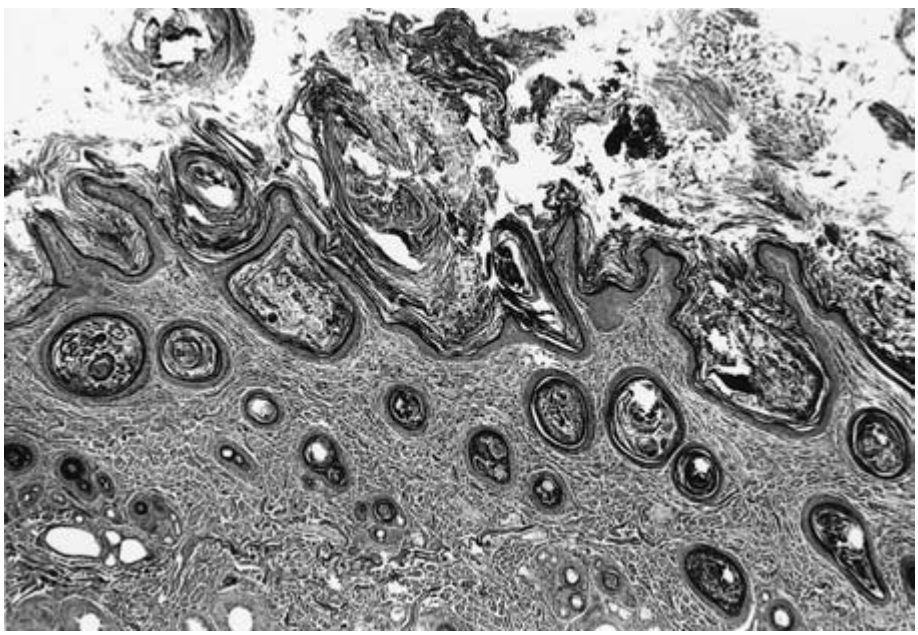


Fig. 8.10 Vitamin A-responsive dermatosis in a Schnauzer. Note massive distention of follicular infundibula with keratin.

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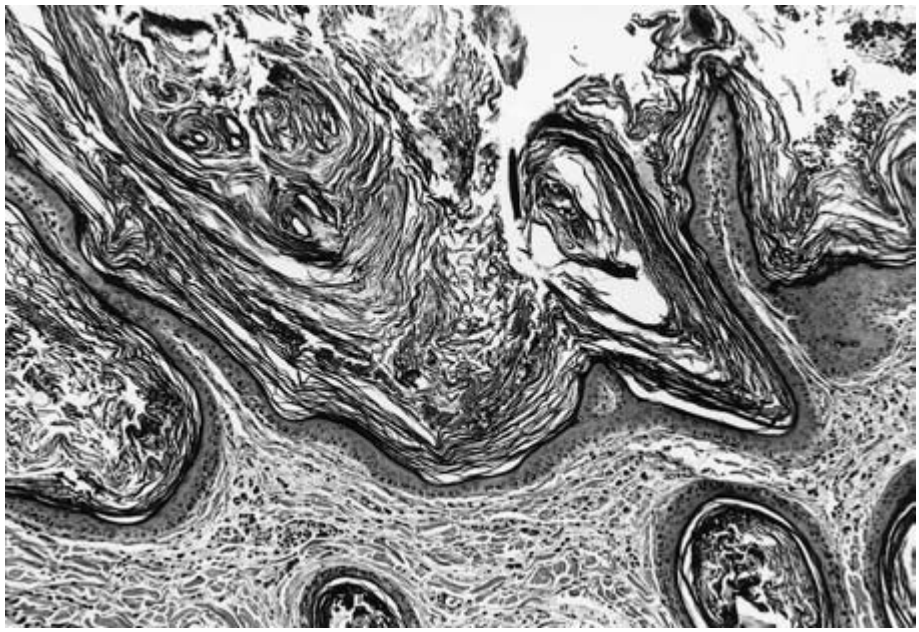


Fig. 8.11 Higher magnification of Fig. 8.10.

superficial follicles is qualitatively similar but is significantly more severe than in primary seborrhea (see p. 161). Differentiation between severe primary seborrhea and vitamin A-responsive dermatosis may be difficult but unimportant; histologic similarity suggests etiopathogenic overlap of these two syndromes.

CANINE EAR MARGIN SEBORRHEA

(Synonym: canine ear margin dermatosis)

Clinical features (Figures 8.12 and 8.13)

Canine ear margin seborrhea is a relatively common presumed abnormality in cornification. Lesions are confined to the margins of the pinnae. Marked breed predilection for the Dachshund and features in common with other cornification abnormalities suggest a hereditary basis for most cases. Ear margin seborrhea also may present as a clinical feature of hypothyroidism.

Adherent keratinous deposits are present on both the lateral and medial margins of the pinna. Considerable variation occurs in the character and color of the keratinous accumulations, which vary from greasy to waxy, tenacious to exfoliative, and yellow to brown. Follicular casts or plugs sometimes entrap hair. Partial alopecia of the pinnal margin is common, and keratin mats the remaining hair. A waxy, seborrheic odor often is present. Aggressive removal of tenacious debris may cause erosion or ulceration. The syndrome usually is asymptomatic, although pruritus may be seen. Fissuring and secondary bacterial infection can occur in unusually severe, chronic cases (Scott et al., 2001). Most dogs with ear margin seborrhea have lesions confined to the pinnae. When ear margin seborrhea is seen secondary to hypothyroidism, other skin lesions suggestive of hypothyroidism usually are present (see Chapter 19).



Fig. 8.12 Canine ear margin seborrhea in a Doberman Pinscher. Adherent keratinous deposits are present on the partially alopecic margin of the pinna. (Photograph courtesy H.T. Power; case material University of California, Davis.)

Canine ear margin seborrhea is seen most commonly in Dachshunds, although it may be seen in other breeds of dogs with pendulous ears. Ear margin seborrhea secondary to hypothyroidism may be seen in any breed. Age or sex predilections have not been noted.

Clinical differential diagnoses for ear margin seborrhea are few. The syndrome may resemble early vasculitis of

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the pinnal margin (which is initially characterized by scaling and hair loss), and early, localized canine sarcoptic acariasis. With the exception of ischemic dermatopathy/canine dermatomyositis (see Chapter 3), overt vasculitis of the pinnae causes gross tissue destruction in all but the very earliest clinical stages. Ischemic dermatopathy/canine dermatomyositis does not preferentially affect the margins of the pinnae. Canine sarcoptic acariasis is very pruritic, in contrast to ear margin seborrhea.



Fig. 8.13 Closer view of the pinna of the dog in Fig. 8.12. Follicular casts entrap hair on the margin of the partially alopecic pinna. (Photograph courtesy H.T. Power; case material University of California, Davis.)

Biopsy site selection

A small portion of the margin of the pinna with adherent keratinous deposits should be sampled. Cosmetically acceptable as well as representative biopsy specimens may be obtained using a single-edged razor blade or a scalpel blade to amputate a small portion of the rounded margin of the pinna. Care should be taken not to dislodge attached keratinous material.

Histopathology (Figure 8.14)

Ear margin seborrhea is characterized by severe hyperkeratosis, predominantly manifested by follicular keratosis. Keratin distends follicular ostia and may give the epidermal surface a pronounced pseudopapillomatous appearance. Keratin encircles protruding hair shafts to produce follicular 'fronds'. Parakeratosis and neutrophilic serocellular crusting are variable. Acanthosis is mild to moderate and may not be present diffusely within the specimen.

Superficial and periadnexal mixed dermal inflammation is variable and may be absent. The inflammatory infiltrate may include lymphocytes, plasma cells, macrophages, and neutrophils.

Lesions of ear margin seborrhea closely resemble vitamin A-responsive dermatosis or severe primary seborrhea. Knowledge of site affected is important diagnostically and may be revealed if pinnal cartilage is included in the specimen. Follicular frond formation in ear margin seborrhea also is similar to sebaceous adenitis; delineation



Fig. 8.14 Ear margin seborrhea in a dog demonstrating pronounced follicular keratosis.

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Fig. 8.15 Nasal hyperkeratosis in a middle-aged Basset Hound. The planum nasale exhibits prominent, dry, adherent keratinous material.



Fig. 8.16 Digital hyperkeratosis in a 9-year-old Cocker Spaniel. Excess keratin has been worn off the weight-bearing surfaces leaving proliferative frond-like material at the periphery of the pawpads.

is based on the general absence of sebaceous glands in sebaceous adenitis. Differentiation of these two entities may be complicated by the fact that ear margin biopsy specimens may be superficial, resulting in lack of visible sebaceous glands.

NASODIGITAL HYPERKERATOSIS

(Synonym: idiopathic nasodigital hyperkeratosis)

Clinical features (Figures 8.15 and 8.16)

Nasodigital hyperkeratosis is an idiopathic disorder of cornification affecting the planum nasale and pawpads. The syndrome is common in the older dog and uncommon to rare in the cat. Nasodigital hyperkeratosis increases in occurrence and severity with age and probably represents a senile change. Lesions may involve either the planum nasale, the pawpads, or both.

The normally smooth, pliable, shiny planum nasale becomes dry, firm, and hyperplastic. Wide variation occurs in surface changes. Prominent, adherent, dry keratinous material may accentuate the normal cobblestone pattern of the planum nasale. Conversely, either frond-like keratinous proliferations or verrucous, ridged proliferations with feather-like splitting may obscure the normal cobblestone architecture. Inflammation is not a feature of uncomplicated nasal hyperkeratosis. However, fissuring can lead to secondary inflammation, and bacterial and *Malassezia* infection. Although digital hyperkeratosis affects the entire surface of all pawpads, excess keratin is worn off weight-bearing surfaces leaving proliferative debris predominantly at the pad margins (Scott et al., 2001). Abnormalities in cornification involving haired skin are not seen with this syndrome and affected dogs are otherwise healthy.

Nasal hyperkeratosis is rare in the cat and digital hyperkeratosis is uncommon. A case observed by one author (T.L.G.) had isolated callus-like lesions on three individual pads. One author (E.J.W.) has seen two Bengal cats with hyperkeratosis that partially occluded the nares, resulting in respiratory difficulty.

The syndrome usually begins either in late middle-aged or elderly dogs. Although some sources indicate that breed predilections are not seen (Scott et al., 2001), the authors believe this syndrome to be much more common in Cocker Spaniels, Beagles, and Basset Hounds. Sex predilections have not been noted. Bengal cats may be at increased risk.

Nasodigital hyperkeratosis of older dogs is visually distinctive and is generally not confused with other diseases. Early discoid lupus erythematosus or pemphigus erythematosus involving only the planum nasale may mimic nasal hyperkeratosis if these diseases have only minimally disturbed the normal planum architecture. Similarly, digital hyperkeratosis could be confused with pemphigus foliaceus that is restricted to the pawpads. Nasal parakeratosis of Labrador Retrievers (see p. 170) may be similar, but occurs in dogs less than 1 year of age. Familial pawpad hyperkeratosis also may appear similar but has specific breed predilections and earlier age of onset (see p. 179). 'Hard pad disease' may be seen in conjunction with distemper virus infection; associated systemic

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signs are present. Leishmaniasis may affect pawpads, but lesions also should be present elsewhere.

Biopsy site selection

Lesions are best sampled by 4 mm punch biopsy of the lateral planum nasale or the margins of the less weight-bearing pawpads. Cosmetically, less obvious deformation of the planum nasale results from lateral biopsy. Hemostasis may be difficult at these locations.

Histopathology (Figure 8.17)

The primary lesion of uninflamed nasodigital hyperkeratosis is irregular mild to moderate acanthosis accompanied by moderate to severe orthokeratotic hyperkeratosis. There is variable hypergranulosis. Fissuring of the keratin layer is associated with secondary neutrophilic serocellular crusting and parakeratosis. Crusting and parakeratosis may be distributed in columns or may become diffuse and severe. Dermal inflammation is variable and depends on the degree of disruption of the keratin layer. Neutrophils are intermingled with lymphocytes, plasma cells, and macrophages; pigmentary incontinence may be present. In the single feline case observed by one author (T.L.G.) there was orthokeratotic hyperkeratosis with subjacent hypergranulosis, similar to dogs. Hyperkeratosis in the two observed Bengal cats (E.J.W.) was similar and severe.

Differential diagnoses are few, as the hyperkeratotic features in skin from the pad or nasal planum are fairly typical. Familial pawpad hyperkeratosis may be indistinguishable (see p. 179) and consideration of age and breed affected may be important in differentiation. In cases with secondary diffuse parakeratosis, zinc-responsive skin disease and nasal parakeratosis of Labrador Retrievers may need to be considered (see p. 188 and below). Nasal and pedal lesions only are not generally expected in zinc-responsive dermatosis. Clinical differentiation from nasal parakeratosis of Labrador Retrievers may be required.

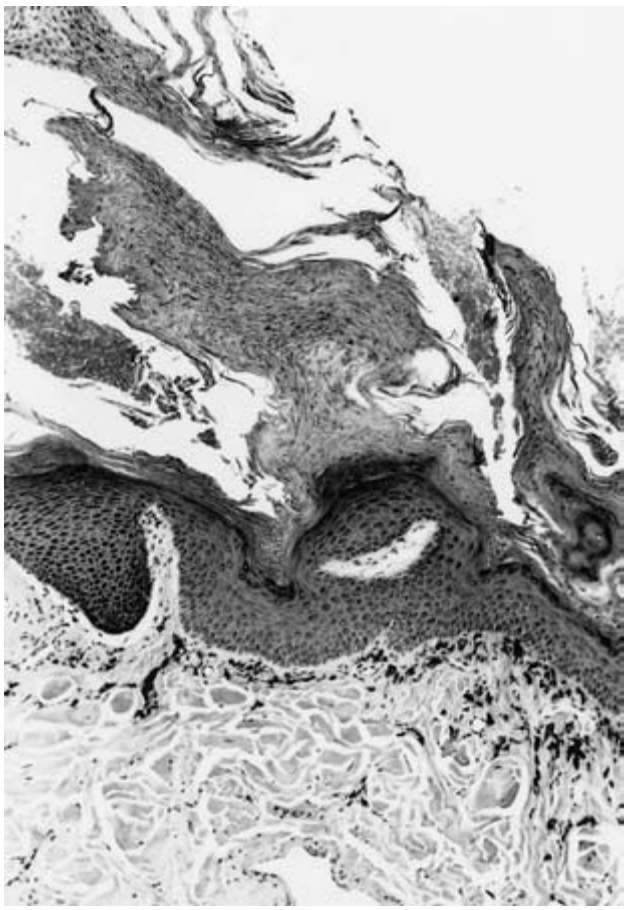


Fig. 8.17 Nasodigital hyperkeratosis. The orthokeratotic and parakeratotic layer is fragmented or fissured.

NASAL PARAKERATOSIS OF LABRADOR RETRIEVERS

Clinical features (Figure 8.18)

Nasal parakeratosis of Labrador Retrievers is a rare syndrome characterized by proliferative changes of the planum nasale. The strong breed predilection supports the likelihood of a hereditary basis, and an autosomal



Fig. 8.18 Nasal parakeratosis of Labrador Retrievers. Rough, proliferative keratinous debris is present on the planum nasale.

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recessive mode of inheritance has been hypothesized (Page et al., 2003). Although electron microscopic features indicated an altered cornification process, it is not known if the syndrome is a primary defect in cornification or an inflammatory disease that affects the cornification process adversely (Page et al., 2003).

Affected dogs develop dry, rough, proliferative, adherent keratinous debris on their planum nasale. In the early stages the process does not ablate the normal cobblestone appearance; later severe lesions may be ablative. Lesions are more severe on the dorsal surface of the planum. A color change from black to gray or brown may accompany the proliferation. In severely affected dogs, fissuring can lead to secondary inflammation and bacterial infection. Several owners have noted that the surface of the planum nasale becomes a paler shade of grey or brown after the surface is wet (Page et al., 2003). Affected dogs are otherwise healthy.

Grossly similar lesions affected the pawpads in two of 18 reported dogs; histopathologic analysis was not available and thus it is unknown whether those lesions represent the same condition (Page et al., 2003). Familial pawpad hyperkeratosis is parakeratotic in this breed (see p. 179), but the relationship of these two conditions is not known.

The syndrome has been seen exclusively in Labrador Retrievers or their crossbreeds. Black, yellow, and chocolate Labrador Retrievers are affected (Peters et al., 2003). Dogs develop lesions between 6 months and 1 year of age (Page et al., 2003). Thirteen of 18 affected dogs were males (Page et al., 2003).

Differential diagnosis is not problematic, as nasal parakeratosis of Labrador Retrievers is visually distinctive, develops at less than 1 year of age, and occurs exclusively in Labrador Retrievers and their related crossbreeds. Nasal parakeratosis of Labrador Retrievers shares some clinical features with nasodigital hyperkeratosis. However, nasodigital hyperkeratosis occurs in middle aged or elderly dogs and may be seen in a variety of breeds. Lesions seen with zinc-responsive dermatosis rarely are limited to the planum nasale and are seen predominantly in northern breed dogs. In contrast to nasal parakeratosis, autoimmune diseases that affect the planum, such as discoid lupus erythematosus and pemphigus foliaceus, alter the normal cobblestone architecture of the planum nasale early in the progression of the disease. Skin biopsy is required for definitive diagnosis.

Biopsy site selection

Biopsy specimens are best acquired with punch biopsy technique. A 4 mm punch can be used to sample the lateral aspects of the planum nasale. Cosmetically, less obvious deformation of the planum nasale is noted when specimens are taken laterally.

Histopathology (Figures 8.19 and 8.20)

There is mild to severe parakeratosis with moderate acanthosis. The keratin layer may be arranged in peaks. Serum lakes and smaller vacuoles accumulate in the keratin layer, often strikingly, and are accompanied by degenerating

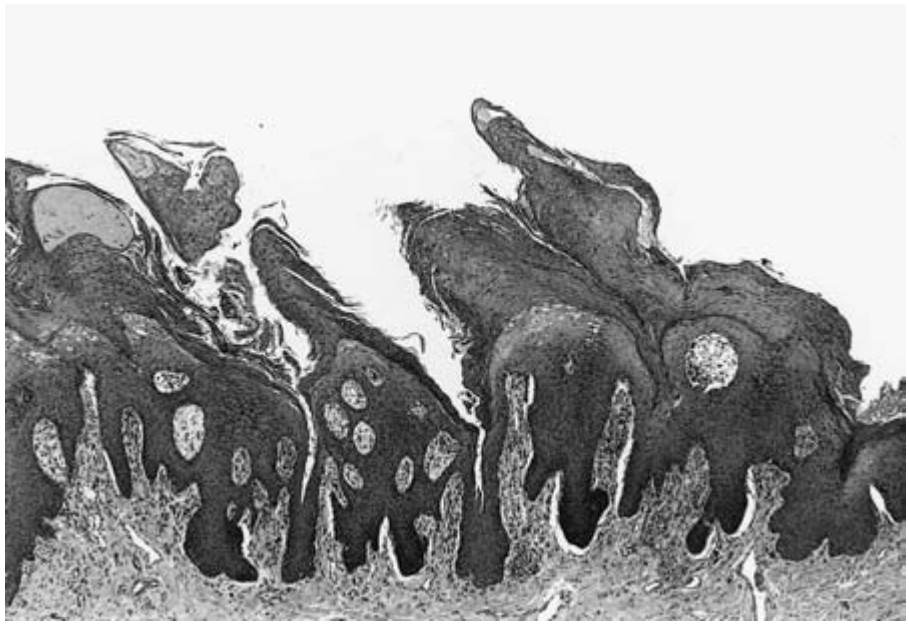


Fig. 8.19 Nasal parakeratosis of Labrador Retrievers. Note peaked parakeratosis, foci of epidermal pallor, and large serum lakes at left.

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Fig. 8.20 Higher magnification of nasal parakeratosis demonstrating large serum lakes within parakeratosis. There is acanthosis and superficial dermatitis.

neutrophils. There are rare, brightly eosinophilic and shrunken (apoptotic or dyskeratotic) keratinocytes in the spinosum, often contiguous to the overlying parakeratotic layer. There may be a zone of epidermal pallor just beneath the parakeratotic layer, characterized by ballooning cytoplasmic vacuolation of keratinocytes. Neutrophils and lymphocytes migrate through the epidermis.

The dermis features superficial perivascular to band-like inflammation consisting of lymphocytes, macrophages, plasma cells, and scattered neutrophils. There is moderate to severe superficial dermal edema, and pigmentary incontinence, particularly in severe lesions of the nasal planum. Fibrosis was reported (Page et al., 2003). Immunoperoxidase staining for IgG was negative in four dogs tested (Page et al., 2003).

The principal differential diagnosis for nasal parakeratosis is zinc-responsive dermatosis. If epidermal pallor is present beneath parakeratosis, then superficial necrolytic dermatitis may be considered. As zinc-responsive skin disease and superficial necrolytic dermatitis have very different clinical presentations (see p. 188 and Chapter 4), knowledge of lesion distribution and breed affected will allow differentiation. Serum lakes may be found in zinc-responsive dermatosis, but are often organized in columnar or peaked configuration. Lakes of serum are not a typical feature of superficial necrolytic dermatitis. Small vacuoles within the parakeratotic layer are a common feature of many parakeratotic conditions and are not specifically diagnostic (Senter et al., 2002; Peters et al., 2003). However, the numbers of vacuoles seen in nasal parakeratosis of Labrador Retrievers are, in general, greater than in other parakeratotic conditions (Peters et al., 2003).



Fig. 8.21 Congenital follicular parakeratosis in a Rottweiler. Adherent keratinous debris surrounds the planum nasale. (Photograph courtesy D.W. Scott.)

CONGENITAL FOLLICULAR PARAKERATOSIS

Clinical features (Figures 8.21 through 8.24)

Congenital follicular parakeratosis is a rare disorder of cornification (Lewis et al., 1998; Scott & Miller, 2000). The syndrome is presumed to be heritable, as six of seven cases reported in the literature are Rottweilers. An X-linked mode of inheritance is suggested by the fact that all cases reported to date have been in female dogs (Scott et al., 2001). Two Labrador Retrievers seen by the authors responded to vitamin A therapy.

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Fig. 8.22 Closer view of the dog in Fig. 8.21. Keratinous debris adheres to the skin and ensheathes the hair of the pinna. (Photograph courtesy D.W. Scott.)



Fig. 8.23 Congenital follicular parakeratosis in a Labrador Retriever. In this view there is the illusion of subtle partial alopecia caused by clumping of the hair. (Photograph courtesy S. Radowicz.)

Affected dogs have a generalized exfoliative dermatitis. Thick keratinous debris adheres to the skin and ensheathes and clumps the hair in yellow, brown, or black, waxy follicular casts. Lesions may first develop on the muzzle and pinnae but rapidly generalize. Hair loss may be present at sites of focal adherent debris. Relatively glabrous regions such as the groin and axillae may be less severely affected. Linear hyperplastic lesions on the trunk following the lines of Blaschko (a visually striking, repetitive, curvilinear pattern seen with certain heritable skin diseases in humans; Bolognia et al., 1994) were present in two of the six Rottweilers (Lewis et al., 1998; Scott & Miller, 2000). The planum nasale and pawpads are strikingly spared (Lewis et al., 1998; Scott & Miller, 2000). Affected Labrador Retrievers may give the visual appearance of greater hair loss than actually is present, as debris ensheathes and clumps the hair. Secondary pyoderma or



Fig. 8.24 Closer view of the dog in Fig. 8.23. Thick, keratinous debris adheres to the skin. (Photograph courtesy S. Radowicz.)

Malassezia dermatitis is common and, when present, increases pruritus. Affected puppies may be stunted. Multiple, noncutaneous congenital defects have been seen in both affected dogs and their littermates (Lewis et al., 1998; Scott & Miller, 2000).

Lesions are present at birth but rapidly increase in severity. Six of seven cases reported have been Rottweilers; the seventh was a Siberian Husky. Two cases were observed by the authors in young Labrador Retrievers. All known affected dogs have been female.

Clinical differential diagnoses are few as this is a highly characteristic, early onset genodermatosis. Ichthyosis shares some clinical features, but commonly also affects the planum nasale and pawpads. The linear hyperplastic lesions seen with congenital follicular parakeratosis also may be similar to those seen in inflamed linear epidermal nevus (see Chapter 7); however, dogs with the latter syndrome do not exhibit generalized exfoliative disease.

Biopsy site selection

Multiple areas with maximum involvement should be sampled. Care should be taken that adherent keratinous deposits are not dislodged during procurement.

Histopathology (Figures 8.25 and 8.26)

There is moderate to severe acanthosis of the epidermis and superficial hair follicles, and severe parakeratosis (Lewis et al., 1998; Scott & Miller, 2000). Parakeratosis affects the hair follicles predominantly and distends infundibula; conical projections may be seen (Scott & Miller, 2000). Severe folliculitis or furunculosis may occur. There may be milder parakeratosis of the interfol-

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Fig. 8.25 Congenital follicular parakeratosis in a Labrador Retriever. There is accompanying folliculitis.



Fig. 8.26 Higher magnification of congenital follicular parakeratosis in a Labrador Retriever with accompanying inflammatory debris and dermatitis.

licular epidermis (Lewis et al., 1998) or the interfollicular epidermis may have orthokeratotic hyperkeratosis (Scott & Miller, 2000). Laminar intracellular edema of the stratum spinosum and granulosum may be present. The granular layer is variable in prominence. Variably sized vacuoles are present throughout the parakeratotic layer, and were identified as lipid on ultrastructural evaluation (Lewis et al., 1998). Although vacuoles are a common feature of parakeratotic diseases in general, very large vacuoles (>5 μm) are reportedly seen only in congenital follicular parakeratosis (Senter et al., 2002). *Malassezia* were found in one case which also featured bacterial folliculitis (Scott & Miller, 2000).

Dermal inflammation varies from perivascular to lichenoid, and consists of lymphocytes and plasma cells. A similar band-like infiltrate may encircle hair follicles. Sebaceous hyperplasia may be followed by squamous metaplasia of glands in later stages of the disease (Lewis et al., 1998).

The principal differential diagnosis of congenital follicular parakeratosis is inflamed linear epidermal nevus, which it closely resembles (see p. 191). There are also clinical similarities and careful clinical differentiation may be required. The parakeratotic lesions of congenital follicular parakeratosis are too massive and too predominantly folliculocentric to be confused with most other parakeratotic conditions such as zinc-responsive dermatosis, generic dog food dermatosis, acrodermatitis, or superficial necrolytic dermatitis.

ICHTHYOSIS

Clinical features (Figures 8.27 through 8.30)

Ichthyosis is a very rare hereditary skin disease that has been reported in the dog and, more recently, in the cat. Although both clinical and histopathologic similarities exist between ichthyosis in dogs and cats and a heterogeneous group of heritable skin diseases in humans termed ichthyosis or ichthyosiform dermatoses, reported cases in animals do not completely match the human syndromes (Helman et al., 1997; Credille et al., 1998; Lewis et al.,

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Fig. 8.27 Canine ichthyosis in a yellow Labrador Retriever. Tightly adherent scales entrap hairs.



Fig. 8.28 Closer view of the dog seen in Fig. 8.27. The affected area was clipped to show the adherent dark, keratinous deposits.

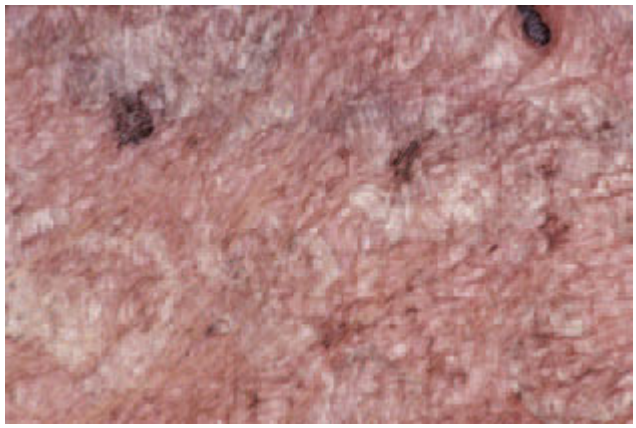


Fig. 8.29 Ichthyosis in an Australian Terrier. Dark keratinous debris is adherent to the skin.

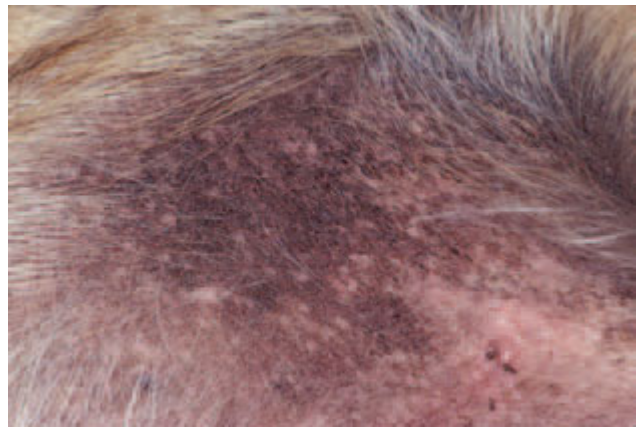


Fig. 8.30 Ichthyosis in a Norfolk Terrier. Tightly adherent, light brown scales cover the abdomen.

1998; Olivry & Mason, 1998). Many subgroups of ichthyosis are recognized in humans and approximately a dozen have been most extensively characterized (DiGiovanna, 2003).

In veterinary medicine, classification of ichthyosis into epidermolytic and nonepidermolytic subtypes has gained favor (Credille et al., 1998; Olivry & Mason, 1998). Most reported cases of canine ichthyosis are nonepidermolytic; some of these have features in common with human lamellar ichthyosis. The causes of nonepidermolytic ichthyoses are heterogeneous. Defects in any component of the stratum corneum, such as intercellular lipids, cornified envelope and, in rare cases, keratins or internal desmosomal components, may result in this phenotype in humans (Kelsell et al., 1995; Sako et al., 1998; Norgett et al., 2000; Yang et al., 2001). Few specific etiologies have been documented. A Jack Russell Terrier with nonepidermolytic ichthyosis has been described (Lewis et al., 1998). An additional Jack Russell Terrier with an identical phenotype had an attenuated cornified envelope and low transglutaminase 1 expression and activity, similar to forms of autosomal recessive (lamellar) ichthyosis in humans (Credille, K.M. & Dunstan, R.W., personal communication, 2003); transglutaminase 1 is key in the formation and stabilization of the cornified envelope (Credille et al., 2001). Electron microscopic data further underscore the heterogeneity of ichthyosiform dermatoses in small animals (Helman et al., 1997; Credille et al., 1998; Lewis et al., 1998; Olivry & Mason, 1998).

Epidermolytic ichthyoses are invariably associated with a defect in keratin synthesis. This leads to an impaired cytoskeleton and lysis of keratinocytes. Norfolk Terriers with epidermolytic ichthyosis have a defect in keratin 10 due to a splice site mutation (Credille et al., 2003); this keratin is paired with keratin 1 in the upper epidermis and stratum corneum (DiGiovanna, 2003).

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The cases of nonepidermolytic ichthyosis identified to date are heterogeneous in their clinical presentation. In severe cases typified by lamellar ichthyosis of the Jack Russell Terrier, there are tightly adherent, parchment-like, gray or light brown scales over most body regions including pawpads and the planum nasale. Keratinous debris may adhere to the haircoat and remain entrapped during hair growth, resulting in parallel rafts of keratin layered throughout the haircoat. Coarse, thick scales with elevated margins give the skin a rough, irregular texture that may enhance the normal skin surface architecture. These coarse scales may appear similar visually to dried, cracked mud in an empty riverbed. The haircoat is sparse and the remaining hair is bound in keratinous deposits, which heightens the appearance of alopecia. A hand lens may show crateriform enlargements of follicular ostia. Lamellar keratinous projections are prominent, especially on flexural surfaces. Fissures develop in the areas of thickest scale accumulation. Keratinous deposits are shed continuously. In more severe cases of pawpad involvement, thick, dry keratinous proliferations build up, fissure, and crumble from the pad margins. Excess keratinous material may extend outward and upward from the margins of the pads forming bizarre projections. The keratin of the claws may be affected. Fissuring of the pawpads and elsewhere leads to secondary infection with bacteria or *Malassezia*.

Severity of disease is extremely heterogeneous, and ranges from subtle to severe, and local to generalized. Although most cases are generalized, one author (P.J.I.) has seen clinically subtle ichthyosis affecting predominantly the relatively glabrous ventral abdomens of young Australian Terriers, Cairn Terriers, Norfolk Terriers, and Jack Russell Terriers. Golden Retrievers usually have mild generalized scaling with facial involvement, which may wax and wane with periods of relative normalcy. Adherent scale plus dry powdery scale that is loose in the haircoat may go unnoticed. Other breeds such as the American Bulldog may also be mildly affected.

Norfolk Terriers and others with epidermolytic ichthyosis have cobblestoned hyperpigmented skin. Prominent hyperkeratosis has been reported (Mecklenburg et al., 2000); however, scaling is not a prominent feature in all cases (Credille et al., 2003; Credille, K.C., personal communication, 2003). The skin of the muzzle, periocular and perianal regions, pawpads, elbows, axillae, and groin were preferentially affected in the reported mixed breed dog (Mecklenburg et al., 2000). Erosions may be initiated by mild trauma due to increased keratinocyte fragility; in the reported Norfolk Terriers, drying with a towel produced blisters (Credille et al., 2003).

Accompanying erythema is more likely to be seen in young animals and may diminish with age. Ectropion is an occasional complication of severe facial disease. Lymphadenopathy may occur, especially if secondary infection is present.

Feline ichthyosis may be even rarer than canine ichthyosis. One Abyssinian kitten with ichthyosis has been reported, and had diffuse erythema and shiny abdominal skin (Credille et al., 1998).

Breeds that have been noted to develop nonepidermolytic ichthyosis include the West Highland White Terrier, Golden Retriever, Doberman Pinscher, Irish Setter, Collie, American Bulldog, Pit Bull Terrier, Boston Terrier, Labrador Retriever, Jack Russell Terrier, Manchester Terrier, Australian Terrier, Cairn Terrier, Norfolk Terrier, Yorkshire Terrier, Soft Coated Wheaten Terrier, as well as mixed-breed dogs. Epidermolytic ichthyosis has been observed in a Rhodesian Ridgeback and Labrador

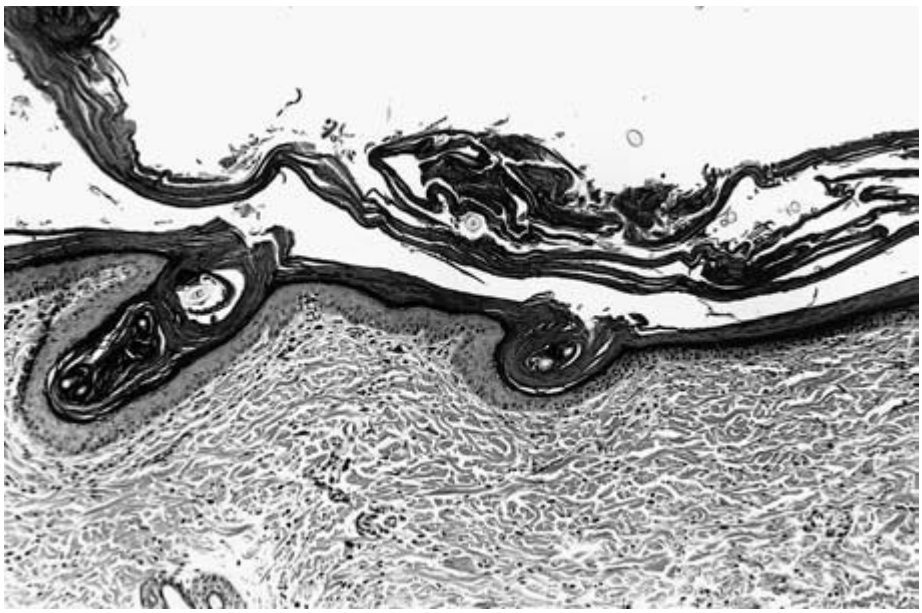


Fig. 8.31 Canine nonepidermolytic ichthyosis. Laminated hyperkeratosis extends to follicles.

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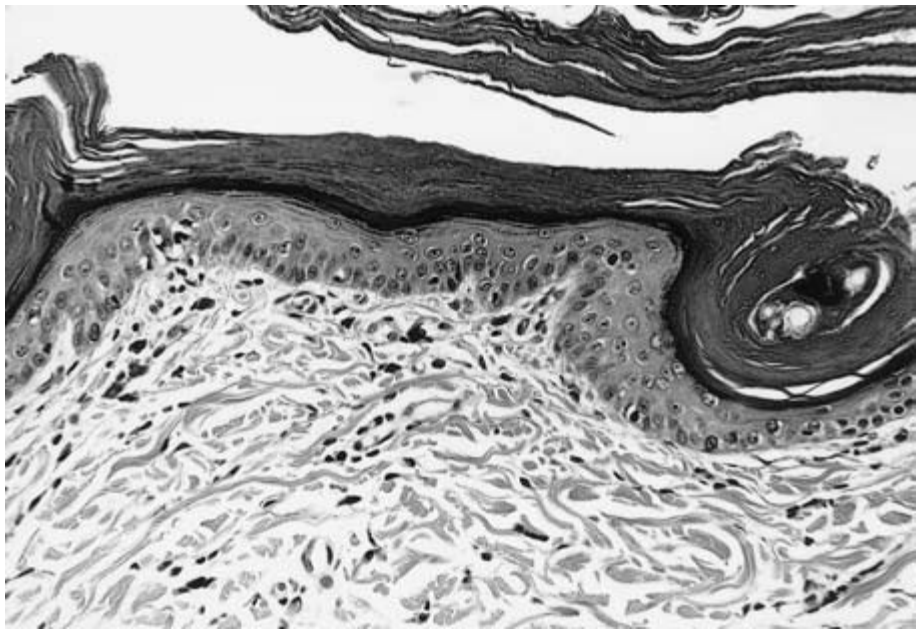


Fig. 8.32 Higher magnification of Fig. 8.31. Note layered keratin, mild acanthosis, and mild hypergranulosis.

Retriever cross (Hargis, A. M., personal communication, 2002; Mecklenburg et al., 2000), as well as in Norfolk Terriers (Credille et al., 2003). Most cases of canine ichthyosis have been reported as present from birth or shortly thereafter. Sex predilections have not been noted. Although 'ichthyosis' has been reported in the Cavalier King Charles Spaniel (Alhaidari et al., 1994), histologic findings closely resemble those of primary seborrhea of the Cocker Spaniel and other spaniel breeds (see p. 161). Appropriate classification awaits further study.

Ichthyosis is visually distinctive. If clinical signs are reported to have been present since birth, or the presented animal is very young, diagnosis is not difficult. If prior clinical history is not available, differential diagnoses should include other diseases characterized by prominent, adherent keratinous debris such as primary seborrhea, sebaceous adenitis, and demodicosis. If an adult dog is examined without benefit of historical information, diagnostic evaluation should include skin scrapings, fungal cultures, and skin biopsy. Histopathology is necessary to confirm a diagnosis of ichthyosis.

Biopsy Site selection

Areas with the most prominent adherent scaling should be selected. Care should be taken not to dislodge the keratin during procurement of the specimen for biopsy. Multiple specimens should be taken.

Histopathology (Figures 8.31 through 8.36)

Nonepidermolytic ichthyosis is the most commonly recognized form of ichthyosis in dogs, often of terrier breeds,

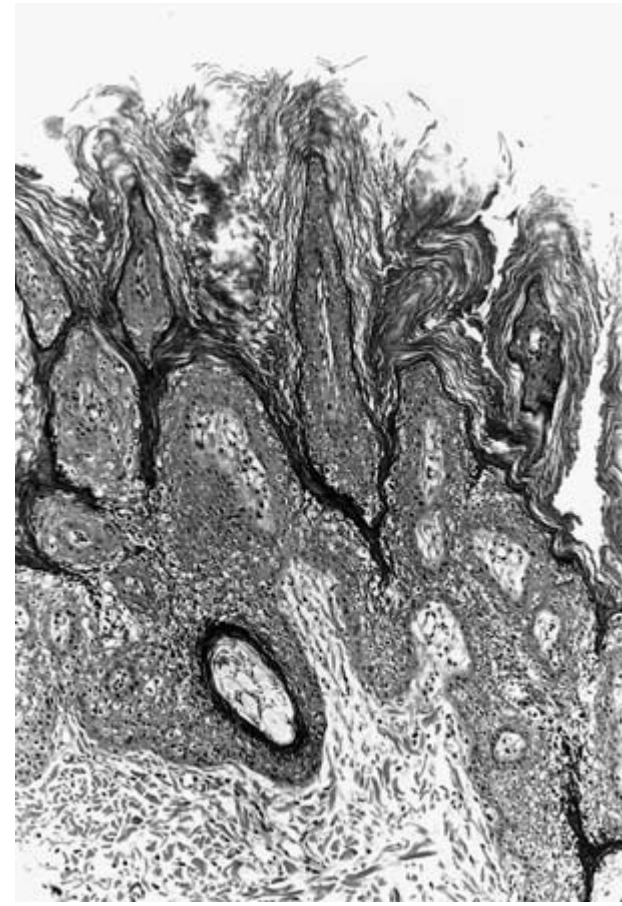


Fig. 8.33 Epidermolytic ichthyosis in a Rhodesian Ridgeback, demonstrating characteristic ballooning of keratinocytes throughout the epidermis and follicular infundibula. (Case material courtesy A.M. Hargis.)

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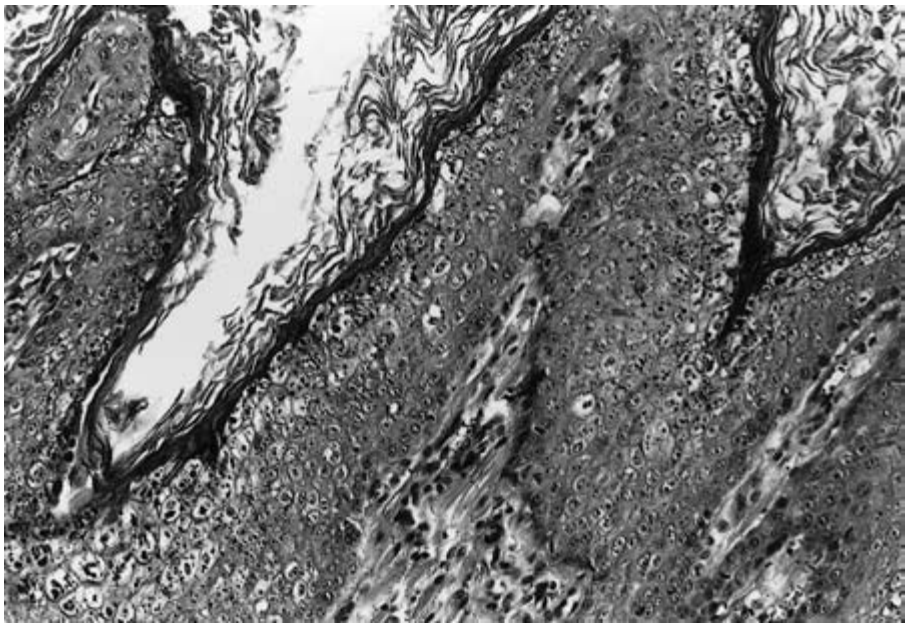


Fig. 8.34 Higher magnification of epidermolytic ichthyosis in the dog of Fig. 8.33. Note coarse and irregular keratohyalin granules within ballooned keratinocytes.

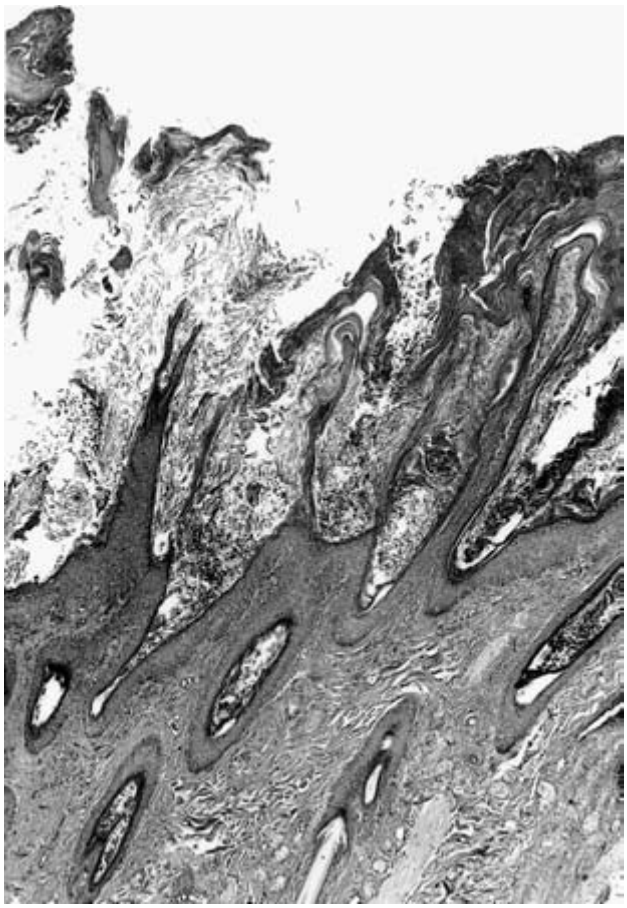


Fig. 8.35 Ichthyosis in a Cavalier King Charles Spaniel. Follicular infundibula are distended with keratin. (Case material courtesy A.M. Hargis.)



Fig. 8.36 Higher magnification of Fig. 8.35 showing severe follicular keratosis. Note linear, thin parakeratotic spires at edges of follicular ostia.

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and is characterized by a lamellar or laminated to compact stratum corneum that is disproportionately thicker than the underlying nucleated epidermis. There are several phenotypic subtypes of ichthyosis, particularly evident on electron microscopy (Credille et al., 1998; Olivry & Mason, 1998). In general, the epidermis is mildly to moderately acanthotic, and laminated hyperkeratosis is mild to severe. Follicular infundibula are affected, but usually are not greatly distended with keratin; hair shafts remain normal. Laminated keratin is relatively compact, but has spaces or clefts visible between layers (filo dough effect). In phenotypically mild cases, such as in Golden Retrievers, the presence of abnormal keratin, rather than an overall increase in thickness of the keratin layer, is most common. Focal parakeratosis has been described (Helman et al., 1997; Credille et al., 1998). A characteristic finding is lifting or flaking of the abnormal keratin layer from the surface. The granular layer of the epidermis is often variable, even within individual cases, and ranges from normal, to increased or decreased.

Epidermolytic ichthyoses are generally characterized by lysis of the upper spinous and granular layers with concurrent hypergranulosis and a laminated to compact stratum corneum that is hyperkeratotic. In epidermolytic ichthyosis, as observed in a Labrador Retriever cross and a Rhodesian Ridgeback, there is diffuse ballooning of keratinocytes above the basal layer, accompanied by numerous irregular keratohyalin granules, including giant and irregular forms. Eosinophilic intracytoplasmic bodies were described which correlated with aggregated tonofilaments ultrastructurally (Mecklenburg et al., 2000). There are occasional small foci of parakeratosis. A milder and more superficial form of epidermolytic ichthyosis, characterized by mild acanthosis, orthokeratotic hyperkeratosis, superficial epidermolysis with separation primarily of the granular layer, and numerous large keratohyalin granules, was described in a family of Norfolk Terriers (Credille et al., 2003).

Electron microscopic features of ichthyosis in dogs have been variable. The ultrastructural findings of nonepidermolytic ichthyosis include numerous lamellar bodies (Credille et al., 1998), irregular tonofilaments (Lewis et al., 1998), and curvilinear structures (Credille et al., 1998). Cytolysis and decreased tonofilaments (Credille et al., 2003), as well as perinuclear clumped tonofilaments with decreased tonofilaments in the remaining cytoplasm (Mecklenburg et al., 2000) have been reported in epidermolytic ichthyosis.

Ichthyosis of Cavalier King Charles Spaniels has very mild histologic evidence of epidermolysis; further, the electron microscopic finding of intact tonofilament–desmosome attachments is in contrast to the epidermolytic ichthyoses in humans (Alhaidari et al., 1994). Multifocal and very mild swelling of superficial keratinocytes is associated with a few coarse and irregular keratohyalin granules. Keratin is loose and distends follicles. This pattern of keratin accumulation is highly reminiscent of primary seborrhea of the Cocker Spaniel (see p. 161). Secondary inflammation (usually absent in other identified types of ichthyosis) may mimic seborrheic dermatitis, and includes the presence of parakeratotic and serocellular caps, epaulets, or thin spires at the edges of follicular ostia. The superficial dermis has mild inflammation composed of lymphocytes, plasma cells, and neutrophils. This entity may be better classified with primary seborrhea until further study.

In the single cat reported with nonepidermolytic ichthyosis, histologic features were laminated to compact orthokeratotic hyperkeratosis with involvement of superficial infundibula. Acanthosis was mild. Refractile vacuoles were present in the thickened stratum corneum. Keratohyalin granules were found only in the lower follicular epithelium (Credille et al., 1998). Rare keratohyalin granules, dispersed tonofilaments, and lamellar bodies were observed with electron microscopy (Credille et al., 1998). The ultrastructural features suggested possible similarity to human ichthyosis vulgaris (Credille et al., 1998).

Ichthyoses, particularly those with epidermolytic change, are characteristic histologically, and differential diagnosis is usually uncomplicated. Differential diagnosis of nonepidermolytic ichthyosis principally includes primary seborrhea. In general, the hyperkeratosis of ichthyosis is more compact and laminated than that of primary seborrhea. In cases of orthokeratotic hyperkeratosis resembling ichthyosis but occurring in an atypical clinical setting, ruling out a reaction to persistent contact irritants may be required, specifically frequent shampooing (see Chapter 4). Persistent contact irritation usually features at least some parakeratosis, in contrast to ichthyosis.

FAMILIAL PAWPAD HYPERKERATOSIS

(Synonym: palmoplantar hyperkeratosis)

Clinical features (Figure 8.37)

Familial pawpad hyperkeratosis is a rare canine cornification defect with lesions restricted to and involving all pawpads of all feet. This clinically distinctive but heterogeneous genodermatosis probably is a subgroup of ichthyosis. An autosomal recessive mode of inheritance has been hypothesized for the disease in Irish Terriers (Binder et al., 2000). Familial pawpad hyperkeratosis clinically resembles human hereditary palmoplantar keratodermas (Stevens et al., 2003). This is a complex of diseases resulting from various mutations in proteins

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Fig. 8.37 Familial pawpad hyperkeratosis in a Dogue de Bordeaux. Keratinous proliferations give the appearance of irregular cutaneous horns. (Photograph courtesy M. Paradis.)

involved in the terminal differentiation of the cornified envelope, including several different keratins, desmosomal proteins, loricin, connexins, and cathepsins (Kimyai-Asadi et al., 2002). In a recent report, evaluation of lesions of Irish Terriers by polymerase chain reaction (PCR) analysis did not causally implicate mutations in keratins 2 and 9, or desmoglein 1 (Schleifer et al., 2003).

All surfaces of all pawpads develop dramatic and severe keratinous proliferation. Lesions may be preceded by the development of 'smooth, parchment-like' pawpads that rapidly give rise to severe keratinous proliferations with 'lateral cone-like protrusions' (Binder et al., 2000). Keratinous proliferation may take the form of irregular cutaneous horns (Paradis, 1992). Fissuring and splitting give rise to secondary bacterial and *Malassezia* infection. Claws grow more rapidly than normal, and cross-sections may be circular rather than U-shaped (Binder et al., 2000). Lameness is common. Other skin lesions or systemic signs are not present.

Familial pawpad hyperkeratosis has been seen predominantly in several families of Dogues de Bordeaux (French Mastiffs) and Irish Terriers (Paradis, 1992; Binder et al., 2000). Kerry Blue Terriers, Labrador Retrievers, Golden Retrievers, and mongrels also have been identified (Scott et al., 2001). Lesions develop before 6 months of age. Sex predilection has not been noted.

Clinical differentiation is not difficult if lesions are seen by 6 months of age in an otherwise healthy puppy, particularly of a previously reported breed. If compatible lesions are seen in a healthy adult dog with an unknown history, diseases such as nasodigital hyperkeratosis, pemphigus foliaceus restricted to the pawpads, and canine distemper virus-associated skin disease (hard pad disease) must be considered. Systemic signs are not a feature of familial pawpad hyperkeratosis.



Fig. 8.38 Familial pawpad hyperkeratosis in a Labrador Retriever demonstrating marked ballooning and parakeratosis in layers and columns.

Biopsy site selection

Punch biopsy specimens should be obtained from the margin of the accessory carpal or tarsal pads. Biopsy of the central pads is more likely to initiate lameness.

Histopathology (Figures 8.38 and 8.39)

Familial pawpad hyperkeratosis may vary in pattern and appearance depending on the breed affected. In Irish Terriers the epidermis is reportedly moderately acanthotic and has severe orthokeratotic hyperkeratosis (Binder et al., 2000). There is hypergranulosis. The stratum corneum appears ruptured and lacks normal cohesion. Electron microscopic abnormalities are not found (Binder

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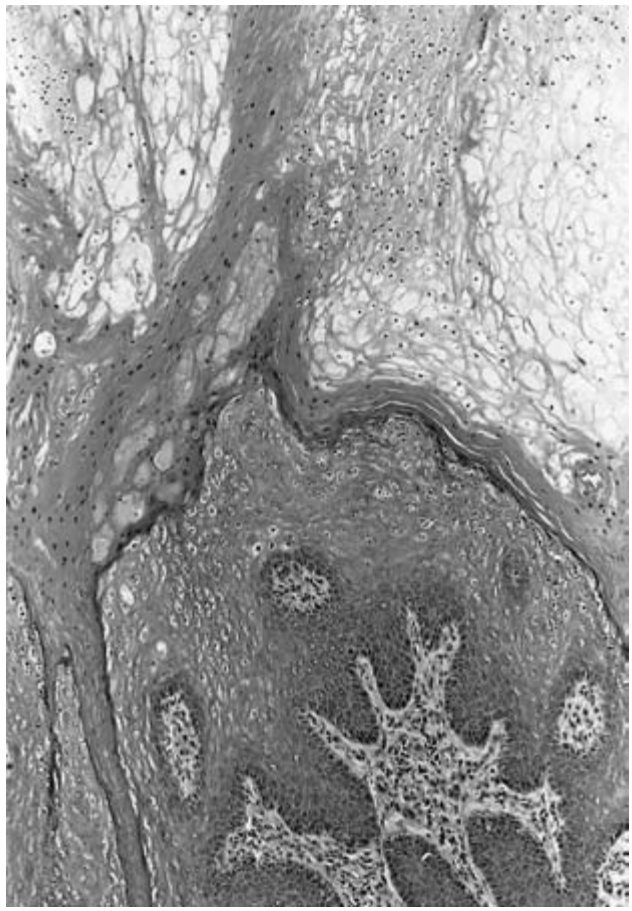


Fig. 8.39 Higher magnification of familial pawpad hyperkeratosis in a Labrador Retriever. Note retention of balloon change within massive parakeratotic layer.

et al., 2000). In Dogues de Bordeaux papillated epidermal hyperplasia and diffuse orthokeratotic hyperkeratosis are present (Paradis, 1992).

In cases of pawpad hyperkeratosis of the Labrador Retriever observed by the authors (perhaps better termed 'pawpad parakeratosis' in this breed), superficial keratinocytes are massively swollen and mostly retain their nuclei, resulting in severe parakeratosis. Massive ballooning change often is retained within the cornified layer. Vacuolated keratin may be strikingly layered, and in columnar arrangement, with areas of severely ballooned keratin interspersed among dense parakeratosis. There is usually an increased granular layer and granules may be somewhat variable in size. The relationship of this disorder to nasal parakeratosis of Labrador Retrievers is not known; it is of interest that two of the reported dogs with that disorder also had pad lesions (see p. 170); histopathology of those sites was not performed.

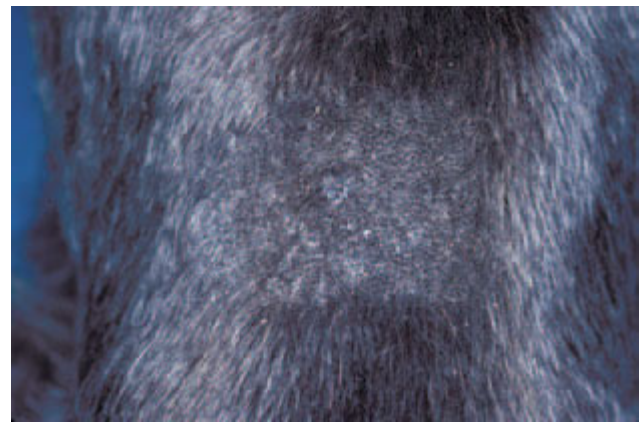


Fig. 8.40 Schnauzer comedo syndrome. Dark keratinous material in comedones creates pixel-like hyperpigmentation. (Photograph courtesy T. DeManuelle; case material University of California, Davis.)

Pawpad hyperkeratosis of the Labrador Retriever superficially resembles epidermolytic ichthyosis (see p. 174). However, the increase in number and size of keratohyalin granules occurring in epidermolytic ichthyosis is more severe. Also, swelling of keratinocytes is generally superficial in pawpad hyperkeratosis of the Labrador Retriever, in contrast to the transepidermal alteration seen in more classical epidermolytic ichthyosis. Further studies are required.

Orthokeratotic pawpad hyperkeratosis, as seen in Irish Terriers and Dogues de Bordeaux, resembles nasodigital hyperkeratosis of older dogs (see p. 169). Consideration of age and breed affected may be important in differentiation.

SCHNAUZER COMEDO SYNDROME

Clinical features (Figure 8.40)

Schnauzer comedo syndrome is a relatively common, predominantly asymptomatic skin disease seen almost exclusively in Miniature Schnauzers. The marked breed predilection is a likely indicator of heritability. This syndrome probably represents a developmental follicular disorder of cornification (Paradis & Scott, 1989). Schnauzer comedo syndrome bears some resemblance to a developmental hair follicle dysplasia seen in humans, termed nevus comedonicus (Silver & Ho, 2003).

Comedones develop in a band along the dorsal spine. Substantial variation in character and severity of clinical lesions is seen among individual dogs. Lesions may be palpable rather than visual. Occasionally, the principal change is a dorsal band of darkly colored or diffusely

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erect hair. In more typical cases, crusted papules, small nodules, or frank comedones are observed. Lesions may not appear grossly follicular if the follicular ostia are not dilated; this leads to the visual impression of dense, dark material accumulating in discrete foci beneath the epidermis. Comedones may be small, and require use of a hand lens for identification. More obvious comedones are characterized by peripherally inflamed, dilated hair follicles which contain inspissated, dark, keratinous or caseous debris that may be extruded with digital pressure. Hair is lost from severely affected follicles. Mild scaling and erythema may be seen with more severe lesions. Confluence of comedones creates the illusion of hyperpigmentation. Secondary bacterial folliculitis accompanied by erythema and scarring is noted in more severe cases. Lesions occur along the midspinal area from the shoulders to the sacrum, usually within 5 cm of the spine. Pruritus may be present if lesions are severe or secondary infection is present.

Schnauzer comedo syndrome is seen almost exclusively in Miniature Schnauzers and their related crossbreeds. However, a seemingly identical syndrome is seen occasionally in Cairn Terriers and other rough-coated terriers. Age or sex predilections have not been reported. Differential diagnosis is not problematical as Schnauzer comedo syndrome is a visually distinctive disease.

Biopsy site selection

Multiple specimens should be taken from the most severe lesions. Skin biopsy of larger persistent comedones may be curative for these more troublesome lesions. If present, pustules should be obtained to confirm the presence of secondary pyoderma.

Histopathology (Figures 8.41 and 8.42)

Distension of superficial hair follicles with keratin is the diagnostic feature of Schnauzer comedo syndrome. The size of the follicular ostium may remain nearly normal, resulting in a cystic (comedonal) appearance of the keratin-dilated infundibulum. Other affected follicles may have dilated ostia. The follicular infundibular wall is generally of normal thickness to mildly acanthotic. Epidermal hyperkeratosis usually is mild. Superficial crusting, originating from secondary pyoderma, may be prominent. Acanthosis is moderate to severe, and varies with the degree of secondary inflammation present.

Most specimens submitted for skin biopsy are inflamed. Folliculitis, or furunculosis with comedonal rupture may be observed. Pustular inflammation may be loosely distributed in the superficial dermis, and may involve apocrine sweat glands in severe cases. Chronic lesions have mixtures of neutrophils, macrophages, and plasma cells in superficial and periadnexal distribution.

Comedo formation in Schnauzer comedo syndrome is in contrast to the follicular keratosis of primary seborrhea. In primary seborrhea, follicular ostia are uniformly dilated by infundibular engorgement with keratin, whereas in Schnauzer comedo syndrome, follicular ostia often remain relatively closed. Other skin diseases with comedo formation include hyperglucocorticoidism (including to topical corticosteroids), and actinic comedones. In diseases of glucocorticoid excess, there is accompanying follicular atrophy as well as thinning of the infundibular wall. In actinic comedones, a pale concentric layer of collagen usually surrounds the distended follicle. Clinical features also will differentiate

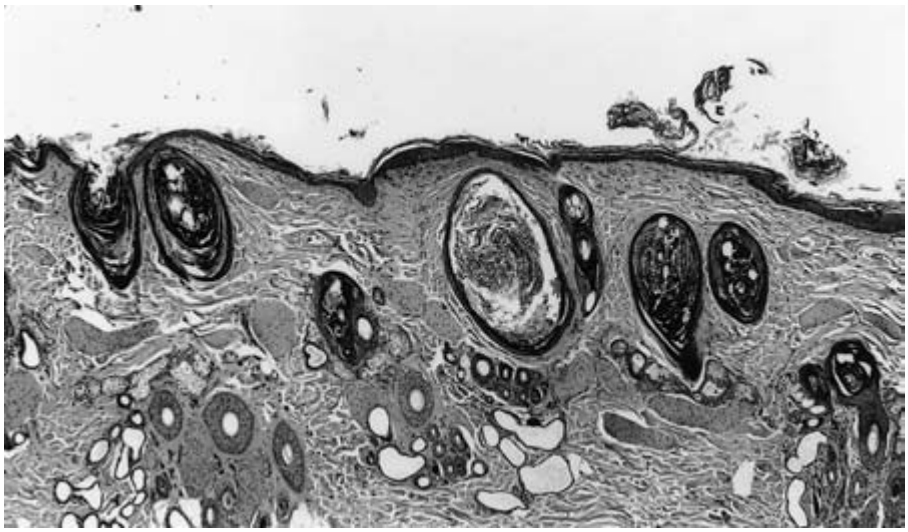


Fig. 8.41 Schnauzer comedo syndrome showing diffuse distention of follicular infundibula with keratin.

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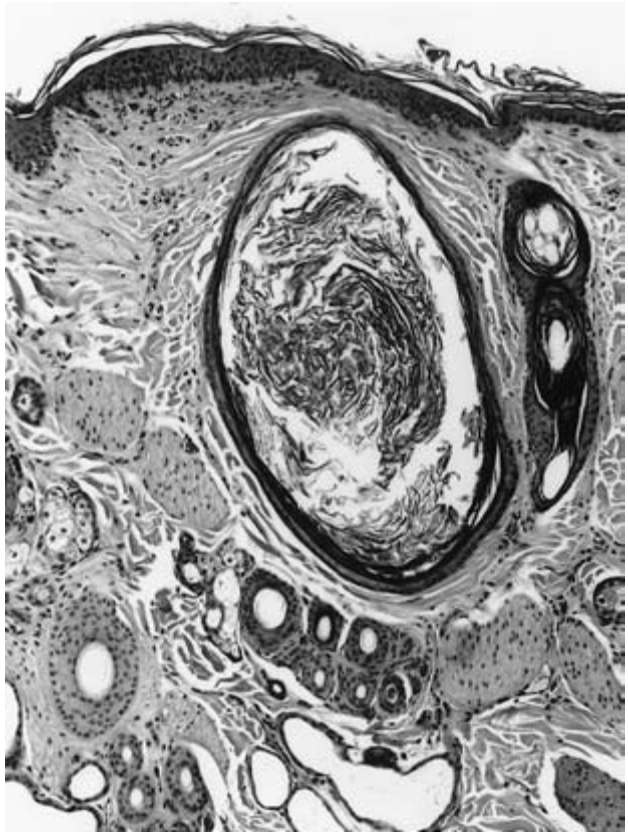


Fig. 8.42 Higher magnification of comedone in Fig. 8.41. Note normal cornification of the epidermis.

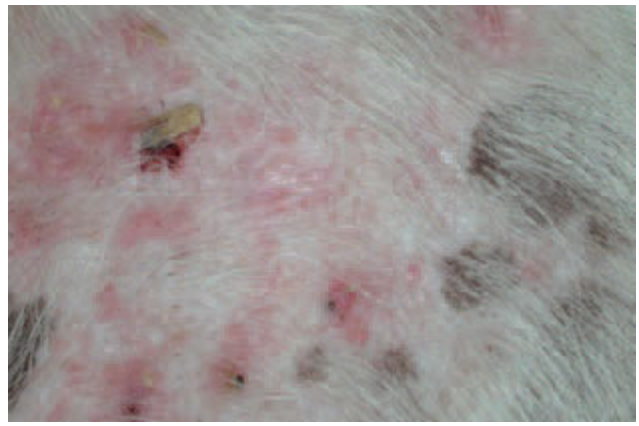


Fig. 8.43 Actinic comedones on the abdomen of a Bull Terrier crossbreed with a history of long-term sunbathing. Dark, inspissated material plugs hair follicles amid erythematous, scaly solar keratoses in the solar-damaged nonpigmented areas. A cutaneous horn growing from an actinic squamous cell carcinoma is seen in the upper left.

Schnauzer comedo syndrome from other skin diseases with histopathologic similarities.

ACTINIC COMEDONES

Clinical features (Figure 8.43)

Actinic comedones are distinctive, solar-induced comedones that occur in conjunction with chronic solar dermatitis, actinic keratoses (see Chapters 7 and 22), and other solar skin lesions. The syndrome is uncommon, but is seen much more frequently in environments with enhanced solar exposure. Comedones and other actinic lesions occur in nonpigmented, lightly haired skin. Affected dogs may be known to sunbathe (Mason, 1999). In addition to preneoplastic and neoplastic changes of keratinocytes, solar irradiation induces dermal damage, including fibrosis and elastosis (see Chapter 15). Actinic comedones follow follicular occlusion secondary to dermal fibrosis.

Actinic comedones most commonly comprise inflamed, dilated hair follicles containing inspissated, dark, keratinous, or caseous debris. Lesions may not appear follicular and may appear as discrete pigmented subepidermal foci or small nodules. Actinic comedones often occur in conjunction with the roughened, crusted, indurated plaques that characterize actinic keratoses (see Chapters 7 and 22). Palpation of comedones in apparently normal skin may reveal irregular firmness and thickening, suggesting more widespread solar-induced change. Actinic furunculosis may arise directly from ruptured actinic comedones (see Chapter 17); coexistent pyoderma may diminish the clinician's ability to recognize comedones. Hemorrhagic crusts may be present if lesions fistulate.

Lesions are restricted to sun-exposed, relatively nonpigmented skin in sparsely haired regions such as the glabrous skin of the abdomen, flank folds, inner thighs, dorsal muzzle, and periorbital region. Most actinic comedones are seen in dogs with visually obvious lack of epidermal pigmentation.

Dalmatians, Whippets, Italian Greyhounds, Greyhounds, American Staffordshire Terriers, Bull Terriers, Beagles, and Basset Hounds are at increased risk for developing actinic lesions. Lesions occur most commonly in older animals, but have been seen in dogs as young as 2 years of age. Animals spending substantial time outdoors in tropical, subtropical, desert, or mountainous regions of the world are at greater risk.

Differential diagnoses for actinic comedones include other comedogenic disorders such as demodicosis (especially in the German Shepherd Dog), hyperglucocorticoidism (especially iatrogenically induced by topical application of glucocorticoids), and Schnauzer comedo syndrome. The presence of comedones in a lightly pig-

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mented breed with habitual access to sun exposure, with or without evidence of other solar-induced lesions, should increase suspicion for actinic comedones. Prompt skin biopsy of lesions suggestive of actinic comedones is strongly recommended, since awareness of solar damage to the skin may prevent more serious disease.

Biopsy site selection

If secondary pyoderma is present, it may be advantageous to delay skin biopsy until the dog has received appropriate systemic antibiotics for at least 3 weeks so that inflammation will not complicate the diagnosis. Multiple comedones should be sampled. If other lesions suggestive of solar damage are present, they should be obtained as well.

Histopathology (Figure 8.44)

The epidermis is variably acanthotic and may demonstrate actinic keratosis or squamous cell carcinoma (see Chapters 7 and 22). Superficial hair follicles are distended with keratin. Follicular ostia are relatively closed, creating a comedone. The infundibular wall is moderately acanthotic, and keratinocyte cytoplasm often appears pale. Usually concentric, compressed layers of pale slightly basophilic collagen surround affected follicles. Interestingly, elastic stains are negative for solar elastosis in this location (see Chapter 15). These comedones may rupture, leading to actinic furunculosis (see Chapter 17). The surrounding dermis is variably inflamed and usually features solar fibrosis and elastosis.

Actinic comedones generally occur in the context of other actinic changes such as actinic keratosis, squamous cell carcinoma, solar elastosis and solar fibrosis, or actinic furunculosis. This usually allows easy differentiation of actinic comedones from other comedonal lesions such as those occurring in callus, hyperglucocorticoidism, topical corticosteroid reactions, or Schnauzer comedo syndrome. Actinic comedones and occasional canine callus lesions may share pericomedonal pale fibrosis; however, the severe epidermal and follicular infundibular hyperplasia (without dysplasia) that is seen in most cases of callus is lacking in actinic comedones.



Fig. 8.44 Actinic comedone. Note circumferential pale fibrosis.

CALLUS

(Synonym: pressure point granuloma)

Clinical features (Figure 8.45)

A callus is a thickened plaque that develops over bony prominences or pressure points in response to repeated pressure or frictional trauma. Lesions termed ‘calluses’ in



Fig. 8.45 Canine callus on the lateral elbow of a Labrador Retriever. The callus is lichenified and alopecic. Secondary callus pyoderma is present near the upper central margin.

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dogs and cats are visually similar but histopathologically distinct from calluses in humans, the latter of which are localized thickenings of the epidermal cornified layer. Calluses are common in dogs and rare in cats. Noninfected calluses act as a normal protective response to perpetual environmental trauma, especially from habitual contact with hard, rough surfaces such as cement, wood, or brick. Callus pyoderma develops as a sequela to repeated trauma to the callus (see Chapter 17). Histopathologic evidence indicates that uninflamed canine calluses frequently contain dilated, keratin-filled hair follicles. Rupture of these dilated hair follicles and traumatic implantation of hairs induces secondary bacterial furunculosis and a foreign body response to the displaced hairs and keratinous debris, creating callus pyoderma.

Thickened plaques with circular or oval smooth borders form over bony prominences or other pressure points. Partial to complete alopecia occurs with chronicity. Developing early calluses usually are erythematous. Noninflamed chronic calluses appear gray or white due to poorly vascularized fibrous tissue, whereas continuously traumatized calluses often are hyperpigmented. Wrinkles occur with chronicity. Follicular dilatation and comedo formation are common, and multiple hairs may emanate from the enlarged follicles. Frank pustules, furuncles, or fistulas may be visible, but secondary pyoderma may not be obvious clinically. It is not known how often subtle or mild callus pyoderma occurs, as calluses rarely are biopsied. Ulceration may be observed with severe and persistently traumatized callus pyoderma. One author (P.J.I.) has seen topical corticosteroid reaction (see Chapter 15) superimposed on canine calluses. Feline calluses may have adherent mats.

The elbow and hock are the most common sites, but calluses may be seen on the sternum, stifle, lateral digits, over bony prominences of the pelvis, and on the dorsal muzzle. Deformities, partial amputation of legs, or other locomotor problems may lead to callus and callus pyoderma on unusual sites in either dogs or cats. Untreated calluses tend to enlarge as the dog ages. The hock is the most common site for feline callus. Obesity predisposes to callus formation in both dogs and cats.

Large and giant breed dogs such as Doberman Pinschers, Great Danes, Saint Bernards, Newfoundlands, and Irish Wolfhounds are at greater risk. Short-legged dogs with short haircoats such as smooth-coated Dachshunds and Basset Hounds, and deep-chested dogs such as Boxers, pointers, and setters are at increased risk for sternal calluses. The Bull Terrier is at increased risk for developing callus on the dorsum of the muzzle due to the peculiar dorsiflexed sleeping position of many members of the breed. Age or sex predilections have not been noted. No breed predilection has been seen in cats.

Canine and feline calluses are visually distinctive due to their characteristic location at prominences under pressure. Acral lick dermatitis visually may superficially resemble canine callus pyoderma, but has different site predilections (see Chapter 7). Plaques of coalescing actinic comedones also may resemble calluses, but are not associated with pressure points. Histopathology will allow differentiation, if needed, and also is useful in detecting clinically occult pyoderma.

Biopsy site selection

Risk versus potential benefit must be weighed when contemplating biopsy of a callus. Classical lesions over bony prominences or pressure points ordinarily should not be sampled, as healing may be difficult and prolonged at these sites. Surgical removal of an entire callus may be fraught with potential difficulties such as poor wound healing. Dehiscence is a common sequel to elbow callus removal unless special surgical techniques are employed. In contrast, wedge or excisional biopsy may be performed on sternal calluses and may be curative.

Histopathology (Figures 8.46 and 8.47)

The epidermis is moderately to severely acanthotic, and hyperplasia usually extends to follicular infundibula, creating an undulating or papillated surface to the lesion. In most cases, follicular infundibula are severely acanthotic, but may be only mildly to moderately affected in some lesions. There is variable epidermal hyperkeratosis and parakeratosis, and crusting or ulceration may be a feature of inflamed lesions.

Uninflamed callus is most specifically characterized by prominent, often cystic, follicular keratosis of multiple contiguous follicles. Rarely, there may be pale encircling fibrosis, as seen in actinic comedones (see p. 183). Dilated cystic follicles contain fragments of hair in addition to keratin. Rupture of these cysts leads to release of hair and keratin which provokes severe traumatic furunculosis (callus pyoderma; see Chapter 17).

Actinic comedones as well as other comedonal diseases, notably Schnauzer comedo syndrome and hyperglucocorticoidism, are characterized by prominent follicular keratosis as seen in canine callus. Multiple contiguous follicular cysts can also occur as a developmental anomaly on the head of young dogs (see Chapter 23). Actinic comedones and occasional canine callus lesions may share pericystic pale fibrosis. These other comedonal syndromes usually do not have the severe epidermal and follicular infundibular hyperplasia that is seen in most calluses. Clinical differentiation may be required for callus in which severe follicular infundibular hyperplasia is not pronounced.

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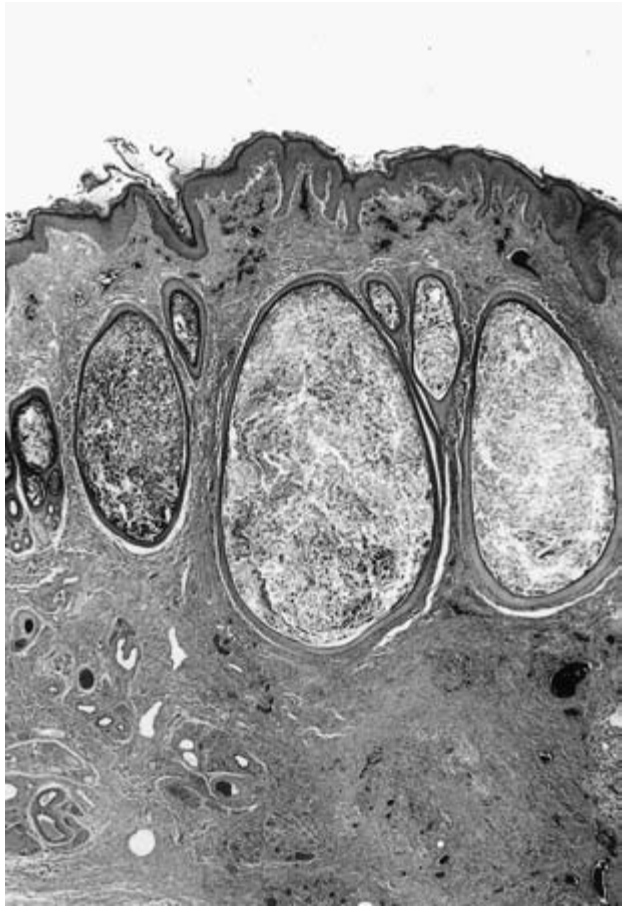


Fig. 8.46 Canine callus featuring large comedones beneath irregular acanthosis.



Fig. 8.47 Higher magnification of comedones in Fig. 8.46. Note thickening of follicular epithelium.

SEBACEOUS ADENITIS

(Synonym: granulomatous sebaceous adenitis)

Clinical features (Figures 8.48 and 8.49)

Sebaceous adenitis is an uncommon canine and rare feline skin disease of uncertain etiology (Scott, 1986, 1989; Rosser et al., 1987; White et al., 1995). Recently, a similar disease has been described in humans (Martins et al., 1997). Strong canine breed predilections suggest a genetic basis. An autosomal recessive mode of inheritance has been proposed in the Standard Poodle (Dunstan & Hargis, 1995) and in the Akita (Reichler et al., 2001).

Hypotheses for the pathogenesis of sebaceous adenitis include heritable and developmental ('predetermined') inflammatory destruction of the sebaceous glands, cell-mediated immunologic destruction, a cornification abnormality leading to sebaceous duct and sebaceous gland inflammation and atrophy, an anatomic defect in sebaceous glands leading to lipid leakage and a foreign body response, and a defect in lipid metabolism leading to a cornification abnormality and sebaceous gland destruction (Scott, 1986; Rosser et al., 1987; Guaguère et al., 1990; Gross & Ihrke, 1992; Dunstan & Hargis, 1995;



Fig. 8.48 Sebaceous adenitis in an adult Samoyed. The remaining haircoat is short and matted due to keratinous deposits.

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Fig. 8.49 Closer view of the dog in Fig. 8.48, demonstrating adherent scale and crusts. Note the coarse dry appearance of the remaining haircoat.

Reichler et al., 2001). Immunohistological studies reveal a preponderance of antigen-presenting dendritic cells and T cells in inflamed lesions. These findings coupled with the absence of detection of autoantibodies further suggest a cell-mediated immunopathogenesis for sebaceous gland destruction (Rybnicek et al., 1998). The salient clinical features of scaling and follicular plugging probably occur as nonspecific sequelae to the cessation of sebum flow resulting from sebaceous gland inflammation and ablation. Similar secondary hyperkeratosis is associated with sebaceous gland destruction in generalized demodicosis, cutaneous leishmaniasis, exfoliative cutaneous lupus erythematosus, and others. It is not clear if there also is a causal relationship between loss of sebaceous glands and abnormal follicular maturation, or if these are simply coexistent features of a common inherited process.

Clinical signs, distribution, and severity of the disease vary substantially among different breeds of dogs. Adherent scaling, forming follicular casts or fronds, is the unifying clinical feature. Coat quality diminishes as the disease progresses, leaving dull, dry, brittle, broken hairs. Lesion distribution is bilaterally symmetric. In general, the dorsal trunk, temporal region, face, and pinnae are often first and ultimately most severely affected. Over 40% of affected dogs had secondary pyoderma in one study (White et al., 1995). Occasionally, striking alopecia and adherent scale on the tail (rat-tail) can be a clinical marker of sebaceous adenitis (White et al., 1995). Pruritus usually is not substantial unless secondary pyoderma is present.

In Standard Poodles, silvery to white keratinous deposits resembling candle-wax drippings most often develop first on the dorsal muzzle, temporal region, and the dorsal neck and thorax. Adherent scale of variable severity with progressive alopecia and poor coat quality is seen in a predominantly dorsal distribution. Frond-like, protruding, keratinous casts may emanate from dilated hair follicles, and tenacious keratinous debris ensheathes hairs. Lesions similar to those of the Standard Poodle, but with a greater tendency towards more discrete plaque formation, are seen in the Samoyed.

In Akitas, typical lesions are similar to those of Standard Poodles, with the additional feature of more complete alopecia, especially of the secondary hairs. Secondary superficial bacterial folliculitis or deep bacterial folliculitis and furunculosis, manifested as papules, pustules, or nodules, is a prominent feature of sebaceous adenitis in this breed. Fever, malaise, and weight loss may be present as additional, as yet unexplained, systemic features of this disorder.

Sebaceous adenitis in German Shepherd Dogs may begin on the tail and progress up the trunk (Scott et al., 2001). Belgian Sheepdogs with sebaceous adenitis commonly have concurrent otitis externa (Guaguère et al., 1997).

A strikingly different clinical presentation is noted in the Vizsla and occasionally in other short-coated breeds, such as the Dachshund. One author (T.L.G.) has observed this presentation in Miniature Pinschers and Plott Hounds. Focal coalescing, firm nodular lesions and annular plaques with alopecia and adherent scale develop predominantly on the trunk. Scale is less adherent than in other forms of the disease. Follicular casting is prominent. Facial lesions also may be seen. Unexplained, cyclical, edematous swellings of the dorsal muzzle, periorbital region, and lips have been noted (Power & Ihrke, 1990; White et al., 1995). These pronounced clinical differences suggest that this form of sebaceous adenitis is a separate disease.

Feline sebaceous adenitis is characterized by multifocal, annular areas of alopecia with scaling, crusting, and follicular casting (Scott, 1989; Scott et al., 2001). Irregularly broken hairs may be noted. Pruritus is variable, but may be present. One author (T.L.G.) has observed transient feline sebaceous adenitis.

Strong breed predilections for sebaceous adenitis have been noted for Standard Poodles, Samoyeds, Akitas, and Vizslas. Dachshunds also may be at increased risk (Scott et al., 2001). However, many other purebred dogs (Old English Sheepdog, Toy Poodle, Springer Spaniel, Lhasa Apso, Boxer, Chow Chow, and Collie), as well as mixed breed dogs have been documented with sebaceous adenitis. Young adult dogs most commonly are affected. Sex predilections have not been noted.

Clinical differential diagnoses for canine sebaceous adenitis characterized by generalized scaling include primary seborrhea and seborrheic dermatitis, ichthyosis, and vitamin A-responsive dermatosis. Demodicosis and generalized dermatophytosis also may mimic sebaceous

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adenitis. The more nodular form of sebaceous adenitis seen in the Vizsla, Dachshund and other short-coated breeds may resemble nodular demodicosis or deep bacterial folliculitis and furunculosis. Dermatophytosis is the prime differential diagnosis for feline sebaceous adenitis. Skin biopsy is required for definitive diagnosis.

Biopsy site selection

Multiple specimens are recommended so that adequate numbers of adnexal units may be observed. Subtle early lesions characterized by adherent scale without alopecia are most useful for documenting active sebaceous gland inflammation. Chronic, extensively alopecic lesions commonly show an absence of sebaceous glands without significant inflammation; multiple specimens are then essential to confirm that the absence of sebaceous glands is widespread, and therefore diagnostic of sebaceous adenitis.

Histopathology (Figure 8.50)

The nodular form of sebaceous adenitis, as seen in Vizslas and others, is discussed in Chapter 17. Most other cases of sebaceous adenitis exhibit mild to moderate acanthosis and generally moderate to severe hyperkeratosis with follicular plugging. Keratin ensheathes hair shafts as they emerge from follicular ostia, often most notably in the Standard Poodle. These protruding follicular casts of keratin, or follicular fronds, may be variably severe, but when present should always be a signal to search for sebaceous glands.

Random sampling of affected dogs (which are most often presented for biopsy with late stage disease) indicates that diffuse absence of sebaceous glands is the most common histopathologic feature of chronic sebaceous adenitis. Isthmus perifollicular inflammation is highly variable, depending on the breed affected and the stage of the disease, but is usually mild, occurring in the vicinity of previous glands (see Chapter 17).

In cats, sebaceous adenitis has mild to severe orthokeratotic hyperkeratosis with variable serocellular crusting. Follicular fronds are not as common as in dogs, but may be observed. Sebaceous glands are absent and there is perifollicular inflammation and mural folliculitis (see Chapter 17).

Differential diagnosis of the hyperkeratotic lesions of sebaceous adenitis includes primary seborrhea, vitamin A-responsive dermatosis, as well as ear margin seborrhea. Associated absence of sebaceous glands is the prime differential feature of sebaceous adenitis. A definitive diagnosis of sebaceous adenitis should not be offered if many sebaceous glands are intact and/or uninflamed.

ZINC-RESPONSIVE DERMATOSIS

Clinical features (Figures 8.51 and 8.52)

Zinc-responsive dermatosis is an uncommon to rare canine skin disease. The term 'nutrient-responsive dermatosis' is used to designate syndromes characterized by nutrient deficiency, nutrient imbalances, or the genetic inability to absorb or metabolize a nutrient. Zinc-responsive dermatosis may encompass all three etiologic

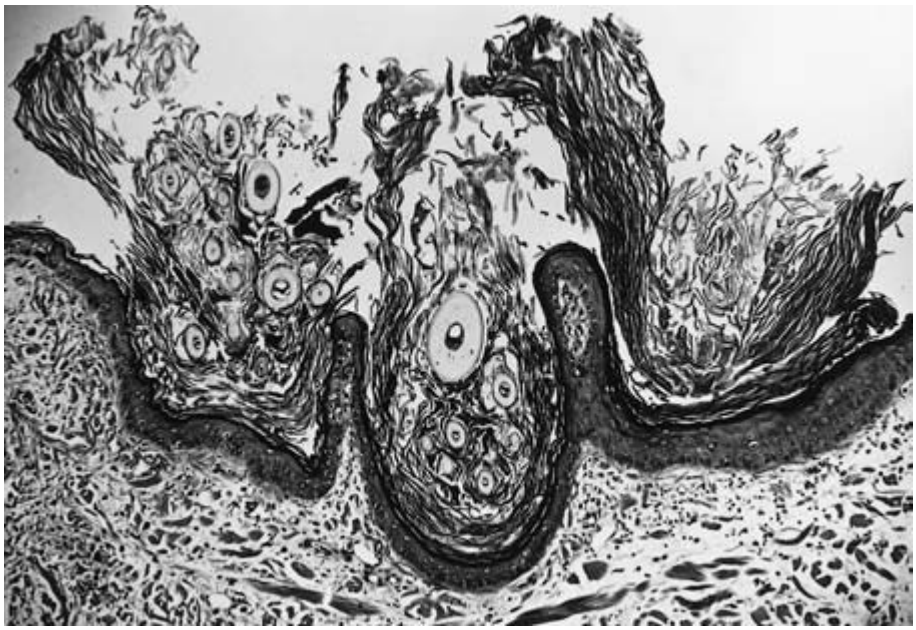


Fig. 8.50 Sebaceous adenitis in a dog. Hair shafts are engulfed by keratin to form follicular fronds.

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Fig. 8.51 Zinc-responsive dermatosis in a Siberian Husky. Alopecia, scaling, and crusting are present near the mucocutaneous junctions of the eye, the mouth, and the planum nasale.



Fig. 8.52 Closer view of the dog in Fig. 8.51. Crusts adhere to the skin beneath the eye.

categories. Zinc plays an integral role in metabolism as a component of many metalloenzymes (Watson, 1998). Although it has been speculated that relative zinc deficiency might impact many skin diseases, more recent work does not support this hypothesis (Logas et al., 1993).

Clinically, zinc-responsive dermatosis has been subdivided into two groups (Kunkle, 1980). Syndrome I is an uncommon skin disease seen almost exclusively in Siberian Huskies and Alaskan Malamutes, and most likely is due to an inherited impairment in the absorption or metabolism of zinc (Kunkle, 1980). Some Malamutes have been shown to have diminished capability to absorb zinc from the gastrointestinal tract (Kunkle, 1980). Other northern-breed dogs such as the Samoyed also may be affected (White et al., 2001). Occasional isolated cases occur in other breeds (White et al., 2001). In the opinion of one author (P.J.I.), accounts of this syndrome in Bull Terriers may represent heterozygous expression of acrodermatitis of Bull Terriers (see p. 193). Syndrome I is seen in dogs of all ages and occurs in dogs fed a balanced diet (White et al., 2001).

Syndrome II has become rarer in developed countries during the past decade due to an increased knowledge of the appropriate formulation of pet food. It is seen in rapidly growing large-breed puppies receiving either a diet high in plant phytates that may prevent appropriate zinc absorption, a commercial or home prepared diet that is zinc-deficient, or a diet that is over-supplemented with calcium and other vitamins or minerals that may impact zinc absorption. In the past, producers of inexpensive dog food did not take into account the differences in digestibility among various rations (Huber et al., 1986). Considerable range in severity is seen in dogs from the same litter eating the same diet. This may indicate individual variation in the ability to absorb zinc.

Syndrome I is characterized clinically by erythema, thick adherent scaling, crusting, alopecia, and lichenification. Mucocutaneous junctions, genitals and pressure points are commonly affected. Lesions commonly are well demarcated from adjacent apparently normal skin. More severe erythema, exudation, suppuration, crusting, and fissuring may be seen in dogs with secondary pyoderma or *Malassezia* dermatitis. In order of diminished frequency, lesions are seen in the periorbital region, perioral region, pawpads, pinnae, nasal planum, genital region, distal legs, perianal region, and elbows (White et al., 2001). In the majority of dogs, lesions are somewhat bilaterally symmetric (White et al., 2001). In severe cases, the muzzle, genitals, and legs can be encased in thick keratinous debris.

The clinical features seen with Syndrome II mimic those seen with Syndrome I; however, severity commonly is greater. Thick, well-demarcated crusted, lichenified plaques with erosions or ulcers are noted. Some dogs have constitutional signs such as anorexia and depression, while others have only skin disease; this range of clinical signs might be explained by variability in the severity of zinc deficiency, or the presence of a combined trace mineral deficiency. Clinical features of zinc-responsive dermatosis coupled with constitutional signs may warrant a diagnosis of generic dog food dermatosis (see Chapter 4).

Syndrome I is seen almost exclusively in northern-breed dogs. Clinical signs develop in early adulthood, usually between 1 and 3 years of age. Sex predilections have not been noted but estrus may exacerbate lesions (White et al., 2001). One study showed that most dogs in North America developed lesions between autumn and winter (September to January); this finding is unexplained

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(Colombini & Dunstan, 1997). Syndrome II is seen in rapidly growing, predominantly large breed puppies and young adult dogs.

The clinical differential diagnoses of Syndrome I include dermatophytosis and demodicosis for mild disease. More severe cases of Syndrome I and Syndrome II may mimic superficial necrolytic dermatitis, generic dog food dermatosis, autoimmune skin diseases such as pemphigus foliaceus and systemic lupus erythematosus, demodicosis, dermatophytosis, or mild cases of acrodermatitis of Bull Terriers. The occurrence of Syndrome I in northern breeds is useful diagnostically. The young age of onset of Syndrome II and higher occurrence in large-breed dogs should increase the index of suspicion for the diagnosis. Differentiation requires skin scrapings, surface cytology, chemistry screening profiles, dermatophyte culture, an antinuclear antibody (ANA) test, and histopathology.

Biopsy site selection

Areas of most severe crusting and scaling should be obtained. Care should be taken to avoid areas of erosion or ulceration, since an intact epidermis is necessary to establish a diagnosis.

Histopathology (Figures 8.53 and 8.54)

Moderate to severe acanthosis is present. Parakeratosis is a consistent feature and varies from mild and multifocal to diffuse and moderate. Extension of parakeratosis into hyperplastic follicular infundibula is a characteristic histopathologic feature of zinc-responsive dermatosis. There may be absence of the underlying granular layer (hypogranulosis). Parakeratosis may form peaks or spikes at the edges of follicular ostia, resulting in a digitated configuration to the skin surface. Serum may be present between the parakeratotic layers in these foci, suggesting 'squirting' from the underlying superficial dermis. There may be slight multifocal pallor of the superficial epidermis. Associated orthokeratotic hyperkeratosis has been reported (White et al., 2001).

Serocellular crusting with erosion is variable and may be severe, resulting in effacement of the parakeratotic layer. Occasionally, shrunken, eosinophilic keratinocytes are seen just beneath parakeratosis, suggesting dyskeratosis. Mild to moderate diffuse spongiosis is present and may also affect superficial follicles. Dermal inflammation is superficial, perivascular to interstitial, and is comprised of lymphocytes, macrophages, eosinophils, and neutrophils. Inflammation may extend around subjacent adnexal appendages.

Parakeratosis may be a feature of spongiotic inflammation in general, such as that provoked by allergic or irritant skin diseases. Parakeratosis usually is diffuse in zinc-responsive dermatosis, but this feature may not always allow differentiation from other skin disease. For example, some cases of irritant contact dermatitis are diffusely parakeratotic (see Chapter 4). Clinical differentiation may be required.

Lesions of zinc-responsive dermatosis may resemble chronic lesions of superficial necrolytic dermatitis when

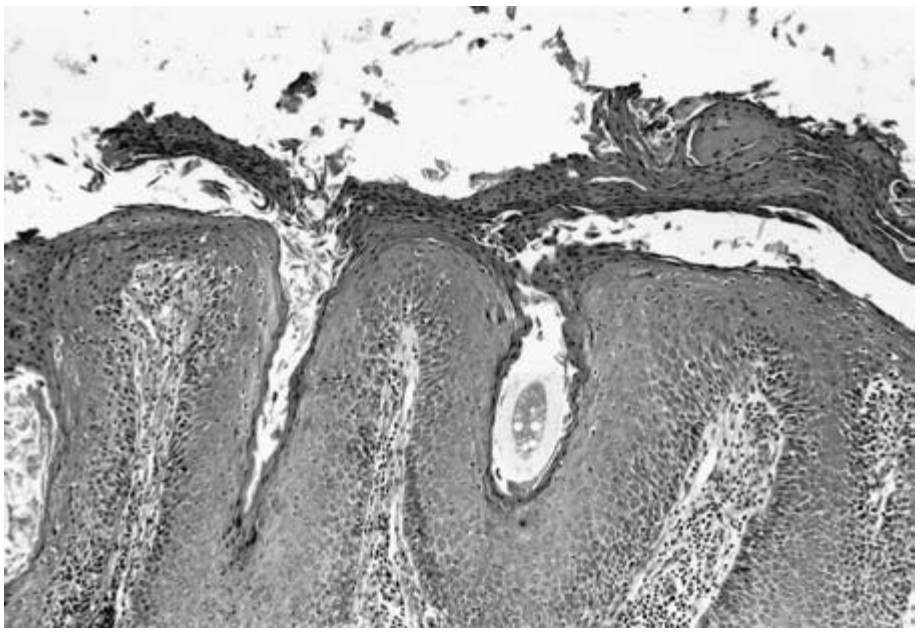


Fig. 8.53 Zinc-responsive dermatosis in a Siberian Husky. Parakeratosis overlies an acanthotic and spongiotic epidermis; note extension to superficial follicles and dermal inflammation.

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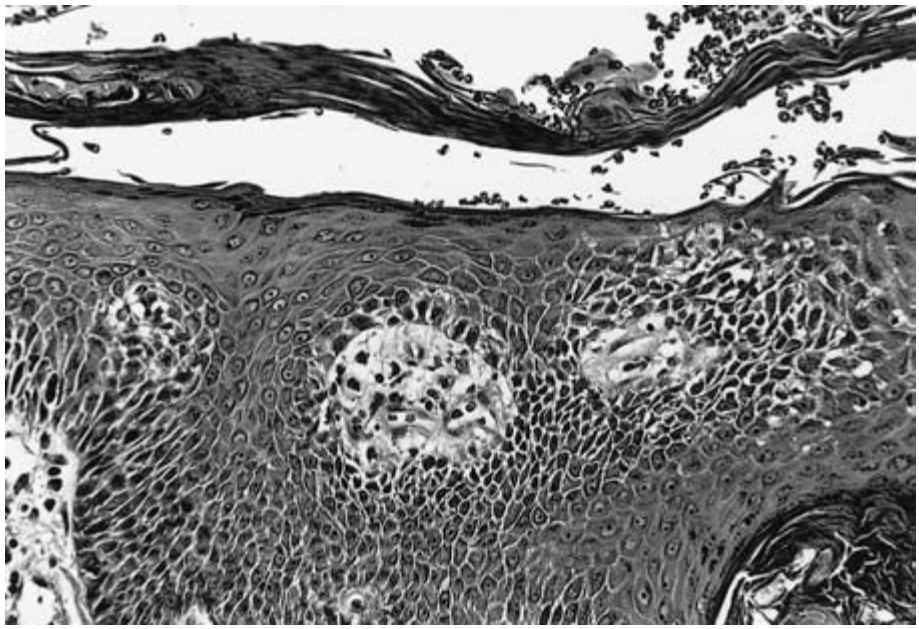


Fig. 8.54 Higher magnification of zinc-responsive dermatosis in a Siberian Husky demonstrating spongiosis and parakeratosis.

necrolysis is absent. Clinical evidence of diffuse pawpad involvement or hepatic disease may be required to differentiate chronic superficial necrolytic dermatitis from zinc-responsive dermatosis. Zinc-responsive dermatosis resembles generic dog food dermatosis; however, generic dog food dermatosis generally has superficial epidermal edema or necrolysis (similar to superficial necrolytic dermatitis) in addition to parakeratosis. Zinc-responsive dermatosis also resembles lethal acrodermatitis; however, parakeratosis in lethal acrodermatitis usually is more severe. Nasal parakeratosis of Labrador Retrievers is similar histologically, but includes larger and more numerous serum lakes within the parakeratotic layer; columnar or peaked configurations of these serum accumulations, as seen in zinc-responsive skin disease, are not found. Zinc-responsive skin disease is generally not confined to the planum nasale as is nasal parakeratosis of Labrador Retrievers.

SUPERFICIAL NECROLYTIC DERMATITIS

(Synonyms: metabolic epidermal necrosis, hepatocutaneous syndrome)

Clinical features

See Chapter 4.

Biopsy site selection

See Chapter 4.

Histopathology (Figure 8.55)

On low power, the distinctive epidermal feature of superficial necrolytic dermatitis (SND) is the pink, white and blue layering, referred to by some as the 'French flag'. The 'necrolytic' and variable apoptotic changes that characterize this entity have been described (see Chapter 4). In some chronic lesions, the pale middle layer is absent or minimal, and parakeratosis with crusting predominates. Unusually large parakeratotic nuclei may be observed. Superficial necrolytic dermatitis is identical histopathologically in cats and may be accompanied by *Malassezia* colonization (see Chapter 4).

The reaction pattern of SND is unique in cats and not shared by other recognized entities, to the authors' knowledge. Superficial necrolytic dermatitis in cats should prompt a search for secondary *Malassezia* colonization. The differential diagnosis for chronic lesions of SND in dogs in which laminar epidermal edema and degeneration and/or apoptosis are absent is zinc-responsive dermatosis. If the lesions are occurring on the skin of the pad and in the context of appropriate clinical distribution, then SND should be strongly considered even if laminar degeneration is absent. The presence of unusually large parakeratotic nuclei is a useful clue in lesions of SND.

INFLAMED LINEAR EPIDERMAL NEVUS

Clinical features (Figure 8.56)

See Chapter 7.

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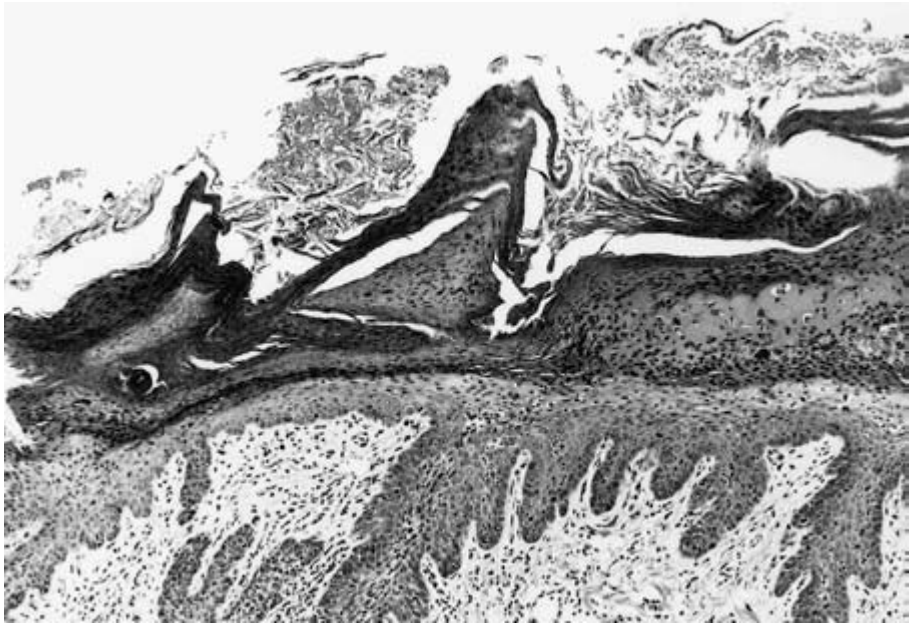


Fig. 8.55 Superficial necrolytic dermatitis in a dog demonstrating prominent parakeratosis. Laminar epidermal pallor is subtle in this lesion.

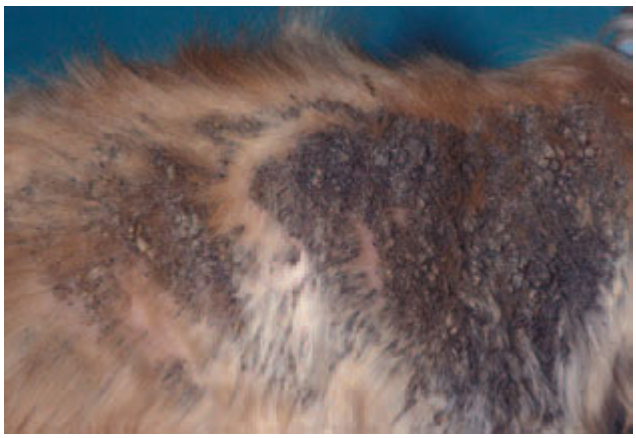


Fig. 8.56 Inflamed linear epidermal nevus displaying severe proliferation and lichenification; note the partially linear pattern of distribution. (Photograph courtesy S.D. White.)

Biopsy site selection

See Chapter 7.

Histopathology (Figures 8.57 and 8.58)

Inflamed linear epidermal nevus has severe irregular acanthosis (see Chapter 7), accompanied by generally very severe parakeratosis. The proliferative and parakeratotic changes extend to superficial follicles, which are often massively dilated. Areas of hypergranulosis, featuring coarse keratohyalin granules, alternate with areas of hypogranulosis in which keratohyalin granules are absent.

The thickened keratin layer is embedded with neutrophilic crusts, often in layers. Frank neutrophilic pustules may be present superficially and within follicular infundibula (folliculitis). Acantholytic and slightly dyskeratotic keratinocytes may be seen at the base of occasional pustules. Colonies of staphylococci are prominent within crusts. Surface colonization by *Malassezia* sp. has been reported (White et al., 1993). Idiopathic linear pustular acantholytic dermatosis also features epidermal and follicular epithelial hyperplasia and follicular pustules with acantholysis (Beningo & Scott, 2001), and may be a related phenomenon of blaschkitis (see Clinical features, Chapter 7).

Dermal inflammation is most prominent beneath areas of pustulation and crusting, and is minimal to mild in other locations. Mild areas have lymphocytes and some macrophages, while more inflamed foci show neutrophils, plasma cells, and occasional eosinophils. Sebaceous glands may be hyperplastic.

The principal differential diagnosis of inflamed linear epidermal nevus is congenital follicular parakeratosis, which it closely resembles (see p. 172). Careful clinical differentiation may be required. The parakeratotic lesions of inflamed linear epidermal nevus are too massive to be confused with most other parakeratotic conditions, such as zinc-responsive dermatosis or chronic superficial necrolytic dermatitis. Also, the severe irregular acanthosis in inflamed linear epidermal nevus should allow differentiation from these.

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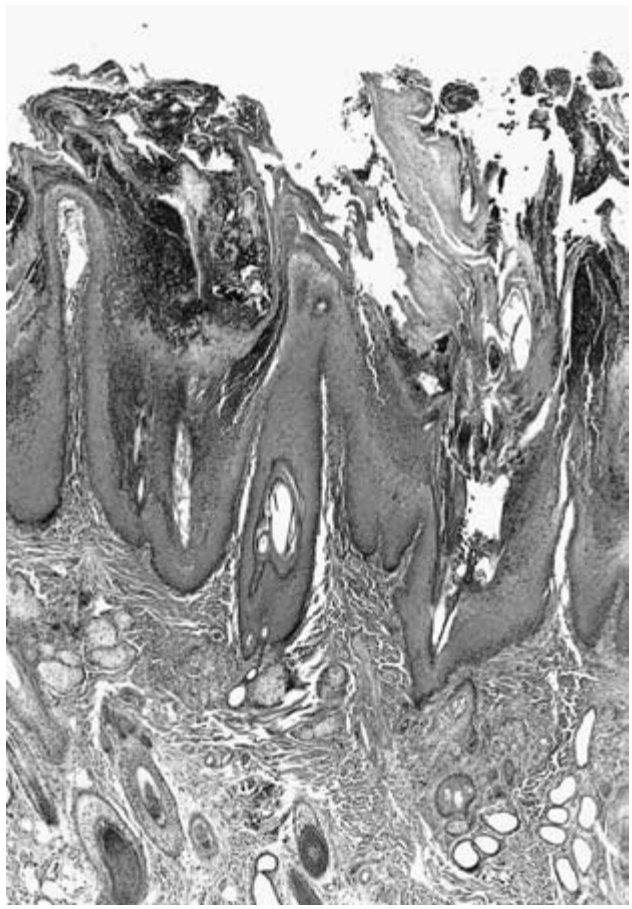


Fig. 8.57 Inflamed linear epidermal nevus in a dog demonstrating massive follicular parakeratosis and neutrophilic intrafollicular crusting.



Fig. 8.58 Higher magnification of inflamed linear epidermal nevus in the dog of Fig. 8.57. Note neutrophils accompanying follicular parakeratosis.

ACRODERMATITIS OF BULL TERRIERS

(Synonym: lethal acrodermatitis of Bull Terriers)

Clinical features (Figures 8.59 through 8.61)

Acrodermatitis of Bull Terriers is a rare, inherited autosomal recessive metabolic disease (Jezyk et al., 1986; McEwan, 1993; McEwan et al., 2000). The term 'lethal acrodermatitis' has been advocated since homozygously affected dogs have a median survival age of 7 months and rarely live beyond 18 months of age (Jezyk et al., 1986). However, the authors have seen several affected dogs reach 3 years of age without intensive therapy. The syndrome is seen exclusively in white Bull Terriers.

Previously, this syndrome was thought to be associated solely with defects in zinc absorption and metabolism (Jezyk et al., 1986; Mundell, 1988). Since affected puppies have concurrent pigment dilution, copper deficiency also has been suspected; serum copper and zinc



Fig. 8.59 Acrodermatitis in a Bull Terrier puppy. An erythematous, exfoliative dermatitis is seen on the distal extremities and surrounding the mucocutaneous junctions of the mouth, eyes, and ears. Note characteristic splaying of the feet. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

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Fig. 8.60 Closer view of mouth of the dog in Fig. 8.59. An abnormally arched hard palate is characteristically impacted with decayed, malodorous food. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)



Fig. 8.61 Closer view of paws of the dog in Fig. 8.59. The feet show abnormal keratinization of the pawpads, characterized by villous hypertrophy, fissures, and exfoliation. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

concentrations are significantly lower than those in dogs without this syndrome, indicating likely abnormalities in both zinc and copper metabolism (Uchida et al., 1997). These trace minerals are integral components of over 300 metalloenzymes that participate in many metabolic processes. Decreased serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), increased cholesterol, nonregenerative anemia, leukocytosis with neutrophilia, dysgammaglobulinemia, and decreased lymphocyte blastogenesis reflect the widespread effects of this disease (Jezyk et al., 1986). Not surprisingly, some of the cutaneous and systemic clinical signs are similar to those of other metabolic skin diseases such as severe zinc-responsive dermatitis and generic dog food dermatosis.

A hereditary disease seen in humans, termed acrodermatitis enteropathica, shares multiple clinical, histopathologic and presumed pathophysiologic features with acrodermatitis of Bull Terriers (Jezyk et al., 1986). Recently, it has been suggested that mutations in a group of mammalian zinc transporter genes may be responsible for initiating acrodermatitis enteropathica in humans (Neldner, 2003).

Acrodermatitis is characterized clinically by progressive dermatitis, growth retardation, abnormal behavior, diarrhea, and bronchopneumonia. Often by 8 weeks of age, affected Bull Terriers develop an erythematous, exfoliative, papular or pustular dermatitis of the distal extremities, skin surrounding the mucocutaneous junctions, and sometimes the mucous membranes at the mucocutaneous junctions. Ulcerated and crusted lesions are prominent on the muzzle and ears. Generalized superficial bacterial folliculitis and ceruminous otitis may be present. Secondary infection with *Malassezia* or *Candida* is common (McEwan, 2001). Splayed feet show abnormal cornification of the pawpads, characterized by villous hypertrophy, fissures, and exfoliation. There is concurrent paronychia, and claws may be dystrophic. An abnormally arched hard palate impacted with decayed, malodorous food is a characteristic clinical marker for the disease.

Chronic diarrhea and bronchopneumonia are the most serious systemic signs, and bronchopneumonia is the most common cause of death. Sires, dams, and siblings of affected dogs may exhibit an increased frequency of secondary pyoderma and *Malassezia* dermatitis, suggesting that heterozygote expression of this genetic disease may increase the risk for secondary skin infections. In the opinion of one author (P.J.I.), accounts of zinc-responsive skin disease in Bull Terriers may represent heterozygous expression of acrodermatitis.

The syndrome is seen only in white Bull Terriers and develops shortly after birth. Sex predilections have not been noted. Acrodermatitis of Bull Terriers is clinically distinctive; clinical differential diagnoses are few. Theoretically, generic dog food dermatosis and zinc-responsive dermatosis in Bull Terrier puppies might be similar clinically. Lesions may resemble those seen with superficial necrolytic dermatitis, but age and breed predilections facilitate differentiation.

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Biopsy site selection

Multiple biopsy specimens should be taken from affected areas. Care must be taken not to dislodge adherent crusts.

Histopathology (Figures 8.62 and 8.63)

Acrodermatitis is characterized by massive parakeratosis, organized in compact layers. The epidermis is moderately to severely acanthotic and occasionally mildly spongiotic. There is hypogranulosis. Small to moderately-sized serocellular crusts may be imbedded in the keratin layer, and entrapped colonies of staphylococci are prominent. Neutrophils may migrate through the epidermis to form small intraepidermal spongiotic pustules that become confluent superficial pustules and crusts. Erosion and ulceration may be present. Laminar pallor of the superficial epidermis is sometimes observed, but keratinocytes generally appear viable. Rarely, there is loss of nuclear definition or cellular outline; intracytoplasmic vacuolation may be



Fig. 8.62 Acrodermatitis in a Bull Terrier. Massive parakeratosis shows abrupt transition with the subjacent acanthotic epidermis. Epidermal pallor is in laminar distribution, and neutrophils are migrating to form small pustules. Hair follicles are also affected.

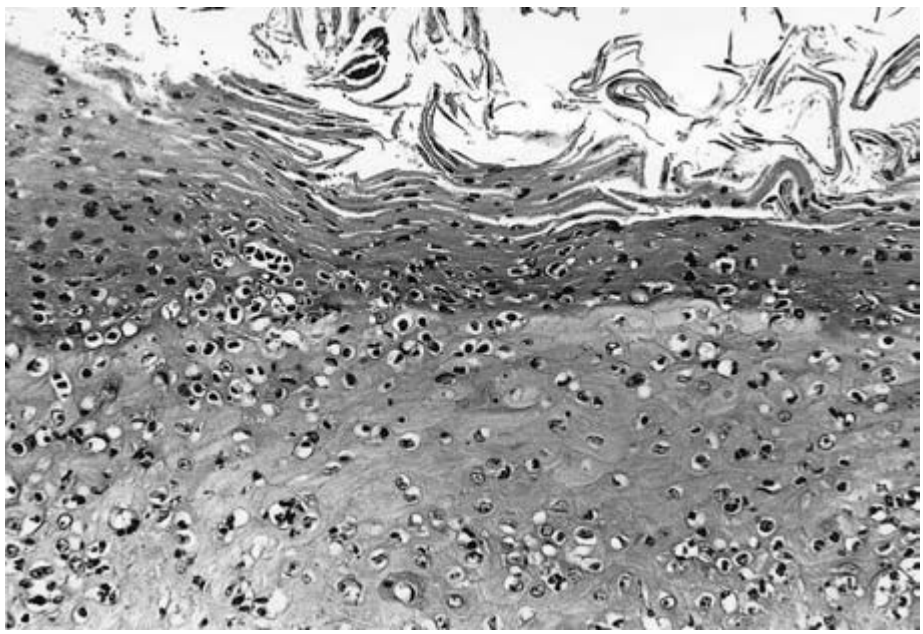


Fig. 8.63 High magnification of acrodermatitis in the Bull Terrier of Fig. 8.62. Severe parakeratosis overlies pale epidermis.

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seen. Shrunken, brightly eosinophilic, presumptively dyskeratotic keratinocytes may occur occasionally beneath the parakeratotic layer. The deeper keratinocytes may have a slightly gray cast and may appear slightly disordered. Similar histopathologic changes extend to dilated follicular infundibula.

Dermal inflammation is absent, or mild to moderate, and is composed of lymphocytes, macrophages, plasma cells, and neutrophils, the latter accumulating beneath overlying foci of pustulation.

Differential diagnosis is generally not difficult if the characteristic breed occurrence and clinical signs of acrodermatitis are known. Zinc-responsive dermatosis, generic dog food dermatosis, and superficial necrolytic dermatitis are characterized by parakeratosis, but not to the degree observed in acrodermatitis. Generic dog food dermatosis and superficial necrolytic dermatitis tend to have more prominent laminar necrolytic epidermal degeneration than the laminar pallor seen in acrodermatitis. Congenital follicular parakeratosis is similar, but has not been reported in Bull Terriers. Also, parakeratosis is folliculocentric in congenital follicular parakeratosis, but is diffuse in acrodermatitis.

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See Chapter 4.

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Part II

Diseases of the Dermis

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Chapter 9

Perivascular diseases of the dermis

Perivascular dermatitis is a relatively nondiagnostic pattern in the skin characterized by inflammatory cells around vessels of the dermis. Inflammation does not remain strictly perivascular but also spreads to the adjacent dermal interstitium. Diseases of this group tend to have inflammation that appears perifollicular or periadnexal because blood vessels are numerous in that location. The majority of the diseases in this group have an allergic cause; histopathologic differentiation among them is often very difficult. Identification of the primary inflammatory cell present may allow partial differentiation; however, definitive diagnosis will depend heavily upon clinical assessment, including response to therapy. Most of these diseases also are characterized by hyperplasia of the epidermis and superficial follicular epithelium, and were discussed in Chapter 7 under the general heading of Chronic hyperplastic dermatitis.

Most inflammatory diseases of the skin are characterized by perivascular infiltrates at some stage in the histogenesis of the lesions, as blood vessels are the source of all inflammation in tissue. The diseases included in this chapter are those which have perivascular inflammation as a principal and predominant pattern.

SUPERFICIAL SPREADING PYODERMA

Clinical features (Figures 9.1 and 9.2)

See Chapter 1.

Biopsy site selection

See Chapter 1.

Histopathology (Figures 9.3 and 9.4)

Epidermal lesions have been described (see Chapter 1). Dermal inflammation consists of superficial perivascular neutrophils that predominate in early lesions and usually are intermingled with macrophages and lymphocytes. Some eosinophils are invariably present and may be as numerous as neutrophils; this may be due not only to associated hypersensitivity dermatitis, but also to the influence of bacterial superantigens. Mast cells may also be increased in number. Plasma cells are seen in chronic lesions. Mild to moderate edema may be present. Vessels may be mildly to moderately dilated and congested. There may be marginating neutrophils and swollen endothelial cells. Inflammation may extend to surround the middle (isthmus) portion of hair follicles and associated glands.

The perivascular inflammation of superficial spreading pyoderma may be indistinguishable from chronic hyperplastic dermatitis, more specifically allergic dermatitis, if typical epidermal lesions are lacking in the specimen for biopsy. A predominance of neutrophils and/or plasma cells may suggest superficial pyoderma, but dermal inflammation alone is not sufficient to indicate the diagnosis. Clinical differentiation is required.

ATOPIC DERMATITIS

Clinical features (Figures 9.5 through 9.7)

Atopic dermatitis is a common, genetically predisposed allergic skin disease (Olivry et al., 2001; Sousa & Marsella, 2001). It occurs in animals with atopy, a hereditary tendency to develop IgE-mediated allergic reactions to various environmental allergens. These may include house dust mite proteins, plant pollen, mold spores, and various other allergens. Atopic dermatitis may begin either as a seasonal or nonseasonal disease; seasonal cases frequently progress to perennial (Griffin & DeBoer, 2001). Atopic dermatitis is reasonably well characterized in the dog and considerably less well characterized in the cat.

Current evidence suggests that genetically predisposed animals and humans may predominantly percutaneously absorb allergens that provoke specific immunological events (Leung, 1999; Olivry & Hill, 2001a). Langerhans cells probably play a central role in antigen processing and presentation. Immunostaining of skin biopsy specimens from atopic dogs shows proliferation of Langerhans cells and enhanced expression of tissue bound IgE in

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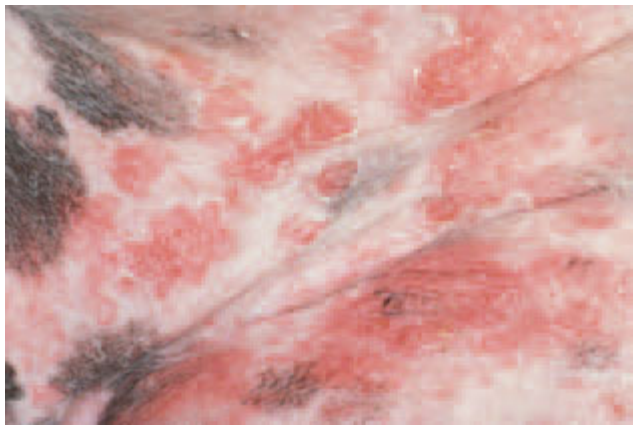


Fig. 9.1 Superficial spreading pyoderma in a Border Collie. Multiple coalescing erythematous macules with peripheral collarettes cover the glabrous skin of the ventral abdomen. The macular hyperpigmentation is the sequela to prior infection.

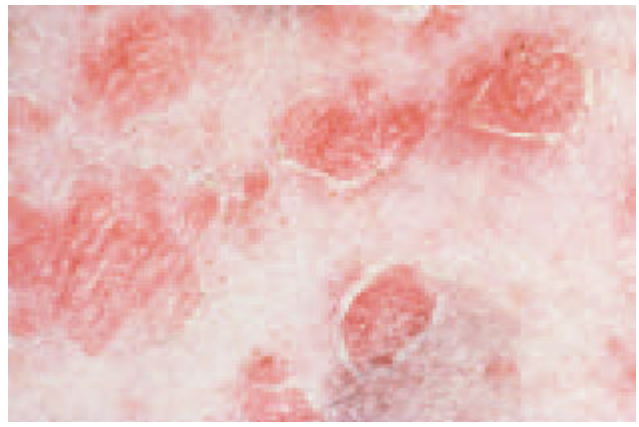


Fig. 9.2 Closer view of the dog in Fig. 9.1. Collarettes peel peripherally from the margins of the macules. Pustules are not present.

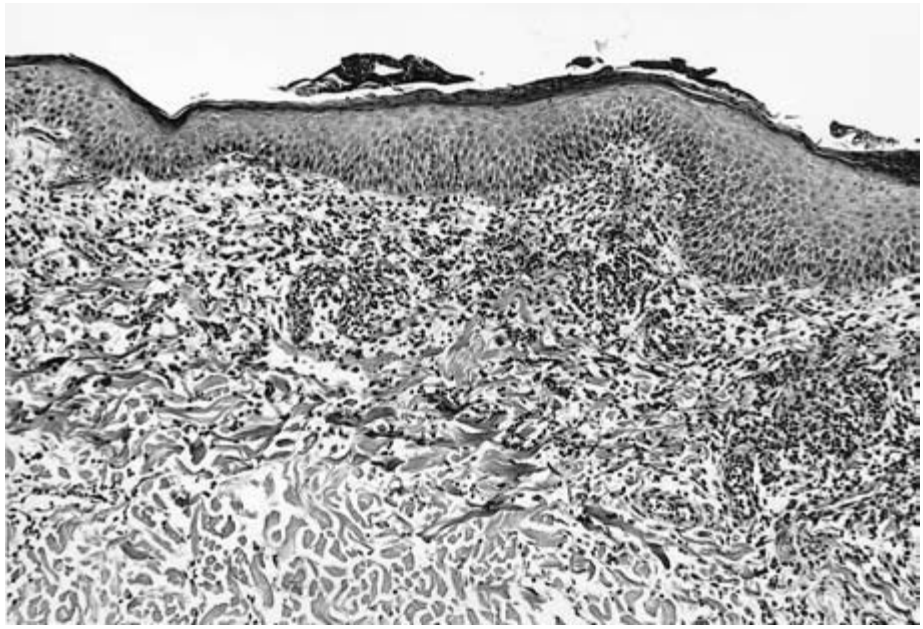


Fig. 9.3 Superficial spreading pyoderma in a dog. Superficial dermal neutrophilic inflammation is accompanied by acanthosis, spongiosis, and crusting.

lesional skin (Olivry et al., 1996; Olivry & Hill, 2001b). Two distinct patterns of cytokine production have been demonstrated in a variety of mammalian species; the T-helper 1 (TH1) and T-helper 2 (TH2) response. A polarization of cytokine response from a TH1- to a TH2-skewed response may be responsible for the development of atopic dermatitis (Hill & Olivry, 2001). These immunologic events lead to the release of pharmacologically active compounds from mast cells (Marsella & Olivry, 2001). Considerable evidence exists that the interaction of the relevant antigen with allergen-specific IgE initiates the events leading to canine atopic dermatitis (Halliwell & DeBoer, 2001). Feline IgE has been identified (DeBoer et al., 1993; Gilbert & Halliwell, 1998). However, conclusive links have not been established between the existence of heterogeneous IgE and clinical disease in cats.

The diagnosis of canine atopic dermatitis requires exclusion of diseases causing similar clinical symptomatology, as pathognomonic clinical features of atopic dermatitis are not present (Willemse, 1986; DeBoer & Hillier, 2001). The modification of Willemse's criteria by Prélaud et al. (1998) states that the clinical criteria for the diagnosis of canine atopic dermatitis be the fulfillment of three of the following five features: (1) corticosteroid-sensitive pruritus, (2) erythema of pinnae, (3) bilateral cranial

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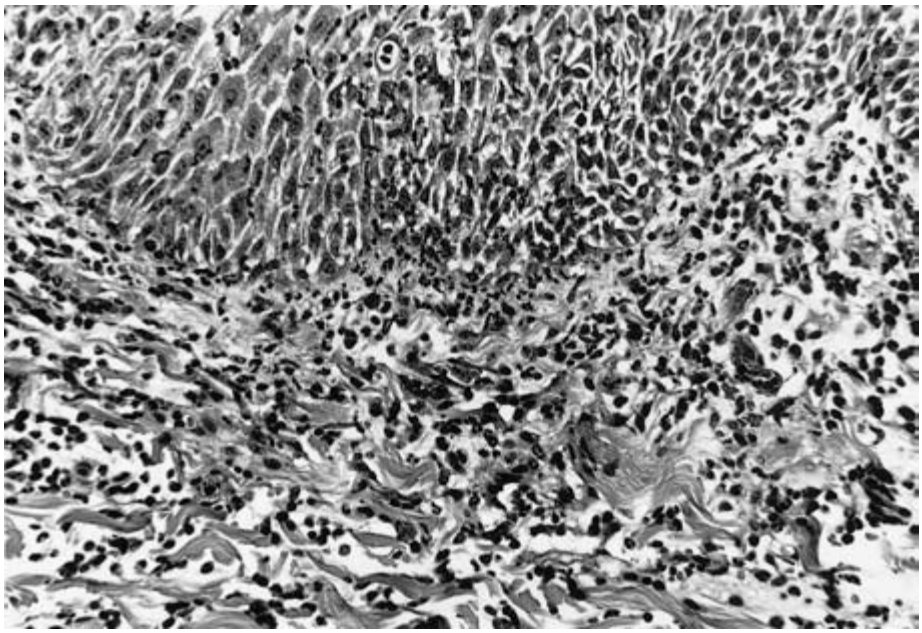


Fig. 9.4 Higher magnification of superficial dermal inflammation in superficial spreading pyoderma. Neutrophils are intermingled with fewer mixed mononuclear cells. Note migration of inflammatory cells into the spongiotic epidermis.



Fig. 9.5 Atopic dermatitis in a Dalmatian. Areas of erythema, excoriation, and self-traumatic alopecia are seen periorally, and on the forelegs, distal extremities, lateral thorax, and ventral abdomen.



Fig. 9.6 Closer view of the dog in Fig. 9.5. Extensive excoriations are present on the elbow and lateral thorax. Note the absence of primary lesions.

erythematous pododermatitis, (4) cheilitis, and (5) appearance of first signs between the ages of 6 months and 3 years.

Feline atopic dermatitis remains controversial (Gilbert et al., 1999; Scott et al., 2001). Estimates of the frequency of occurrence vary widely, genetic predilection has not been proven, and a unifying description of expected clinical features is not available for cats. The strongest evidence to date in support of heritability is the presence of a disease closely resembling atopic dermatitis in three feline littermates (Moriello, 2001).

Pruritus is the unifying clinical feature of atopic dermatitis. Primary skin lesions are rare in canine atopic dermatitis; most skin lesions are due to secondary self-

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Fig. 9.7 Atopic dermatitis in a Bull Terrier. Pruritus has prompted excoriations and self-traumatic alopecia on the dorsum of a forepaw.

trauma. Self-trauma leads to variable degrees of erythema, alopecia, and excoriation. Lichenification and hyperpigmentation are observed in chronically affected dogs. Greasiness or hyperhidrosis also may be present. Salivary staining of the haircoat occurs in dogs with light coat color. The face, paws, caudal carpi, distal extremities, ears, and ventrum are affected most commonly. The caudal aspect of the carpus may be the most diagnostically useful site for increasing index of suspicion for canine atopic dermatitis. Lesions may be generalized. In a previous report, pruritus of the distal extremities was noted in 76% of dogs and otitis externa was noted in 60% of dogs (Zur et al., 2002). Less commonly, pinnal inflammation characterized by erythema and swelling may be the only feature of canine atopic dermatitis and may be seen in conjunction with otitis externa. Secondary pyoderma and *Malassezia* dermatitis are common and contribute greatly to the clinical features and pruritus.

Feline atopic dermatitis is less well characterized clinically. Reported presentations include pruritus and self-induced alopecia; pruritus and self-trauma centered on the head, neck, and pinnae; miliary dermatitis (see Chapter 6); and feline eosinophilic skin diseases such as feline eosinophilic plaque, feline eosinophilic granuloma, and feline indolent ulcer (Scott et al., 2001). Respiratory disease, especially asthma, may be seen alone or in conjunction with skin disease. Self-trauma varies from mild to severe. Cats may conceal evidence of milder pruritus by engaging in clandestine self-trauma to such an extent that owners deny its existence. In those cases, pruritus may need to be deduced clinically via indirect evidence such as trichograms revealing barbered hairs, tufts of hair in the cat's hiding places, vomiting of hair balls, and excess hair in the feces. Self-traumatized areas may be relatively localized or generalized. Similar to dogs, the face, neck, pinnae, forelegs, and ventrum may be more severely affected.

The majority of affected dogs (70%) present with signs of atopic dermatitis between 1 and 3 years of age (Scott et al., 2001). A large recent study indicates a mean of 1.66 years of age and a range from 2 to 3 months to 8 years of age (Zur et al., 2002). Clinical signs of atopic dermatitis rarely begin before 6 months of age or after 7 years of age. Many studies have noted breed predilections, with multiple small terrier breeds at increased risk. Labrador Retrievers, Golden Retrievers, and West Highland White Terriers were at highest risk in a recent study (Zur et al., 2002). Springer Spaniels, Chinese Shar Peis, Bull Terriers, Bichon Frises, and Tibetan Terriers were also at increased risk (Zur et al., 2002). Another recent study in Golden Retrievers and Labrador Retrievers using quantitative estimation of heritability as a tool confirmed a strong genetic component to canine atopic dermatitis in these breeds (Shaw et al., 2004). Although multiple studies have mentioned a female predilection, this was not observed in the recent large study (Zur et al., 2002). Initially, many dogs manifest atopic dermatitis as summer–autumn pruritus, with the time of involvement tending to lengthen each year.

Few signalment data are available for the cat. One source indicates that the clinical signs of miliary dermatitis due to atopic dermatitis are more likely to occur between 6 and 24 months of age (Scott et al., 2001).

The most common canine clinical differential diagnoses include flea allergy dermatitis, food allergy, sarcoptic acariasis, recurrent pruritic superficial pyoderma, *Malassezia* dermatitis, allergic contact dermatitis, and generalized pruritic skin disease associated with intestinal parasite hypersensitivity in the young dog. Differential diagnosis of atopic dermatitis may be hampered by the frequent coexistence of flea allergy dermatitis. Flea allergy dermatitis has a primary papular eruption with prominent dorsal lumbosacral distribution. The pruritus of flea allergy dermatitis frequently is limited to the caudal one-half of the body in contrast to atopic dermatitis. Food allergy is nonseasonal and less corticosteroid-responsive than is canine atopic dermatitis. Both pyoderma and *Malassezia* dermatitis can be differential diagnoses for atopic dermatitis and also can occur secondary to atopic dermatitis. Primary lesions, such as papules and pustules, are seen with pruritic pyoderma. Allergic contact dermatitis is a rare type IV cell-mediated delayed hypersensitivity, usually limited to ventral, sparsely haired skin.

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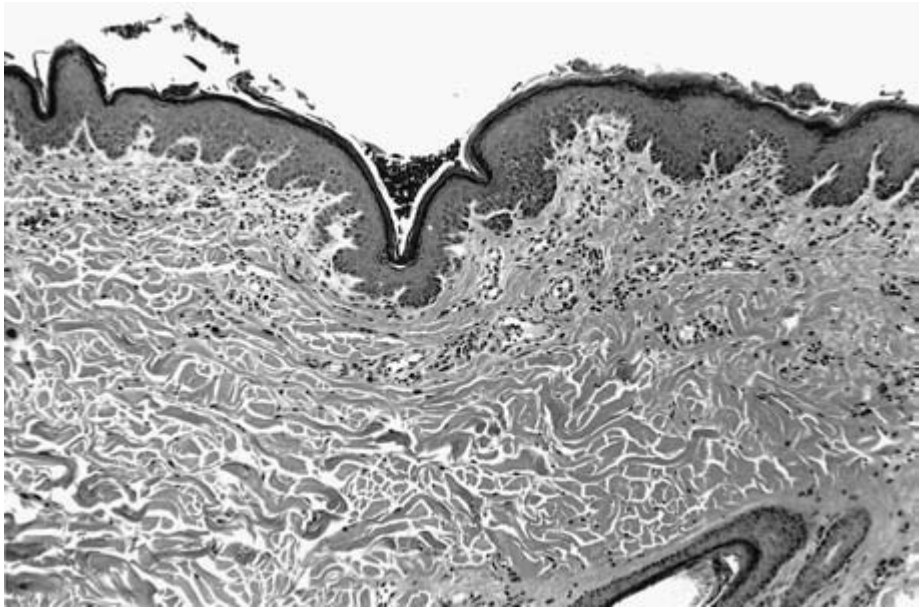


Fig. 9.8 Atopic dermatitis in a dog. Irregular acanthosis overlies mild superficial dermal inflammation. Note mild vascular ectasia.

Feline principal clinical differential diagnoses include flea allergy dermatitis and food allergy. Miliary dermatitis predominantly localized to the neck and dorsal rump is seen with flea allergy dermatitis. Food allergy is nonseasonal, regularly less corticosteroid-responsive, and often affects the head and neck primarily. Feline psychogenic alopecia is a less common differential diagnosis; inflammation is not a feature of feline psychogenic alopecia.

Biopsy site selection

Biopsy is employed primarily to rule out other more histopathologically specific skin diseases in animals with compatible history and physical findings. Areas of erythema with minimal self-trauma should be selected. Chronic areas of lichenification and hyperpigmentation, which are frequently complicated by secondary pyoderma and *Malassezia* dermatitis, should be avoided.

Histopathology (Figures 9.8 through 9.10)

Difficulty in characterizing atopic dermatitis in dogs arises from the potential concomitant presence of other allergic disorders including flea allergy or food allergy, as well as secondary superficial pyoderma (folliculitis or superficial spreading pyoderma). Inflammation caused by concurrent allergic conditions may obscure the frequently subtle inflammation of atopic dermatitis. In uncomplicated cases of atopic dermatitis, epidermal lesions are those of chronic hyperplastic dermatitis due to allergy (see Chapter 7). Mild to severe acanthosis, which also involves follicular infundibula, is present. The epidermis may have

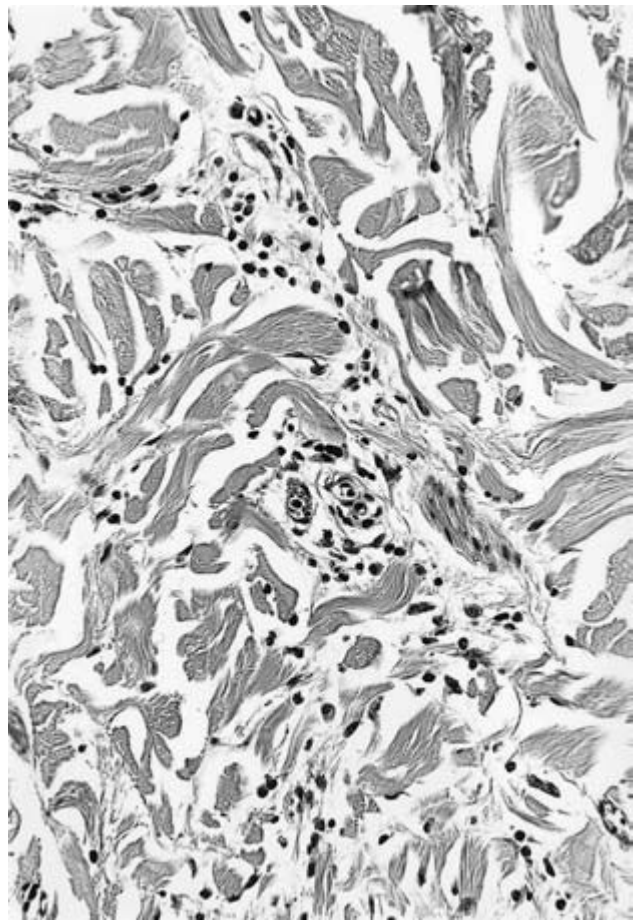


Fig. 9.9 Higher magnification of atopic dermatitis in a dog. Mild accumulations of mononuclear cells are oriented around blood vessels.

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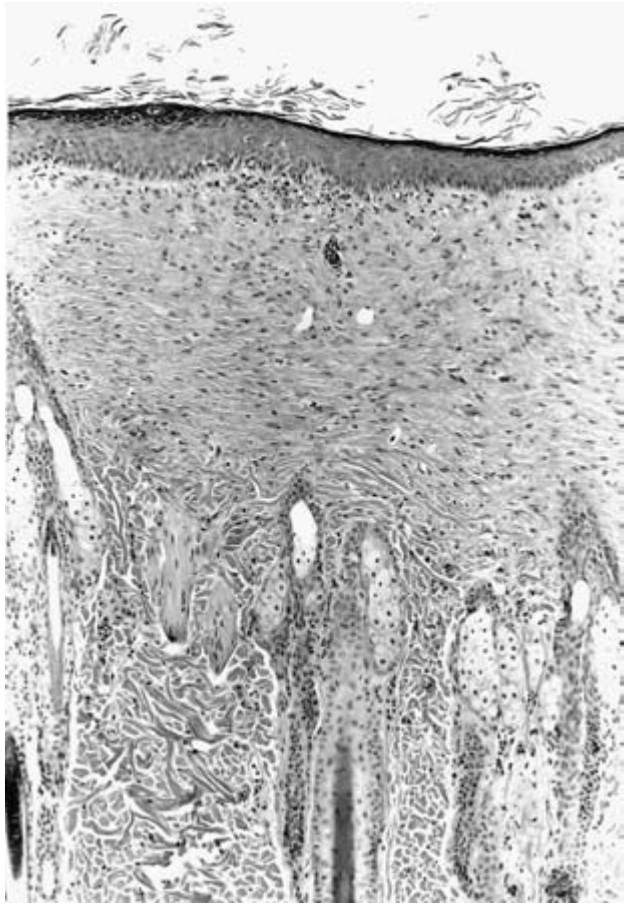


Fig. 9.10 Atopic dermatitis in a cat. Atypically severe laminar fibrosis from persistent self-trauma is mixed with mild superficial inflammation.

patchy, mild spongiosis with exocytosis of lymphocytes, identified previously as T cells (Olivry et al., 1997). Intraepidermal eosinophils, sometimes forming small pustules, were observed in a small percentage of lesions in that study (Olivry et al., 1997). Clusters of intraepidermal mononuclear cells have been identified as Langerhans cells (Olivry et al., 1997). Focal parakeratosis and crusting are variable but usually mild. Dense, brightly eosinophilic, compact keratin is observed and occasionally extends to superficial hair follicles. This type of keratinization usually reflects persistent self-trauma, and occurs in chronic lesions.

The dermis is characterized by a superficial perivascular infiltrate. Inflammation generally is mild in lesions of atopic dermatitis that are not complicated by superficial pyoderma or other allergic conditions. Inflammation may extend to surround the middle (isthmus) portion of hair follicles and their associated glands. The inflammatory infiltrate principally consists of mixtures of lymphocytes and histiocytic cells; the latter have been identified as antigen presenting dendritic cells (Olivry et al., 1997). Perivascular mast cells are frequently increased in number. Eosinophils are rarely detected in routine hematoxylin and eosin (HE)-stained sections, but may be more numerous in sites of direct recent aeroallergen contact, particularly the feet. Eosinophils were reported in small numbers in atopic dogs; increased sensitivity of detection was likely related to the use of Luna's and Giemsa stains, which highlight both intracellular and extracellular eosinophilic granules (Olivry et al., 1997). Neutrophils and plasma cells are seen in small numbers, and their presence may depend on the extent of secondary epidermal pustulation and crusting induced by self-trauma (impetiginization), and/or secondary pyoderma. Superficial dermal blood vessels often are dilated and may be congested. Edema is variable but usually mild.

Sebaceous gland hyperplasia may occur in any longstanding pruritic skin disease of dogs, including atopic dermatitis. Sebaceous glands enlarge and proliferate loosely in the dermis, and this alteration may correlate directly with the degree of oily seborrhea observed. There also may be squamous metaplasia of sebaceous glands which is characterized by replacement of glands by squamous epithelium, usually expanding outward from the ductular region. Apocrine sweat glands may be dilated and lined by hyperplastic epithelium; this feature is also associated with chronic pruritus and may correlate clinically with hyperhidrosis.

Atopic dermatitis in cats is not well characterized, most likely because it is less common. Lesions may resemble allergic miliary dermatitis (see p. 211). Acanthosis, serocellular crusting, and mild spongiosis are as seen in dogs. Eosinophils predominate in superficial and perifollicular inflammatory infiltrates, and are accompanied by lymphocytes and mast cells; this inflammatory pattern also has been reported in clinically confirmed cases of feline atopy (Moriello, 2001). Fewer histiocytes and neutrophils are found. There may be mild sebaceous hyperplasia but apocrine dilatation is uncommon. In contrast to dogs, mild to prominent laminar superficial dermal fibrosis may be present in atopic cats with pruritus-induced self-trauma.

Differential diagnoses in dogs include other allergic skin diseases or skin diseases that evoke persistent self-trauma. Identification of primary lesions, such as pustules in pruritic superficial spreading pyoderma, is helpful; however, superficial spreading pyoderma may accompany atopic dermatitis. Atopic dermatitis may be the tentative histopathologic diagnosis for the pruritic dog when superficial perivascular inflammation is minimal and does not include many detectable eosinophils with routine HE staining. If intraepidermal eosinophilic pustules are found, consideration of allergic contact dermatitis may be required (see Chapter 5). Intraepidermal eosinophilic

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Fig. 9.11 Food allergy in a cat. Severe self-trauma of the head and neck has created extensive alopecia with excoriations and ulcers.



Fig. 9.12 Food allergy in a Dalmatian. Self-traumatic alopecia and erythema are noted on the dorsum of a forepaw.

pustules also have been reported in a small percentage of atopic dogs in one study (Olivry et al., 1997); since percutaneous penetration of allergens also is involved in atopic dermatitis, histologic distinction from allergic contact dermatitis may be impossible in some clinical settings. In cats, the differential feature of a predominantly mononuclear cell infiltrate is not present, as eosinophils prevail in most allergic diseases in this species. Clinical correlation and appropriate confirmatory testing always are required in cats and dogs, as histopathologic findings are not etiologically diagnostic for atopic dermatitis.

FOOD ALLERGY

(Synonyms: adverse food reactions (AFR), food hypersensitivity, food intolerance)

Clinical features (Figures 9.11 and 9.12)

Food allergy is a controversial skin disease of the dog and cat. It is presumed to be a hypersensitivity reaction to ingested allergens. Some cases may be examples of true hypersensitivity, while others may simply be food intolerances due to nonimmunologic idiosyncratic reactions, or physiologic reactions to vasoactive substances in food. Since the underlying pathomechanism of adverse food reaction is rarely proven, 'food allergy' is a term of convenience. The immunologic basis of food allergy in domestic animals is not well characterized. In humans, type I hypersensitivity is documented most frequently, but type III and IV hypersensitivities also have been implicated.

Dermatologic and gastrointestinal signs of food allergy may coexist both in animals and in humans. It has been estimated by most authors that fewer than 20% of animals with dermatologic signs of food allergy have coexistent gastrointestinal signs, and vice versa.

The authors view food allergy as the third most common allergic skin disease in the dog after flea allergy dermatitis and atopic dermatitis. Feline food allergy may be second in frequency to flea allergy dermatitis. Since food allergy is seen more frequently in animals with other allergic diseases, disparate information on the reported incidence of food allergy may be associated with the prioritization of diagnostic tests for allergic disease, as well as the threshold phenomenon.

Clinically, food allergy is one of the most pleomorphic skin diseases encountered in clinical veterinary practice. Nonseasonal pruritus with self-trauma is the most common clinical sign. In both dogs and cats, primary skin lesions frequently are not present, as is seen in atopic dermatitis. When present, primary lesions may include erythema, erythematous papules, wheals, and pustules with crusts. Pruritus leads to the secondary changes of erosion, ulceration, and excoriation with alopecia. Lichenification and hyperpigmentation are seen with chronic food allergy in the dog. Face, ears, extremities, and the ventrum are the most frequently involved sites. Secondary pyoderma and *Malassezia* dermatitis may contribute greatly to both pruritus and lesions. Secondary infections are less common in the cat than in the dog. Otitis externa is a common feature of canine food allergy.

Feline food allergy may be more pruritic and unremitting than canine food allergy. In cats, pruritus centered on

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the head, neck, and pinnae may be severe. Miliary dermatitis may be present (see Chapter 6). Pruritus leading to self-traumatic alopecia only, as in feline psychogenic alopecia (see Chapter 19), is sometimes dramatically bilaterally symmetric (Guaguère, 1996). The coexistence of many eosinophilic skin diseases (feline eosinophilic plaque, feline eosinophilic granuloma, and feline indolent ulcer) with feline food allergy is controversial but has been described (Scott et al., 2001).

Signalment predilections also are controversial. Many breed predilections have been reported; however, food allergy can occur in any breed. In dogs, between one-third and one-half of food allergy cases occur in dogs less than 1 year of age (White, 1986; Carlotti et al., 1990; Harvey, 1993; Rosser, 1993a, 1998). However, food allergy may occur at any age. A breed predilection for Siamese cats and their related crossbreeds may exist (Carlotti et al., 1990; Rosser, 1993b). Age predilections have not been documented for cats. Sex predilections have not been reported in either dogs or cats.

The principal differential diagnosis for canine food allergy is atopic dermatitis. Other clinical differential diagnoses include additional highly pruritic skin diseases such as flea allergy dermatitis, and sarcoptic or notoedric acariasis. Feline mosquito bite hypersensitivity may resemble feline food allergy; however, mosquito bite hypersensitivity is more narrowly focused on the dorsal muzzle and ears, and is markedly seasonal. Food allergy is nonseasonal and may be considerably less glucocorticoid responsive than other allergic skin diseases. Food allergy is diagnosed by appropriate elimination diet followed by rechallenge after improvement has been obtained.

Biopsy site selection

Primary lesions and lesions with minimal self-trauma are preferred sites. In the cat, it is especially important to avoid ulcers. In cats the dorsum of the neck between the shoulder blades is not recommended as a biopsy site, as any traumatic or inflammatory manipulation in this region may lead to the development of feline idiopathic ulcerative dermatosis (see Chapter 6).

Histopathology (Figures 9.13 and 9.14)

The lesions of food allergy are highly variable in both dogs and cats. In dogs, epidermal lesions include those of chronic hyperplastic dermatitis due to allergy (see Chapter 7). Acanthosis may be severe and there may be patchy spongiosis. Dermal lesions include superficial perivascular inflammation that may be diffuse in more severe lesions. Vessels are dilated and congested, and there may be mild to moderate superficial dermal edema.



Fig. 9.13 Food allergy in a dog demonstrating mild superficial perivascular and interstitial inflammation; note mild edema.

Inflammation is mixed and variable in both cell type and intensity. Some cases include predominantly lymphocytes and histiocytes, while others may feature many eosinophils, sometimes in striking perivascular arrangement. Mast cells may be numerous. The presence of neutrophils and plasma cells may depend on the degree of self-trauma-induced epidermal damage or pyoderma. Inflammation may extend around subjacent adnexal appendages. Chronic lesions may be characterized by sebaceous gland and sweat gland hyperplasia, as seen in atopic dermatitis (see p. 200).

In cats, lesions may be manifested as allergic miliary dermatitis (see Chapter 6 and p. 211). Moderate to severe acanthosis may be accompanied by extensive ulceration and exudation in more severe lesions. Eosinophilic plaque-like changes of severe epidermal and superficial follicular spongiosis and mucinosis may be present in areas not typically expected to develop plaque, such as the head. Dermal inflammation often includes eosinophils, intermingled with histiocytes, lymphocytes and variable neutrophils, the latter dependent upon the

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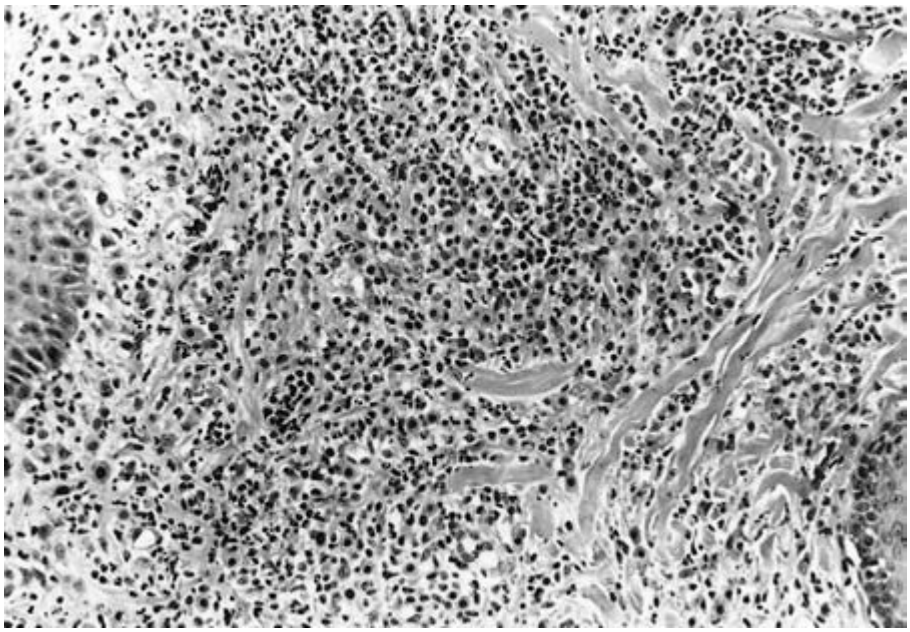


Fig. 9.14 High magnification of food allergy in a cat. Severe eosinophilic and mastocytic inflammation is diffusely present in the dermis.

degree of ulceration. Mast cells may be present in large numbers throughout the superficial and middle dermis, and are often clustered around blood vessels or in rows between collagen fibers. In some instances, lesions of feline food allergy have been confused with cutaneous mast cell neoplasia. Eosinophilic and mixed infiltrates may extend to surround vessels of the deep dermis and upper layers of the panniculus; this deep extension of inflammation is very suggestive of food allergy, particularly when occurring in the context of lesions confined to the head and neck. In occasional cases, there may be small foci of eosinophil degranulation around collagen fibers (flame figures) in a milieu of severe eosinophilic dermatitis. Eosinophilic (luminal) folliculitis has been observed. Eosinophilic mural folliculitis, characterized by the degranulation of eosinophils in the follicular wall and around follicles, may be present rarely. Neutrophils may be clustered around and within superficial to middle hair follicles, constituting putative secondary bacterial folliculitis.

Mild to moderate mononuclear cell dermatitis without eosinophils has been reported in cats with clinically confirmed food allergy (White & Sequoia, 1989). Also, inflammation is minimal in the rare food allergic cat that presents for alopecia only. These cases clinically and histologically mimic feline psychogenic alopecia (see Chapter 19), but generally include a few scattered eosinophils as evidence of an underlying allergic stimulus to hair pulling.

Differential diagnoses in the dog and cat include other allergic skin diseases, particularly those characterized by eosinophils. These include canine flea allergy dermatitis, feline allergic miliary dermatitis, feline mosquito bite hypersensitivity, and sarcoptic and notoedric acariasis. Flea allergy may be indistinguishable. Uncomplicated canine atopic dermatitis is generally less inflamed and does not include significant numbers of eosinophils, as do most cases of canine food allergy. In the cat, a predominance of mast cells or severe and deep extension of eosinophilic inflammation is suggestive for food allergy, particularly when lesions are known to be confined to the head and neck. However, the deep eosinophilic inflammation of feline mosquito bite hypersensitivity may be virtually identical. Feline mosquito bite hypersensitivity may have prominent eosinophil degranulation, in contrast to feline food allergy in which these lesions are less common and mild. In feline cases of food allergy that mimic psychogenic alopecia, scattered eosinophils may suggest an underlying allergic cause. Definitive histopathologic identification of food allergy in dogs and cats is not possible, and clinical differentiation is required.

CANINE FLEA ALLERGY DERMATITIS

(Synonyms: FAD, flea bite hypersensitivity, flea bite dermatitis)

Clinical features (Figures 9.15 through 9.17)

Canine flea allergy dermatitis is an extremely common pruritic skin disease caused by hypersensitivity to salivary antigens of the flea. Flea allergy dermatitis is the most common cause of canine skin disease globally in environmental regions supportive of flea populations. Type I immediate hypersensitivity, type IV delayed hypersensi-

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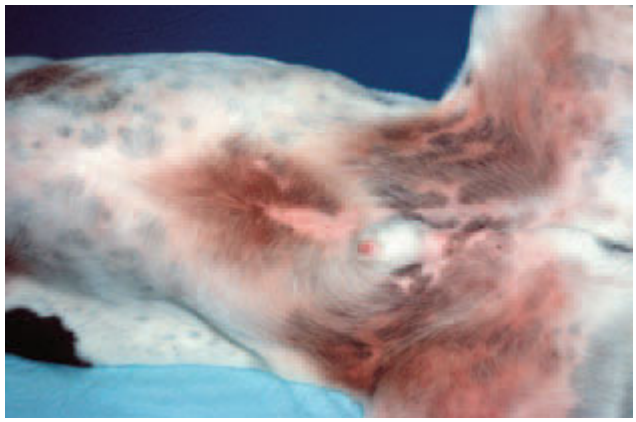


Fig. 9.15 Acute canine flea allergy dermatitis. Salivary staining, erythema, and papules are present bilaterally symmetrically on the ventral abdomen. Note characteristic involvement of the umbilicus. (Photograph courtesy M.D. Song; case material University of California, Davis.)



Fig. 9.16 Chronic flea allergy dermatitis in a Samoyed crossbreed. Classic lesions consisting of bilaterally symmetric alopecia, hyperpigmentation, and severe lichenification are seen in the dorsal lumbosacral region.

tivity, and cutaneous basophil hypersensitivity to salivary antigens all have been documented as immunologic participants (Gross & Halliwell, 1985; Halliwell & Schemmer, 1987). A late-phase IgE-mediated reaction also may contribute to the pathogenesis.

Pruritus is the single most important clinical sign of flea allergy dermatitis. Crusted papules occur in a somewhat bilaterally symmetric pattern and involve the dorsal lum-



Fig. 9.17 Closer view of the lateral tail fold of the dog in Fig. 9.16. The erythematous papules of acute flea allergy dermatitis are superimposed on chronic skin lesions.

bosacral region, tailbase, perineum, and the medial and caudal thighs. Lesions and pruritus are predominantly localized to the caudal one-half of the dog. The umbilical fold commonly is affected in male dogs. Lesions vary from subtle to severe. Alopecia, lichenification, and hyperpigmentation indicate chronicity, and are contingent on the degree of self-trauma. Fibropruritic nodules may form in susceptible individuals (see Chapter 7). Occasionally, pruritus may be generalized. The wearing down of the incisors and hair embedded beneath the gum line are other visual indicators of the pruritus seen with flea allergy dermatitis. Secondary pyoderma and *Malassezia* dermatitis are common; flea allergy can predispose to recurrent infection.

Flea allergy dermatitis can occur in any breed. However, breed predilections have been reported for the Chow Chow, Labrador Retriever, Fox Terrier, Pekingese, Brittany Spaniel, and setters in France (Carlotti & Costargent, 1992). In an unpublished study performed in the United States, the Airedale, Irish Setter, Lhasa Apso, and Golden Retriever were at statistically significant increased risk for being diagnosed with flea allergy dermatitis at North American schools of veterinary medicine (Sischo, W.M. & Ihrke, P.J., unpublished data, 1989). Similar to sarcoptic acariasis (see p. 216), breed predilections could reflect the propensity to develop the intensity of hypersensitivity required to yield highly characteristic, readily diagnosable clinical disease. Flea allergy develops most often in dogs between 1 and 3 years of age, but may commence later in life in dogs that have had minimal previous flea exposure. Rarely, signs may be seen in dogs younger than 6 months of age. A definite seasonality (summer and autumn) is seen with flea allergy dermatitis in areas of the world with cold winters. Sex predilection has not been noted.

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Major clinical differential diagnoses include pruritic superficial spreading pyoderma, superficial bacterial folliculitis, canine atopic dermatitis, and food allergy. Coexistence of some of these diseases may hamper differential diagnosis. In pyoderma, pustules are the primary lesion, the axillae and groin commonly are involved, and lesions spread peripherally and form collarettes. Atopic dermatitis and food allergy both have more facial and pedal involvement, and pruritus is not localized to the caudal one-half of body.

Biopsy site selection

Areas of papular eruption and erythema with minimal self-trauma are preferred sites for skin biopsy. Sites of obvious secondary infection should be avoided.

Histopathology (Figures 9.18 and 9.19)

Epidermal lesions are those of chronic dermatitis due to allergy (see Chapter 7). These include irregular acantho-

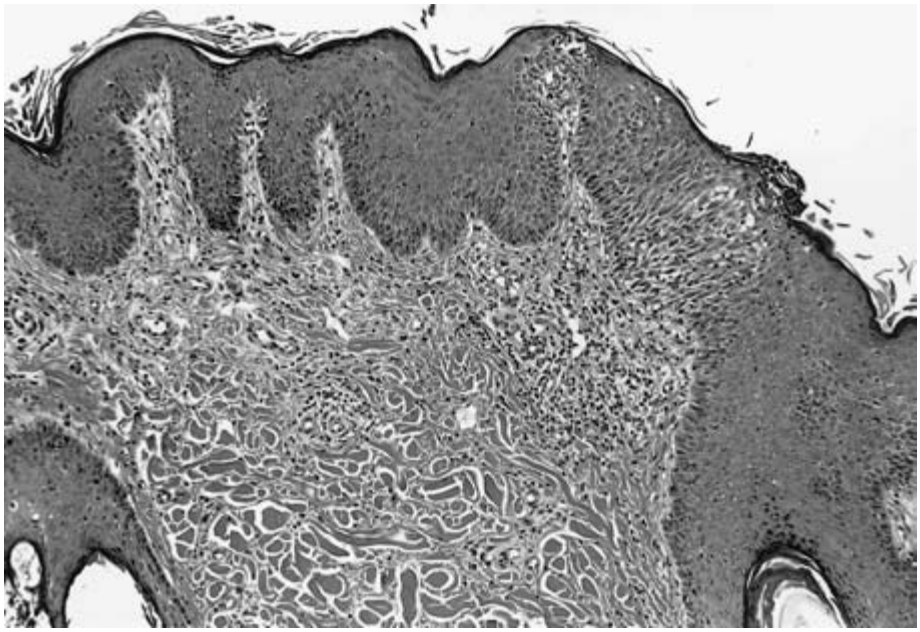


Fig. 9.18 Canine flea allergy dermatitis. Irregular acanthosis accompanies superficial perivascular inflammation. Note discrete spongiotic foci with crusting.

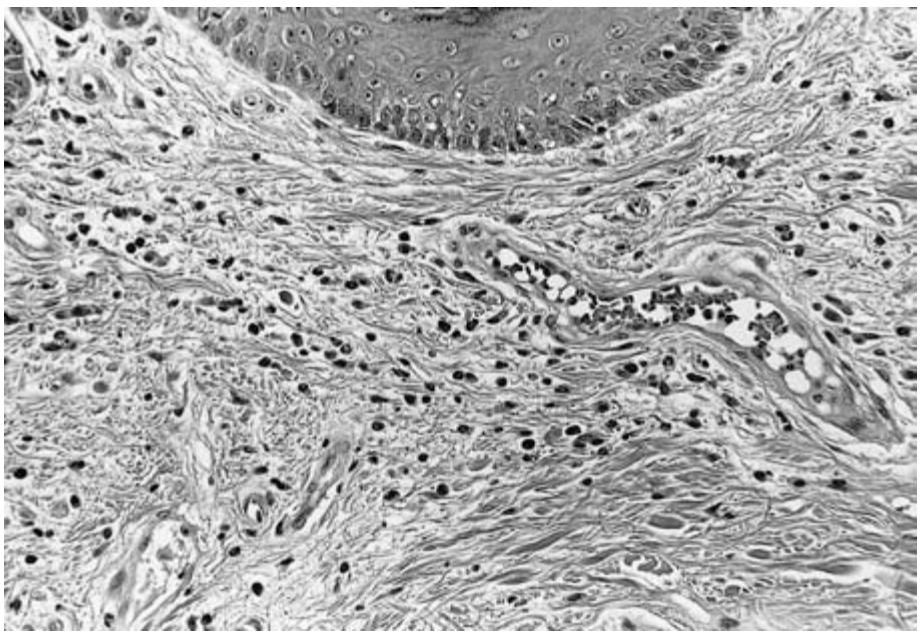


Fig. 9.19 Higher magnification of canine flea allergy dermatitis. Eosinophils and mononuclear cells are accumulating around superficial dermal blood vessels.

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sis with patchy spongiosis, serocellular crusting, and patchy parakeratosis.

In experimentally induced flea allergy dermatitis in dogs, eosinophils and edema predominated in the immediate response (15 minutes to 4 hours); eosinophils persisted and were accompanied by mononuclear cells in late reactions (24 to 48 hours) (Gross & Halliwell, 1985). This biphasic pattern of inflammation supports both type I and type IV hypersensitivity. Additionally, Halliwell & Schemmer (1987) showed that cutaneous basophils are a significant component of the delayed response to flea bites in dogs, implicating cutaneous basophil hypersensitivity. Basophils are not identifiable by routine fixation, processing, and staining of skin biopsy specimens.

In specimens from natural cases of canine flea allergy dermatitis, dermal inflammation is superficial, perivascular to diffuse, and generally mild to moderate. Eosinophils and mast cells are mixed with lymphocytes and macrophages. Neutrophils and plasma cells also may be prominent, and the presence of these cells may depend on the degree of secondary self trauma and pyoderma. Melanophages may be observed. There are variable superficial edema and vascular ectasia. Inflammation frequently extends around adnexal appendages. There may be secondary superficial bacterial folliculitis (see Chapter 16). As in atopic dermatitis, sebaceous gland hyperplasia and apocrine gland ectasia are present in chronic lesions (see p. 200, atopic dermatitis). Mild to moderate dermal fibrosis occurs with chronicity. Rarely, fibropruritic nodules are present (see Chapter 7); however, these lesions are not routinely obtained for histopathologic confirmation of flea allergy. Feline flea allergy dermatitis is discussed in the context of feline allergic miliary dermatitis (see below).

Lesions of flea allergy dermatitis closely resemble those of other allergic dermatitides. Eosinophils may be a key feature in separating flea allergy from atopic dermatitis, as specimens from cases of uncomplicated atopic dermatitis usually do not exhibit eosinophils on routine evaluation with hematoxylin and eosin (HE) staining. Food allergy may be indistinguishable. Other parasitic allergic diseases, such as sarcoptic acariasis or hookworm dermatitis, also will closely resemble flea allergy dermatitis if parasites are not found in tissue. Clinical differentiation is required.

FELINE ALLERGIC MILIARY DERMATITIS

Clinical features (Figure 9.20)

See Chapter 6.

Biopsy site selection

See Chapter 6.



Fig. 9.20 Feline allergic miliary dermatitis. Minute, discrete, erythematous, crusted papules are seen where the haircoat is parted.

Histopathology (Figure 9.21)

Epidermal lesions have been described (see Chapter 6) and include discrete serocellular crusts or spongiotic eosinophilic pustules associated with variable erosion, ulceration, and acanthosis. The dermal inflammatory infiltrate is mild to moderate, and consists of eosinophils, lymphocytes, mast cells, and fewer histiocytes. Dermal inflammation is perivascular to interstitial and extends from the superficial to the middle (follicular) dermis. Perivascular inflammation of the deep dermis also may be present, and when severe, may be suggestive of food allergy (see p. 206), although confirmed flea allergy has been seen occasionally in these cases. Neutrophils may be prominent beneath epidermal erosion or ulceration.

Edema and mucinosis of the superficial dermis may occur in conjunction with inflammation, and vessels may be dilated. Superficial dermal fibrosis is a feature of chronically or severely self-traumatized lesions. Eosinophilic luminal folliculitis is an occasional finding in some cats with severe allergic miliary dermatitis and may be associated with food allergy in some cases (see p. 206). Neutrophilic superficial folliculitis is not uncommon (see Chapter 16), and may be secondary to bacterial infection following ulceration.

Histopathologic differential diagnoses are few, but the diagnosis of allergic miliary dermatitis is not etiologically specific, as many allergic skin diseases of cats can manifest this pattern of dermatitis. Eosinophilic plaque is qualitatively similar to allergic miliary dermatitis, but is more dramatically spongiotic, mucinotic, inflamed, and ulcerated, and involves a larger expanse of skin. Since eosinophilic plaque and miliary dermatitis both may be manifestations of allergic skin disease in the cat (and can exist concurrently), histopathologic separation may not be critical diagnostically.

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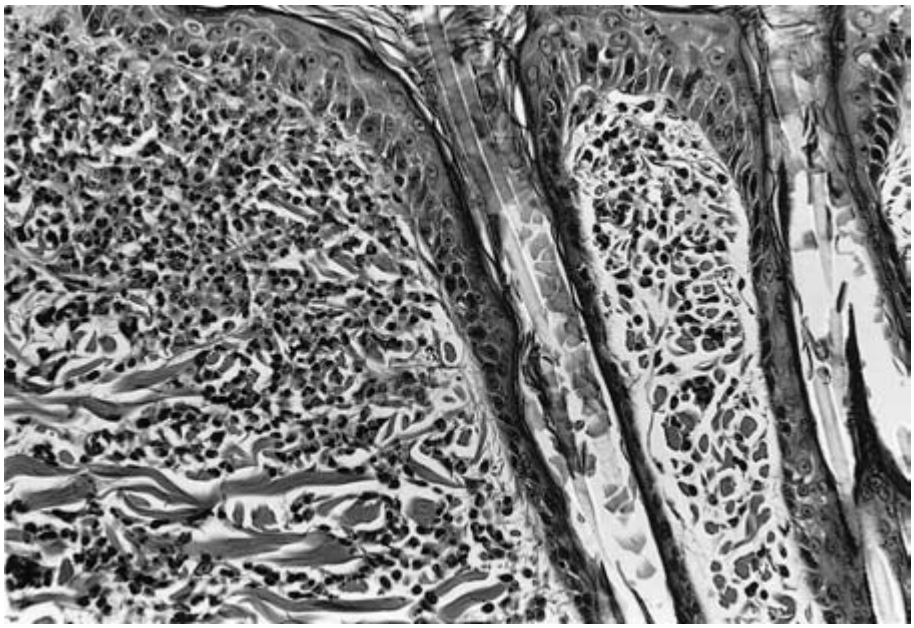


Fig. 9.21 Feline allergic miliary dermatitis. Moderate numbers of eosinophils are infiltrating the superficial dermis.



Fig. 9.22 Urticarial allergic eruption in a crossbreed dog. Erythema and a papular eruption are present, but dermal edema is not visually obvious.

URTICARIAL ALLERGIC ERUPTION

Clinical features (Figure 9.22)

Urticarial allergic eruption is a canine reaction pattern characterized clinically by macular erythema, erythematous papules, wheals, or edema. This reaction pattern is a distinct histopathologic diagnosis, but is not recognized as a distinct clinical entity. Urticarial allergic eruptions are assumed to be associated with hypersensitivity reactions. A similar reaction pattern has been reported in human medicine (Ackerman, 1978). Initiating causes most commonly have been adverse drug reactions, stinging or biting arthropods, and food allergy. However, this reaction pattern also could be initiated by contact allergens, vaccines, bacteria or other immunologic stimuli.

Clinical features are diverse and include erythroderma with or without a papular eruption or visually obvious edema. Frank wheals may be present, as in urticaria (see Chapter 10). Erythematous lesions may not blanch with diascopy, which indicates extravasated red blood cells due to vascular damage. Petechial hemorrhage may be noted. Lesions may be visually more obvious and striking in comparatively glabrous regions and in short-coated dogs. Pruritus is variable and, if present, may induce self-trauma that can obscure primary lesions. As in urticaria, site involvement may be contingent on cause (see Chapter 10). Signalment predilections have not been noted.

Clinical differential diagnoses include urticaria, if wheals are present, and other hypersensitivity reactions, if wheals are not present. If lesions do not blanch with diascopy, other causes of vasculopathy, as well as vasculitis, must be considered. Superficial pyoderma (especially in short-coated dogs) may closely mimic urticarial allergic eruption grossly. Folliculocentric inflammation and accompanying edema can cause groups of hairs to stand upright, resembling urticaria.

Biopsy site selection

Representative lesions uncomplicated by self-trauma should be selected. If both wheals and papules are present, both lesions should be selected. Nonblanching erythema always should be sampled to rule out vasculitis.

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Histopathology (Figures 9.23 through 9.25)

Superficial to mid-dermal, moderate to severe edema, and superficial vascular congestion are consistent features of urticarial allergic eruption in dogs. Blood vessels may be prominently dilated in some cases. Perivascular to interstitial inflammation often is very mild but may be moderate, and extends from the superficial to the midfollicular dermis. Inflammation may appear periadnexal due to the high density of blood vessels in this location. Eosinophils, lymphocytes, histiocytes, and variable neutrophils are observed.

In cases with nonblanching erythema, vasculopathic change may be indicated by swollen endothelial cells and perivascular hemorrhage ('microhemorrhage'). There may be margination of neutrophils and/or eosinophils within blood vessels, but there is an absence of vascular inflammation (vasculitis). There is mild acanthosis. Features of persistent self-trauma, such as parakeratotic crusting, severe acanthosis, and sebaceous hyperplasia, generally are lacking.

Other allergic dermatitides, including atopic dermatitis, may be considered in the differential diagnosis of urticarial allergic eruption. Mild reactions to ticks or other

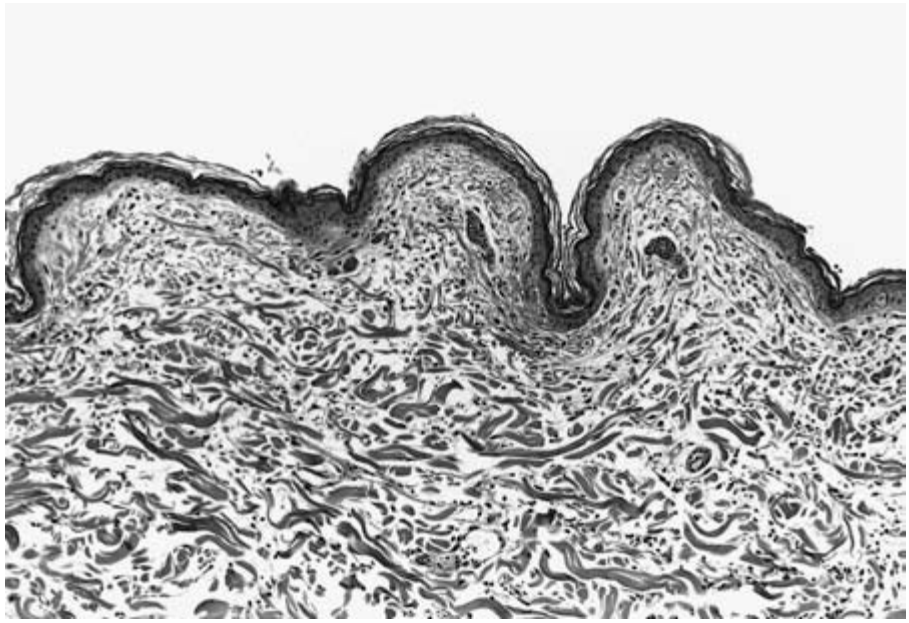


Fig. 9.23 Urticarial allergic eruption in a dog featuring diffuse moderate edema and mild superficial inflammation.

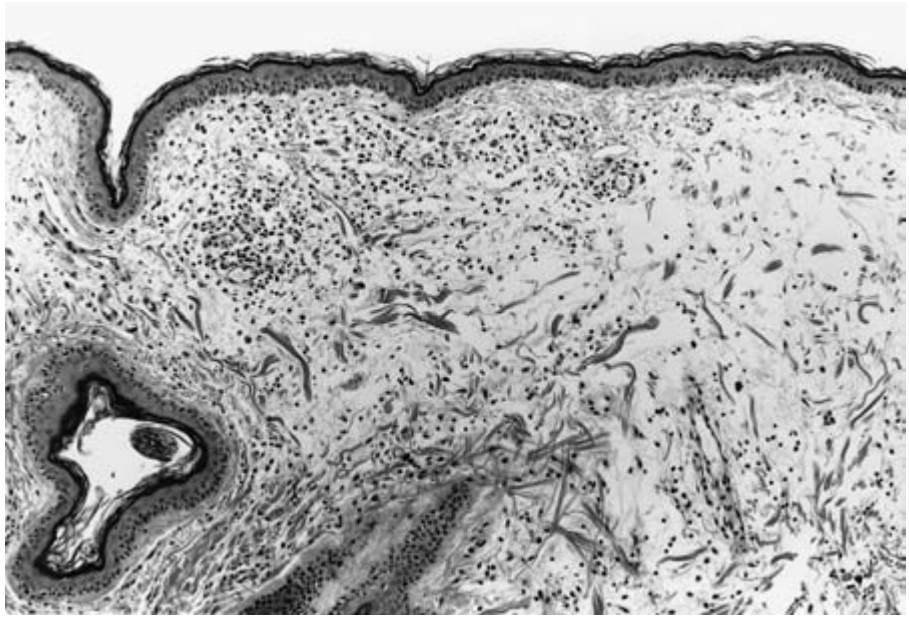


Fig. 9.24 Higher magnification of urticarial allergic eruption in a dog. Both inflammation and edema are more severe than in Fig. 9.23. Note vascular dilatation.

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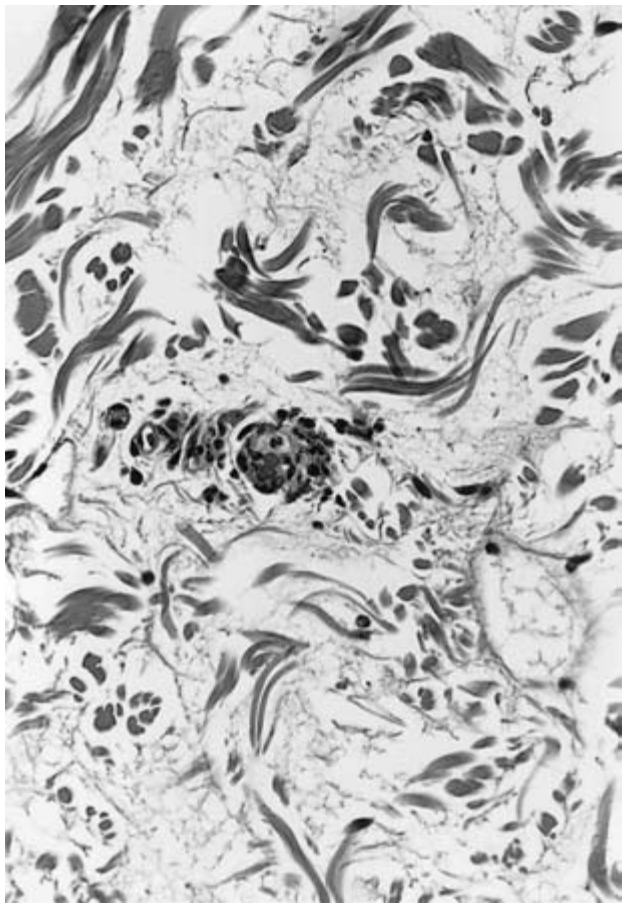


Fig. 9.25 High magnification of urticarial allergic eruption. Note perivascular neutrophils and marked edema.

arthropods may appear similar (see Chapter 14). However, urticarial allergic eruption tends to demonstrate more prominent dermal edema in proportion to the degree of dermal inflammation than most other allergic dermatitides. Ultimately, specific etiological differentiation via histopathology may be unimportant since many different allergic stimuli probably can initiate urticarial allergic eruption. Urticarial allergic eruption with pronounced vasculopathic change is similar to neutrophilic immunologic vasculitis (see Chapter 10) but lacks true vascular inflammation.

ALLERGIC CONTACT DERMATITIS

Clinical features (Figures 9.26 through 9.28)

See Chapter 5.

Biopsy site selection

See Chapter 5.



Fig. 9.26 Acute allergic contact dermatitis of the ear of a Dalmatian due to the neomycin in a topical otic preparation. An exudative and vesicular papular eruption extends beyond the confines of the ear canal.



Fig. 9.27 Allergic contact dermatitis in a dog. Note erythema, alopecia, and hyperpigmentation of the muzzle.

Histopathology (Figures 9.29 and 9.30)

Acute and chronic lesions of the epidermis have been described (see Chapter 5), and consist of spongiotic vesicles which progress to crusting and acanthosis. In some cases of confirmed allergic contact dermatitis, including

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within patch tests, dermal inflammation predominates and epidermal spongiosis and inflammation are not observed.

Dermal inflammation of allergic contact dermatitis is superficial to mid-dermal, and can be mild to multifocally severe, the latter particularly in lesions with severe self-trauma. Perivascular distribution usually is observed, but interface reactions have been reported in natural cases (Calderwood Mays, 1993; Olivry, 1993). In a single case of allergic contact dermatitis to wool, confirmed by patch



Fig. 9.28 Chronic allergic contact dermatitis involving the ventral interdigital web of a Labrador Retriever. Lichenification, alopecia, and erythema are present. (Photograph courtesy C.E. Griffin; case material University of California, Davis.)

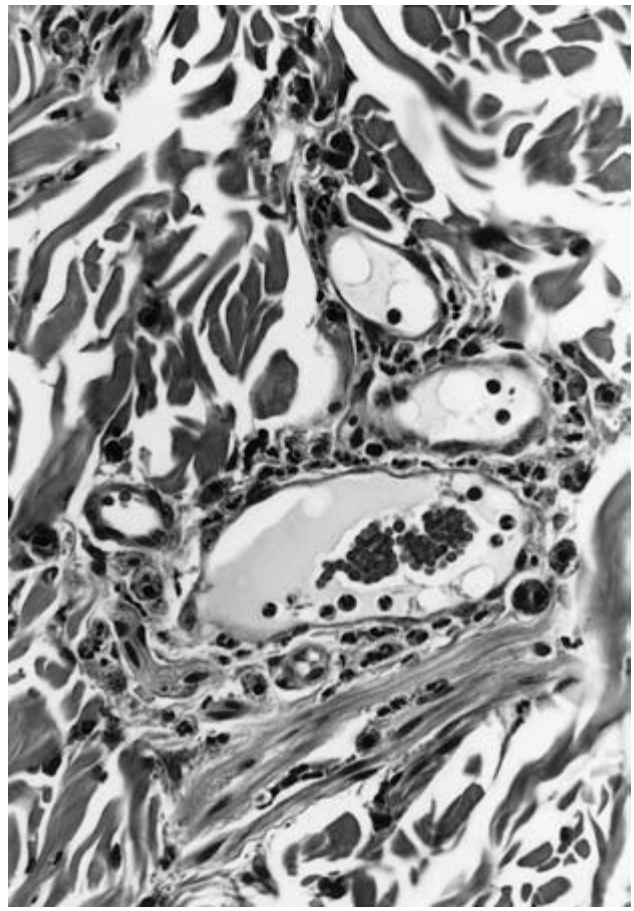


Fig. 9.30 High magnification of allergic contact dermatitis to wool in a dog. Note perivascular eosinophils.

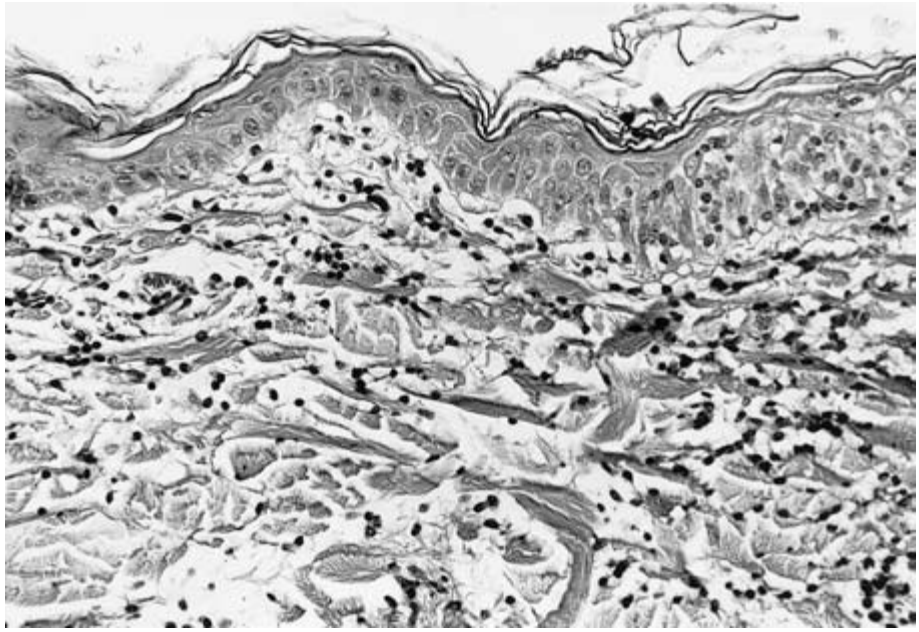


Fig. 9.29 Allergic contact dermatitis in a dog. Superficial perivascular inflammation consists principally of mixed mononuclear cells. Note epidermal spongiosis with migration of lymphocytes at right.

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Fig. 9.31 Canine sarcoptic acariasis in a German Shepherd Dog. Alopecia and crusting are present on the pinna.

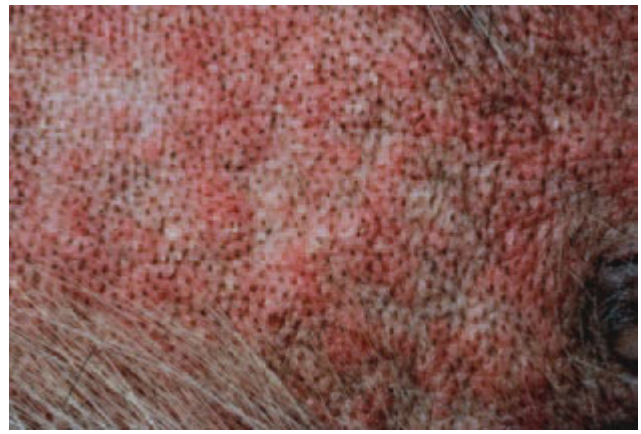


Fig. 9.32 Close view of the lesions of sarcoptic acariasis on the ventral abdomen of a dog. A diffuse, erythematous, maculopapular rash is present.

testing, inflammation was superficially diffuse and band-like in distribution.

Lymphocytes and histiocytes may be most prominent, but fewer neutrophils and eosinophils often are seen. Mast cells may be numerous. Neutrophils are more intense when there is severe erosion or ulceration due to secondary self-trauma. Eosinophils may be prominent in some cases; a single case was observed by one author (T.L.G.) due to *Tradescantia fluminensis* in which both the natural lesions and positive patch test reaction featured eosinophils. The intensity and variable distribution of individual inflammatory cell types may vary between natural lesions and patch test sites in the same animal. Edema is variable and is probably consistently most prominent in patch test reactions.

Allergic contact dermatitis mimics allergic dermatitis of any cause. Histopathologic changes, unless from a known positive patch test site, do not allow definitive diagnosis. Epidermal features, including lymphocytic exocytosis with spongiosis, or eosinophilic intraepidermal pustulation, may be suggestive if the clinical presentation is appropriate (see Chapter 5). Differentiation usually is difficult and will require clinical demonstration of contact exposure.

CANINE SARCOPTIC ACARIASIS

(Synonyms: canine scabies, sarcoptic mange)

Clinical features (Figures 9.31 through 9.33)

Canine sarcoptic acariasis is a highly contagious, intensely pruritic, transmissible skin disease caused by the burrowing epidermal mite *Sarcoptes scabei* var. *canis*. Recent data suggest that the genus *Sarcoptes* is composed of a single heterogeneous species (Zahler et al., 1999). The canine

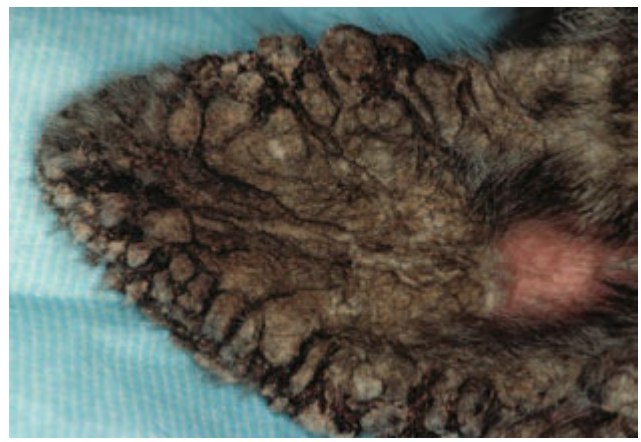


Fig. 9.33. Pinna of an Akita with severe, chronic sarcoptic acariasis. Thick, adherent crusts cover the almost totally alopecic pinna.

mite is relatively host specific but can cause at least transient pruritic disease in other host species including cats and humans. Scabies of canine origin is the most common pruritic zoonosis. Canine scabies appears to be increasing in frequency in geographic regions where modern insect-specific, low-volume application parasiticides that do not reliably kill acarids are used for flea control.

A preponderance of evidence in all mammalian species studied indicates that sarcoptic acariasis is a complex hypersensitivity reaction (Bornstein & Zakrisson, 1993; Arlian et al., 1995; Lower et al., 2001; Scott et al., 2001). Dogs with clinical signs of sarcoptic acariasis seroconvert to various mite antigens 4 to 5 weeks post infection; exposed dogs that do not develop the clinical lesions of sarcoptic acariasis do not seroconvert (Bornstein & Zakrisson, 1993). Enzyme-linked immunosorbent assays (ELISAs) show IgG response to scabies antigens (Lower

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et al., 2001). A biphasic increase and decrease of CD1a+ Langerhans cells has been documented in the epidermis of dogs sensitized and then challenged with scabies mites (Stemmer et al., 1996). T-lymphocytes (CD3 epsilon +), CD11c+, major histocompatibility complex (MHC) class II+, and CD1a+ cells in the dermis play a major role in a successful immune response to scabies mites in experimentally infested dogs (Stemmer et al., 1996). Similarly, scabies in humans is believed to be a complex hypersensitivity reaction involving both humoral and cell-mediated hypersensitivity, and circulating immune complexes.

Most of the clinical features (including extreme pruritus) that characterize sarcoptic acariasis in all species probably are associated with a hypersensitivity reaction to various mite antigens including proteins in the cuticle and the feces. Allergic crossreactivity between various mite species is likely, as shared antigens exist in mite cuticles and feces. The majority of dogs with sarcoptic acariasis in one study displayed both positive intradermal testing and serological reactivity to house dust mites that disappeared after successful treatment for scabies (Prélaud & Guaguère, 1995). Crossreactivity between scabies mite antigens and dust mites complicates serologic testing; IgE directed at 17 different scabies mite proteins has been documented in the sera of atopic dogs without known exposure to scabies mites (Schumann et al., 2001).

Variation in the intensity of the immunologic reaction to scabies mite antigens probably fosters variability in severity of clinical signs, the development of asymptomatic carriers, and a decrease in mite numbers as the disease progresses. One author (P.J.I.) and other dermatologists have documented scabies mites on asymptomatic dogs living in households with dogs with clinically apparent disease. Dogs with compromised immune systems (due to coexistent immunosuppressive disease or therapy with corticosteroids or cytotoxic drugs) may harbor much larger populations of mites in so-called 'Norwegian scabies'. Similarly, high mite counts are seen most commonly in human patients who are immunocompromised with diseases such as acquired immunodeficiency syndrome (AIDS) (Stone, 2003).

Pruritus is the prime clinical feature of canine sarcoptic acariasis. An erythematous maculopapular eruption with crusting and alopecia is accompanied by secondary self-traumatic excoriations. The crusts are often thick and yellowish white. Extensive alopecia, lichenification, and hyperpigmentation may be seen in chronic cases. The margins of the pinnae are most often affected and may be the initial site of involvement, especially in young dogs. The ventral truncal abdomen, chest, lateral elbows and face also are involved commonly. The preference of mites for sparsely haired skin results in a predominantly ventral truncal distribution; the dorsum of the trunk remains relatively spared.

Generalized dermatopathic lymphadenopathy often is present. Secondary pyoderma and *Malassezia* dermatitis may occur, especially in chronic cases. Corticosteroid administration in anti-inflammatory dosages may impede the clinical diagnosis by decreasing the severity of lesions. However, the mites may be more readily found on skin scrapings in dogs receiving corticosteroids. Immunocompromised dogs with so-called 'Norwegian scabies' exhibit much more florid clinical signs in conjunction with large mite populations. Affected dogs have severe generalized thick, adherent crusts with marked alopecia.

The Labrador Retriever, Cocker Spaniel, and Doberman Pinscher are at statistically significant increased risk for being diagnosed with canine sarcoptic acariasis at North American schools of veterinary medicine (Sischo, W.M. & Ihrke, P.J., unpublished data, 1989). The great majority of dogs of all breeds exposed to sarcoptic acariasis probably develop a clinically apparent hypersensitivity reaction. Marked breed predilections (with assumed uniform risk for acquiring the disease) might be due to the propensity to develop the more intense hypersensitivity reaction required to yield highly characteristic, readily diagnosable clinical disease. One author (P.J.I.) believes the Cocker Spaniel may be at increased risk for the development of 'Norwegian scabies'. This apparent predilection might be explained by a breed-based tendency for an immunologic defect fostering intense replication of scabies mites, similar to demodicosis. An age predilection for young dogs is seen and may correlate with increased opportunity for exposure in large breeding farms and pet stores. Immunologic factors also could favor young dogs developing overt clinical disease. Sex predilections are not seen.

Clinical differential diagnoses should include pruritic skin diseases such as flea allergy dermatitis and pruritic superficial pyoderma, both of which may present with similar crusted papules. Other pruritic canine skin diseases such as atopic dermatitis and food allergy usually do not exhibit primary lesions. The typical site predilections for canine sarcoptic acariasis (margins of the pinnae, ventral abdomen and chest, and lateral elbows) will aid in the differentiation from other pruritic skin diseases. Skin scrapings and fecal flotation for ingested mites and eggs are recommended diagnostic procedures. Since scabies mites may be difficult to demonstrate in skin scrapings, empirical treatment for canine sarcoptic acariasis based on clinical impression is a useful diagnostic tool. Skin biopsy is helpful to reveal mites where skin scrapings have proved negative.

Biopsy site selection

Erythematous papules from sparsely haired areas, such as the ventrum, are ideal biopsy sites. Biopsy site selection

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also should include crusted lesions, since these may be more likely to reveal the offending parasite. Multiple specimens should be obtained to increase the potential for finding mites in tissue section. Excoriated lesions or frank pustules indicative of secondary pyoderma should be avoided. Ear margins should not be selected for biopsy, unless exclusively affected, since sampling may result in scarring and distortion of the pinna.

Histopathology (Figure 9.34)

Histologic features vary depending upon whether mites are fortuitously present in section; this variability has been previously reported (Morris & Dunstan, 1996). That report postulated that variability of spongiosis and inflammation in the immediate vicinity of individual mites was indicative of the stage of the inflammatory reaction to these organisms. Spongiosis and inflammation were minimal in assumed early lesions, became intense in fully developed lesions, and waned in late lesions (Morris & Dunstan, 1996).

Inflammatory changes usually are more severe in specimens where mites are present than in specimens where they are absent, although the reaction to individual mites may vary. In mite-associated specimens the epidermis has moderate to severe acanthosis and variable spongiosis, accompanied by parakeratosis and serocellular crusting. Parakeratotic crusting may be distributed in mounds; in some lesions mild to moderate parakeratosis is diffuse. Cross-sections of mites (200 to 400 μm) or their oval eggs (100 to 150 μm) are embedded in the keratin layer or superficial cell layers of the epidermis. Eosinophils may migrate through the epidermis in the vicinity of the mites and may form small discrete pustules. These foci may have a flat surface or may appear slightly indented ('nibbles').

The epidermis of lesional skin that does not contain mites resembles chronic allergic dermatitis of any cause. There is acanthosis, but spongiosis is minimal to mild. Compact hyperkeratosis may predominate over parakeratosis and probably reflects persistent self-trauma. Eosinophilic intraepidermal pustules were reported as rare in lesional skin that did not contain mites (Morris & Dunstan, 1996).

Dermal inflammation consists of eosinophils and mast cells intermingled with mild to moderate superficial perivascular infiltrates of lymphocytes and histiocytes. There may be mild to moderate edema. Neutrophils and plasma cells may be prominent in specimens obtained from sites of epidermal erosion and crusting. Inflammation is milder and less proportionately eosinophilic in sections without mites. Sebaceous hyperplasia and apocrine dilatation, features of chronic self-trauma, are often present (see atopic dermatitis, p. 200).

Large numbers of mites embedded in thick crusts may be present in dogs that have severe infestation due to immunologic compromise ('Norwegian scabies'). In these cases layers of parakeratotic and serocellular crusts are intermingled with numerous mites. The thickness of the crust may be six to eight times that of the underlying acanthotic epidermis. Other inflammatory changes are similar to standard sarcoptic acariasis.

The histopathologic appearance of sarcoptic acariasis without mites present is nonspecific diagnostically. Dif-



Fig. 9.34 Canine sarcoptic acariasis. Mites are imbedded in the superficial epidermis and overlying crust. Note superficial inflammatory infiltrate.

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ferential diagnoses principally include other allergic diseases that feature eosinophils, including flea allergy dermatitis or food allergy. If mites are not present in tissue section, clinical differentiation by discovery of the offending mites or response to appropriate therapy is required. If mites are present, cheyletiellosis may be considered. On average, adult sarcoptic mites are smaller and of a more round configuration than the elongated mites of *Cheyletiella* spp.

FELINE NOTOEDRIC ACARIASIS

(Synonyms: feline scabies, notoedric mange, head mange)

Clinical features (Figure 9.35)

Feline notoedric acariasis is a highly contagious, intensely pruritic, transmissible skin disease caused by the burrowing epidermal mite *Notoedres cati*. The disease is rare in most parts of North America but may be found in localized enzootic areas, especially in larger cities with substantial feral cat populations. As with canine sarcoptic acariasis, the mite is relatively host-specific but can cause pruritic disease in other host species including dogs and humans (Scott et al., 2001). A complex hypersensitivity reaction similar to that proposed in canine sarcoptic acariasis is suspected (see p. 216). Feline notoedric acariasis appears to be increasing in frequency in geographic regions where modern insect-specific, low-volume application parasiticides that do not reliably kill acarids are used for flea control.



Fig. 9.35 Feline notoedric acariasis. Note the adherent crusts, alopecia, and excoriations. (Photograph courtesy I.J. Ameti.)

Pruritus is the prime clinical feature of feline notoedric acariasis. An erythematous papular rash rapidly eventuates in thick, adherent, yellow-gray crusts. Severe self-trauma produces excoriation. Alopecia is progressive and may be severe. Lichenification varies with chronicity. Similar to canine sarcoptic acariasis, the margins of the pinnae are most often affected initially. Lesions spread rapidly over the entire pinnae, face, eyelids, neck, and forelegs as areas of involvement increase by peripheral extension. Cats that remain untreated may develop generalized disease. Generalized dermatopathic lymphadenopathy is a consistent feature. Breed, age, or sex predilections have not been noted.

Clinical differential diagnoses should include other severely pruritic skin diseases with a predilection for the face and ears. Otodectic acariasis, food allergy, pemphigus foliaceus, and atopic dermatitis should be considered. Skin scrapings and fecal flotations for ingested mites and eggs should be performed. Skin scrapings may be a more useful diagnostic tool than in canine sarcoptic acariasis, since notoedric mites may be more prevalent on affected cats. Empirical treatment based on clinical impression also is a useful diagnostic tool.

Biopsy site selection

Biopsy site selection should include severely crusted lesions, since they may reveal the offending parasite. Multiple sites should be sampled to increase the potential for finding mites in tissue. Severe excoriations should be avoided. Ear margins should not be selected for biopsy, unless exclusively affected, since sampling may result in scarring and distortion of the pinna.

Histopathology (Figure 9.36)

Orthokeratotic hyperkeratosis and parakeratosis overlie moderate acanthosis. Parakeratosis with serocellular crusting is often distributed in mounds or caps. Mild spongiosis is present. Histopathologically, parasites are discovered more readily in feline notoedric acariasis than in canine sarcoptic acariasis. *Notoedres cati* may be seen in variable numbers embedded in the superficial layers of the epidermis. *Notoedres cati* are slightly smaller than *Sarcoptes scabei* (see p. 216).

The dermis has superficial, perivascular to diffuse, mild to moderate inflammation composed of eosinophils, histiocytes, mast cells, neutrophils, and lymphocytes. Mild edema and vascular ectasia may be present.

In the absence of mites the lesions of notoedric acariasis are not specifically diagnostic and resemble other allergic skin diseases. Dermal inflammation of food allergy is often more severe and deeply extensive than the inflammation of notoedric acariasis. Discovery of mites in tissue

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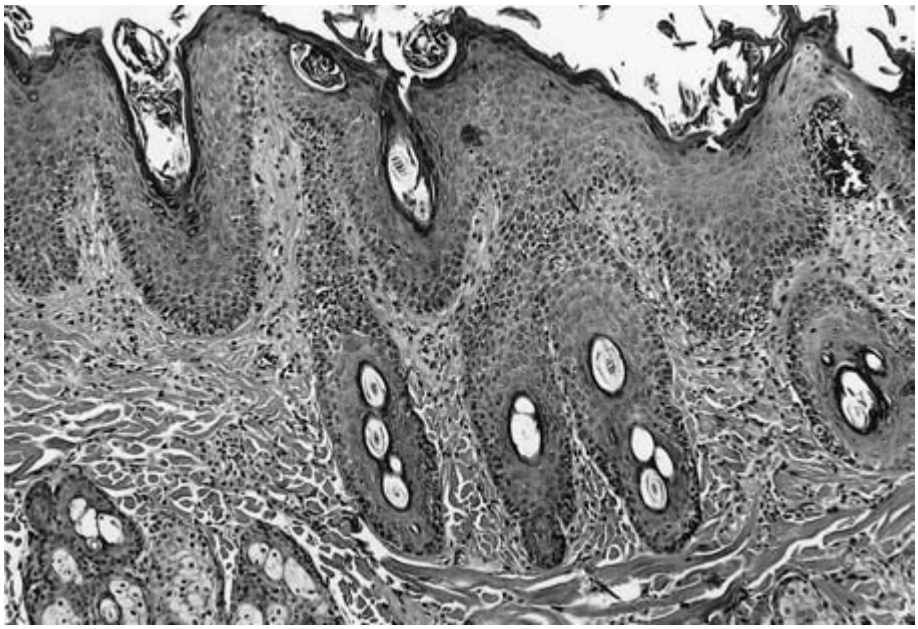


Fig. 9.36 Feline notoedric acariasis. Mites are imbedded in the superficial acanthotic epidermis and within keratin. Mild superficial dermal inflammation is evident.



Fig. 9.37 Cheyletiellosis in a Cocker Spaniel demonstrating severe scaling and crusting on the trunk.



Fig. 9.38 Cheyletiellosis in a dog. Mild scaling without erythema affects the dorsal trunk.

is the key differential feature. If mites are present, cheyletiellosis may be considered. On average, adult notoedric mites are smaller and of a more round configuration than the elongated mites of *Cheyletiella* spp.

CHEYLETIELLOSIS

(Synonym: *Cheyletiella* dermatitis)

Clinical features (Figures 9.37 and 9.38)

Cheyletiellosis is a mild, variably pruritic, transmissible skin disease caused by surface-living mites of the genus *Cheyletiella*. The mite appears to be only partially host-specific. Dogs are thought to be parasitized primarily by *Cheyletiella yasguri*, cats by *Cheyletiella blakei*, and rabbits by *Cheyletiella parasitovorax*. However, multiple mammalian species (including humans) in the same environment may be parasitized by the same species of *Cheyletiella* mites. Cheyletiellosis is an under-reported zoonosis (Wagner & Stallmeister, 2000). Although the entire life cycle is completed on the host, adult female mites may be able to survive in the environment transiently, thus increasing the likelihood of transmission to other animals. Infestations may be enzootic in catteries. Cheyletiellosis is seen most commonly in areas of the world where vigorous flea control is either not necessary or not practiced, as the mites usually are sensitive to many parasiticides. Cheyletiellosis may be increasing in frequency in geographic regions where modern insect-

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specific, low-volume application parasiticides that do not reliably kill all *Cheyletiella* mites are used for flea control.

The immunology of cheyletiellosis is largely unexplored. The host access to mite antigens may be less than seen with burrowing sarcoptic mites, since the *Cheyletiella* mite does not invade the living epidermis. However, it is probable that *Cheyletiella* mites can induce a complex hypersensitivity reaction in some animals, which is similar to that seen with the sarcoptiform mites (see p. 216). Variations in the tendency to develop a hypersensitivity response could explain the marked variability in clinical signs and pruritus seen with cheyletiellosis. Recently, allergic crossreactivity between *Cheyletiella* mite antigens and both common house dust mites has been shown, providing evidence that hypersensitivity to *Cheyletiella* mite products may be part of the pathogenesis of the disease (White et al., 2001). Mite counts and severity of the disease are commonly reported to be increased in kittens and puppies less than 3 months of age. The lack of a mature immune system could account for greater mite counts; the increased severity of disease is unexplained.

The clinical features of cheyletiellosis are highly variable. Cheyletiellosis of both dogs and cats can be subdivided into those cases with exfoliation as a principal feature with little or no pruritus, and those with substantial pruritus and inflammation. *Cheyletiella* spp. mites are large; adult mites and their eggs may be visible to the naked eye or with the use of a hand lens. Entrance and egress of the mites from the nostrils of cats has been noted (Stein, B.P., personal communication, 1982; Power, H.T., personal communication, 1988). The activity of *Cheyletiella* mites may increase in the evening, as they are best observed crossing the muzzle of the cat at that time (Power, H.T., personal communication, 1988).

The most common canine presentation of cheyletiellosis is predominantly truncal scaling and mild crusting. Lesions may generalize with chronicity. Pruritus usually is mild to absent. Mild lymphadenopathy may be noted. Rarely, dogs may develop a more generalized exfoliative erythroderma and severe pruritus.

Feline cheyletiellosis usually is characterized clinically by mild scaling and crusting. Inapparent carriers are common. The dorsal trunk most commonly is affected but lesions may be generalized. Alopecia and poor haircoat quality may be subtle but progressive. Pruritus usually is mild to nonexistent. However, florid cases with severe pruritus occasionally are seen in cats (Power, H.P., personal communication, 2003). Clinical signs and pruritus may increase with chronicity. Truncal miliary dermatitis (see Chapter 6) is noted in conjunction with more severely pruritic cases.

Although any breed may become affected, a marked breed predilection for Cocker Spaniels has been hypothesized by the authors and in a previous report (Moriello, 1993). Clinical disease is noted most commonly in dogs and cats less than 6 months of age. Infested adults are more likely to be inapparent carriers. Sex predilections have not been reported.

Clinical differential diagnoses for cheyletiellosis vary according to the predominant clinical signs. In cats, if scaling with little or no pruritus is the presenting complaint, then differential diagnoses should include poor coat quality due to poor nutrition or systemic illness such as diabetes mellitus or liver disease. If pruritus is substantial, differential diagnoses should include notoedric acariasis and the causes of allergic miliary dermatitis (see Chapter 6). In dogs, if exfoliation with minimal or no pruritus is the presenting complaint, then disorders of cornification such as primary seborrhea or ichthyosis should be considered (see Chapter 8). Multiple affected animals of one or more species in a household should increase the index of suspicion. If pruritus is severe, sarcoptic acariasis, flea allergy dermatitis, food allergy, and atopic dermatitis are possible differential diagnoses. Flea combing, superficial skin scrapings, acetate tape preparations, and fecal flotations are useful in finding the mites. Generally, *Cheyletiella* mites are found more readily than the causative organisms of most other contagious ectoparasitic skin diseases. Response to therapy may be used as a diagnostic tool if cheyletiellosis is suspected but mites are not found.

Biopsy site selection

Areas of maximal scaling and crusting should be selected. Care should be taken not to dislodge surface crust as that is the habitat of the mite.

Histopathology (Figures 9.39 through 9.41)

The epidermis is irregularly acanthotic and has moderate to severe orthokeratotic hyperkeratosis. Variable numbers of mites, measuring 350 to 500 µm in length, are entrapped in the keratin. Eggs are observed rarely and measure 200 µm. In clinically more severe, pruritic cases there may be extensive serocellular crusting and erosion. Mite numbers may be reduced in these more severe lesions, presumably due to removal by scratching.

The superficial dermis has a mixed inflammatory infiltrate that is perivascular to interstitial and includes eosinophils, lymphocytes, histiocytes, and plasma cells. Inflammation ranges from mild to severe; intensity probably varies with clinical severity and degree of pruritus. Variable edema is observed.

Differential diagnoses principally include sarcoptic acariasis in dogs and notoedric acariasis in cats. Hyperkeratosis may be more prominent in cheyletiellosis than

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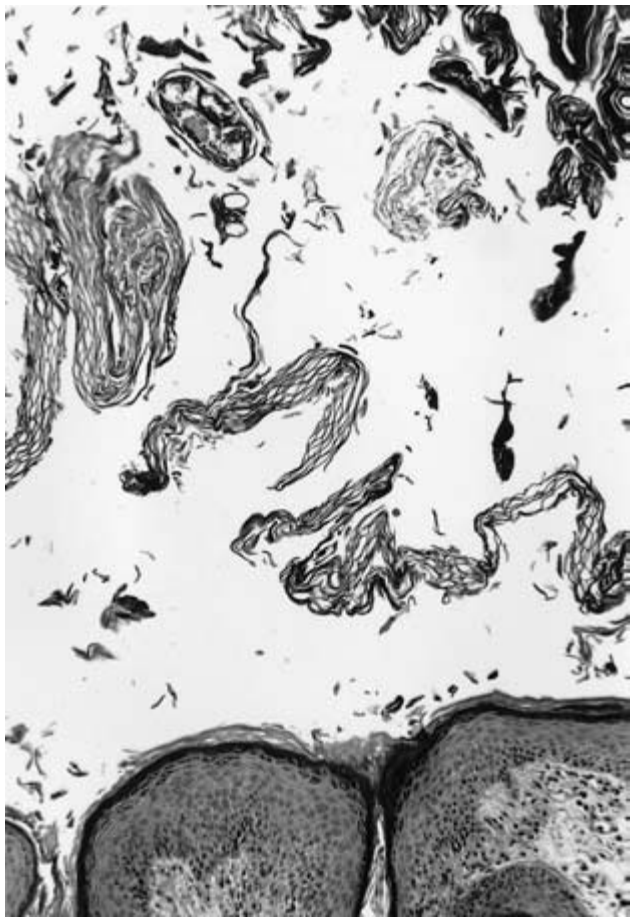


Fig. 9.39 Cheyletiellosis in a dog. Note mite within abundant keratin.

in sarcoptic or notoedric acariasis. On average, adult sarcoptic and notoedric mites are smaller and of a more round configuration than the elongated mites of *Cheyletiella* spp. Additionally, large numbers of mites characterize cheyletiellosis in dogs, as mites are rare in random specimens from dogs with sarcoptic acariasis.

FELINE SUPERFICIAL DEMODICOSIS

(Synonyms: demodectic mange, demodectic acariasis)

Clinical features (Figures 9.42 and 9.43)

Feline demodicosis is a rare or regional parasitic skin disease caused by an overpopulation of one of at least three different species of the host-specific mites, *Demodex* spp. *Demodex cati* is a feline follicular mite with morphologic features resembling *Demodex canis* in dogs (Scott et al., 2001). *Demodex gatoi* is a considerably shorter, nonfollicular species of demodicid mite that predominantly inhabits the stratum corneum (Desch & Stewart, 1999). A third as yet unnamed species of mite that resembles *Demodex gatoi*, but is larger, also has been identified (Chesney, 1988; Desch & Stewart, 1999). Wide clinical variability is noted; feline demodicosis may be localized and follicular, or generalized and follicular with features resembling canine generalized demodicosis (*Demodex cati*; see Chapter 17). Alternatively, feline demodicosis may be generalized and contagious with the mites inhabiting predominantly the surface stratum corneum (*Demodex gatoi*) (Morris & Beale, 1997; Beale,



Fig. 9.40 Higher power magnification of mite in Fig. 9.39.

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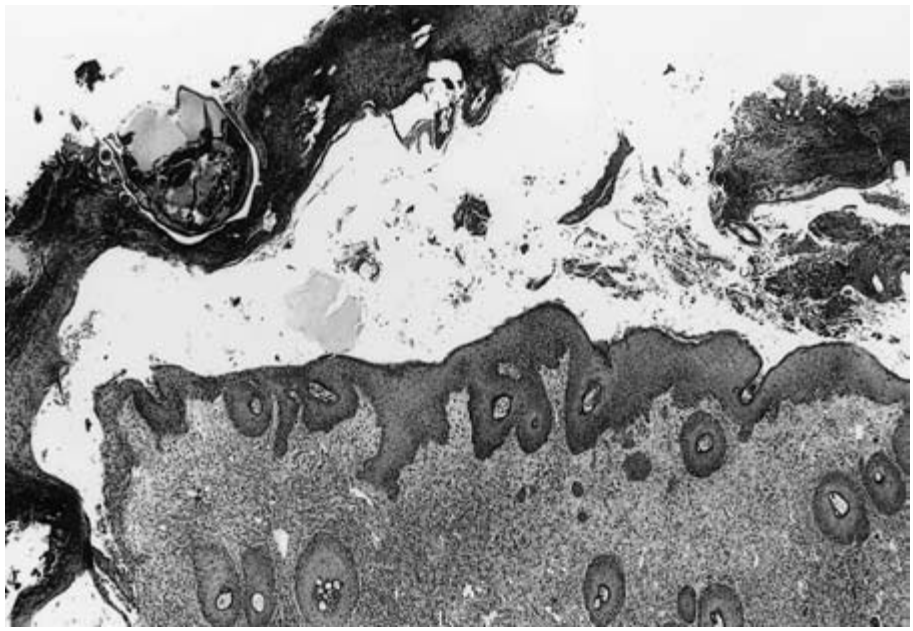


Fig. 9.41 Inflamed cheyletiellosis in a pruritic cat demonstrating severe crusting, acanthosis, and dermatitis. Note single large mite within crust at left.



Fig. 9.42 Feline superficial demodicosis in a Siamese cat. The cat exhibits bilaterally symmetric, partially self-traumatic alopecia affecting the caudal trunk, lateral thighs, and shoulder regions. (Photograph courtesy K.M. Beale.)



Fig. 9.43 Feline superficial demodicosis in a Siamese cat. Note the patterned partial alopecia. The cat was mildly pruritic.

1998; Guaguère, 2000; Scott et al., 2001). Feline superficial demodicosis appears to be caused predominantly by *Demodex gatoi*.

Demodicosis due to *Demodex gatoi* is markedly different from other forms of demodicosis as it is a contagious, transmissible, frequently pruritic skin disease (Morris & Beale, 1997; Beale, 1998). Marked variability in pruritus from nonexistent to severe suggests a role for hypersensitivity in the pruritic cats. Feline demodicosis due to *Demodex gatoi* seemingly has a contagious pathogenesis reminiscent of nonfollicular sarcoptiform mites (Beale, K.M., personal communication, 2002). The disease is perceived to be rare in most of North America, but may be found more commonly in localized enzootic regions of the southern and southeastern USA. Feline demodicosis due to *Demodex gatoi* may be increasing in frequency in geographic regions where modern insect-specific, low-volume application parasiticides that do not reliably kill acarids are used for flea control.

The clinical features of feline superficial demodicosis vary from asymptomatic alopecia alone, to alopecia with self-trauma due to pruritus (Morris & Beale, 1997; Beale,

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1998). The presence or absence of pruritus dictates the clinical features. If pruritus is absent, affected cats can present with diffuse, bilaterally symmetric alopecia, with or without associated scaling, usually affecting the ventral and lateral trunk and caudal legs. If pruritus is present, usually it is intense; affected cats present with similar lesions plus erythema, crusting, and excoriation (Morris & Beale, 1997; Beale, 1998). Owners or veterinarians may not be aware of excessive feline grooming, since grooming behavior may occur when an animal is alone. Additionally, some pruritic cats may present with multifocal erythematous plaques with broken hair stubble and hyperpigmentation. Siamese and Burmese cats may be predisposed to feline generalized demodicosis caused by *Demodex gatoi* (Guaguère, 2000; Scott et al., 2001).

Clinical differential diagnoses for feline generalized demodicosis should include virtually all feline skin diseases characterized by pruritus (allergic skin diseases, feline notoedric acariasis), alopecia due to excessive grooming (feline psychogenic alopecia), and all other causes of alopecia that are not due to self-trauma. Skin scrapings of pruritic cats may not yield mites or eggs of *Demodex gatoi* since excessive grooming removes the surface-living mites (Beale, 1998). Conversely, skin scrapings of nonpruritic cats usually yield large numbers of mites and eggs (Beale, 1998). If mites are not found, skin biopsy is recommended. Skin biopsy may identify unsuspected feline demodicosis, as many clinicians have a low index of suspicion for all varieties of feline demodicosis.

Biopsy site selection

Areas that are less inflamed or sites where the cat is less able to lick are ideal for biopsy. Multiple lesions should be sampled to increase the likelihood of discovering the mites histologically.

Histopathology (Figures 9.44 through 9.46)

In some cases of feline superficial demodicosis there is minimal inflammation, accompanied by acanthosis and lamellar hyperkeratosis. Mites are dispersed amongst the keratin layers. *Demodex gatoi* is a shorter and fatter mite than *Demodex cati* of feline follicular demodicosis (see Chapter 17). This mite resembles *Demodex criceti* of hamsters. *Demodex gatoi* measure 80 to 115 μm in length (Desch & Stewart, 1999). *Demodex gatoi* accumulate in the stratum corneum and are not found within hair follicles, with the possible exception of follicular ostia.

In other cases, probably those that correlate with clinical pruritus, there is epidermal erosion and ulceration with crusting, accompanied by mild to moderate perivascular to diffuse infiltrations of lymphocytes, histiocytes, eosinophils, and mast cells. Neutrophils are prominent if there is overlying epidermal damage and inflammation. In correlation with the finding of reduced mites on skin scrapings from pruritic cats, mite numbers are decreased to absent in inflamed specimens, particularly in areas of epidermal erosion or ulceration.

Definitive diagnosis is easy to accomplish if mites are identifiable in tissue. In severely inflamed specimens that

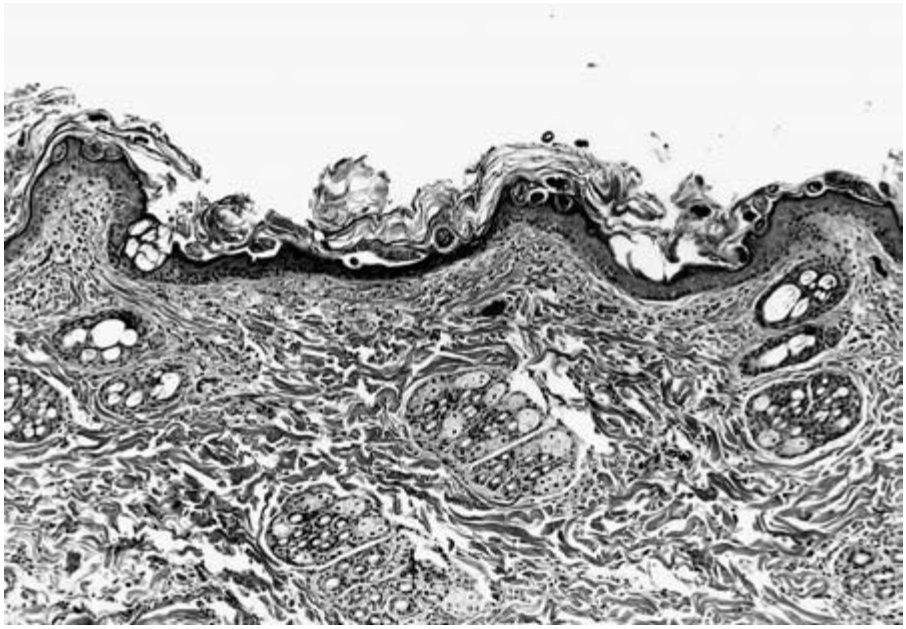


Fig. 9.44 Feline superficial demodicosis. Note numerous small superficial mites and mild inflammation.

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Fig. 9.45 Higher magnification of feline superficial demodicosis demonstrating mites in superficial keratin.

lack mites, severely self-traumatized allergic dermatitis of other causes may be considered.

CUTANEOUS MICROFILARIASIS

Clinical features (Figures 9.47 and 9.48)

Cutaneous microfilariasis is a group of rare skin diseases caused by a host response to the microfilariae of a number of species of nematodes of the superfamily Filaroidea. To date, cutaneous microfilariasis has been reported in the dog, but not in the cat. Microfilariae migrate to the dermis and subcutaneous tissues, and are presumed to elicit a hypersensitivity reaction. In addition, solitary cavitating nodules harboring aberrant migrating adult heartworms have been reported in dogs, cats, and humans (Scott et al., 2001; Cornegliani, 2003). Described syndromes of microfilariasis include two forms of cutaneous dirofilariasis due to *Dirofilaria immitis*, microfilarial skin disease caused by an unnamed species of *Acanthocheilonema*, and a disease resembling the papular pruritic form of dirofilariasis caused by *Acanthocheilonema reconditum* (Scott, 1979; Gross & Ihrke, 1992; Mozos et al., 1992; Hargis et al., 1999). Histopathologic confirmation is lacking in some of the published case reports.

Two distinct syndromes of cutaneous dirofilariasis have been reported (Scott, 1979; Scott & Vaughn, 1987; Mozos et al., 1992). The first subgroup of cutaneous dirofilariasis is characterized by a multifocal nodular dermatitis with erosions and ulcerations. Previous reports

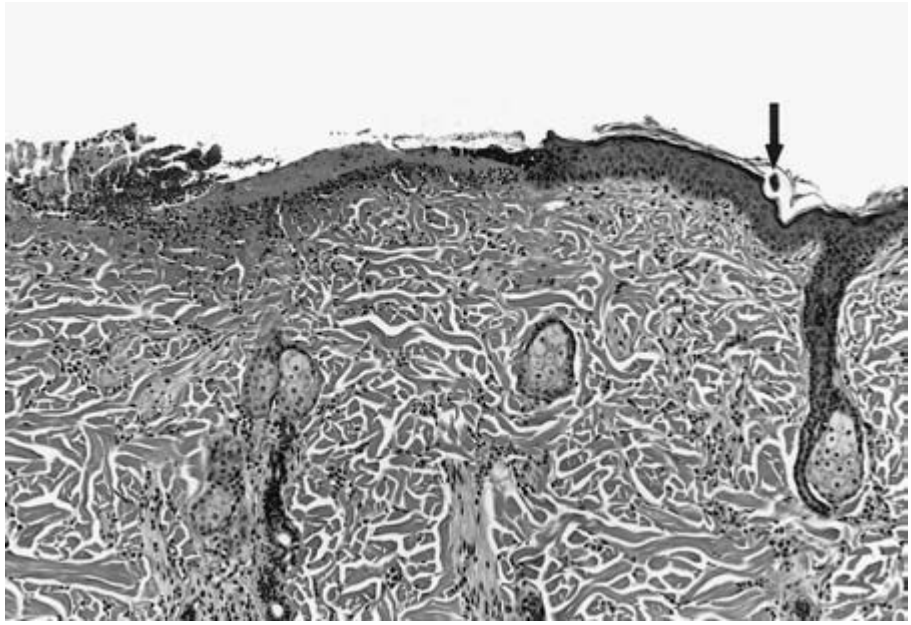


Fig. 9.46 Inflamed superficial demodicosis in a pruritic cat; note erosion and crusting due to self trauma. A small superficial mite fragment is at right (arrow).

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Fig. 9.47 Shoulder and neck of a Collie with cutaneous microfilariasis due to *Dirofilaria immitis*. A finely papular eruption with alopecia is present.



Fig. 9.48 Caudal thighs of the dog in Fig. 9.47. Note hyperpigmentation as a manifestation of chronic pruritic self-trauma.

described prominent facial involvement (Scott, 1979; Scott & Vaughn, 1987). Erythematous papules coalesce and eventuate in firm alopecic nodules. The lesions are chronic, slowly progressive, and mildly pruritic. The dorsum of the muzzle, lips, and pinna are affected most frequently, but lesions also are seen on the trunk and limbs (Scott, 1979; Scott & Vaughn, 1987). A second subgroup of cutaneous dirofilariasis is described as a highly pruritic papular dermatitis clinically resembling canine sarcoptic acariasis (Mozos et al., 1992). This syndrome is characterized by a generalized, maculopapular, erythematous eruption with severe pruritus. In both reported syndromes, complete resolution of the skin disease in response to therapy for heartworms was used as a method of validating the diagnosis.

The microfilarial skin disease associated with an unnamed species of *Acanthocheilonema* reported by Hargis et al. (1999) was characterized by solitary or multifocal, erythematous, alopecic, crusted papules or plaques with ulceration and scarring. Most dogs were pruritic (Hargis et al., 1999). The authors have seen a microfilariae-related skin disease in a dog with a pruritic plaque on the head that exhibited many similarities with these reported dogs. The observed dog tested negative for *Dirofilaria immitis* infection using direct assay and enzyme-linked immunosorbent assay (ELISA). An additional dog seen by the authors for generalized pruritic, erythematous, and papular skin disease was positive for *Acanthocheilonema reconditum* (*Dipetalonema reconditum*) (Gross & Ihrke, 1992). Biopsy was not permitted. This second dog bore closest clinical resemblance to the highly pruritic form of cutaneous dirofilariasis reminiscent of scabies.

Case sampling for the various forms of cutaneous microfilariasis is too small to infer signalment data. However, many of the reported cases of all syndromes have been in mature, large-breed dogs, perhaps with greater environmental access to infective larvae.

Clinical differential diagnoses for multifocal nodular microfilarial dermatitis should include diseases characterized by multifocal nodules, such as infectious granulomas, sterile granuloma and pyogranuloma syndrome, and reactive histiocytosis. Clinical differential diagnoses for the highly pruritic papular dermatitis caused by either *Dirofilaria immitis* or *Acanthocheilonema reconditum* should include sarcoptic acariasis, pruritic superficial pyoderma, and other pruritic skin diseases of similar distribution. The diagnosis of cutaneous microfilariasis is supported by compatible clinical and histopathological findings coupled with response to therapy.

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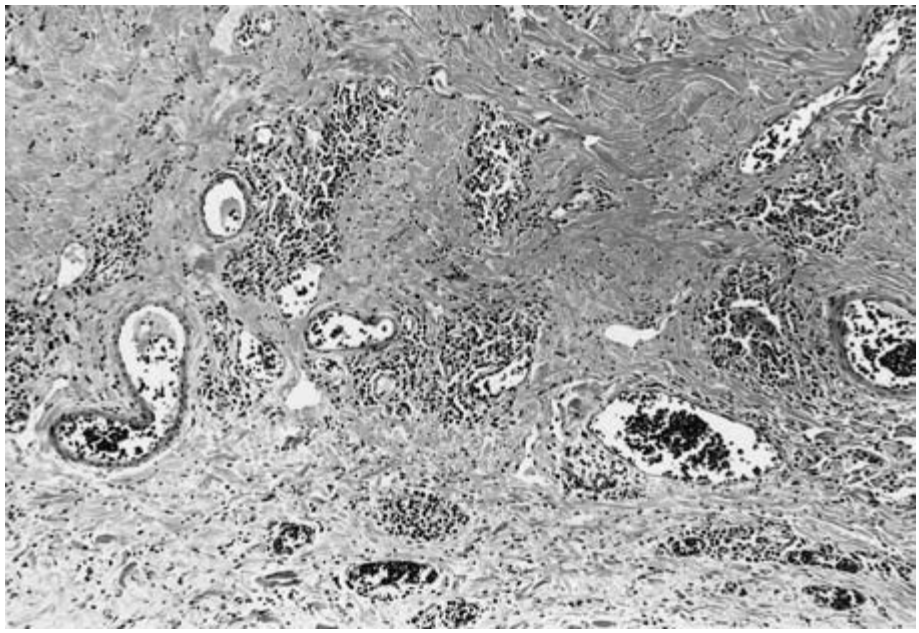


Fig. 9.49 Cutaneous microfilariasis due to *Dirofilaria immitis* in a dog. Inflammatory cells are accumulating in a tightly perivascular pattern. (Case material courtesy J.R. Hill.)

Biopsy site selection

Multiple specimens should be obtained from well-developed nodular lesions or generalized papular eruptions. Lesions of all stages should be sampled.

Histopathology (Figures 9.49 through 9.51)

In lesions of cutaneous dirofilariasis the epidermis is moderately acanthotic or ulcerated. Epidermal pustulation and crusting may be present. The dermis is characterized by superficial and deep perivascular infiltrations of macrophages, eosinophils, neutrophils, lymphocytes, and plasma cells. Macrophages predominate and often form nodular or granulomatous configurations around or near vessels. Segments of microfilariae are seen, usually in small numbers, within vessels as well as within extravascular inflammatory foci. Deeper sectioning of these granulomas may be required to identify the organisms. Granulomatous hidradenitis with microfilariae has been reported (Mozos et al., 1992).

In the reported cases of dermatitis associated with an unnamed species of *Acanthocheilonema*, lesions were similar to those of cutaneous dirofilariasis. Inflammation was often intense, and was superficial and deep, perivascular to interstitial, and predominantly eosinophilic and plasmacytic (Hargis et al., 1999). Neutrophils, lymphocytes, and macrophages were variable. Inflammation extended to the panniculus, and deep scarring was reported. Small granulomas were found in association with the eosinophilic and plasmacytic inflammation and scarring in the dermis or panniculus, and often but not invariably contained portions of microfilariae. Deeper

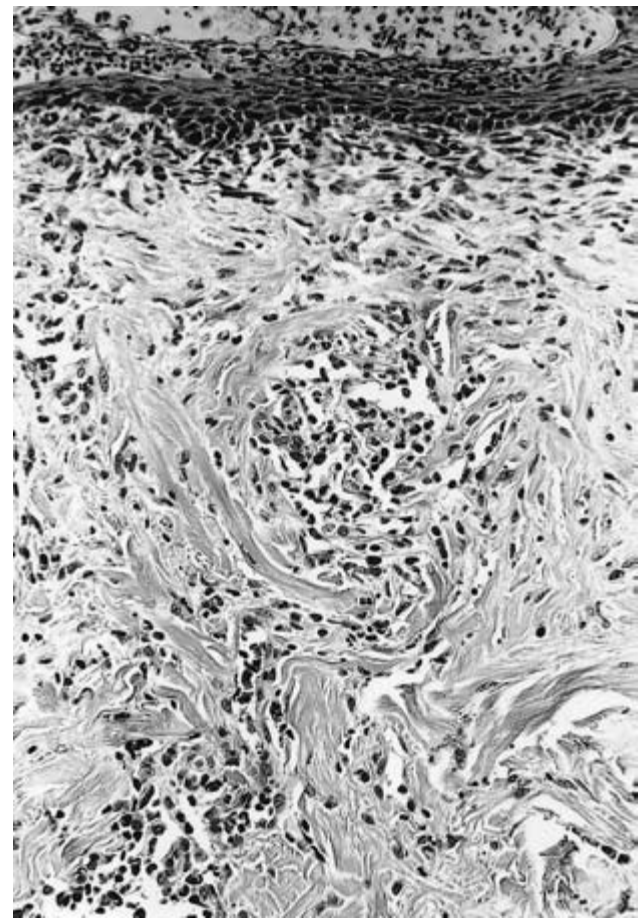


Fig. 9.50 Higher magnification of microfilariasis due to *Dirofilaria immitis* in the dog of Fig. 9.49. Note mononuclear cells in a nodular pattern around superficial dermal vessels. (Case material courtesy J.R. Hill.)

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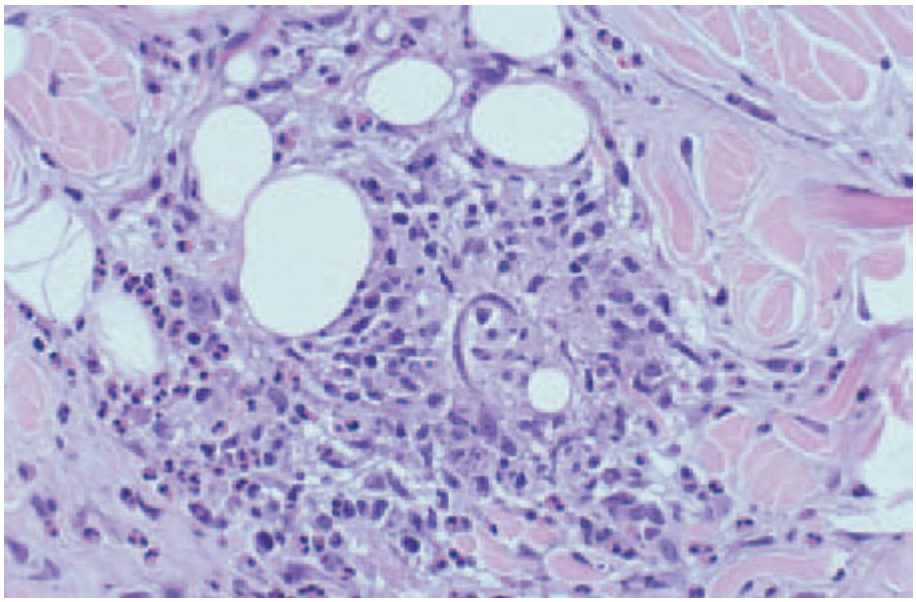


Fig. 9.51 Cutaneous microfilariasis. Note fragment of microfilaria within mixed inflammatory infiltrate that includes eosinophils. (From Hargis, A.M., Lewis, T.P., Duclos, D.D. et al. (1999) Dermatitis associated with microfilariae (Filaroidea) in 10 dogs. *Vet Dermatol* **10**, 95–107. Reprinted with permission.)

sections identified the organisms in several cases. Microfilariae also were free within the dermis or panniculus but were not seen within blood vessels (Hargis et al., 1999).

Differential diagnoses include other skin diseases characterized by eosinophilic perivascular dermatitis. The deep extension of the inflammation is atypical for most other allergic dermatitides, and the formation of extravascular or perivascular granulomas is suspicious for cutaneous microfilariasis. Discovery of microfilariae in tissue may be difficult. Identification of organisms in intravascular spaces only is not diagnostic; intravascular microfilariae may be incidental findings in dogs living in enzootic areas of *Dirofilaria immitis* and *Dipetalonema reconditum* infestation. Microfilariae must be found at the centers of inflammatory foci. Response to therapy, involving eradication of all stages of heartworms or other filarid parasites, is the best method of definitive diagnosis in these cases.

HOOKWORM DERMATITIS

(Synonyms: cutaneous ancylostomiasis and uncinariasis)

Clinical features (Figures 9.52 and 9.53)

Hookworm dermatitis is an uncommon to rare skin disease incidental to larval migration associated with the normal life cycle of the hookworms *Ancylostoma braziliense*, *Ancylostoma caninum*, and *Uncinaria stenocephala* in the dog. Hookworm dermatitis has been seen in cats (Scott et al., 2001), but is rare. The syndrome is more common in local enzootic areas and is a disease associated with poor sanitation where larval numbers are greatly increased. Hookworm dermatitis is presumed to be due to a hypersensitivity reaction to migrating larvae; coexistent arthritis suggests a more complex immunologic etiopathogenesis (Baker, 1981). Third-stage larvae enter the skin in soil-contact areas, principally the distal extremities. Hookworm dermatitis is reported to occur more frequently in association with *Uncinaria stenocephala* and is more common in Ireland, southwestern England (Baker & Grimes, 1970; Baker, 1981), the southeastern United States, and other humid areas of the world where hookworms are common.



Fig. 9.52 Hookworm dermatitis on the dorsum of the paw of a Doberman Pinscher. Erosions and ulcers are present around the margins of the nailbeds. (Photograph courtesy G.A. Kunkle.)

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Fig. 9.53 Ventral paw of the Doberman Pinscher in Fig. 9.52. Note the ulcers of the pawpads and the surrounding skin. (Photograph courtesy G.A. Kunkle.)



Fig. 9.54 Cutaneous anatrichosomiasis in a dog living in Arizona in the southwestern United States. The pawpads of all four feet exhibited proliferation of white-grey keratin. Note secondary fissuring and ulceration. (Photograph courtesy M.D. Song.)

Clinical features include erythematous papules and early erythema and swelling followed by alopecia and lichenification. Characteristic changes in the texture of the pawpads occur. The pad margins become soft and friable, and sometimes separate from the underlying dermis. Claw deformation and paronychia with loss of the claw are seen in chronic cases. The distal extremities often are most severely affected, but other areas of soil contact such as the xiphoid, posterior sternal region, ventral abdomen, and the skin over bony prominences may be affected (Baker & Grimes, 1970; Baker, 1981). Pruritus is mild to moderate. Concomitant arthritis of the distal interphalangeal joints has been reported (Baker, 1981).

Breed, age, and sex data are not available. However, hookworm dermatitis is predominantly a disease of sporting dogs kenneled on poorly sanitized earth or grass runs. As expected, there is a marked seasonal incidence in spring and summer.

Clinical differential diagnoses include other ectoparasitic diseases such as demodicosis, pelodera (rhabditic) dermatitis, and canine sarcoptic acariasis. Irritant or allergic contact dermatitis could present with similar clinical features. A history of poor housing and sanitation in an enzootic area should increase suspicion of hookworm dermatitis.

Biopsy site selection

Affected sites in constant contact with soil that exhibit erythema, papules, alopecia, and lichenification should be selected for skin biopsy. Multiple samples will increase the likelihood of diagnosis. Submission of fresh tissue specimens to a parasitologist for maceration and examination is ideal for identifying hookworms.

Histopathology

The epidermis is acanthotic and may be eroded. Multifocal spongiosis, parakeratosis, and serocellular crusts are common features. Tracts caused by migration of larvae have been characterized by linear accumulations of neutrophils and eosinophils that extend through the epidermis to the dermis (Scott et al., 2001).

The dermis is characterized by superficial, mild to moderate, perivascular to interstitial eosinophilic inflammation. Neutrophils, lymphocytes, and macrophages are present in variable numbers. Larvae rarely are discovered in tissue section, but may be recovered via maceration and dissection of skin specimens, best undertaken by a parasitologist.

Differential diagnoses include allergic dermatitides that feature eosinophils, such as other parasitic skin diseases (flea allergy dermatitis, sarcoptic acariasis), and food allergy. Geographic location and opportunity for exposure must be considered in the diagnosis of hookworm dermatitis if etiologic agents cannot be demonstrated in tissue.

CUTANEOUS ANATRICHOSOMIASIS

Clinical features (Figure 9.54)

Anatrichosomiasis is a rare, but possibly under-reported, regional feline and canine skin disease caused by the aphasmid nematode *Anatrichosoma* sp. (Lange et al.,

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1980; Ramiro-Ibáñez et al., 2002). Adult *Anatrichosoma* sp. inhabit the mucosal epithelium of the nasal passages, stomach, eye, skin, and oral cavity of a variety of different species of mammals and reptiles; their life cycle is incompletely understood (Ramiro-Ibáñez et al., 2002). In North America, the opossum (*Didelphis virginiana*) is the natural reservoir host for *Anatrichosoma buccalis* (Ramiro-Ibáñez et al., 2002). This organism is postulated to be the cause of aberrant infestations seen in domestic animals in North America (Ramiro-Ibáñez et al., 2002). Since all reported cases of anatrichosomiasis in North America have been from the southwestern United States, this may imply ideal geographic or climactic conditions favorable for aberrant infestation (Ramiro-Ibáñez et al., 2002). Both the cat reported by Ramiro-Ibáñez et al. (2002) and a dog seen by Song (Song, M., personal communication, 2002) presented with pododermatitis and resided in Arizona.

Ulcerative pododermatitis involving the pawpads of all four feet was described in a cat (Ramiro-Ibáñez et al., 2002). Swelling and exfoliation was followed by vesicle formation, erosion and ulceration. Depression was noted, probably in response to pain. Similar lesions were noted in the dog seen by Song (Song, M., personal communication, 2002). Affected pawpads were proliferative and had adherent excessive white-gray keratinized material and fissures. Focal ulceration was noted. The dog was in pain and reluctant to stand.

Clinical differential diagnoses for feline anatrichosomiasis should include pemphigus foliaceus, plasma cell pododermatitis, and eosinophilic granuloma of the pawpad. Canine differential diagnoses should include pemphigus foliaceus, superficial necrolytic dermatitis, familial footpad hyperkeratosis, nasodigital hyperkeratosis, and canine distemper virus-associated skin disease (hard pad). Index of suspicion should be increased in otherwise healthy animals living in the southwestern United States. Cytology of the exudate may reveal multiple ova. Histopathology is required for definitive diagnosis.

Biopsy site selection

Punch biopsy specimens should be obtained from the margin of affected accessory carpal or tarsal pads, as biopsy of the central pads is more likely to initiate lameness. Ulcers should be avoided as parasites are mostly found in the epidermis.

Histopathology (Figures 9.55 through 9.57)

Based on a single canine case observed, there is mild to moderate acanthosis accompanied by mild to moderate erosion and crusting. A superficial perivascular mixed infiltrate is mild to moderate and includes lymphocytes, plasma cells, macrophages, and neutrophils. Embedded in the epidermis are numerous cross-sections of nematodes, measuring 250–300 μm in diameter. These have prominent hypodermal bacillary bands, typical of the genus *Anatrichosoma*. Imbedded in the stratum corneum, and sometimes surrounded by neutrophilic debris, are bioperculated, yellow, oval eggs, measuring 75 μm × 40 μm.

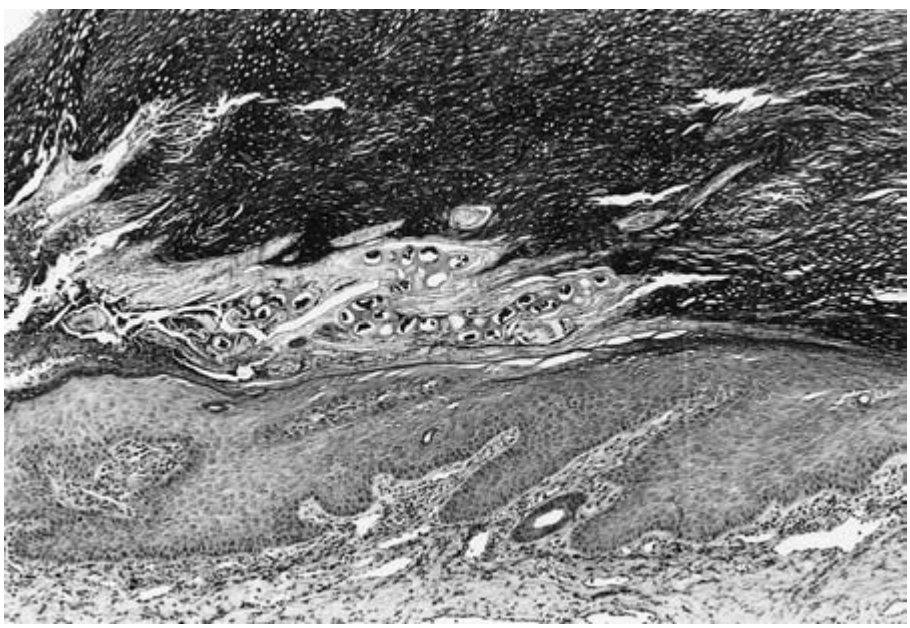


Fig. 9.55 Cutaneous anatrichosomiasis in a dog. Numerous dark parasitic ova are present in thickened pawpad keratin. Note superficial dermatitis.

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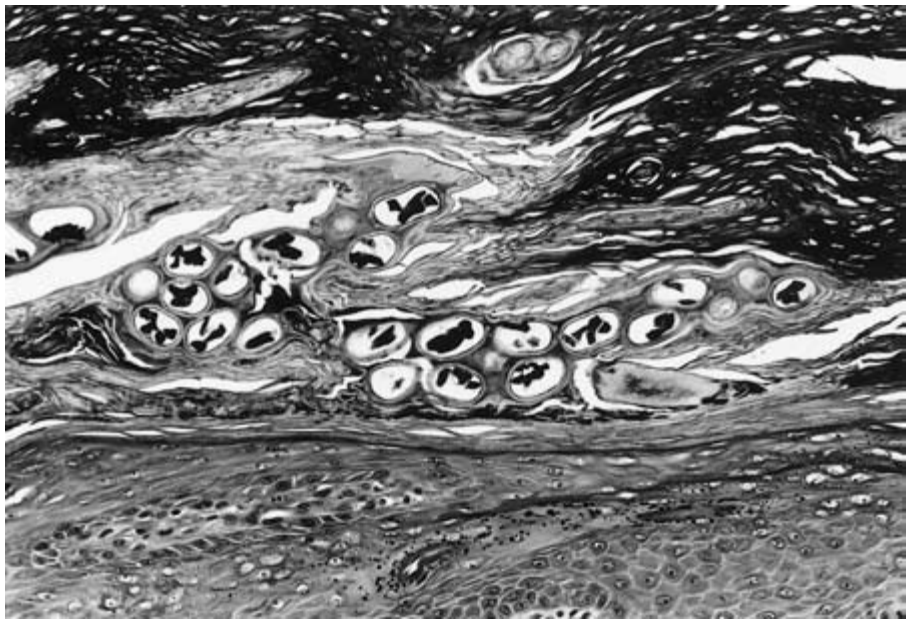


Fig. 9.56 Higher magnification of Fig. 9.55 demonstrating ova of *Anatrichosoma* sp. within pawpad keratin.



Fig. 9.57 High magnification of cross sections of *Anatrichosoma* sp. nematodes in epidermis from the dog in Figs 9.55 and 9.56.

In the reported feline case, inflammation was more intense and extended perivascularly to the deep dermis as well. Parasites colonized the superficial dermis as well as the epidermis, and were associated with intense dermal inflammation that included eosinophils (Ramiro-Ibáñez et al., 2002).

Differential diagnosis is uncomplicated due to the highly characteristic appearance and location of the organisms. *Pelodera* dermatitis, also due to a nematode, is folliculocentric (see Chapter 17).

VITILIGO

Clinical features (Figure 9.58 through 9.61)

Vitiligo is an acquired melanocytopenic hypomelanosis characterized by progressive, well-circumscribed loss of pigment. Vitiligo is relatively uncommon in the dog and rare in the cat. Marked breed predilections seem to indicate that vitiligo in the dog is heritable. The term vitiligo in human medicine is used rather specifically to denote a

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Fig. 9.58 Vitiligo in a Belgian Tervuren. Note the depigmentation of the planum nasale, muzzle, lips, and periorbital skin, as well as the pigment loss from the facial haircoat. (Photograph courtesy B.A. Atlee; case material University of California, Davis.)



Fig. 9.59 Vitiligo of the pawpads in the Belgian Tervuren in Fig. 9.58. A mottled loss of pigmentation has occurred on all pawpads. (Photograph courtesy B.A. Atlee; case material University of California, Davis.)

common, heritable, acquired disorder characterized by 'milky-white', well circumscribed macules that are devoid of any melanocytes on histopathology (Mosher et al., 1999). The diagnosis of vitiligo in humans carries with it the significant risk for ocular abnormalities, thyroid disease, diabetes mellitus, Addison's disease, and pernicious anemia (Mosher et al., 1999). Concurrent vitiligo

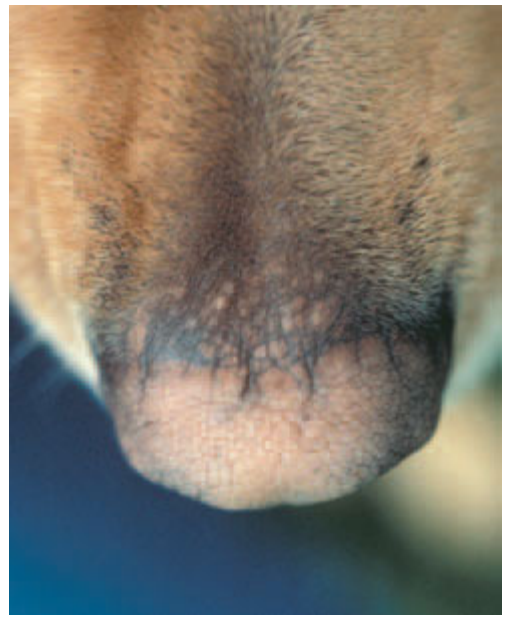


Fig. 9.60 Depigmentation affecting only the planum nasale and the adjacent muzzle in a Labrador Retriever. This subgroup of vitiligo has been termed 'Dudley nose' by dog breeders.

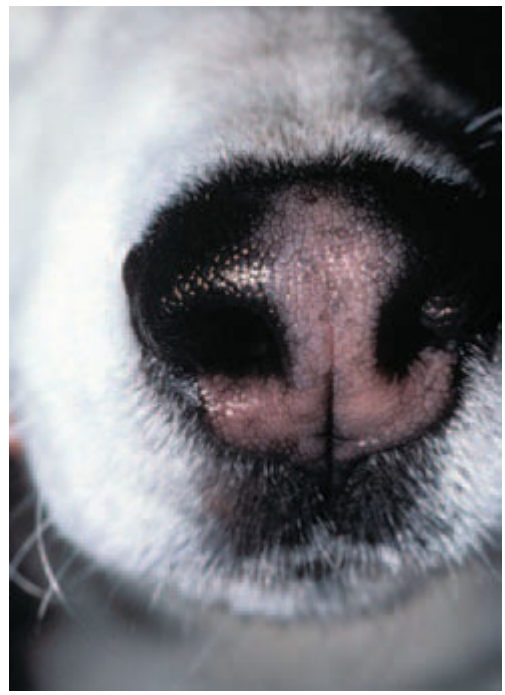


Fig. 9.61 Vitiligo affecting only the planum nasale in a Siberian Husky. Focal loss of pigmentation was the only abnormality noted. This subgroup of vitiligo has been termed 'snow nose' by dog breeders.

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and juvenile-onset diabetes mellitus has been reported in a Dachshund (Scott et al., 2001).

In veterinary medicine, the term 'vitiligo' has been used considerably more generically to encompass various types of leukoderma and leukotrichia. The authors have chosen to use vitiligo more narrowly to delineate animals with features similar to vitiligo in humans. The cardinal difference between vitiligo in humans and domestic animals is that concomitant leukotrichia is a common feature in domestic animals. Leukotrichia may be seen in vitiligo in humans, but humans are glabrous in comparison to domestic animals, affording less opportunity for leukotrichia.

Vitiligo in humans was long thought to be a heritable disease of autosomal dominance and variable expression. Similar heritability has been hypothesized in the Belgian Tervuren Dog (Mahaffey et al., 1978). However, current human literature indicates that the heritability pattern is incompletely characterized (Mosher et al., 1999; Ortonne et al., 2003).

The etiopathogenesis of vitiligo in humans and domestic animals is unclear. Composite research data from human medicine indicate that vitiligo may have a complex pathogenesis, involving the lack of normal protective mechanisms that eliminate toxic melanin precursors (self-destruct hypothesis), neurochemical mediators that inhibit melanogenesis or destroy melanocytes (neural hypothesis), and the induction of autoantibodies against various antigens in the melanogenic system (autoimmune hypothesis) (Mosher et al., 1999; Ortonne et al., 2003).

The primary clinical feature is progressive macular depigmentation. If the macules occur in haired regions, leukotrichia usually occurs simultaneously. Lesions may be partially bilaterally symmetric, especially lesions involving the face and distal extremities. Nonhaired predisposed sites include the planum nasale, lips, buccal mucosa, and pawpads. Depigmentation of the claws may occur. The muzzle, elsewhere on the face, and the distal extremities are common predisposed haired sites; this pattern of involvement is termed 'acrofacial'. Lesions may be strikingly periorificial and surround the mouth, nares, eyes, anus, and genitals, as is seen in humans. Transient erythema and scaling have been described rarely in vitiligo both in the veterinary and human literature. The evolution of vitiligo is unpredictable. Affected areas may repigment, remain unchanged, or wax and wane. Usually, the full extent of hypopigmentation occurs within 3 to 6 months of onset. Lesions are asymptomatic.

A marked breed predilection exists for the Belgian Tervuren. Other breeds at increased risk include the Rottweiler, German Shepherd Dog, Doberman Pinscher, German Shorthaired Pointer, Old English Sheepdog, and Dachshund (Alhaidari et al., 1999). Vitiligo has been seen occasionally as an isolated event in a variety of other breeds. Vitiligo has been described in Siamese cats (Alhaidari et al., 1999). Vitiligo develops most frequently in animals less than 3 years of age. Sex predilections have not been published, although reported Siamese cats all have been female.

Idiopathic depigmentation restricted to the planum nasale in dogs also has been termed 'vitiligo', 'Dudley nose', and 'snow nose'. The etiology of this syndrome is not known. Breeds at increased risk include Golden Retrievers, yellow Labrador Retrievers, and arctic breeds such as the Siberian Husky and Alaskan Malamute.

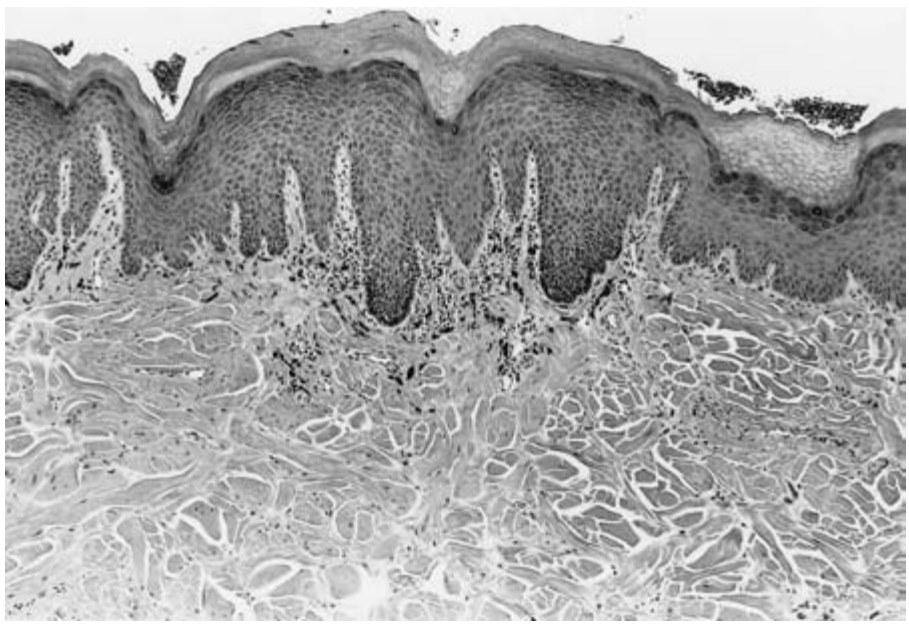


Fig. 9.62 Vitiligo in a Rottweiler. Note uneven distribution of epidermal pigment and pigmentary incontinence.

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Fig. 9.63 Higher magnification of vitiligo in a Rottweiler. Mild superficial lymphocytic inflammation migrates into the overlying epidermis.

Facially oriented vitiligo affecting the planum nasale and muzzle must be differentiated from Vogt–Koyanagi–Harada-like syndrome, discoid lupus erythematosus, and systemic lupus erythematosus. Vitiligo is a syndrome seen during young adulthood and is asymptomatic. Diagnostic aids include detection of uveitis by ophthalmological examination (Vogt–Koyanagi–Harada-like syndrome), or a positive antinuclear antibody (ANA) test (systemic lupus erythematosus). Histopathology will aid in differentiation. Vitiligo with accompanying leukotrichia is clinically striking and highly characteristic of vitiligo. If vitiligo is suspected, a general physical examination, complete blood count, and chemical screening profile are recommended to rule out concurrent disease.

Biopsy site selection

Skin biopsy is recommended as early as possible in the development of the disease. Ideal sites are from junctions of lesions, and should include adjacent normally pigmented skin. Larger punch biopsy (8 mm) or wedge technique will best allow the evaluation of the lesion, transition zone, and adjacent normal skin.

Histopathology (Figures 9.62 and 9.63)

The affected epidermis is characterized by a marked reduction to complete absence of epidermal melanocytes and melanin. Comparison with adjacent pigmented skin is often striking. Other epidermal lesions are not observed.

The dermis is often normal except for small to moderate numbers of melanophages. However, there also may be minimal to mild superficial perivascular accumulations of lymphocytes and fewer histiocytes and plasma cells. Lymphocytes often migrate into the overlying epidermis. Inflammation is presumed to characterize early stages of vitiligo, but temporal correlation with clinical lesions has not been made.

Differential diagnosis is not difficult for specimens characterized by obvious loss of epidermal melanin in the face of minimal to absent inflammation. Since these lesions can mimic normal nonpigmented skin (in which melanocytes are inapparent), knowledge of the clinical lesions is critical to the histopathologic diagnosis. Vitiligo with more obvious perivascular inflammation may need to be distinguished from mild atopic dermatitis or other allergic diseases with postinflammatory depigmentation.

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Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis, Second Edition
Thelma Lee Gross, Peter J. Ihrke, Emily J. Walder, Verena K. Affolter
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Chapter 10

Vascular diseases of the dermis

Vascular diseases of the dermis, as classified here, include those in which cutaneous vessels are the primary target. Some vascular diseases are grouped by histomorphologic characteristics and not by clinical appearance. Tight histopathological classification is difficult because inflammation may vary by stage, as reported (Nichols et al., 2001). Most cutaneous vasculitides recognized in dogs and cats are of small vessel type.

Most cutaneous vasculitides of animals may be attributed to immunoreactive mechanisms that are, as yet, poorly characterized. These may be triggered by drugs (including vaccines), hereditary factors, infectious agents, solar exposure, or, most commonly, undiscovered stimuli.

Vasculitis is characterized by inflammation directed to the vessel wall, as well as vascular lesions that include frank necrosis, fibrinoid change, endothelial swelling, and thrombosis. Microhemorrhage is common. Leukocytoclasia, a feature of small vessel vasculitis, is fragmentation of granulocytic nuclei as they exit affected vessels, and is typified by nuclear fragments or dust in perivascular distribution. In some cases, leukocytoclastic debris is the prime feature of vasculitis, as vascular lesions may be subtle in random samples. 'Cell poor' vasculitis or, more precisely, 'vasculopathy' is characterized by vascular damage and often vascular depletion, but with sparse inflammation. Typical vasculopathic features include loss of endothelial cells and thickening of the vessel wall.

Diascopy, the pressing of a clear microscope slide on erythematous skin to determine if erythema is due to dilated blood vessels or hemorrhage into the skin, is a useful clinical tool in the diagnosis of vascular diseases of the skin. Erythema that does not blanch with diascopy confirms hemorrhage and suggests vasculitis or vasculopathy.

SEPTIC VASCULITIS

Clinical features (Figure 10.1)

Septic vasculitis is a rare disorder seen secondary to catastrophic bacterial infection in both dogs and cats. Septic vasculitis may occur as a sequela to severe deep pyoderma in dogs, especially when the bacterial infection is secondary to generalized demodicosis or a defect in the host immune response. Cutaneous septic vasculitis may occur from 'bacterial shower' derived from internal infections such as bacterial endocarditis. Rocky Mountain spotted fever, a cause of septic vasculitis in humans (Kao et al., 1997), is an uncommon etiology in dogs. Septic vasculitis associated with ehrlichiosis and vasculitis due to systemic infection with *Erysipelothrix rhusiopathiae* has been described in the dog (Crawford & Foil, 1989).

Clinical signs partially parallel those seen with other causes of vasculitis. Swelling, erythema, purpura, erythematous plaques, hemorrhagic bullae, necrosis, and ulceration may be generalized or localized to areas of less extensive collateral circulation such as the distal extremities and pinnae. Affected regions may vary in firmness and texture. Necrotizing ulcers may be crateriform. The erythema seen with septic vasculitis does not blanch with diascopy (see above). Coexistent cellulitis and deep folliculitis and furunculosis may be present, especially if septic vasculitis is secondary to demodicosis. Fistulous tracts may form. Devitalized tissue may be firm and discolored. Pain is variable but usually is present if tissue necrosis is marked. Systemic signs, including fever, malaise, and anorexia, are common and may indicate coexistent visceral vasculitis. Septic vasculitis always is life threatening; coma and death are possible sequelae.

Breed, age, or sex predilections have not been noted for septic vasculitis. Septic vasculitis secondary to severe generalized demodicosis probably shares the breed and age predilections for that condition.

Clinical differential diagnoses should include all other vasculitides, including neutrophilic immunologic vasculitis, severe cell poor vasculitis, and cryopathies, as well as deep pyoderma and disseminated intravascular coagulation. Generalized lesions and documentation of sepsis by blood culture are suggestive of septic vasculitis.

Biopsy site selection

Early lesions, characterized by erythema or petechial hemorrhage, are preferred over advanced lesions with exten-

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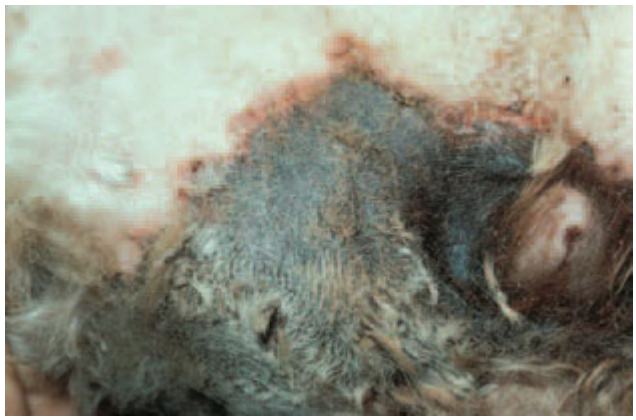


Fig. 10.1 Septic vasculitis of the ventral abdomen of a dog secondary to septicemia. Firm and darkly discolored devitalized tissue is surrounded by a margin of erythema, swelling, and ulceration.



Fig. 10.2 Urticaria due to insect bites on the ventral abdomen of an English Bulldog. Multiple, erythematous, well-demarcated wheals are present.

sive tissue necrosis and ulceration. Larger punch biopsy (8 mm) or wedge biopsy specimens are more likely to yield a diagnosis, as smaller punch biopsy may result in disruption of friable, devitalized tissue. If distal extremities are sampled, collateral circulation must be adequate to nourish distal tissue and provide for healing of the biopsy site.

Histopathology

Necrosis and ulceration of the epidermis are common in advanced lesions as hypoxic tissue damage proceeds in the skin. There may be fibrinosuppurative or sanguinopurulent exudation. Dermal vascular lesions resemble those of neutrophilic immunologic vasculitis (see p. 244) but usually are more severe and deeper. Neutrophilic inflammation occurs murally and around vessels, and there may be mild to severe leukocytoclasia (see introduction, p. 238). Vascular fibrinoid necrosis and fibrin thrombi may be prominent, including in large vessels. Severe hemorrhage, edema, and dermal necrosis (infarction) may be found. Mixed mononuclear inflammation is variable and is perivascular to interstitial depending on chronicity and degree of secondary tissue damage. The inflammatory process often extends into the subcutis. Bacterial emboli may be present in florid cases.

The lesions of septic vasculitis may resemble severe neutrophilic immunologic vasculitis (see p. 244); hyaline thrombi are observed more often in septic vasculitis, with the exception of severe neutrophilic immunologic vasculitis in Shar Peis. Infarcted tissue suggests sepsis over immunologic vasculitis, particularly when bacteria are identified within tissue. Deep septic vasculitis with infarction may resemble vasculitis of thermal burns (see Chapter 21). However, septic vasculitis sufficient to create



Fig. 10.3 Closer view of the dog in Fig. 10.2. Several steep-walled wheals have coalesced.

coagulative necrosis resembling a burn usually is more severe than vasculitis associated with even the most severe burns. Also, septic vasculitis often is associated with severe systemic illness, whereas dogs with thermal burns usually are clinically normal. Historical and clinical information may be required for differentiation.

URTICARIA AND ANGIOEDEMA

(Synonym: hives)

Clinical features (Figures 10.2 through 10.4)

Urticaria and angioedema are edematous cutaneous reactions characterized by the formation of wheals. Urticaria is distinguished by edema that is limited to the dermis. Extension of edema to the subjacent subcutaneous tissue creates angioedema. Both reaction patterns are uncom-

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Fig. 10.4 Angioedema of the face of a Doberman Pinscher puppy caused by a stinging insect. The eyes are swollen shut and the muzzle is severely distorted by edema.

mon in the dog and rare in the cat. Urticaria may be initiated by immunologic or nonimmunologic factors (Soter & Kaplan, 2003). Angioedema is almost always associated with hypersensitivity reactions.

The most frequently reported immunologic causes of urticaria and angioedema include drug reactions, food allergy, stinging or biting arthropods, vaccines, bacterins, blood transfusions, infections, contact with certain plants, and atopic dermatitis (Scott et al., 2001; Soter & Kaplan, 2003). One author (P.J.I.) has seen angioedema due to buffalo gnat bites. Nonimmunologic or physical causes include heat, cold, sunlight, and water (Soter & Kaplan, 2003). Dermatographism is a rare form of urticaria in which pressure to the skin produced by a blunt instrument initiates wheals.

A wheal is a discrete, erythematous, edematous circular swelling with a flat top and steep-walled margins. Wheals vary from less than 1 cm to 3 cm in diameter. Multiple wheals may coalesce and form unusual arcuate patterns. Rarely, bizarre geographic (map-like) patterns may be seen in the dog. The number of wheals varies considerably and may range from less than five to hundreds. Urticaria is most visible in comparatively glabrous body regions such as the ventral abdomen and the axillary region. Similar lesions may be present in haired regions, but are often much less apparent. Urticaria is more obvious in short-coated dogs, as edema results in groups of hairs standing erect over the wheals. Pruritus is variable and, if present, may induce self-trauma that can obscure primary lesions.

Sites of involvement are contingent upon the cause. Urticaria from venomous arthropods is seen more commonly on the face and on the comparatively glabrous areas such as the groin. Cold- or water-induced urticaria occurs at the sites of contact.

Angioedema is physically similar to, but considerably less well demarcated than urticaria, since the edema is not confined to the dermis. Poorly defined areas of swelling are present. Angioedema from an injection usually occurs at the site of injection, but may extend to surrounding areas. Angioedema from causes other than injection seems to be most common on the face.

Breed, age, or sex predilections have not been substantiated for either urticaria or angioedema. Short-coated breeds such as the English Bulldog, Bull Terrier, Doberman Pinscher, and Dalmatian may be at increased risk for urticaria. However, this clinical impression may be due to the increased visibility of urticaria in these short-coated dogs that also have comparatively glabrous abdomens.

The predominant clinical differential diagnoses for urticaria are urticarial allergic eruption (see Chapter 9) and superficial folliculitis. Superficial folliculitis (especially in short-coated dogs) may closely mimic urticaria grossly. Folliculocentric inflammation and accompanying edema can cause groups of hairs to stand upright, resembling wheals. In addition, wheals or wheal-like lesions may characterize early erythema multiforme, neutrophilic immunologic vasculitis, mast cell tumors, cutaneous mastocytosis, and focal mucinosis. Differential diagnoses for angioedema include early juvenile cellulitis, early bacterial cellulitis, and neutrophilic immunologic vasculitis. Histopathology will allow differentiation.

Biopsy site selection

Expeditious skin biopsy is recommended, since wheals are transient lesions. If pruritus is present, wheals may be obscured by secondary self-trauma. The inclusion of a biopsy specimen from adjacent normal skin may be helpful, since the dermal edema of urticaria may be subtle.

Histopathology (Figure 10.5)

Urticaria manifested by pure edema is rare in biopsy specimens; most lesions conform to urticarial allergic eruption (see Chapter 9). In one author's opinion (P.J.I.), this may be due to lack of sampling of clinically obvious urticarial wheals, which are purely edematous microscopically. Rather, atypical edematous lesions that characterize urticarial allergic eruption are more likely to be biopsied; these may be more likely to reveal an inflammatory component.

Epidermal changes usually are not present in untraumatized wheals. Dermal histopathologic changes may be subtle. Edema may widen spaces between collagen fibers

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Fig. 10.5 Urticaria in a dog. Edema is widening spaces between collagen fibers. Note absence of inflammation.



Fig. 10.6 Idiopathic telangiectasia in an aged Golden Retriever. Diffuse intense erythema is present on the antebrachial region. (Photograph courtesy T.C. DeManuelle; case material University of California, Davis.)

in the dermis, but can be missed if not severe. Urticaria should be suspected in any case for which no obvious histopathologic changes are present in tissue ('invisible dermatosis'). In more severe urticaria, prominent edema may expand the superficial dermis and result in secondary dermal–epidermal separation. Angioedema is characterized by severe edema that extends to the subcutis.

Urticaria is distinctive, although its detection can be difficult in the absence of inflammation. In cases where edema is subtle, correlation with appropriate clinical presentation of wheals or hives is required for definitive diagnosis. Urticarial allergic eruption varies only by the inclusion of perivascular inflammation.

TELANGIECTASIA, PHLEBECTASIA, AND CUTANEOUS FLUSHING

Clinical features (Figure 10.6)

Telangiectasia, phlebectasia, and cutaneous flushing are uncommon (phlebectasia) to rare (telangiectasia, cutaneous flushing) syndromes that give the appearance of localized, poorly blanching erythema. They are grouped for convenience as they resemble each other clinically and putatively appear similar histopathologically. Telangiectasia is defined as a permanent dilatation of pre-existing blood vessels and is very rare in the dog (DeManuelle et al., 1999). Cutaneous phlebectasia, a type of telangiectasia, is defined as a focal abnormal dilation, extension, or reduplication of small veins and is seen most commonly as a clinical marker of canine hyperadrenocorticism (Scott, 1985). Similar lesions are observed in topical corticosteroid reactions (see Chapter 15). Cutaneous flushing is due to the dilatation of apparently normal cutaneous blood vessels and can either be persistent or paroxysmal (Miller, 1992).

Cutaneous flushing in humans can be caused by a wide variety of phenomena including neoplasia (especially carcinoid syndrome), endocrinopathy, mastocytosis, menopause, and drugs (Hurst & Heffernan, 2003). In dogs, persistent flushing has been seen with adverse drug reactions and mast cell tumors (Miller, 1992). Flushing has been induced experimentally in the dog via the intradermal injection of fluoroquinolones; increased histamine

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release is the probable mechanism (Kurata et al., 1995). Paroxysmal flushing has been seen with pheochromocytomas and mast cell tumors (Miller, 1992).

Idiopathic telangiectasia in an aged Golden Retriever was characterized by diffuse erythema affecting both antebrachial regions (DeManuelle et al., 1999). Other clinical signs, including pruritus, were not noted.

Cutaneous phlebectasias are asymptomatic, usually multifocal, erythematous macular to papular lesions commonly less than 6 mm in diameter (Scott, 1985). They occur most frequently on the ventral and medial thighs. They are a cutaneous marker of canine hyperadrenocorticism and are seen in up to 40% of affected dogs (Scott, 1985). Lesions blanch partially with diascopy (see introduction, p. 238).

Cutaneous flushing is characterized clinically by either regional or generalized erythema (Miller, 1992). Lesions blanch partially with diascopy. Pruritus may or may not be a feature depending on underlying cause. Paroxysmal flushing due to mast cell tumors and paroxysmal or persistent flushing due to an adverse drug reaction may be pruritic.

Signalment predilections are contingent upon the underlying cause of the vascular abnormality. Cutaneous flushing due to underlying neoplasia should occur more commonly in older dogs. Cutaneous phlebectasia secondary to hyperadrenocorticism should share breed and age predilections for that disease (see Chapter 19).

Clinical differential diagnoses for cutaneous phlebectasia are few, but include very early sun-induced telangiectasia or hemangioma (see Chapter 28). Certain types of early progressive angiomatosis may mimic phlebectasia (see Chapter 28). Dogs exhibiting persistent, widespread cutaneous flushing must be differentiated from the myriad causes of generalized erythroderma; these include generalized demodicosis, thallium toxicosis, early epitheliotropic lymphoma, and cutaneous mastocytosis. The presence or absence of pruritus may aid in differentiation. Of the above-mentioned diseases, all but thallium toxicosis may be pruritic. The differential diagnosis of generalized erythroderma requires routine hematology and other procedures more specific for each disease.

Biopsy site selection

A lesion or region of maximum erythema should be selected for skin biopsy. Multiple specimens should be obtained to ensure that unusual differential diagnoses are ruled out.

Histopathology (Figure 10.7)

Idiopathic telangiectasia is characterized by superficial dermal vascular ectasia. There may be the appearance of vascular proliferation. True proliferation has not been proven and the impression may result from increased vascular prominence due to dilatation and congestion. Alkaline phosphatase staining was reportedly negative in dilated vessels, indicating venular rather than arteriolar origin (DeManuelle et al., 1999); alkaline phosphatase activity is a normal finding in endothelium of arterioles, but is lacking in venules. There may be mild to moderate acanthosis. Inflammation, edema and necrosis are absent.

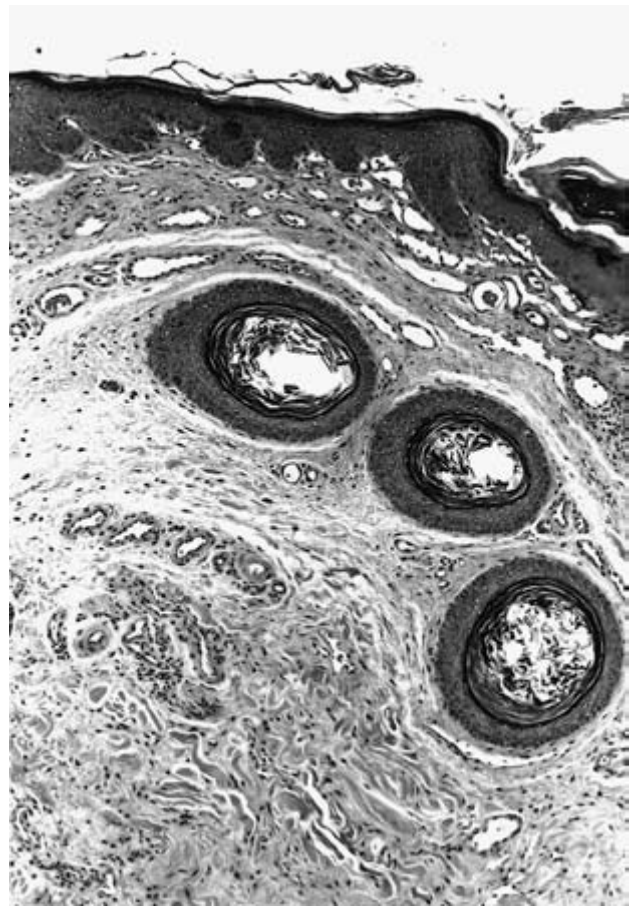


Fig. 10.7 Telangiectasia in a dog. Vascular dilatation gives the appearance of vascular proliferation.

Phlebectasia (telangiectasia) due to Cushing's disease is uncommonly sampled for histology. As reported, early lesions had dilatation of superficial vessels; older papular lesions had a lobular proliferation of dilated vessels, often with partial 'collaring' by the overlying epidermis (Scott, 1985). Similar telangiectasia is a common accompaniment to topical corticosteroid reactions (see Chapter 15). Telangiectasia also may be seen with chronic solar damage, and is often accompanied by solar vascular neoplasms (see Chapter 28).

The histopathology of cutaneous flushing is unknown. Based on a previous report that documented increased

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blood flow in cutaneous flushing secondary to fluoroquinolones, vascular dilatation is likely (Kurata et al., 1995).

The histologic features of telangiectasia or phlebectasia are characteristic. Differentiation between idiopathic telangiectasia and cutaneous flushing probably requires correlation with clinical findings. Phlebectasia (telangiectasia) associated with chronic solar damage, topical corticosteroids, and Cushing's disease should have accompanying morphologic changes compatible with those entities (see Chapters 15 and 19). Progressive angiomatosis should not be confused with telangiectasia due to the more proliferative nature of the condition and the depth of involvement (see Chapter 28).

CRYOGLOBULINEMIA AND CRYOFIBRINOGENEMIA

(Synonym: cutaneous cryopathies)

Clinical features (Figure 10.8)

Cryoglobulinemia and cryofibrinogenemia are rare diseases affecting multiple organ systems. They are characterized by vascular insufficiency due to the precipitation of immunoglobulins or immune complexes within the peripheral vasculature. The skin is a prime organ for cryopathic disease (Cornelius & Lawley, 2003). Cutaneous cryopathies are rarely reported as a cause of skin diseases in the dog and cat (Green et al., 1977; Godfrey & Anderson, 1994; Bridle & Littlewood, 1998; Nagata et al., 1998). The names 'cold agglutinin disease', 'cold hemagglutinin disease' and 'cryopathic hemolytic anemia' have been used to describe autoimmune disease associated with cold-reacting autoantibodies (usually IgM) that are directed against erythrocytes (Scott et al., 2001).



Fig. 10.8 Cold agglutinin disease in a Chihuahua. Infarction has severely damaged the margins of the pinnae; note severe bilaterally symmetric crusting. (Photograph courtesy T. Olivry.)

Cryoglobulins are defined as circulating immunoglobulins that have formed complexes with other immunoglobulins or other proteins (Cornelius & Lawley, 2003). Cryofibrinogens are cryoproteins composed of fibrinogen that are present in noncoagulated blood or plasma. Both cryoglobulins and cryofibrinogens reversibly precipitate with exposure to cold (Cornelius & Lawley, 2003). The accepted classification of cryoglobulinemia used in veterinary medicine parallels the scheme used in human medicine (Scott et al., 2001; Cornelius & Lawley, 2003). Type I cryoglobulins are composed of a single, monoclonal immunoglobulin, and are most commonly associated with B cell malignancies such as multiple myeloma or B cell lymphoma (Cornelius & Lawley, 2003). Type II cryoglobulins are immune complexes composed of both monoclonal and polyclonal immunoglobulins, and are most commonly associated with autoimmune or connective tissue diseases (Cornelius & Lawley, 2003). Type III cryoglobulins are immune complexes composed of polyclonal immunoglobulins, and are associated either with autoimmune and connective tissue diseases, or infections (especially viral hepatitis in humans) (Cornelius & Lawley, 2003). Cryoglobulins precipitate over a wide temperature range between 32°F and 86°F (0°C and 30°C) and can precipitate as a gel, flocculent precipitate, or as crystals (Cornelius & Lawley, 2003). Cutaneous and visceral signs are associated with various types of vascular insufficiency leading to ischemic damage.

Cutaneous lesions include purpura, erythema, tissue necrosis, and ulceration. Acrocyanosis, a bluish or whitish discoloration of the skin of the extremities associated with diminished blood supply, may be noted. Gangrenous necrosis may occur in more severe cases. Pain is variable, but may be an important feature. Distal extremities including the pinnae, tip of the tail, pawpads, planum nasale, and adjacent haired skin are most commonly affected. Anemia may be seen. Extracutaneous signs of cryopathies may be under-reported in veterinary medicine; serious extracutaneous signs seen in humans can include renal disease and peripheral polyneuropathies (Cornelius & Lawley, 2003).

Clinical differential diagnoses include all other causes of vasculitis, as well as vasculitic autoimmune skin diseases such as systemic lupus erythematosus, ischemic necrosis associated with vasoconstrictive toxins, disseminated intravascular coagulopathy and, where appropriate, frostbite. Hematologic evaluation for cryoglobulins or cryofibrinogens is required for a definitive diagnosis.

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Fig. 10.9 Neutrophilic immunologic vasculitis affecting the pinna of a Chihuahua. Necrosis and ulceration have led to loss of tissue along the pinnal margin; note accompanying crusting.



Fig. 10.10 Neutrophilic immunologic vasculitis in a Chinese Shar Pei. This breed-based 'acute febrile neutrophilic vasculitis' has created extensive, full thickness cutaneous necrosis. (Photograph courtesy R. Malik.)

Biopsy site selection

Care must be taken when sampling affected tissue to ensure that healing will occur after biopsy. If possible, affected tissue of a distal extremity should be resected such that remaining tissue has an adequate blood supply.



Fig. 10.11 Neutrophilic immunologic vasculitis in another Chinese Shar Pei. Multifocal, crateriform full-thickness necrotic ulcers are present on the trunk. (Photograph courtesy R. Malik.)

Histopathology

As reported, diffuse vascular thrombosis occurs, accompanied by acute coagulation necrosis of the epidermis and dermis (Nagata et al., 1998). Blood vessels throughout the dermis are dilated and contain an amorphous eosinophilic substance. This is either fibrinogen or immunoglobulin, and is periodic acid–Schiff (PAS)-positive (Barnhill & Busam, 1997). Inflammation including vasculitis is not reported (Nagata et al., 1998). Chronic lesions of one early report were ulceration and edema, perivascular mixed inflammatory cells, macrophages containing iron and erythrocytes, hyaline thickening of vessel walls, and an absence of intravascular fibrin; *in vivo* fibrinolysis was postulated (Green et al., 1977).

Differential diagnoses for the necrotic and thrombotic lesions of cryoglobulinemia and cryofibrinogenemia may include severe thermal burn, and infarctive severe vasculitis, such as septic vasculitis. These syndromes usually feature vascular inflammation and generally do not have the widespread intravascular fibrin of typical cryopathies. In the absence of intravascular fibrin, differentiation from lesions of thermal burn or ischemic necrosis from severe vasculitis may be more difficult. Clinical differentiation is required.

NEUTROPHILIC IMMUNOLOGIC VASCULITIS

Clinical features (Figures 10.9 through 10.11)

Neutrophilic immunologic vasculitis is a rare subgroup of nonseptic vasculitis seen in dogs and cats. Inflammatory changes in the walls of blood vessels lead to swelling, purpura, and necrosis. The etiology is multifactorial; most neutrophilic immunologic vasculitis probably is due to

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immune-complex disease (type III hypersensitivity), but type I hypersensitivity also may effect its initiation. Immunologic vasculitis may be leukocytoclastic or non-leukocytoclastic (see below). Viral disease, adverse reactions to drugs, and connective tissue disease may be precipitating factors (McEwan et al., 1987; Gross, 1999). Systemic vasculitis with skin involvement in association with leishmaniasis has been reported in a dog (Pumarola et al., 1991). Most cases are idiopathic. Coexistent visceral lesions may be seen and vary with the underlying cause. In humans, vasculitis can range from a self-limiting single-organ disorder to life-threatening multiple-organ failure and death (Fiorentino, 2003); a similar spectrum of severity is seen in veterinary medicine.

Clinical signs parallel those of other vasculitides. Swelling, erythema, purpura, erythematous plaques, ulceration, and necrosis are noted. Crateriform necrotic ulcers may be present. The erythema seen with vasculitis does not blanch with diascopy (see introduction, p. 238). Devitalized tissue may be firm and discolored. Lesions may be localized to distal extremities or areas of less extensive collateral circulation including the tip of the tail, pawpads, pinnae, lips, or planum nasale. The lips and oral mucosa also may be affected. Generalized disease may be present.

Pain is variable, but usually is present in conjunction with marked tissue necrosis. Systemic signs can include fever, malaise, and anorexia, and should alert the clinician to the possibility of coexistent visceral vasculitis. In humans, paraesthesia, fever, and the absence of cutaneous pain are risk factors for systemic involvement and a less favorable prognosis (Sais et al., 1998).

A markedly severe subgroup of neutrophilic immunologic vasculitis has been reported in Chinese Shar Pei dogs (Malik et al., 2002) Clinically, the affected Shar Peis developed widespread skin discoloration characterized by hemorrhagic papules, macules or plaques, and edema that lead to life-threatening full-thickness cutaneous necrosis (Malik et al., 2002).

Firm, erythematous truncal papules and nodules with variable ulceration were seen in conjunction with leukocytoclastic immunologic vasculitis due to feline infectious peritonitis in a Sphinx cat (Gross, 1999). The cat was icteric due to vasculitis-induced hemolysis. Lesions were transient and likely were detected due to the hairlessness of the breed affected; thus the true incidence of vasculitis in cats with this infection is unknown. Vasculitis, most likely as a severe adverse reaction to cimetidine, initiated exfoliative lesions of the pinnae, face, and distal legs in another cat (McEwan et al., 1987).

A breed-based acute, febrile neutrophilic vasculitis was reported in young Chinese Shar Pei dogs in Australia (Malik et al., 2002). This syndrome also has been seen recently in Costa Rica (Berrocal & Alfaro, 2003). Other breed and age predilections have not been reported.

Clinical differential diagnoses should include other causes of vascular disease, including septic vasculitis, disseminated intravascular coagulation, cryoglobulinemia and cryofibrinogenemia, and frostbite. History, environment, laboratory findings and evidence of systemic disease may aid in differentiation of these clinically similar diseases. Skin biopsy is required for diagnosis.

Biopsy site selection

Early lesions of hemorrhage and swelling are preferred over chronic lesions of ulceration. Multiple specimens should be submitted, if possible, as diagnostic lesions of vasculitis may be difficult to find in tissue.

Histopathology (Figures 10.12 through 10.15)

Most cases of neutrophilic vasculitis involve small vessels of the dermis. Rarely, vasculitis also may affect vessels of the panniculus (superficial subcutis); vasculitides of the

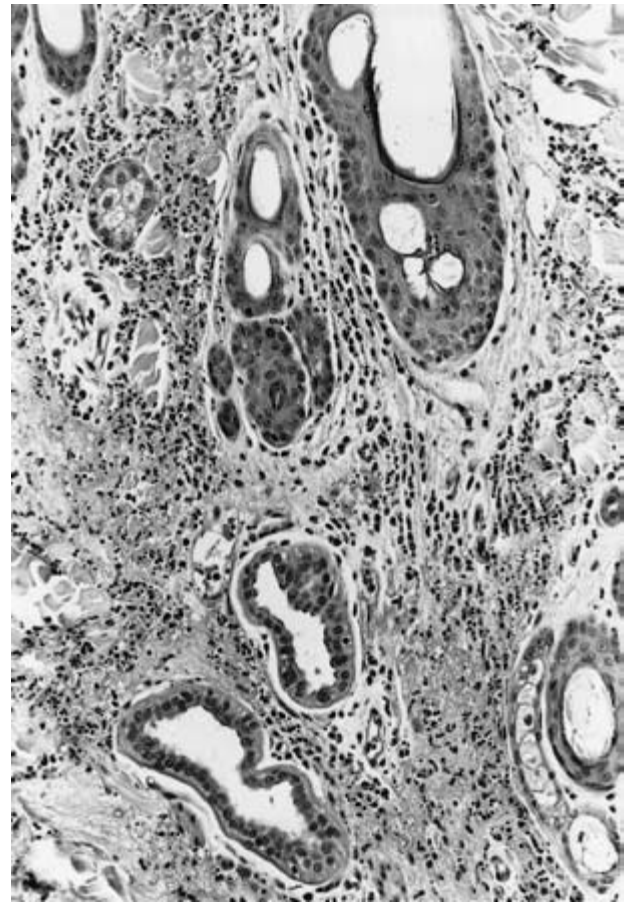


Fig. 10.12 Neutrophilic immunologic vasculitis in a dog featuring prominent leukocytoclastic debris surrounding periadnexal vessels. Inflamed blood vessels are not observed in this view.

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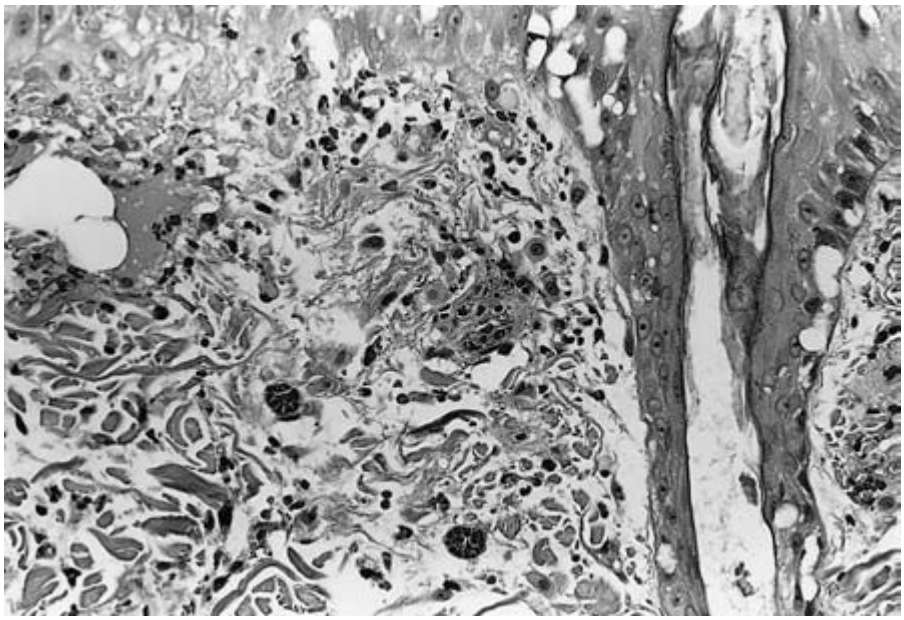


Fig. 10.13 Neutrophilic immunologic vasculitis in a cat with feline infectious peritonitis (FIP). A small blood vessel to the left of a follicle is necrotic and surrounded by leukocytoclastic neutrophils and fibrin.

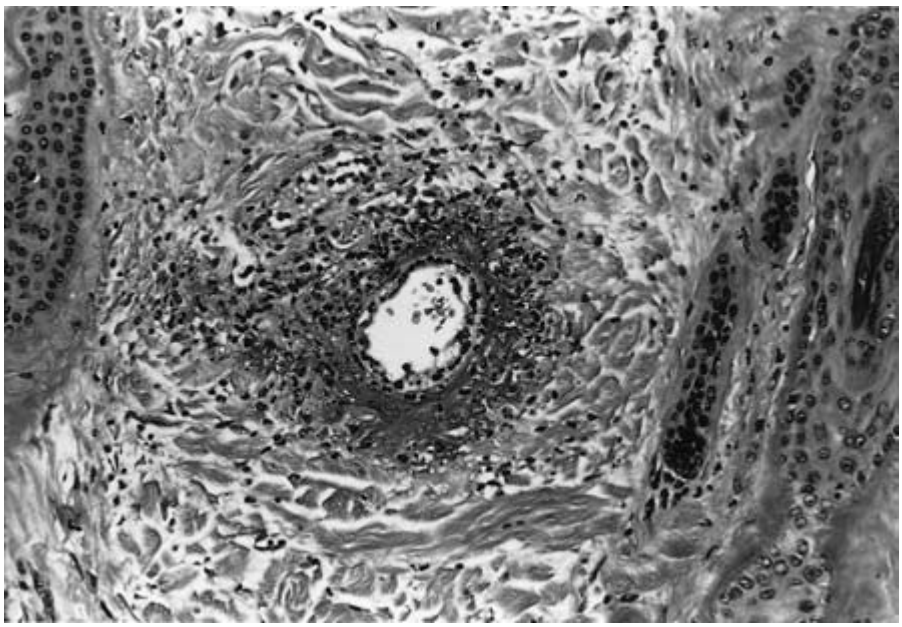


Fig. 10.14 Neutrophilic immunologic vasculitis in a dog. A severely affected vessel is necrotic and inflamed; note marked perivascular fibrin.

panniculus (vasculitic septal panniculitis and vasculitic panniculitis of thermal burns) are discussed in Chapter 21. Deeply extensive lesions and large vessel involvement are characteristic of Shar Peis with neutrophilic vasculitis (Malik et al., 2002), and also characterized systemic vasculitis with cutaneous involvement in a dog with leishmaniasis (Pumarola et al., 1991).

Primary epidermal lesions are not a feature of neutrophilic immunologic vasculitis. Exudation, crusting, and ulceration may develop secondary to hypoxic tissue damage induced by loss of subjacent vascular integrity. In affected Shar Peis, the epidermis is often diffusely necrotic and secondarily separated from the dermis; deep cavitating ulceration develops as lesions progress (Malik et al., 2002).

Neutrophilic inflammation usually centers upon postcapillary venules and may be leukocytoclastic or nonleukocytoclastic. Leukocytoclasia is manifested by fragmented neutrophilic debris around vessels ('nuclear dust') and may be subtle to severe. In some cases, leukocytoclasia may be the principal evidence of vascular inflammation. Neutrophilic inflammation cuffs vessels

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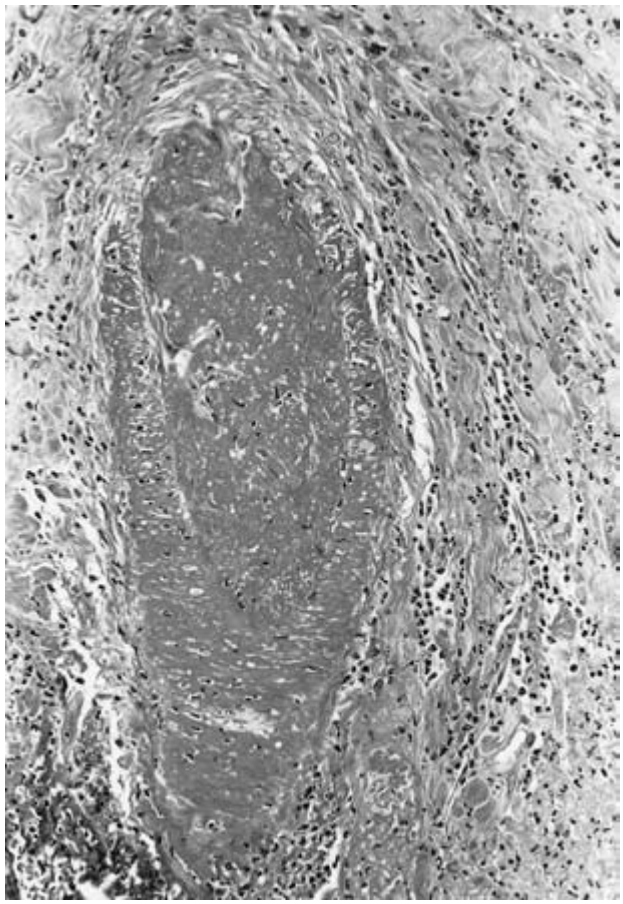


Fig. 10.15 Severe neutrophilic vasculitis of a Shar Pei. A large deep vessel is thrombosed; note perivascular neutrophils. (Case material courtesy K.L. Bosward.)

and spreads variably to the adjacent dermis. Fibrinoid necrosis of vessels is common, and intravascular fibrin thrombi may occur. Endothelial cells are swollen. Perivascular hemorrhage (microhemorrhage) and fibrin are often present. Edema is severe in some cases. Deep ischemic necrosis with severe and diffuse neutrophilic inflammation has been reported in conjunction with neutrophilic vasculitis of Shar Peis (Malik et al., 2002); large vessel thrombosis may occur.

Neutrophilic vasculitis is rarely a purely neutrophilic process. Eosinophils may be intermingled, and lymphocytic, histiocytic, and plasmacytic infiltrates are not uncommon. Mixed mononuclear inflammation may overshadow the neutrophilic infiltrates. However, mixed inflammatory infiltrates are largely perivascular to interstitial; the neutrophil remains the primary inflammatory cell that is directed to the vessel wall. Variation in the proportion and intensity of various inflammatory cell types may have as much to do with the stage of lesion examined and the presence of ulceration and necrosis, as with participation of specific immunologic reactions, such as cell-mediated immunity.

A Sphinx cat with feline infectious peritonitis developed leukocytoclastic vasculitis with granulomatous inflammation. Neutrophils surrounded and often obscured small blood vessels throughout the dermis, particularly in the perifollicular plexus. There was marked leukocytoclasia. Neutrophils were accompanied by numerous large macrophages. Perivascular hemorrhage and fibrin exudation was observed; red blood cells appeared fragmented. Immunohistochemistry demonstrated coronavirus (feline infectious peritonitis virus) antigen within macrophages (Gross, 1999).

Histopathologic evidence of vascular inflammation and necrosis may be difficult to document in cases of clinically suspected vasculitis. Suspicion for vasculitis may be based on histopathologic evidence of ischemic necrosis, prominent and closely oriented perivascular neutrophilic inflammation, subtle leukocytoclasia, and dermal hemorrhage and edema.

Histopathologic differential diagnoses for neutrophilic immunologic vasculitis are few if vascular inflammation and necrosis are found. Septic vasculitis is comparable, but often produces more severe attendant necrosis (infarction). In particular, neutrophilic vasculitis of Shar Peis closely resembles septic vasculitis (Malik et al., 2002). Urticarial allergic eruption with vasculopathic change is similar to neutrophilic vasculitis (see Chapter 9) but lacks true vascular inflammation.

CELL POOR VASCULITIS

(Synonyms: cell poor vasculopathy, ischemic dermatopathy)

Clinical features (Figures 10.16 and 10.17)

See also Chapters 3 and 21.

Cell poor vasculitis is a term used to group multiple clinical syndromes in dogs that are unified by similar histopathologic features. Ischemic dermatopathy/canine dermatomyositis, which includes five clinical subgroups, is the prototype for canine cell poor vasculitis (see Chapter 3). The vasculitis reported in Jack Russell Terriers (Parker & Foster, 1996) is a manifestation of ischemic dermatopathy in that breed (see Chapter 3). Cell poor vasculitis has not been observed in cats to the authors' knowledge.

Although severity and anatomic sites vary, clinical features correlate with those expected with long-term lack of cutaneous vascular sustenance (Vitale et al., 1999). Presumably, multifocal immunologic damage to blood vessels results in ischemic damage to the skin and other susceptible organs. Cutaneous hypoxia leads to follicular

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Fig. 10.16 Cell poor vasculitis in an Irish Terrier with generalized idiopathic ischemic dermatopathy. Patchy alopecia and macular hyperpigmentation are present. (Photograph courtesy T. Olivry; case material University of California, Davis.)



Fig. 10.17 Closer view of truncal lesions of the dog in Fig. 10.16. Alopecic macules are hyperpigmented. (Photograph courtesy T. Olivry; case material University of California, Davis.)

atrophy and, clinically, alopecia and associated chronic skin changes. In human dermatomyositis, complement-associated microvascular injury leading to ischemia is considered to be the pathophysiologic basis of skin lesions (Crowson & Magro, 1996). Similarly, complement C5b-9 membrane attack complex was demonstrated in small blood vessels within muscle from one dog with vaccine-induced ischemic dermatopathy featuring cell poor vasculitis (Vitale et al., 1999). This supports a role for complement-mediated microangiopathy, as seen in the cell poor vasculitis of human dermatomyositis (Crowson & Magro, 1996).

The unifying clinical features of cell poor vasculitis include alopecia with crusting and postinflammatory mottled pigmentary changes, including hyper- and hypopigmentation (see Chapter 3). Erosions or ulceration occur in more severe cases, especially if trauma or secondary infection is present. Scarring is a feature of chronicity. Lesions occur over bony prominences due to susceptibility to trauma, and on distal extremities where collateral circulation does not allow appropriate vascular sustenance, such as the pinnae, tail tip, and distal legs.

Several older dogs with chronic unilateral leg swelling, sometimes extending to the inguinal region, have exhibited cell poor vasculitis of the panniculus and subcutis; a variant of rabies vaccine reaction is suspected by one author (T.L.G.) (see Chapter 21); however, the relationship to deep injection in these sites has not been proven. Lesions in another dog with cell poor vasculitis were limited to periorbital swelling.

Clinical differential diagnoses should include other causes of vascular disease, such as septic vasculitis, cryoglobulemia and cryofibrinogenemia, and frostbite. Alopecia and other characteristic lesions occurring in a region susceptible to ischemic damage should increase the index of suspicion for cell poor vasculitis. Biopsy is generally confirmatory.

Biopsy site selection

Early lesions showing alopecia in conjunction with skin changes are preferred sites for biopsy. Secondarily infected or scarred lesions are less optimal for demonstration of typical histopathologic changes.

Histopathology (Figures 10.18 through 10.20)

The vascular lesions of cell poor vasculitis in ischemic dermatopathy/canine dermatomyositis are often subtle. There may be loss of endothelial cells, mummification, or mild hyaline mural alteration in small vessels. These changes are often easiest to identify in the superficial dermis, but occur throughout the lesional area. Density of small vessels may be decreased (Vitale et al., 1999) similar to obliterative microangiopathy of human dermatomyositis (Crowson & Magro, 1996).

Occasionally, active mural inflammation includes fragmented degenerating nuclear debris of neutrophils (leukocytoclasia), or infrequently, mononuclear cells. Fibrinoid degeneration is rare, but may be striking in some cases. Larger blood vessels are uncommonly affected. Although perivascular lymphocytes may be present in some cases of ischemic dermatopathy, there is no morphologic evidence that primary lymphocytic vasculitis is present. Complement C5b-9 membrane attack complex was demonstrated in small blood vessels within muscle from a dog with vaccine-induced cell poor vasculitis, supporting a role for complement-mediated microangiopathy, as seen in human dermatomyositis (Crowson & Magro, 1996; Vitale et al., 1999).

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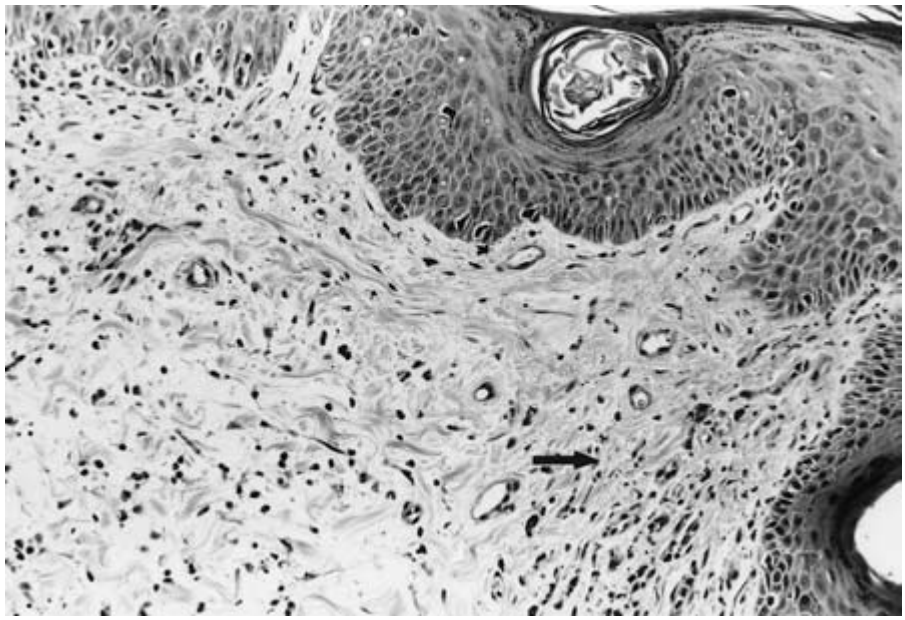


Fig. 10.18 Cell poor vasculitis in a German Shepherd Dog. Blood vessels have decreased endothelial cells. Note subtle leukocytoclastic debris around some blood vessels at right (arrow), and ischemic pallor of collagen.

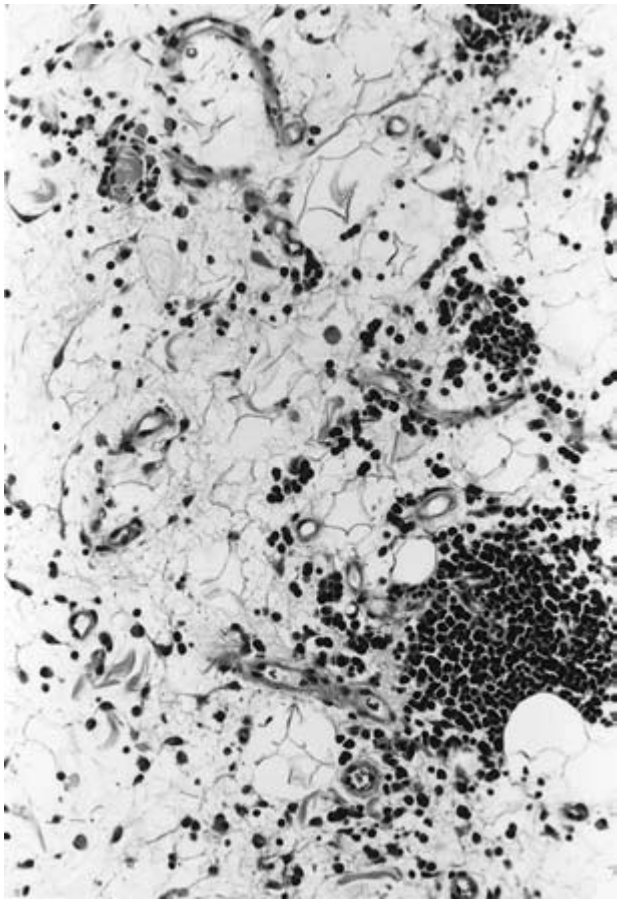


Fig. 10.19 Cell poor vasculitis in a dog. Many blood vessels have decreased endothelial cells; note microhemorrhage. Normal vessels for comparison are visible at bottom edge.



Fig. 10.20 Cell poor vasculitis in a dog with a chronically swollen hindleg. Small granulomas are forming around collagen fibers, most prominently at center (arrow).

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Evidence of cell poor vasculitis, or 'vasculopathy', often relies heavily on the recognition of ischemic changes in the skin (ischemic dermatopathy). These include pale-staining, mucinous, or 'smudged' collagen, and marked 'fading' atrophy of hair follicles (see Chapters 3 and 19). Interface dermatitis and mural folliculitis are often evident, and are likely further manifestations of the immunologic reaction occurring in the skin.

Cell poor vasculitis accompanies postrabies vaccination panniculitis in dogs (see Chapter 21). Affected vessels in the panniculus are often tightly cuffed by lymphocytes and plasma cells. Cell poor vasculopathy is evident in the overlying dermis as well; dermal lesions are identical to ischemic dermatopathy (see Chapter 3).

Cell poor vasculitis occurs in the clinical syndrome of chronic leg swelling; one author (T.L.G.) suspects a persistent reaction to deep rabies vaccination at this site. In addition to typical features of cell poor vasculitis, blood vessels of the deep dermis and superficial subcutis (panniculus) are often cuffed with lymphocytes, histiocytes, and variable plasma cells, as seen in classic postrabies vaccination panniculitis (see Chapter 21). This inflammation extends to the deep subcutis and there is generally severe diffuse edema. Lymphocytes and/or macrophages may surround collagen fibers to form small granulomas. The formation of these granulomas, which may be palisading in conformation, may be striking in some cases, and has been observed sporadically in other types of cell poor vasculitis (including classical canine familial dermatomyositis) as well as in typical postrabies vaccine panniculitis. This phenomenon is believed to represent an ischemic sequel to localized vascular disease, as described in humans (Magro et al., 1996).

Cell poor vasculitis encompasses a large clinical group of diseases. Few differential diagnoses exist, but it is important to correlate the findings of cell poor vasculitis with the appropriate clinical context, if possible. Neutrophilic immunologic vasculitis may be cell poor in chronic stages, but this form of vasculitis generally fails to induce the associated ischemic dermal and follicular changes observed with cell poor vasculitis. This may be due to the slow and gradual obliteration of vessels in cell poor vasculitis which permits more gradual effects of persistent hypoxia over time.

FAMILIAL CUTANEOUS VASCULOPATHY OF GERMAN SHEPHERD DOGS

Clinical features (Figures 10.21 and 10.22)

Familial cutaneous vasculopathy of German Shepherd Dogs is a rare vascular disease affecting predominantly the pawpads of puppies (Weir et al., 1994). Pedigree analysis indicates the likelihood of an autosomal recessive inheritance (Weir et al., 1994). The majority of published cases (26 dogs) have been seen in Canada. One case was from the United States, and a dog with similar symptomatology was reported from Italy (Weir et al., 1994; Fondati et al., 1998).



Fig. 10.21 Familial cutaneous vasculopathy of German Shepherd Dogs. Widespread ulceration occurs on swollen pawpads. (Photograph courtesy J. Declerq.)



Fig. 10.22 Closer view of ulcerated pads of the dog in Fig. 10.21. (Photograph courtesy J. Declerq.)

A hypersensitivity reaction involving immunologic attack on collagen has been hypothesized (Weir et al., 1994). Interestingly, a temporal association with multivalent puppy vaccine and recrudescence with repeat vaccination has been noted in some dogs, similar to Group 2 ischemic dermatopathy (see Chapter 3) (Weir et al., 1994). One author (T.L.G.) has seen identical lesions in the pawpads of a young Fox Terrier and Miniature Schnauzer, both of which had lesions of ischemic dermatopathy involving the muzzle and ears. The authors

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suspect that pawpad vasculopathy may be simply one manifestation of ischemic dermatopathy in some breeds (possibly overlooked in milder cases); vaccine association lends credence to that supposition.

The characteristic clinical feature is depigmented, swollen pawpads. Erosions and ulceration with adherent crusting occur. The pads may lose pigment prior to ulcerating. Although the pawpads are the predominantly affected tissues, similar lesions (as in other ischemic vascular diseases) may be present on the pinnae, tail tip, and nasal planum. Alopecia is noted around the pad margins and in other affected regions.

Lymphadenopathy is variable. Reported systemic signs include pain, lethargy, and pyrexia (Weir et al., 1994). Lethargy may be associated with pain on ambulation.

All reported cases to date have been in German Shepherd Dogs. However, the authors have recently observed an identical syndrome in a 5-month-old Fox Terrier and 7-month-old Miniature Schnauzer. Since these are two breeds that are affected with juvenile onset ischemic dermatopathy (Group 2; see Chapter 3), and since German Shepherd Dogs with this disorder may have other signs commensurate with juvenile onset ischemic dermatopathy, this suggests that pawpad involvement is simply a manifestation of juvenile onset ischemic dermatopathy that is most commonly seen in German Shepherd Dogs. Clinical signs first appear between 4 and 7 weeks of age (Weir et al., 1994). Sex predilections have not been noted.

Clinical differential diagnoses are few, as other vascular diseases do not predominantly affect the pawpads and do not have a predilection for young German Shepherd Dogs or puppies in general. Lesions compatible with this syndrome in a young German Shepherd Dog conceivably could be caused by septic vasculitis (for example, in conjunction with generalized demodicosis), disseminated intravascular coagulation, cryopathies, and frostbite.

Biopsy site selection

Biopsy of affected tissue near the margin of the pawpad is recommended, as pawpad biopsies can heal slowly, especially if there is vascular compromise. Marginal biopsy may provoke less pain.

Histopathology (Figures 10.23 and 10.24)

Parakeratosis and mild serocellular crusting accompany moderate acanthosis and variable ulceration. There is nodular to diffuse, superficial and deep dermatitis and panniculitis, with degenerate neutrophils intensely oriented around collagen (see Chapter 14). Leukocytoclastic debris may be abundant and there may be mild edema or fibrin exudation. Mild interface dermatitis has been described in depigmented lesions (Weir et al., 1994).



Fig. 10.23 Familial cutaneous vasculopathy in a Fox Terrier puppy, featuring nodular to diffuse inflammation of the skin of the mucocutaneous junction of the pawpad.

Vascular lesions are subtle in some cases, and may be best seen in arterioles of the deep dermis and panniculus. These have swollen endothelial cells and mural infiltration by lymphocytes, macrophages, and occasional neutrophils. As reported, vascular changes also may be seen in postcapillary venules as well as large arteries (Weir et al., 1994). Occasionally large numbers of neutrophils are seen murally (Weir et al., 1994).

Differential diagnoses relate predominantly to the diffuse dermatitis (see Chapter 14), as vascular lesions are subtle. Vascular inflammation of this type may be observed in several forms of cell poor vasculitis (see p. 247), but those vascular lesions do not occur in the context of diffuse dermatitis and panniculitis or with the prominent degenerate foci centered on collagen.

VASCULOPATHY OF GREYHOUNDS

(Synonyms: cutaneous and renal glomerular vasculopathy, 'Alabama rot', Greenetrack disease)

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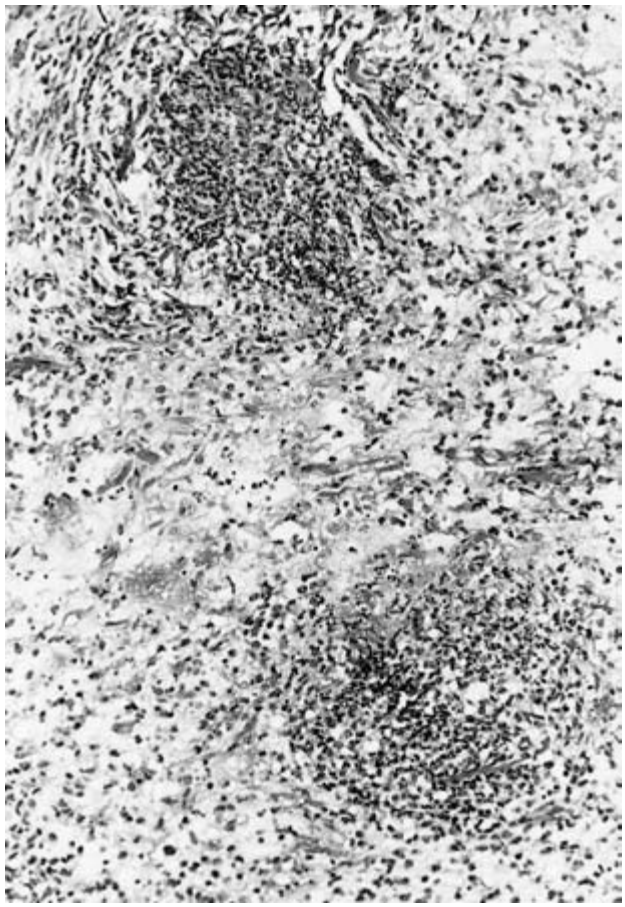


Fig. 10.24 Higher magnification of familial cutaneous vasculopathy in a 9-week-old German Shepherd Dog. Neutrophils are partially leukocytoclastic within nodular foci; note mild edema and fibrin.



Fig. 10.25 Early vasculopathy of Greyhounds. The groin is diffusely erythematous; these lesions precede sloughing of the skin. (Photograph courtesy S. Torres.)



Fig. 10.26 Closer view of the dog in Fig. 10.25. Diffuse erythema extends to the distal hindleg. (Photograph courtesy S. Torres.)

Clinical features (Figures 10.25 and 10.26)

Vasculopathy of Greyhounds is a highly characteristic regional cutaneous and renal disease that is observed almost exclusively in young adult Greyhounds from a racing environment (Carpenter et al., 1988; Cowan et al., 1997). A shiga-like toxin produced by *Escherichia coli* O157:H7 has been implicated in a similar renal disease in humans (hemolytic uremic syndrome) after ingestion of contaminated undercooked meat (O'Brien et al., 1993; Waters et al., 1994). Although skin lesions are uncommon in the human syndrome, a similar pathogenesis in the setting of breed predilection has been proposed for the canine disease, as racing Greyhounds in the United States are fed a diet composed predominantly of raw, condemned ground beef (Cowan et al., 1997).

Cutaneous lesions consist of coalescing well-demarcated deep ulcers. The earliest reported changes are areas of erythema that rapidly eventuate to dark red to black lesions; these slough, leaving deep ulcers (Cowan et al., 1997). The majority of the lesions occur on the legs. Ulcers are seen occasionally on the trunk or inguinal region, but not on the head or mucocutaneous junctions (Cowan et al., 1997). Most dogs exhibit seven to more than ten ulcers that range from 1 to 5 cm in diameter (Cowan et al., 1997). Usually, new lesions do not develop after the initial lesions begin to heal. Pitting edema of the distal leg is common. The associated renal glomerular vasculopathy varies in severity. Lethargy, malaise, fever, polydipsia, polyuria, vomiting, diarrhea, and acute renal failure may be noted to variable degrees in severely affected dogs (Cowan et al., 1997).

This syndrome has been observed predominantly in Greyhounds involved in the racing industry. Recently, this syndrome was also reported in a Great Dane (Rotermund et al., 2002). Most affected dogs are between 1 and 5

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years of age. Sex predilection has not been noted (Cowan et al., 1997).

Clinical differential diagnosis is not difficult, as vasculopathy of Greyhounds is highly distinctive clinically. Concomitant renal disease increases the clinical suspicion for this syndrome. If the geographic location is appropriate, venomous snakebite must be considered for cases with few ulcers.

Biopsy site selection

Multiple punch biopsy specimens should be obtained from newly developing lesions. Older ulcerative lesions are less likely to yield diagnostic results. Care should be taken not to biopsy the digits or lesions over joints or pressure points, as these regions may heal slowly.

Histopathology

As reported, skin lesions in vasculopathy of Greyhounds include thrombosis and necrosis of arterioles, venules, and capillaries (Carpenter et al., 1988). The vascular lesions often extend into the subcutis, where arteries are strikingly affected. Deep dermal and subcutaneous arteries show evidence of necrosis (pyknosis, karyorrhexis, and occasional fibrinoid necrosis). There is accompanying hemorrhagic infarction; the severity and depth of tissue destruction vary with the degree of vascular damage and the size and number of blood vessels affected. Hemorrhage, edema, and necrosis are associated with severe craterous, cavitating ulceration, often reaching to the subcutis. There is variable fibrosis in chronic lesions. Ulcer beds are covered by suppurative exudate containing colonizing staphylococci (Carpenter et al., 1988). Essentially identical lesions were reported in a Great Dane (Rotermund et al., 2002).

Differential diagnosis is uncomplicated if the breed affected is known and if concurrent renal glomerular pathology is present (Carpenter et al., 1988). Histologically, the severely infarcted lesions may suggest cryopathy or septic vasculitis (see pp. 243 and 238) if considered out of the clinical context.

PROLIFERATIVE THROMBOVASCULAR NECROSIS OF THE PINNAE

Clinical features (Figure 10.27)

Proliferative thrombovascular necrosis is an uncommon or underdiagnosed syndrome of unknown etiology that is seen in the dog. It is characterized by wedge-shaped devitalization and necrosis of the distal pinnae. Although Griffin first mentioned this syndrome in 1985, little additional information is available (Griffin, 1994). The characteristic proliferative changes in the small dermal arterioles may be difficult to find, leading to underdiagnosis.



Fig. 10.27 Proliferative thrombovascular necrosis of the pinnae in a dog. Swelling, erythema, discoloration, and exudation are present on the distal pinna. Note dark areas of necrosis at the tip of the pinna and at the extremity of a tortuous blood vessel. (Photograph courtesy I. Fillecia.)

Swelling, erythema, and discoloration of the center of the apex on the medial aspect of the pinnae is the initial clinical sign. Early lesions of erythema fail to blanch with diascopy (see introduction, p. 238) confirming the presence of dermal hemorrhage. As vasculopathy progresses, erosion and ulceration begin centrally and then extend in a wedge-shaped 'V' expanding peripherally in the direction of the ear tip (Griffin, 1994). Beginning at the ear tip, there may be necrosis and loss of tissue. In short-coated dogs or if the pinnae are clipped, trans-pinnal illumination with a powerful light source reveals lack of vascular supply distal to the initial area of necrosis. Mottled hypopigmentation occurs with chronicity. Although the lesions commonly occur bilaterally, unilateral involvement has been seen. The lesions are painful. Systemic signs are not evident. The syndrome is slowly progressive and chronic. Age, breed, or sex predilections have not been reported.

Clinical differential diagnosis should not be difficult as this syndrome is highly characteristic. However, appreciation of the distinctive lesions requires careful observation. Most other vasculopathic diseases affecting the pinnae should also affect other distal extremities such as the tail tip and the distal legs.

Biopsy site selection

Biopsy of the affected regions of the pinna is not easily accomplished. The pinna may be trimmed back to unaffected tissue under general anesthesia to provide surgical

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Fig. 10.28 Proliferative thrombovascular necrosis of the pinna with infarction in a dog. There is a central full-thickness defect containing hemorrhage and inflammatory debris; devitalized pale tissue is at top. Note thrombus in large vessel at lower right.

biopsy specimens as well as a clinical cure. Alternatively, a smaller margin of transitional tissue can be cut from the pinna under tranquilization.

Histopathology (Figures 10.28 through 10.30)

The walls of small dermal arterioles are thickened, often markedly. Concentric spindle cell proliferation is observed in some vessels while others are expanded due to acellular sclerosis. Fibrinoid degeneration is present, and fibrin thrombi may be seen. Vasculitis is not evident. Intimal and subintimal proliferation with infolding into the lumina is evident in fortuitous samples, but is not a uniform feature of random samples; some of these lesions may represent end stage recanalization of a previously thrombosed vessel.

There are secondary changes of ulceration, inflammation, hemorrhage, and dermal fibrosis. In severe lesions there may be total infarction of the distal pinna. Pinnal cartilage may be segmentally necrotic and may protrude through the ulcer defect. Neutrophils cluster within the ulcer bed and necrotic tissue. Melanophages and hemosiderophages are present in small to moderate numbers. Fibrosis extends loosely throughout the dermis, interspersed amongst affected vessels, and is not confined to the ulcer. A mixed infiltrate of neutrophils, lymphocytes, and plasma cells is present. Inflammation and fibrosis are more severe when secondary tissue damage is extensive, and may largely obscure underlying vascular lesions.

Differential diagnosis of proliferative thrombovascular necrosis is facilitated by the presence of typical proliferative changes of arterioles and the site affected. Chronic



Fig. 10.29 Higher magnification of Fig. 10.28 demonstrating an organizing thrombus within a dilated vessel; note necrosis and ulcer of adjacent epidermis. Hemorrhage is severe.

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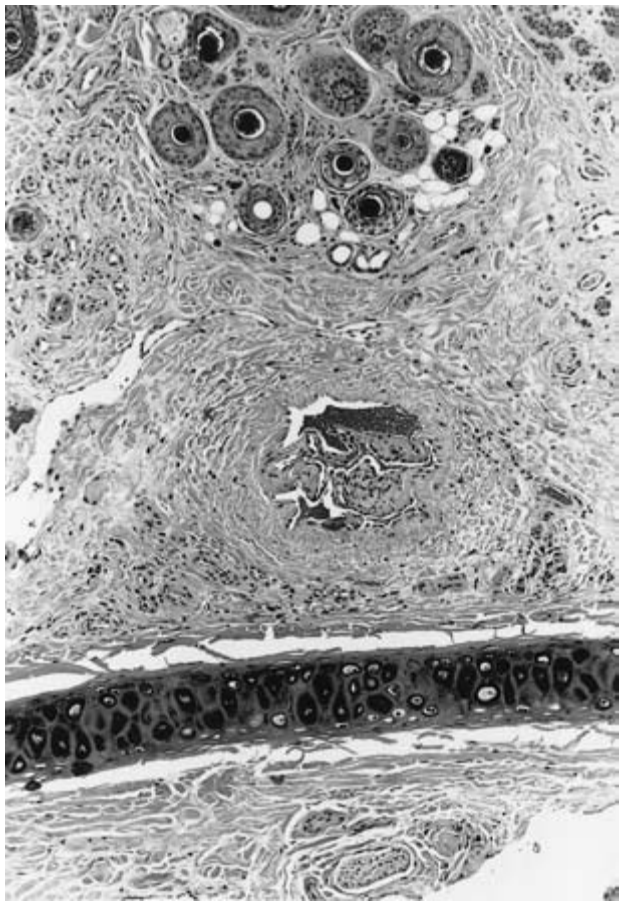


Fig. 10.30 Proliferative thrombovascular necrosis of the pinnae in a dog. The central vessel shows proliferative changes that are partially filling the lumen.

ulceration and fibrosis may obscure typical vascular lesions in some cases, making differentiation from external trauma difficult.

PROLIFERATIVE ARTERITIS OF THE NASAL PHILTRUM

(Synonym: arteritis of the nasal philtrum)

Clinical features (Figure 10.31)

Proliferative arteritis of the nasal philtrum is a rare and distinctive vascular disease affecting the nasal philtrum, details of which have been published to date in only five dogs (Torres et al., 2002). The etiology is unknown. However, since four of the five dogs were Saint Bernards and three of four were closely related, an inherited disorder is suspected (Torres et al., 2002). The authors have recently seen similar lesions in a Newfoundland.



Fig. 10.31 Proliferative arteritis of the nasal philtrum in a Saint Bernard. A well-demarcated deep ulcer is present in the center of the philtrum. (Photograph courtesy S. Torres.)

As reported, clinical features shared by all five dogs were solitary, well-demarcated linear ulcers affecting the nasal philtrum (Torres et al., 2002). Ulcers ranged in size from 3 to 5 cm in length, 2 to 15 mm in width, and 2 to 5 mm in depth. Adherent hemopurulent crusts were noted. All dogs experienced either mild or severe episodes of arterial hemorrhage from the ulcers. Other cutaneous or noncutaneous abnormalities were not noted (Torres et al., 2002).

Four of five dogs were Saint Bernards, and the fifth dog reported was a Giant Schnauzer (Torres et al., 2002). The authors observed a case in a 4-year-old Newfoundland. Large breed dogs may be predisposed. The syndrome is tardive in onset and affects adult dogs between 3 and 6 years of age (Torres et al., 2002).

Proliferative arteritis of the nasal philtrum is highly distinctive visually. The authors have not seen any other syndrome that causes solitary well-demarcated linear ulcers affecting the nasal philtrum. Skin biopsy confirms the diagnosis.

Biopsy site selection

Punch biopsy of the margin of the ulcer should be performed. A 4 mm biopsy punch is recommended, as larger biopsy sites of the planum nasale may not heal as readily.

Histopathology (Figures 10.32 and 10.33)

As reported by Torres et al. (2002) and recently observed in a Newfoundland, large, sometimes V-shaped ulcers are accompanied by subjacent necrosis, hemorrhage, and neutrophilic inflammation. There may be surface exudate. Peripheral to the ulcer, lymphocytes and plasma cells predominate, and there is subepidermal fibrosis and

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Fig. 10.32 Proliferative arteritis of the nasal philtrum. A large ulcer is covered by a large partially detached crust. The affected vessel is seen in the deep dermis (arrow).

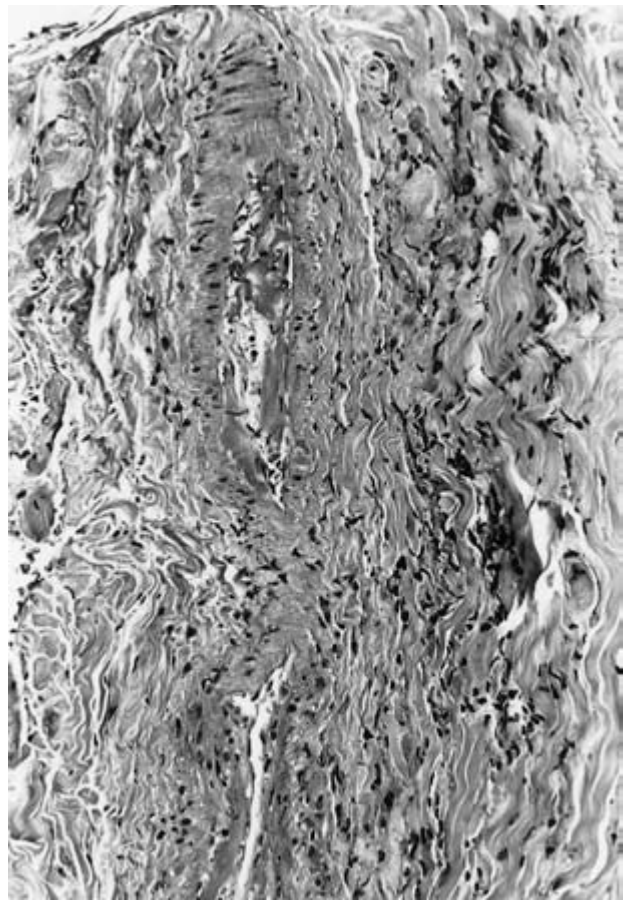


Fig. 10.33 Higher magnification of the blood vessel in Fig. 10.32. There is homogeneous subintimal material intermingled with a few spindle cells. Note narrowing of the lumen.

pigmentary incontinence. The epidermis bordering the ulcer is severely hyperplastic and parakeratotic, and demonstrates exocytosis of neutrophils and lymphocytes.

Deep dermal arteries and arterioles beneath the ulcer show distinctive subendothelial intimal proliferation of spindle cells. Amongst the spindle cells is prominent extracellular mucinous collagenous matrix, which reportedly stained blue with alcian blue stain (pH not given) and blue with Masson's trichrome stain for collagen (Torres et al., 2002). The proliferative changes result in marked intimal thickening and variable stenosis of the affected vessels. Spindle cells are positive for smooth muscle actin and vimentin, and occasionally positive for desmin, consistent with myofibroblastic or smooth muscle origin (Torres et al., 2002). Although 'arteritis' is not a consistent or profound feature, and was not seen in the Newfoundland observed, some affected vessels reportedly have mural hemorrhage, neutrophilic and lymphocytic inflammation, and leukocytoclastic debris of probable neutrophilic origin (Torres et al., 2002).

The histologic findings of proliferative arteritis of the nasal philtrum are striking. There are some similarities to proliferative thrombovascular necrosis of pinnae; however, thrombi, mural fibrinoid degeneration, and acellular sclerosis are not features of proliferative arteritis. Knowledge of site affected, which is usually apparent in the section (aural cartilage and haired skin of the pinna versus non-haired skin of the planum), also will allow differentiation.

SOLAR VASCULOPATHY

Clinical features (Figures 10.34 and 10.35)

Solar vasculopathy is an uncommon but probably underdiagnosed canine skin disease of suspected solar and immunologic cause. Solar vasculopathy may be an important feature of cases previously clinically diagnosed with canine 'nasal solar dermatitis'. However, the subtlety of vascular lesions may have led to a lack of recognition of solar vasculopathy in the past.

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Fig. 10.34 Solar vasculopathy affecting the dorsal and lateral muzzle, planum nasale, and lips of a Doberman Pinscher. Mottled loss of pigmentation, erythema, and crusting are present. (Photograph courtesy A.G. Cannon.)



Fig. 10.35 Closer view of the dog in Fig. 10.34. Bilateral symmetry of the lesions on the dorsal muzzle and planum nasale is marked; note erosions. (Photograph courtesy A.G. Cannon.)

Solar vasculopathy may occur in either naturally lightly or nonpigmented skin, or in previously pigmented skin that has become depigmented. More specifically, the syndrome may be seen in conjunction with underlying depigmenting diseases, such as discoid lupus erythematosus or vitiligo. Some cases occurring in naturally lightly pigmented or nonpigmented skin have been linked temporally to adverse chemical reactions that may be photoactivated (photoactivated vasculitis).

Solar vasculopathy is characterized clinically by variable degrees of erythema, swelling, exudation, crusting, alopecia, erosion, and ulceration. Well-demarcated erythematous plaques may develop and coalesce. Scarring occurs with chronicity. Lesions blanch partially or not at all with diascopy (see introduction, p. 238). Skin disease is restricted to sparsely haired or nonhaired, nonpigmented, sun-exposed skin. As adjacent regions lose pigmentation and hair due to inflammation, newly exposed skin becomes affected. The dorsal muzzle and planum nasale are preferentially affected sites. Pruritus and pain may be seen with chronic lesions. Solar vasculopathy may accompany and complicate discoid lupus erythematosus or other depigmenting diseases.

Breed, age, or sex predilections are not available. Breeds at risk for depigmenting diseases, such as discoid lupus erythematosus, are likely at increased risk. Additionally, breeds with lightly pigmented skin and sparse hair coats may be preferentially affected.

Clinical differential diagnoses include discoid lupus erythematosus, systemic lupus erythematosus, pemphigus foliaceus, pemphigus erythematosus, ischemic dermatopathy/canine dermatomyositis, and infectious follicular diseases such as dermatophytosis, demodicosis, and bacterial pyoderma. However, since discoid lupus erythematosus can coexist with solar vasculopathy and the two diseases may complicate each other, all dogs suspected of having either disease should be biopsied. Solar vasculopathy is a more likely diagnosis in dogs exhibiting the triad of lack of pigmentation, sparse hair coat, and solar exposure. Lesions should not extend into surrounding normally pigmented skin or planum nasale.

Biopsy site selection

Multiple punch biopsy specimens should be obtained from nonulcerated affected sites. If the planum nasale and adjacent skin are affected, both regions should be sampled.

Histopathology (Figures 10.36 through 10.38)

The epidermis is variably acanthotic and may be eroded or ulcerated. Scattered shrunken, eosinophilic, presumptively apoptotic keratinocytes may be present. Degenerate keratinocytes may be true 'sunburn' cells, or may result from ischemia due to underlying vasculopathy.

Superficial blood vessels have thickened, smudged, or sclerotic walls. There may be endothelial swelling or loss of endothelia. Neutrophils cluster around and occasionally within the wall of blood vessels, and mild leukocytoclasia (fragmentation of neutrophilic nuclei indicative of vascular damage and inflammation) usually is evident. Lymphocytes and macrophages are intermingled. Hemorrhage may be observed. The inflammatory, leukocytic process 'spills over' to the adjacent basement membrane where neutrophils and their fragments are distributed, often sparsely but occasionally more intensely, just beneath and along the membrane. There is accompanying

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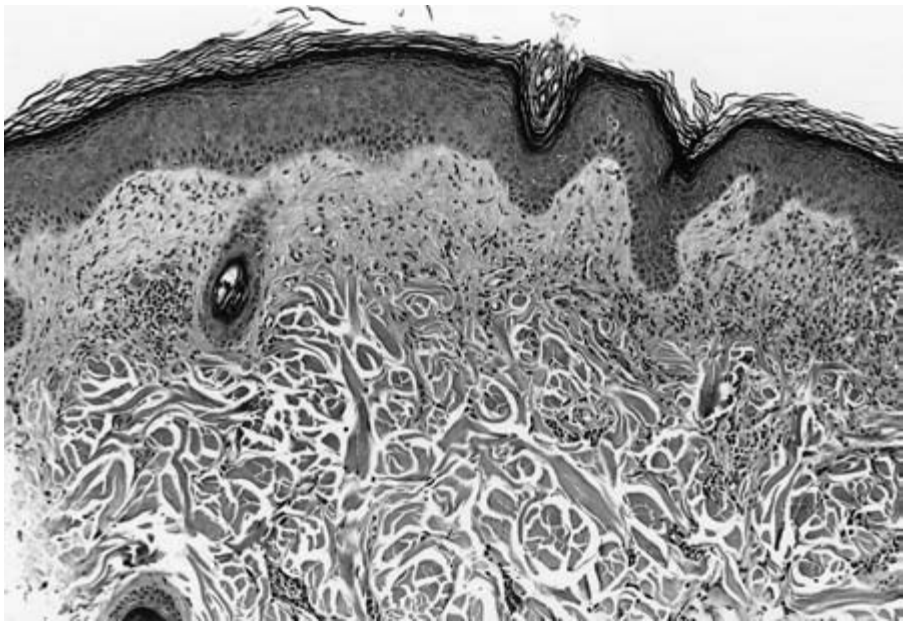


Fig. 10.36 Solar vasculopathy in a white Boxer. Note sclerotic, pale appearance of superficial dermal collagen.

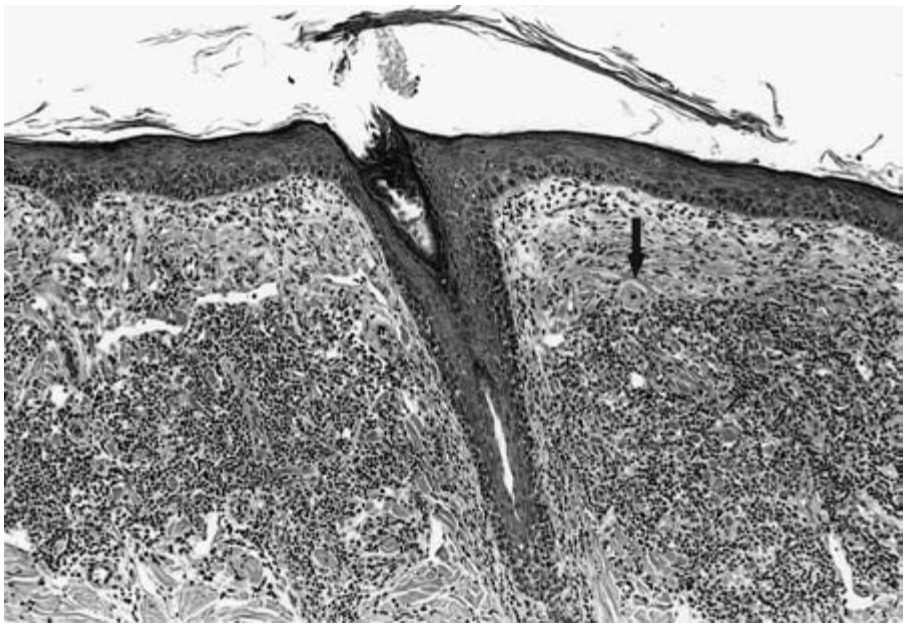


Fig. 10.37 Solar vasculopathy in the clinical setting of discoid lupus erythematosus. A superficial hypocellular zone of altered collagen is subtended by a lichenoid band of inflammation. Note sclerotic blood vessels (arrow).

fibrin deposition in the basement membrane region, and the basement membrane zone may be smudged or poorly defined. Scattered basal cell degeneration and vacuolation often are observed. Theoretically, low oxygen tension due to vascular damage may result in secondary degeneration of the basement membrane zone. Alternatively, the inflammatory process may target vessels and the basement membrane zone alike.

The superficial dermis is pale and hypocellular in appearance. Superficial dermal collagen may appear wispy, homogeneous, and sclerotic, or mucinous and edematous, similar to ischemic dermatopathy (see Chapter 3). This creates a superficial laminar zone of pallor. Solar elastosis may be present (see Chapter 15) and may abut the basement membrane. Older lesions show laminar superficial dermal fibrosis, which may represent concurrent solar fibrosis (see Chapter 15) and/or may be the result of local ischemic damage. Lymphocytes, histiocytes, and plasma cells are variable and may extend around adnexal appendages. If occurring in the context of discoid lupus erythematosus, the superficial dermal zone of pallor may be subtended by lichenoid and periadnexal inflam-

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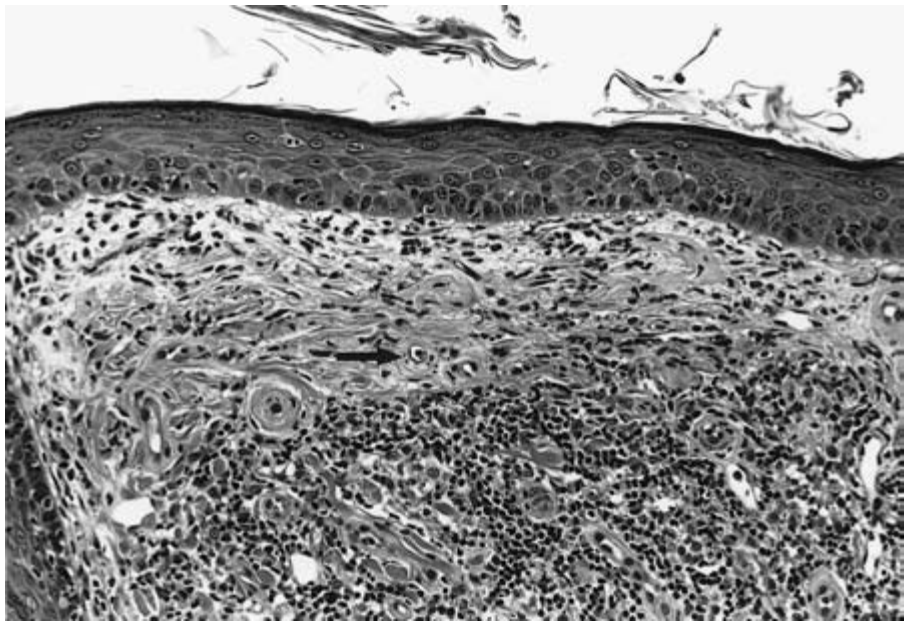


Fig. 10.38 Higher magnification of Fig. 10.37 demonstrating sclerotic blood vessels. Leukocytoclastic debris is present subtly within some affected vessels (arrow) as well as just below the basement membrane.

mation of that condition (see Chapter 11), creating a two-toned effect of light over dark.

Differential diagnosis of solar vasculopathy may be difficult because superficial vascular changes often occur in the milieu of an underlying inflammatory depigmenting disease, such as discoid lupus erythematosus. The lesions are somewhat similar to cell poor vasculitis of ischemic dermatopathy (see p. 247); however, the vascular and ischemic changes of solar vasculopathy are very superficial and consistently are associated with neutrophilic inflammation. Neutrophilic immunologic vasculitis (see p. 244) should not have accompanying ischemic changes of the collagen, nor elastosis or fibrosis. The clinical context is important in the definitive diagnosis of solar vasculopathy.

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Chapter 11

Lichenoid diseases of the dermis

Lichenoid diseases of the dermis are characterized by dense superficial band-like or laminar dermal inflammation that is oriented just beneath the dermal–epidermal junction. The terms 'lichenoid' and 'interface' are often used interchangeably by others.

For descriptive clarity, the authors prefer to define interface dermatitis as mild, superficial dermal inflammation that is oriented tightly to and often obscures the dermal–epidermal junction. Basal cell damage is a consistent feature of interface dermatitis. Interface dermatitides are discussed in Chapter 3. In contrast, lichenoid inflammation may occur with or without interface change; lichenoid inflammation with interface damage may be termed 'lichenoid-interface'. Lichenoid inflammation without interface change often evolves from a perivascular pattern; both patterns are generally evident in tissue.

Lichenoid dermatitides often have a persistent immunologic reaction as their proven or proposed pathogenic mechanism. Lichenoid dermatitis (generally with interface change) occurs in the context of several autoimmune skin diseases, for example (see Chapter 3). Lichenoid dermatitis without interface change may be most common at or near mucocutaneous junctions. Histopathologic differentiation of the diseases of this group often will depend upon differences in any epidermal lesions, as well as variation in the composition of the dermal infiltrate.

MUCOCUTANEOUS PYODERMA

Clinical features (Figures 11.1 and 11.2)

Mucocutaneous pyoderma is a relatively uncommon syndrome characterized clinically by erythema, swelling, and adherent crusts around mucocutaneous junctions (Ihrke & Gross, 1995). Mucocutaneous pyoderma affecting the lips and perioral skin is clinically highly distinctive, but at other sites is considerably less so.

Problems occur in the melding of clinical and histopathologic classifications of mucocutaneous pyoderma. The histopathologic features are nonspecific, and a diagnosis of mucocutaneous pyoderma may be applied inappropriately by pathologists. For example, chronic secondary bacterial inflammation that occurs as a sequel to ulceration of the planum nasale caused by diseases such as discoid lupus erythematosus or pemphigus foliaceus is histopathologically identical to mucocutaneous pyoderma. Mucocutaneous pyoderma and bacterial intertrigo (skin-fold pyoderma) are clinically distinct from each other; lesions of mucocutaneous pyoderma do not originate in and are not confined to folded skin. However, bacterial intertrigo also shares histopathologic features with mucocutaneous pyoderma.

Intertrigo is a relatively common, usually minor inflammatory disease that develops as a result of deep, tightly apposed skin folds that create a moist, warm environment allowing retention of secretions or excretions and intense surface bacterial overgrowth which initiates inflammation. *Malassezia* may contribute to this inflammation. Bacterial intertrigo most commonly affects the lip folds, but also can affect deep facial folds, perivulvar folds and tail folds. Bacterial intertrigo rarely extends beyond the intertriginous zone formed by the anatomic 'defect' leading to the skin fold. Clinical diagnosis is uncomplicated; lesions are rarely biopsied.

The pathogenesis of mucocutaneous pyoderma is not understood. Response to combined systemic and topical antibacterial therapy supports the role of bacterial infection in the etiology of the disorder. However, response to antibacterial therapy is often slow, and repetitive relapses are common. The authors speculate that mucocutaneous pyoderma may have a more complex immunologic pathogenesis.

Classically, mucocutaneous pyoderma of the lips and perioral skin is characterized by erythema, swelling, and crusting. Crusts entrap hairs. Affected lips become markedly erythematous and uniformly swollen. The lateral commisures frequently are severely affected. Fissuring, erosion and ulceration with adherent crusting may occur in more severe cases. Depigmentation of the lips can occur with chronicity and may be clinically striking. Salivary staining may be present surrounding the lip lesions,

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Fig. 11.1 Mucocutaneous pyoderma in a Brittany. Note erythema, swelling, and crusting involving the lips and adjacent skin of the muzzle. Salivary staining is present on the haircoat ventral to the lower lip.



Fig. 11.2 Closer view of the dog in Fig. 11.1. Swelling is extensive where the upper canine tooth contacts the lower lip. Inflammatory debris mats the hair surrounding the lesions.

and tenacious exudate may mat surrounding hair. Lip and perioral lesions commonly are bilaterally symmetric. The adjacent philtrum also may be affected. Pruritus is mild to moderate, and pain may be present. Affected dogs may rub their faces on carpeting or furniture. Dogs with more severe lesions resent palpation. Mild odor may be present. Regional lymphadenopathy may be present.

Similar, but less distinctive lesions can affect the planum nasale, prepuce, and perianal region. The mucocutaneous junction of one or both nares of the planum nasale may be affected, creating fissuring with adherent keratinous crusts. Somewhat surprisingly, bilateral symmetry is not seen in lesions involving the nares. Bacterial involvement secondary to other inflammatory diseases affecting the planum nasale can create antibiotic-responsive lesions that are identical histopathologically but clinically dissimilar to mucocutaneous pyoderma.

German Shepherd Dogs and their related crossbreeds may be at increased risk (Ihrke & Gross, 1995). Age or sex predilections have not been noted.

Canine mucocutaneous pyoderma affecting the lips and perioral skin is visually distinctive. Possible clinical differential diagnoses include early discoid lupus erythematosus, advanced lipfold intertrigo, localized demodicosis, zinc-responsive dermatosis, and early lesions of generic dog food skin disease. The swelling of the lips seen with mucocutaneous pyoderma is not a clinical feature of canine discoid lupus erythematosus. In discoid lupus erythematosus, partially bilaterally symmetric lesions usually are present on the dorsum of the muzzle and the planum nasale. Perioral demodicosis generally is seen in younger dogs and has a more rapid onset.

Lipfold pyoderma also may mimic (and can accompany) mucocutaneous pyoderma. Lesions of lipfold pyoderma are confined to a triangular fold on either side of the lower lip; lipfold pyoderma is seen primarily in spaniels.

Biopsy site selection

Areas of inflammation and crusting without ulceration are recommended sites for biopsy. Punch biopsies no larger than 6 mm are preferred to minimize scarring in visible mucocutaneous regions.

Histopathology (Figures 11.3 and 11.4)

The epidermis or mucosal epithelium is hyperplastic. There is exocytosis of lymphocytes with variable spongiosis. These changes extend to superficial hair follicles. There may be scattered brightly eosinophilic, shrunken keratinocytes, consistent with apoptosis, usually above the basal cell layer. Variable, often severe neutrophilic serocellular crusting is observed in lesions complicated by self-trauma, erosion, or ulceration. Neutrophils may migrate in large numbers through the damaged epidermis to form superficial exudative crusts, sometimes subtended or capped by parakeratosis.

The dermis contains a perivascular to lichenoid infiltrate. Perivascular orientation often is seen in milder or peripheral lesions, but has been observed occasionally in severely exudative and ulcerated lesions as well. The infiltrate is composed predominantly of plasma cells, and there are mixtures of lymphocytes, neutrophils, and macrophages. Eosinophils may be observed in some cases. There is close approximation to the overlying epidermis by the inflammatory infiltrate, but the dermal–epidermal interface is not obscured. Blood vessels may be dilated. Pigmentary incontinence may be mild to severe. If speci-

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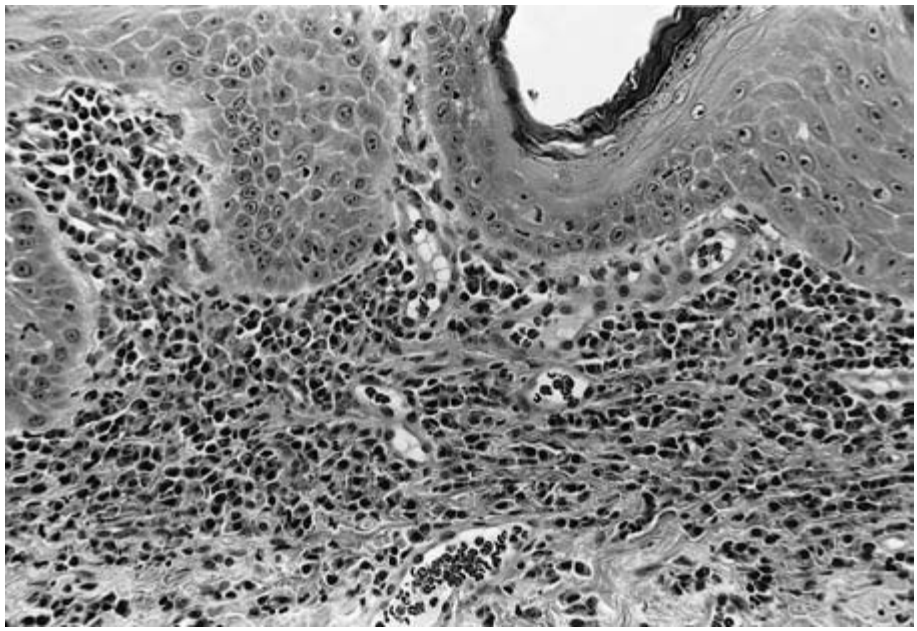


Fig. 11.3 Mucocutaneous pyoderma. A lichenoid band of inflammation in the superficial dermis contains prominent plasma cells.

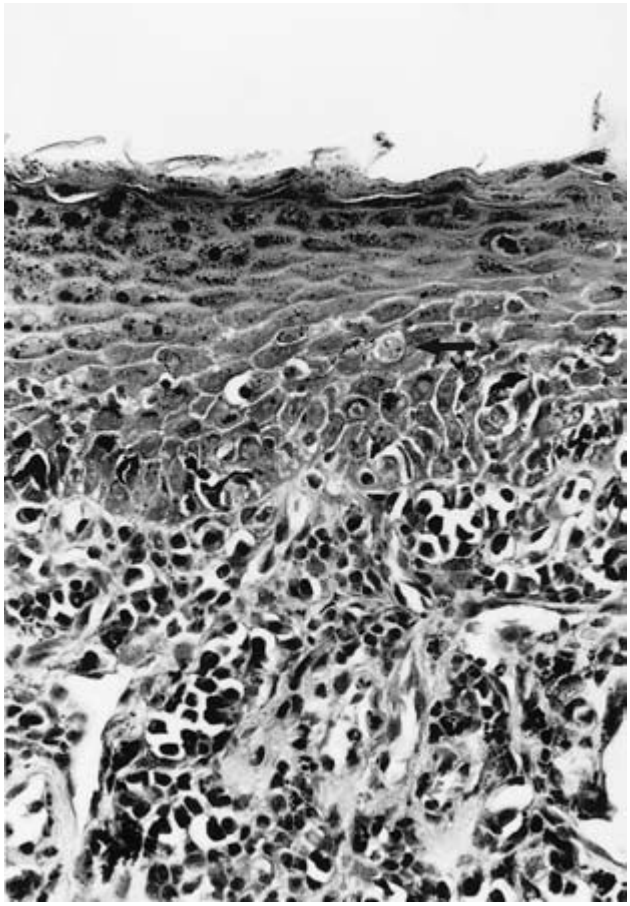


Fig. 11.4 Higher magnification of mucocutaneous pyoderma, demonstrating plasma cells in the superficial dermal infiltrate; note apoptotic keratinocytes (arrow).

mens are obtained from haired skin, similar inflammation often surrounds subjacent adnexal appendages. In some lesions the superficial dermal and periadnexal inflammation is confluent, creating a continuous and deep lichenoid band to the level of the deep adnexal dermis.

Chronic inflammation of any mucocutaneous junction (as observed in mucous membrane pemphigoid, facial pemphigus foliaceus, discoid lupus erythematosus, etc.) may have features similar to mucocutaneous pyoderma. This may be due to the stereotypic response of these regions to persistent antigenic stimuli such as from chronic bacterial infection. Primary lesions such as subepidermal clefting in mucous membrane pemphigoid, acantholytic pustules in facial pemphigus foliaceus, and basal cell degeneration in discoid lupus erythematosus should allow differentiation, but these may be lacking or subtle in chronic lesions. Clinical differentiation may be required.

Intertrigo (skinfold pyoderma) that is located near mucocutaneous junctions (lip fold and vulvar fold) is histopathologically identical to mucocutaneous pyoderma. Clinical separation of these entities is needed.

DISCOID LUPUS ERYTHEMATOSUS

Clinical features (Figures 11.5 and 11.6)

See Chapter 3.

Biopsy site selection

See Chapter 3.

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Fig. 11.5 Discoid lupus erythematosus in a Border Collie. Depigmentation, ulceration, and crusting involve only the planum nasale.

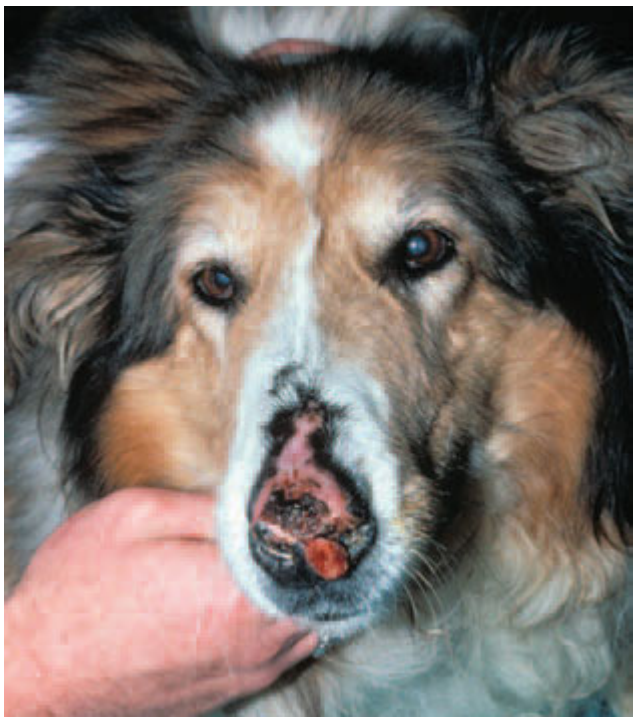


Fig. 11.6 Chronic, severe discoid lupus erythematosus in a Collie. Depigmentation, ulceration, and crusting affect the dorsal muzzle as well as the planum nasale. Severe tissue necrosis has altered the conformation of the planum nasale.

Histopathology (Figure 11.7)

Epidermal lesions of discoid lupus erythematosus (DLE) have been discussed previously (see Chapter 3). These principally include interface basal cell degeneration (apoptosis) and deposition of immunoglobulin and often complement at the basement membrane zone.

The dermis usually has a moderate lichenoid inflammatory infiltrate that includes lymphocytes, macrophages, plasma cells, and fewer neutrophils. Mild interface change features basal cell degeneration and inflammation that obscures the dermal–epidermal interface; this combined pattern is best termed 'lichenoid-interface'. In haired skin there is often a nodular pattern of inflammation around hair follicles and adnexal glands. Pigmentary incontinence usually is present and reflects loss of melanin by damaged basal cells and its incorporation into macrophages in the superficial dermis. Plasma cells may be prominent if lesions from the lip are examined or if lesions are long-standing and/or chronically ulcerated; these lesions resemble mucocutaneous pyoderma (see p. 261). There may be exocytosis of lymphocytes into the overlying epidermis. Neutrophils are variable and their numbers reflect the degree of overlying epidermal erosion or ulceration and superficial crusting.

In putative chronic lesions, there may be a zone of superficial laminar hypocellularity with or without laminar fibrosis and/or edema. This is subtended by a deeper zone of otherwise typical lichenoid inflammation. Fibrosis may be severe in some lesions, preventing hair regrowth (cicatricial alopecia). Superficial neutrophilic vasculitis and fibrinoid vasculopathy may be present in these hypocellular regions, suggesting secondary solar vasculopathy in the face of chronic depigmentation and alopecia (see Chapter 10). Squamous cell carcinoma arising in chronically depigmented lesions of DLE also has been reported (Scott & Miller, 1995).

Increased intraepithelial and intradermal mucin deposition (acid mucopolysaccharide) was demonstrated in dogs with DLE over dogs with other skin diseases (Rosenkrantz et al., 1986). Caution in the use of mucin deposition as a diagnostic aid is advised; strict adherence to the pH requirements of routine mucin stains (Alcian blue at pH 2.5) is critical. In addition, other inflammatory skin diseases may show significant mucin deposition, and thus mucinosis may not be diagnostically specific.

Differential diagnoses for the lichenoid inflammation of DLE include mucocutaneous pyoderma and Vogt–Koyanagi–Harada-like syndrome. Chronic inflammation of mucocutaneous junctions, such as occurs in DLE, may have features of mucocutaneous pyoderma. This may be due to the stereotypic response of these regions to persistent antigenic stimuli such as from secondary bacterial infection. Plasma cells usually are not as prominent in DLE as they are in mucocutaneous pyoderma, but differentiation may be difficult for chronic lesions of DLE in which plasma cells predominate and basal cell degeneration is less obvious. Basal cell degeneration, as usually seen in DLE, is rare in mucocutaneous pyo-

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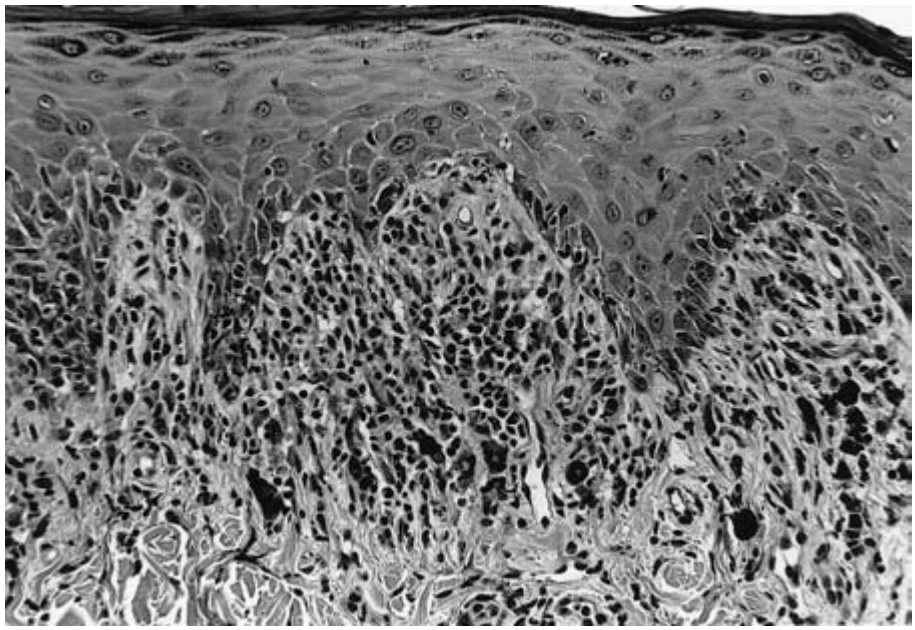


Fig. 11.7 Canine discoid lupus erythematosus with lichenoid infiltrate and pigmentary incontinence; note mild interface degeneration of basal cells.



Fig. 11.8 Pemphigus foliaceus in a dog. Intact vesicopustules span multiple hair follicles on the elbow. Note the asymmetrical shape of the vesicopustules.

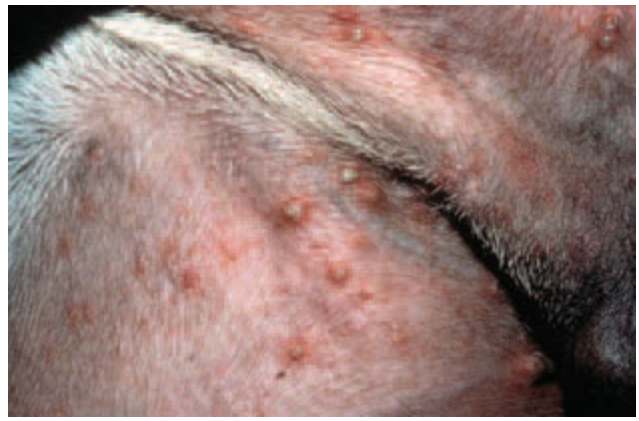


Fig. 11.9 Pemphigus foliaceus in a dog. Intact and ruptured asymmetric pustules are present on the neck.

derma and Vogt–Koyanagi–Harada-like syndrome. Vogt–Koyanagi–Harada-like syndrome generally will have a greater preponderance of large macrophages in the dermal infiltrate than will DLE. Finer melanin granulation is seen within macrophages in Vogt–Koyanagi–Harada-like syndrome in comparison to the heavy clumping of melanin usually observed in DLE.

PEMPHIGUS FOLIACEUS

Clinical features (Figures 11.8 and 11.9)

See Chapter 1.

Biopsy site selection

See Chapter 1.

Histopathology (Figure 11.10)

Epidermal lesions have been described (see Chapter 1) and are principally those of superficial epidermal pustulation with acantholysis, and intercellular deposition of immunoglobulin and often complement.

In some lesions of pemphigus foliaceus (PF), particularly those from the face and mucocutaneous junctions, a lichenoid infiltrate of lymphocytes, macrophages, and plasma cells is present. Eosinophils are generally observed. Inflammation may partially obscure the

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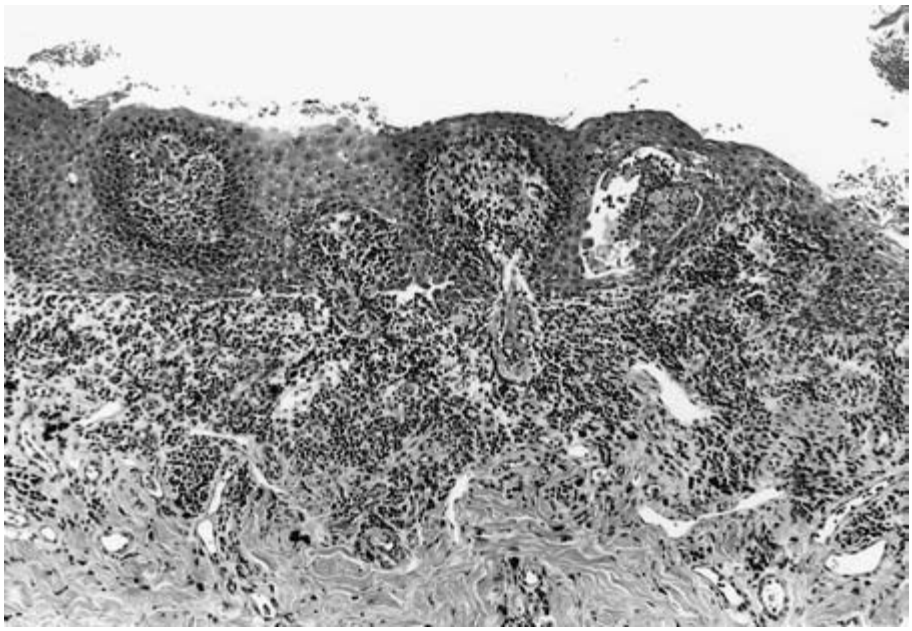


Fig. 11.10 Lichenoid inflammation in canine pemphigus foliaceus. Note intraepidermal pustule with acantholytic cells to right of center.

dermal–epidermal interface, but basal cell degeneration is absent to rare. Pigmentary incontinence is mild to moderate. Inflammation extends in a nodular pattern around subjacent adnexal appendages.

Lichenoid inflammation is most likely a reflection of anatomic location rather than a specific feature of PF; chronic lesions of the planum as in mucocutaneous pyoderma and discoid lupus erythematosus also feature similar lichenoid dermatitis. This may be due to the stereotypic response of these regions to persistent antigenic stimuli such as from bacterial infection. Thus, biopsy specimens from nonpustular facial lesions of PF may yield a false diagnosis for those entities. Eosinophils may be more consistently present in the dermal inflammation of facial PF than in discoid lupus erythematosus, and discoid lupus erythematosus should feature more interface damage than PF. Clinical differentiation may be of benefit in these cases.

The histopathologic lesions, including lichenoid dermatitis, that are observed in facial lesions of PF are similar to those of pemphigus erythematosus. Pemphigus erythematosus features interface dermatitis, as would be expected with pemphigus–lupus crossover disease (see Chapter 3). Without confirmatory immunologic findings, assignment of a diagnosis of pemphigus erythematosus to facially-predominant PF may be difficult. Adherence to the immunologic criteria of pemphigus erythematosus requires that the diagnosis be made only when immunohistochemical or immunofluorescence testing is compatible and when other clinical testing is supportive (positive antinuclear antibody [ANA] test). The principal method of differentiation is through immunofluorescence or immunohistochemical techniques; pemphigus erythematosus exhibits deposition of immunoglobulin along the basement membrane in addition to the typical intercellular deposition of PF.

VOGT–KOYANAGI–HARADA-LIKE SYNDROME

(Synonyms: VKH, uveodermatologic syndrome)

Clinical features (Figures 11.11 through 11.13)

Vogt–Koyanagi–Harada-like syndrome (VKH) is a rare canine disease of probable autoimmune etiology. It is characterized by concurrent granulomatous uveitis and symmetric facial depigmenting skin disease (Bussanich et al., 1982; Kern et al., 1985). Both cell-mediated hypersensitivity and antibodies directed against melanin and related proteins have been demonstrated in humans with VKH (Yamaki et al., 2002). Similar mechanisms have been postulated for the dog. Although similar, substantial differences occur between the human and canine disease (MacDonald, 1993). In humans, a meningoencephalitic phase precedes an ophthalmic–auditory phase (uveitis, deafness, dysacousia) and the final convalescent, or dermatologic phase (Mosher et al., 1999; Ortonne et al., 2003). In dogs, clinical signs compatible with a meningoencephalitic phase are rarely reported (Scott et al., 2001); ophthalmic disease and dermatologic disease both commonly occur, although skin lesions usually occur later in the course of the disease. Deafness has not been documented in the dog; dysacousia could go unnoticed.

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Fig. 11.11 Vogt–Koyanagi–Harada-like syndrome in an Alaskan Malamute. Partially bilaterally symmetric leukotrichia and vitiligo are accompanied by erythema, crusting, and alopecia.



Fig. 11.12 Closer view of periorbital area of the dog in Fig. 11.11. Note swelling, and squinting indicative of uveitis-associated photophobia.

Ophthalmic signs include anterior and posterior uveitis manifested clinically by photophobia, blepharospasm, conjunctival inflammation, and corneal edema. Since blindness may occur if treatment is not expeditious and aggressive, the ophthalmologic component of the disease usually holds far greater portent than the cutaneous component. Skin disease may be largely asymptomatic and is predominantly cosmetically disfiguring. Consequently, diagnosis of the skin disease bears greatest importance as a marker for the ophthalmologic disease.



Fig. 11.13 Closer view of the muzzle of the dog in Fig. 11.11. Diffuse erythema and crusting are present. The depigmented lips were uniformly black prior to the onset of disease.

Bilaterally symmetric facial leukoderma and leukotrichia are accompanied by variable erythema and crusting. Alopecia is less common. The dorsal muzzle, periorbital region, planum nasale, and lips are the predominant sites of involvement. Male dogs commonly have scrotal lesions and female dogs may have vulvar lesions. Lesions also may be seen on the pawpads, perianally, and on the pinnae. Claw disease with onychomadesis was reported in one Siberian Husky (Tachikawa et al., 1995). Depigmentation, erythema, and erosion may occur in the oral cavity, especially on the palatal vault (Vercelli & Taraglio, 1990). On rare occasion, depigmentation of the skin and haircoat may become generalized (Campbell et al., 1986; Herrera & Duchene, 1998). Pruritus is variable but may be marked. Regional lymphadenopathy is common. Photoaggravation of skin lesions has been observed.

Akitas, Samoyeds, Siberian Huskies, Alaskan Malamutes, Chow Chows, and their related mixed breeds are at increased risk. Vogt–Koyanagi–Harada-like syndrome also has been seen in the Shiba Inu, Shetland Sheepdog, white German Shepherd Dog, Old English Sheepdog, Irish Setter, and Dachshund, as well as a number of other breeds. The syndrome may be seen most frequently in dogs between 6 months and 6 years of age (MacDonald, 1993). Sex predilection has not been noted.

Vogt–Koyanagi–Harada-like syndrome clinically most closely resembles other facially-oriented autoimmune skin

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diseases (discoid lupus erythematosus, systemic lupus erythematosus, pemphigus foliaceus, and pemphigus erythematosus), epitheliotropic lymphoma, and vitiligo. If VKH is suspected, a complete ophthalmologic examination should be performed immediately. An anti-nuclear antibody (ANA) test will aid in ruling out systemic lupus erythematosus and pemphigus erythematosus. Skin biopsy will allow differentiation from the above-mentioned differential diagnoses.

Biopsy site selection

Areas of depigmentation, erythema, and scaling, preferably of recent development, are beneficial sites for skin biopsy. The lips and dorsal muzzle are preferred sites, since periocular biopsy may lead to distortion of the eyelid. Secondarily infected or self-traumatized lesions should be avoided.

Histopathology (Figures 11.14 through 11.16)

The epidermis is acanthotic and there may be secondary superficial crusting with variable erosion or ulceration. There may be mild parakeratosis in mounds. Melanin in the basal layer may be decreased or absent in chronic lesions; decreased numbers of epidermal melanocytes have been reported (Kern et al., 1985). Exocytosis of mononuclear cells may be evident, and neutrophils may migrate transepidermally into areas of epidermal damage and crusting. Basal cell degeneration (apoptosis) is rare. Lymphocytic infiltration of the dorsal claw fold epithelium was reported in a dog that had sloughing of the claws in conjunction with confirmatory clinical and histopathological lesions of VKH syndrome (Tachikawa et al., 1995).

In early lesions, dermal inflammation is pronounced and is characterized by perivascular to dense lichenoid inflammation that lies immediately subjacent to the epidermis, touching but only occasionally obscuring the overlying basal cell layer. Inflammatory cells consist of large, often pale macrophages and fewer neutrophils, lymphocytes, and plasma cells. Macrophages often contain very fine, dust-like, granular melanin pigment. Coarsely clumped melanin also may be observed. Occasionally there may be similar inflammation in a nodular pattern around adnexa; this pattern may predominate in some lesions. Chronic lesions of VKH may show only minimal dermal inflammation in the face of decreased or absent epidermal melanin.

Lichenoid inflammation of VKH must be differentiated principally from discoid lupus erythematosus. The predominance of large macrophages and the finely granular appearance of the engulfed melanin pigment are key differentiating features from discoid lupus erythematosus. In addition, basal cell apoptosis is typical of discoid lupus erythematosus, but rare in VKH. Periadnexally predominant lesions may be confused with sterile granuloma and pyogranuloma syndrome (see Chapter 13) or with leishmaniasis (see Chapter 12). Caution is advised, as failure to diagnose VKH may result in untreated sight-threatening uveitis. Correlation with clinical findings may be critical in these cases.

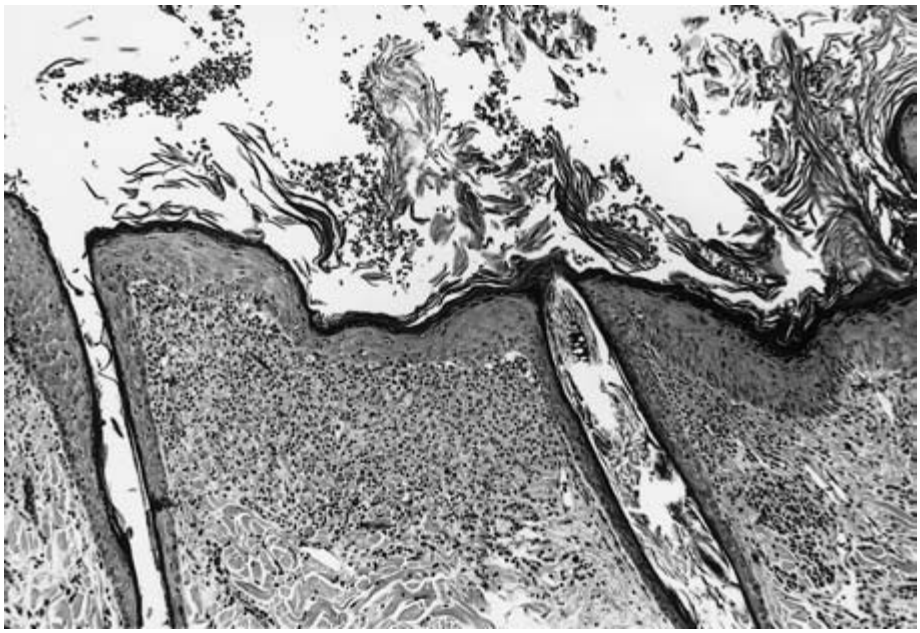


Fig. 11.14 Vogt–Koyanagi–Harada-like syndrome featuring a lichenoid band of predominantly histiocytic inflammation.

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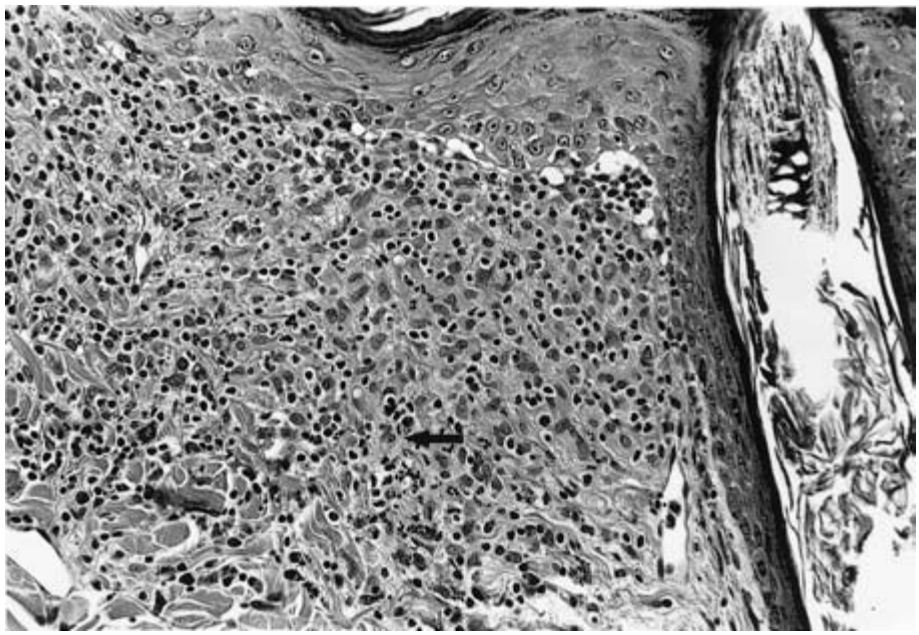


Fig. 11.15 Higher magnification of Fig. 11.14. Note predominance of large epithelioid macrophages, many of which contain a fine, dust-like scattering of intracytoplasmic melanin (arrow).

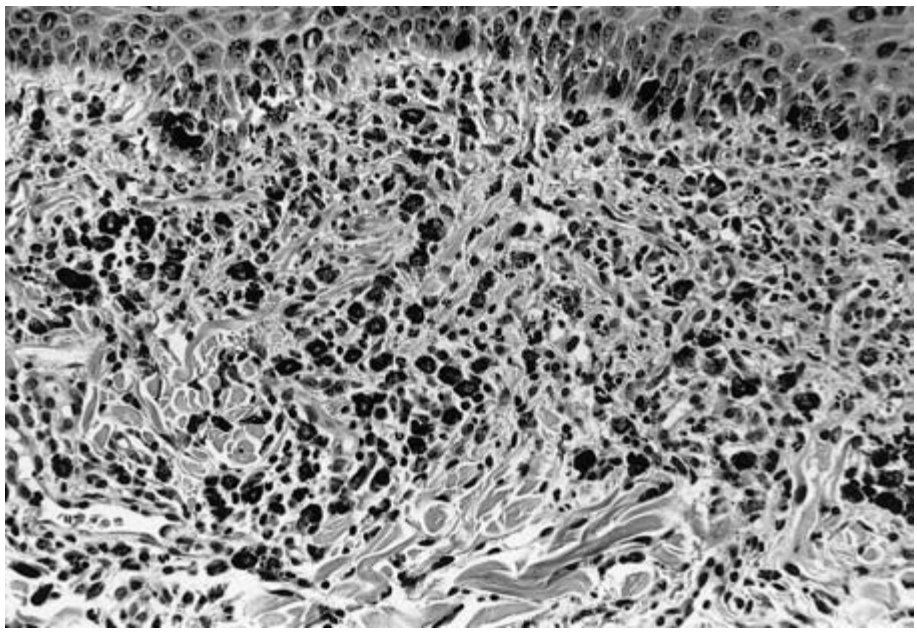


Fig. 11.16 Vogt–Koyanagi–Harada-like syndrome. Melanin granules are distributed abundantly in macrophages.

PSORIASIFORM-LICHENOID DERMATOSIS

Clinical features (Figure 11.17)

See Chapter 7.

Biopsy site selection

See Chapter 7.

Histopathology (Figure 11.18)

Epidermal lesions have been described and consist of psoriasiform hyperplasia with intraepidermal pustulation (see Chapter 7). The dermis contains a dense superficial band consisting primarily of plasma cells. Fewer lymphocytes, histiocytes, neutrophils, and eosinophils are present. Inflammation tends to obscure the dermal–epidermal interface, but basal cell degeneration (apoptosis) is rare. Mild pigmentary incontinence may be present.

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Principal differential diagnoses include discoid lupus erythematosus and mucocutaneous pyoderma. Although dermal lesions are similar amongst these diseases, the epidermal lesions of psoriasiform-lichenoid dermatosis are distinctive and allow differentiation. Lichenoid keratosis is similar to psoriasiform-lichenoid dermatosis and shares its histopathologic differential diagnoses (see p. 271). Clinical differentiation is required; most lichenoid keratoses are solitary.



Fig. 11.17 Psoriasiform-lichenoid dermatosis in a Springer Spaniel. Waxy, crusted, lichenoid plaques are present on the medial surface of the pinnae. (Photograph courtesy R.E.W. Halliwell.)

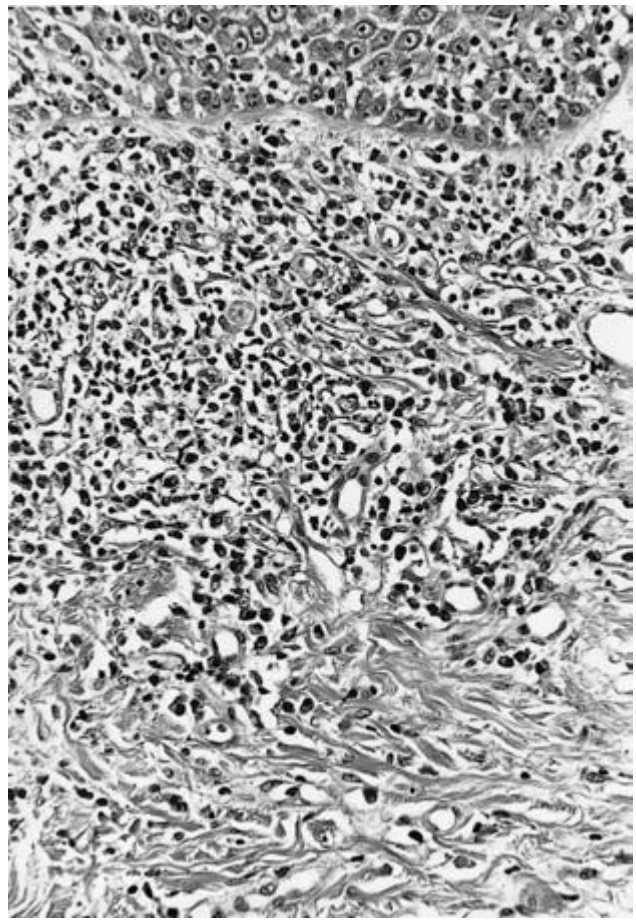


Fig. 11.19 Lichenoid keratosis in a dog. Note dense lichenoid band of mixed inflammation with prominent plasma cells.



Fig. 11.18 Psoriasiform-lichenoid dermatosis. Lichenoid dermatitis is accompanied by irregular acanthosis and discrete intraepidermal pustules.

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LICHENOID KERATOSIS

Clinical features

See Chapter 7.

Biopsy site selection

See Chapter 7.

Histopathology (Figure 11.19)

Epidermal lesions principally include psoriasiform hyperplasia, sometimes accompanied by intraepidermal pustules similar to those of psoriasiform-lichenoid dermatosis (see Chapter 7). Lichenoid dermal inflammation is predominantly lymphocytic and plasmacytic. Variable numbers of macrophages and neutrophils are present. Inflammation may obscure the dermal–epidermal interface, and may extend around subjacent adnexal appendages, or deep dermal vessels. Basal cell degeneration (apoptosis) is rare.

Lichenoid keratosis is similar to psoriasiform-lichenoid dermatosis and shares its histopathologic differential diagnoses, discoid lupus erythematosus and mucocutaneous pyoderma (see pp. 263 and 261). Differences in epidermal lesions as well as clinical distinctions will allow separation from discoid lupus erythematosus and mucocutaneous pyoderma. Differentiation from psoriasiform-lichenoid dermatosis may require knowledge of clinical features; most lichenoid keratoses are solitary.

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Psoriasiform-lichenoid Dermatosis

See Chapter 7.

Lichenoid Keratosis

See Chapter 7.

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Chapter 12

Infectious nodular and diffuse granulomatous and pyogranulomatous diseases of the dermis

Nodular and diffuse granulomatous and pyogranulomatous diseases of the dermis are characterized by multifocal nodular inflammation that tends toward confluence, or a diffuse pattern. Diffuse inflammatory infiltrates often obscure normal dermal architecture and may extend to the underlying subcutis as well. Granulomatous inflammation is composed principally of macrophages, with or without giant cells, which may or may not form discrete granulomas. Pyogranulomatous inflammation has a more prominent component of neutrophils that may be diffusely intermingled with macrophages; discrete pyogranulomas are composed of central neutrophils and rimmed by macrophages. By convention, the presence of discrete granulomas or pyogranulomas is not a requisite for a 'granulomatous' or 'pyogranulomatous' pattern. Diseases included in this chapter are those in which infectious agents incite the inflammatory reaction. Differential diagnosis is facilitated through identification of the offending agent in tissue.

ACTINOMYCOSIS AND NOCARDIOSIS

Clinical features (Figures 12.1 through 12.4)

Actinomycosis and nocardiosis are rare cutaneous/subcutaneous and visceral diseases of the dog and cat, caused by various actinomycetes classified as 'higher' (more evolutionarily advanced) bacteria. Actinomycosis is subdivided clinically into thoracic, abdominal, retroperitoneal, and cutaneous/subcutaneous actinomycosis (Edwards, 1998). Nocardiosis may be subdivided clinically into pulmonary, systemic or disseminated, and cutaneous/subcutaneous nocardiosis (Edwards, 1998).

Actinomycosis and nocardiosis share substantial clinical and histopathologic similarities. *Actinomyces* spp. are Gram-positive, nonacid-fast, filamentous, anaerobic or microaerophilic rods, and *Nocardia* spp. are Gram-positive, partially acid-fast, filamentous, aerobic rods. *Actinomyces viscosus*, *Actinomyces hordeovulnaris*, *Actinomyces odontolyticus*, and *Actinomyces meyeri* are commensal inhabitants of the oral cavity and gastrointestinal tract in many mammalian species. Actinomycetes also may exist as saprophytes. *Nocardia asteroides*, *Nocardia braziliensis*, and *Nocardia caviae* are common saprophytes found in soil and fresh water. Recently, organisms previously classified as members of the *Nocardia asteroides* complex (*Nocardia asteroides*, *Nocardia nova*, and *Nocardia farcinica*) have been separated (Hirsh & Jang, 1999). *Nocardia nova* is believed to be the most common cause of nocardiosis in cats (Hirsh & Jang, 1999).

Actinomycosis and nocardiosis are opportunistic infections initiated most commonly by wound contamination. Differentiation between the two diseases may be difficult both clinically and histopathologically. In the past, nocardiosis may have been overdiagnosed; newer methods of microbiologic differentiation most often identify *Actinomyces* spp. in cases where both clinical and histopathologic characteristics do not allow differentiation (Kirpensteijn & Fingland, 1992).

Infection with higher bacteria can produce 'tissue grains' or granules composed of aggregates of bacteria imbedded in amorphous eosinophilic material that is presumed to consist of antigen–antibody complexes; this material is known as 'Splendore–Hoeppli reaction'. Splendore–Hoeppli reaction forms only in circumstances characterized by a unique, dynamic balance between organism virulence and host response. In humans, the Splendore–Hoeppli phenomenon occurs most commonly in cutaneous and subcutaneous sites; similar lesions can occur in viscera such as the spleen in conjunction with coexistent immunosuppressive disease (Rodig & Dorfman, 2001). Tissue grains formed in actinomycosis commonly are called 'sulfur granules' or 'sulfur grains'. Tissue grains are seen less frequently in nocardiosis. *Nocardia caviae* and *Nocardia braziliensis* are more likely than *Nocardia asteroides* to produce grains.

Actinomycosis results from contamination of penetrating wounds, such as those caused by grass awns, quills,

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Fig. 12.1 Actinomycosis secondary to interdigital grass awn implantation in a dog. A fistulous tract drains sparse purulent exudate.



Fig. 12.2 Nocardiosis in a cat. Large craterous cavitations, fistulous tracts, and nodules are present on the ventral abdomen. (Photograph courtesy L.P. Schmeitzel.)



Fig. 12.3 Nocardiosis in a Doberman Pinscher. A draining nodule is accompanied by severe soft tissue swelling.



Fig. 12.4 Abdominal skin of the dog in Fig. 12.3. Note the large irregular nodule with multifocal ulceration. The overlying intact skin is erythematous to bluish.

cactus spines, and other foreign bodies. Canine interdigital actinomycosis is especially likely to result from foxtail foreign body penetration (Brennan & Ihrke, 1983). Actinomycosis may occur through the creation of an anaerobic inflammatory environment that is conducive to the replication of previously existent commensal organisms. Alternatively, organisms may be acquired with a penetrating foreign body or introduced into the wound secondarily by grooming. Nocardiosis may be associated with wound contamination, inhalation, or ingestion. Although both actinomycosis and nocardiosis are facilitated in animals with impaired host defense mechanisms, nocardiosis may be seen more frequently in immunosuppressed animals.

The most common clinical features of cutaneous and subcutaneous actinomycosis and nocardiosis include abscess formation, cellulitis, draining fistulous tracts, and ulcerated dermal and subcutaneous nodules. The character of the exudate is highly variable, and may range from serosanguinous to sanguinopurulent. Yellow 'sulfur granules' or grains in the exudate are suspicious for actinomycosis since the most common agent of nocardiosis,

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Nocardia asteroides, usually does not form granules. However, on rare occasion, *Nocardia asteroides* may cause the Splendore–Hoeppli phenomenon in tissue, thus giving rise to visible grains (Rodig & Dorfman, 2001). Lesions tend to be grouped; progression is by gradual local extension. The head, neck, thorax, ventral abdomen, and distal extremities are the most common sites in the dog. Paralumbar lesions may indicate retroperitoneal actinomycosis. Feline lesions most commonly affect the distal extremities and ventral abdomen.

Regional lymphadenopathy is common with both actinomycosis and nocardiosis. Actinomycotic osteomyelitis and pulmonary nocardiosis are the most frequent concurrent noncutaneous infections (Kirpensteijn & Fingland, 1992; Edwards, 1998). Systemic signs may be seen with either disease contingent on portal of entry and the coexistence of visceral infection.

Active large dog breeds are reported to be at greater risk, presumably due to increased risk for penetrating wounds and foreign body implantation as a result of rambunctious behavior. The largest study to date indicates a mean age at referral of 3.6 years (Kirpensteijn & Fingland, 1992). Early reports indicated a possible sex predilection for males, perhaps linked to behavioral risk; however, recently sex predilections were not reported in hunting dogs (Edwards, 1998).

Clinical differential diagnoses should include cryptococcosis, other systemic fungi, cutaneous infections of opportunistic fungi and algae, opportunistic mycobacterial infection, bacterial pseudomycetoma, foreign body reactions, and infection by other aerobic or anaerobic bacteria. Differentiation is accomplished by routine and special culture techniques; cytologic examination with special staining of exudates, impression smears, or aspirates; and histopathology. Fungal culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291).

Biopsy site selection

Identification of organisms histopathologically is contingent upon obtaining adequate tissue specimens from affected areas. Aggressive wedge technique or large punch biopsy (8 mm) is recommended to obtain deep nodules, and tissue surrounding and beneath fistulous tracts. Radical surgical ablation of solitary lesions may be curative.

Histopathology (Figures 12.5 and 12.6)

The epidermis is variably acanthotic, and may be ulcerated. The dermis and usually the subcutis are heavily infiltrated with neutrophils and macrophages in a diffuse pattern, or in confluent pyogranulomas. Pyogranulomas are generally large and are formed by extensive accumulations of neutrophils surrounded by cuffs of large epithelioid macrophages. Lymphocytes and plasma cells are present at the periphery of chronic lesions, and there is variable fibrosis surrounding the inflammatory foci. Adipocytes in the panniculus and subcutis may be ruptured to form large cysts.

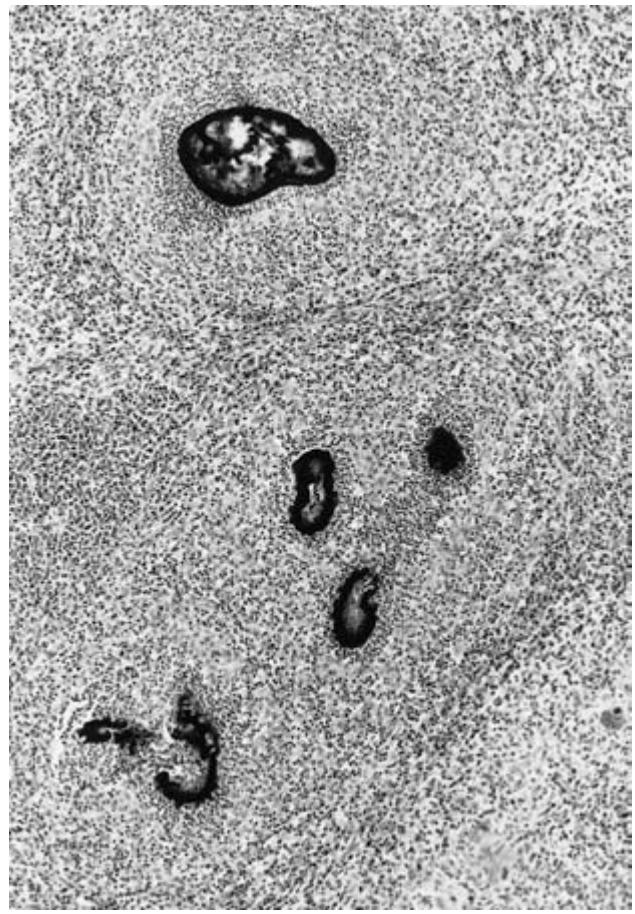


Fig. 12.5 Actinomycosis in a cat. Large tissue grains are within pyogranulomatous inflammation.

Organisms are difficult to identify as they are often not in abundance. Step sections on punch biopsies or multiple sections from large wedge biopsies may aid in detection of a characteristic bacterial colony. Colonies were identified in biopsy specimens of only 11 of 22 dogs in one study (Kirpensteijn & Fingland, 1992). Small to large, often radiating clusters or colonies of tangled, filamentous, and branched bacteria may be found at the centers of pyogranulomas, sometimes in clear spaces. Occasionally, colonies are present within surface suppurative exudate. Tissue grains (or sulfur granules), seen commonly in actinomycosis, are formed by the deposition of

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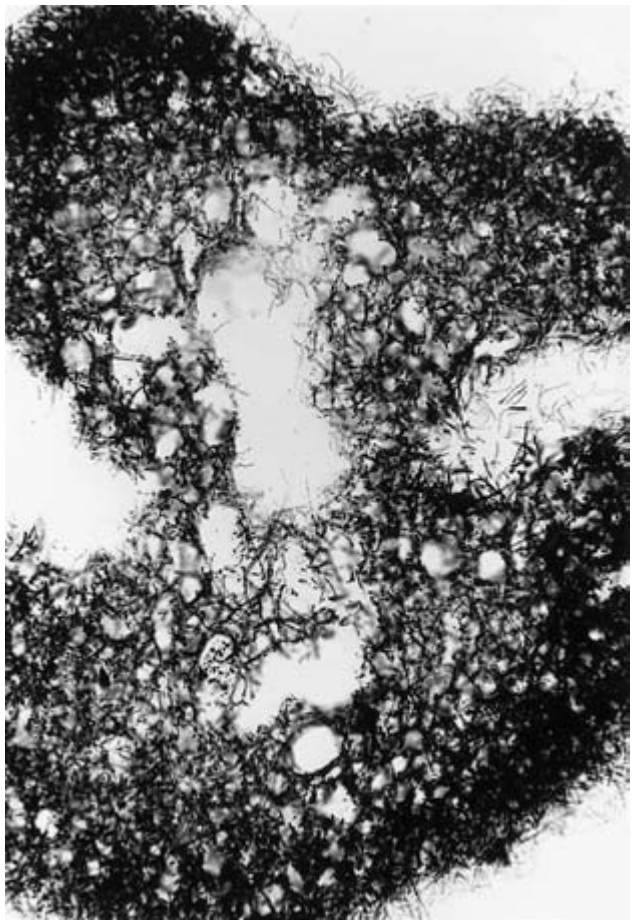


Fig. 12.6 Nocardiosis in a cat. High magnification of colony reveals tangled, filamentous and beaded bacteria that were culturally identified as *Nocardia asteroides* (Brown–Hopps).

brightly eosinophilic, radiating and clubbed deposits, called Splendore–Hoeppli reaction. This represents an antigen–antibody reaction around infectious agents or parasites that occurs at the periphery of organized aggregates of organisms. Large colonies of organisms alone do not constitute tissue grains. The most commonly implicated organism in nocardiosis, *Nocardia asteroides*, uncommonly is associated with tissue grains.

Actinomyces spp. are Gram-positive and nonacid-fast; *Nocardia* spp. are Gram-positive, partially or weakly acid-fast, and may be beaded. A Fite–Faraco modification of the acid-fast stain (Fite's stain) is helpful in the tissue identification of *Nocardia* spp. and its differentiation from *Actinomyces* spp. This stain employs peanut oil to prevent excessive decolorization of organisms during the staining process. Caution is advised when additional sectioning for special staining is performed; sectioning that is too deep may pass through available colonies. If bacteria are not present in deeper tissue, the original hematoxylin and eosin-stained section may be decolorized and stained.



Fig. 12.7 Bacterial pseudomycetoma in a dog. Multiple nodules, both intact and fistulated, are present. Irregular contours indicate scarring and induration. (Photograph courtesy D.W. Scott.)

Differential diagnoses include foreign body reactions, infection due to rapidly growing opportunistic mycobacteria, or bacterial pseudomycetoma (botryomycosis). Foreign body reactions are considered if organisms are not visible in biopsy specimens; differentiation may require careful culture or probing the lesion for foreign material.

Bacterial pseudomycetoma, which is nodular clinically, is characterized by the accumulation of Splendore–Hoeppli material around nonbranching bacteria (usually staphylococci) to form tissue grains, thus resembling actinomycosis. The characteristic morphology and staining characteristics of *Nocardia* spp. and *Actinomyces* spp. in tissue usually allow differentiation from most other infectious agents. *Nocardia* spp. may resemble opportunistic mycobacteria in tissue section, particularly when colonies are found in large tissue spaces created from ruptured adipocytes (see p. 283). However, *Nocardia* spp. accumulate in larger tangled colonies, are only partially or weakly acid-fast, and elicit a more prominent neutrophilic response than do opportunistic mycobacteria.

BACTERIAL PSEUDOMYCETOMA

(Synonyms: cutaneous bacterial granuloma, botryomycosis)

Clinical features (Figure 12.7)

Bacterial pseudomycetoma is a rare (or underdiagnosed) pyogranulomatous skin disease characterized by an unusual, presumed immunologic, reaction to nonbranching bacteria. Dogs and cats may be affected. *Staphylo-*

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coccus spp., *Pseudomonas* spp., *Proteus* spp., or *Streptococcus* spp. bacteria elicit nodular skin disease characterized by the Splendore–Hoeppli reaction in tissue (Scott et al., 2001). Splendore–Hoeppli reaction (an antigen–antibody complex) is also seen in conjunction with higher bacteria such as the actinomycetes (see p. 272), as well as other infectious agents.

Clinical features include solitary or multiple firm nodules with or without obvious fistulation. Nodules may fistulate and drain purulent exudate containing white granules or grains. Scarring and induration are seen with chronicity. Lesions have been seen in the context of canine acne (see Chapter 17). Lymphadenopathy may be present.

Clinical differential diagnoses should include actinomycosis or nocardiosis, foreign body reactions, cryptococcosis and other systemic mycoses, fungal mycetomas, cutaneous infections of opportunistic fungi and algae, and dermatophytic pseudomycetoma. Differentiation is accomplished by routine and special culture techniques, cytologic examination with special staining of exudates, impression smears, or aspirates and histopathology. Fungal culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291).

Biopsy site selection

An entire nondraining nodule should be removed using wedge resection technique. If the lesion is solitary, this has the added benefit of providing a surgical cure.

Histopathology (Figures 12.8 and 12.9)

The epidermis is acanthotic and may be ulcerated. The dermis and often the panniculus and deeper subcutis contain diffuse pyogranulomatous inflammation composed of neutrophils and macrophages. In addition, discrete or confluent pyogranulomas are present. At the centers of the pyogranulomas are discrete and generally large accumulations of bacteria (usually staphylococci) imbedded in brightly eosinophilic, radiating, and clubbed deposits of homogeneous material, constituting tissue grains or granules. The brightly eosinophilic material is Splendore–Hoeppli reaction, which represents an antigen–antibody reaction around infectious agents or parasites that occurs at the periphery of organized aggregates of organisms. If staphylococci are not obvious, Gram's staining for bacteria can be used to further characterize the organisms; staphylococci or streptococci are Gram-positive; *Pseudomonas* and *Proteus* spp. are Gram-negative.

Differential diagnoses are few due to the typical appearance of tissue grains, and principally include actinomycosis (or rarely nocardiosis; see p. 272). Identification of staphylococci (the usual infectious agent of bacterial pseudomycetoma), or other nonbranching, nonfilamentous bacteria, will allow differentiation.

FELINE LEPROSY SYNDROME

Clinical features (Figures 12.10 and 12.11)

Feline leprosy syndrome is a group of uncommon to rare granulomatous mycobacterial skin diseases caused by

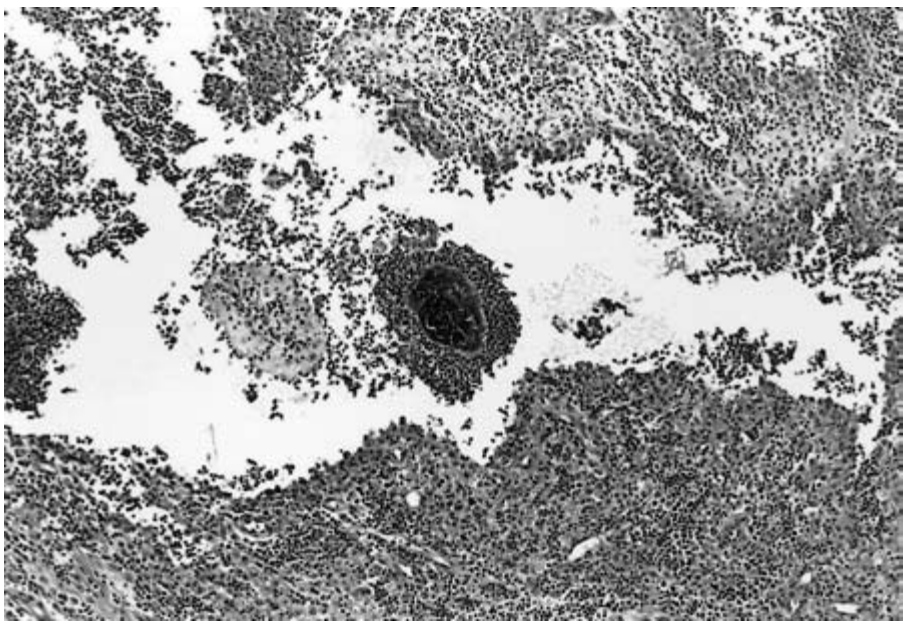


Fig. 12.8 Bacterial pseudomycetoma in a dog with canine acne. A large dark tissue grain is surrounded by a disrupted pustule.

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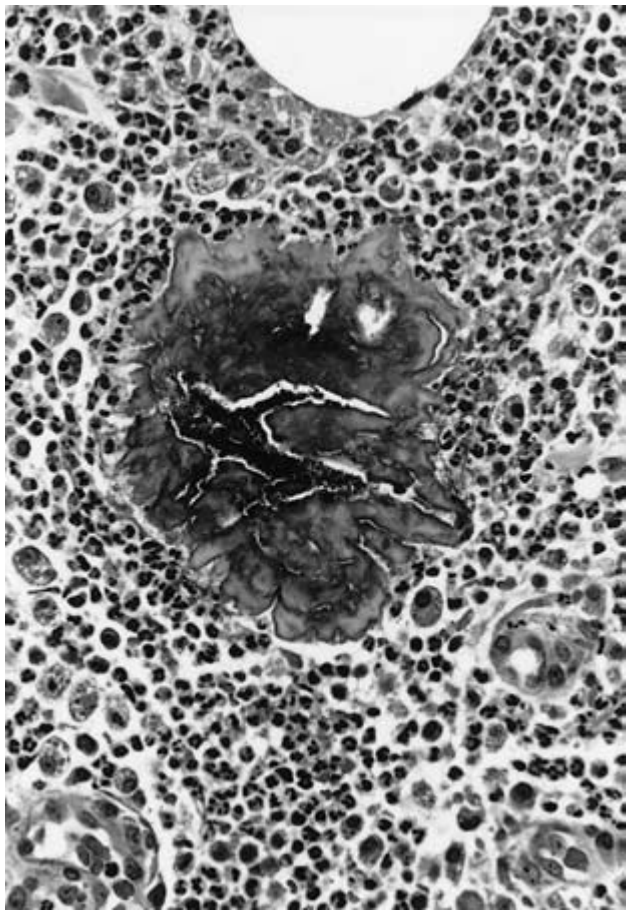


Fig. 12.9 High magnification of bacterial pseudomycetoma in a dog. Granular clusters of staphylococci at center are surrounded by Splendore–Hoeppli reaction.



Fig. 12.10 Feline leprosy in a young, male, outdoor cat from the San Francisco seaport. Two well-demarcated, ulcerated nodules are present on the right foreleg.



Fig. 12.11 Closer view of the cat in Fig. 12.10. A well-demarcated, ulcerated nodule with slightly elevated margins drains a sparse exudate.

various acid-fast bacteria that either cannot be cultured or are not easily cultured using routine laboratory methods. Recent data suggest that the lack of ability to culture *Mycobacterium leprae*, the causative organism of human leprosy, may relate to dramatic gene deletion seen in this organism leaving it with few respiratory enzymes in comparison to other mycobacteria (Rea & Modlin, 2003). The terms 'lepromatous' and 'tuberculoid' leprosy are used traditionally in human medicine for leprosy syndromes that are 'organism rich' or have 'sparse to moderate organisms', respectively (Rea & Modlin, 2003). 'Paucibacillary' and 'multibacillary' are additional terms in use in human medicine (Rea & Modlin, 2003). However, recent classification schemes used in human medicine subdivide leprosy into at least six groups (Rea & Modlin, 2003).

Polymerase chain reaction (PCR)-amplified gene sequencing has lead to an explosion of new information about feline leprosy during the past few years (Hughes et al., 1997; Appleyard & Clark, 2002; Malik et al., 2002). Molecular biology-based analyses have proven conclusively that some cats diagnosed with feline leprosy syndrome have infection caused by *Mycobacterium lepraemurium*, the rat leprosy bacillus (Hughes et al., 1997). Currently, at least two histomorphologic forms of feline leprosy have been recognized, 'lepromatous' and 'tuberculoid' (Malik et al., 2002). Cats identified as having the tuberculoid form of feline leprosy have had *Mycobacterium lepraemurium* identified by PCR testing and DNA sequencing (Malik et al., 2002); similar cases have been confirmed by PCR in the northwestern USA and Hawaii (Foley, J.E., personal communication, 2003). Regional differences likely exist. Cats identified by Malik et al. (2002) in Australia as having the organism-rich, lepromatous form of feline leprosy have infection caused by a distinct, as yet unnamed mycobacterial species.

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However, another distinct mycobacterial species (suggested name, *Mycobacterium visibilis*) has been identified by Appleyard & Clark (2002) as the causative agent of organism-rich lepromatous feline leprosy in Canada, and also in cats with lepromatous leprosy in California (Foley, J.E., personal communication, 2003).

Other species have been identified in cutaneous lesions, including *Mycobacterium szulgai* (Davies et al., 2003) and *Mycobacterium kansasii*, the latter from tuberculoid leprosy (Foley, J.E., personal communication, 2003). Lastly, *Rhodococcus erythropolis* was identified by PCR in a cat with tuberculoid leprosy (Foley, J.E., personal communication, 2003). The significance of this finding is not known; this organism (and other *Rhodococcus* spp.) are common contaminants that have been identified by PCR in uninflamed skin and internal viscera of dogs and cats, as well as in other inflammatory dermatoses (Ramiro-Ibanez, F., personal communication, 2003).

The frequent localization of lesions to the head and neck has led to speculation that the organism may be transmitted by bite wounds from either rats or other cats (McIntosh, 1982; Schiefer & Middleton, 1983). Credence is given to the theory of transmission of *Mycobacterium lepraemurium* from rats by the predominant occurrence of feline leprosy syndrome in seaport cities of western North America, Australia, France, and The Netherlands. The leprosy bacillus of humans has been identified in fleas, mosquitoes, and ticks. Consequently, these vectors also could be involved in the transmission of feline leprosy syndrome. Leprosy in humans commonly is associated with immunodeficiency. Data reflecting the status of the immune system of affected cats are mixed.

Lepromatous leprosy is caused by a novel but as yet unnamed mycobacterial species or another distinct mycobacterial species with the suggested name *Mycobacterium visibilis* (Malik et al., 2002; Appleyard & Clark, 2002). Lepromatous leprosy is more common than tuberculoid leprosy in Australia and New Zealand, and may be in the USA as well. Clinically, lepromatous leprosy usually is characterized by multifocal, slowly progressive nodular and infiltrative skin disease. Based on one report the clinical course is much less aggressive than most cases of tuberculoid leprosy, at least in Australia (Malik et al., 2002). This is in contrast to the more severe clinical course observed in cats with lepromatous leprosy in the western USA and Hawaii (Foley, J.E., personal communication, 2003); affected cats are more likely to have multicentric lesions, recurrence and concurrent disease. Most affected cats reside in rural and semirural environments. Affected cats are older, usually more than 9 years of age. Of four cats tested for immunosuppressive viral infection, two were positive for feline immunodeficiency virus (FIV), but all were negative for feline leukemia virus (FeLV) (Malik et al., 2002). These data, as well as the greater age of affected cats, suggest that diminished immunologic surveillance may be required for this disease.

Tuberculoid leprosy is less common in Australia and New Zealand and probably the USA as well, and is caused by the rat leprosy bacillus, *Mycobacterium lepraemurium* (Malik et al., 2002). Clinically tuberculoid leprosy is most often characterized by localized nodular disease. Most cats are in suburban or rural environments. Cats are young, usually less than 4 years of age (Malik et al., 2002). In one study lesions progressed rapidly, ulcerated, and reportedly displayed an aggressive clinical course (Malik et al., 2002). Widespread cutaneous and subcutaneous lesions developed within a few weeks. Despite widespread lesions, available evidence did not support visceral dissemination in that study. Regional epidemiologic differences may exist globally, however. In a recent study from the Pacific Northwest and Hawaii, six cats with microscopically confirmed tuberculoid leprosy usually had small numbers of lesions that did not recur following excision and/or miscellaneous broad-spectrum antibiotics (Foley, J.E., personal communication, 2003).

In general, in feline leprosy syndrome, single, or multiple, grouped, well-circumscribed, alopecic nodules (5–20 mm in diameter) develop slowly in the skin or the subjacent subcutis. Larger nodules ulcerate and scant exudation occurs. The margins of the ulcers usually are firm and slightly elevated. Less commonly, fistulas may present. The face, forelegs, and trunk are the most common sites. Rarely, lesions involve the facial mucocutaneous junctions. Typically, lesions are asymptomatic. However, cats groom ulcerated nodules, especially on the forelegs.

Regional lymphadenopathy is present, and regional lymph node invasion has been noted in cats with lepromatous leprosy by one author (T.L.G.). Young adult cats predominate, particularly roaming intact male cats from the seaport cities. Breed predilections have not been reported.

Clinical differential diagnoses include cryptococcosis and other systemic mycoses, opportunistic fungal infections, sporotrichosis, sterile granuloma and pyogranuloma syndrome, and neoplasia. Differentiation is accomplished by routine and special culture techniques; cytologic examination with special staining of exudates, impression smears, or aspirates; and histopathology. Fungal culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291). Signs referable to disseminated disease usually are seen with systemic mycoses, but usually are absent in feline leprosy syndrome. The nodules of feline sporotrichosis have draining fistulous tracts (containing abundant organisms easily identified by direct smears) in contrast to the scantily exudative lesions of feline leprosy syndrome.

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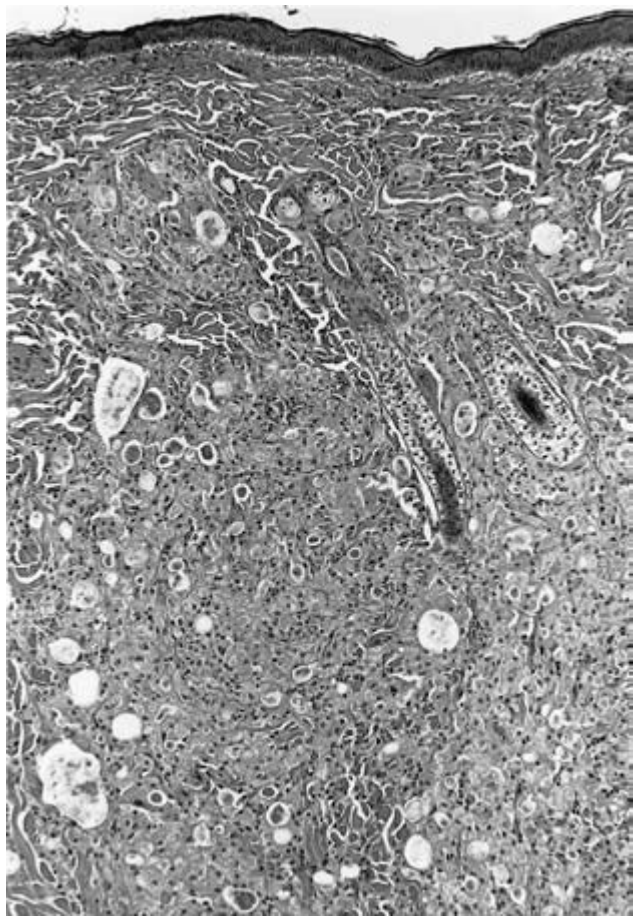


Fig. 12.12 Feline lepromatous leprosy. Diffuse granulomatous inflammation is characterized by foamy, vacuolated macrophages.

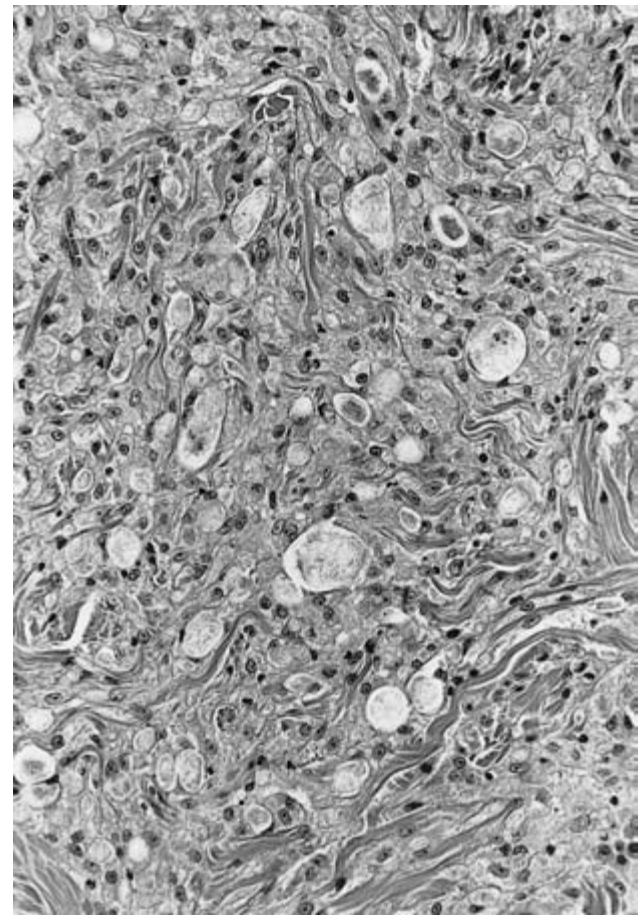


Fig. 12.13 Higher magnification of feline lepromatous leprosy. Note pale vacuolated macrophages; the large, clear spaces contain numerous organisms which are faintly visualized with hematoxylin and eosin.

Biopsy site selection

If feline leprosy syndrome is suspected, an intact nodule should be excised surgically using wedge technique. Gloves should be worn when examining and performing skin biopsies on all cats with ulcerative nodular skin disease, as clinically similar sporotrichosis is a zoonosis (see p. 298). If a solitary lesion is present, complete excision may provide the added benefit of surgical cure.

Histopathology (Figures 12.12 through 12.16)

Two principal forms of feline leprosy syndrome have been recognized, lepromatous and tuberculoid (see above). For the lepromatous form of feline leprosy (organism-rich), the epidermis is mildly to moderately acanthotic. The dermis and often the panniculus and subcutis contain nodular to diffuse infiltrates of predominantly large, pale, foamy, or epithelioid macrophages. There may be large multinucleated giant cells. Giant cells usually are sparse but may be numerous (Malik et al., 2002). In mild lesions, inflammation may be nodular in perivascular and periadnexal orientation. Inflammation obscures normal dermal architecture, but often a thin zone of the superficial dermis is spared (Grenz zone). Large vacuoles may be present among macrophages. Smaller numbers of neutrophils or lymphocytes may be interspersed. Lymphocytes may be in nodules.

Filamentous pale gray organisms may be visible with hematoxylin and eosin (HE) staining, and can be observed in stacked arrangement. Using a routine acid-fast stain, such as Ziehl–Neelsen, numerous acid-fast bacilli are identified within macrophages or dermal vacuoles; organisms are also silver-positive. The presence of these organisms in the face of a negative mycobacterial culture confirms the diagnosis of feline leprosy, as cultural isolation of this organism is not possible under routine laboratory conditions.

In the tuberculoid form of feline leprosy (organism-poor), lesions are distinctly different. There are often large

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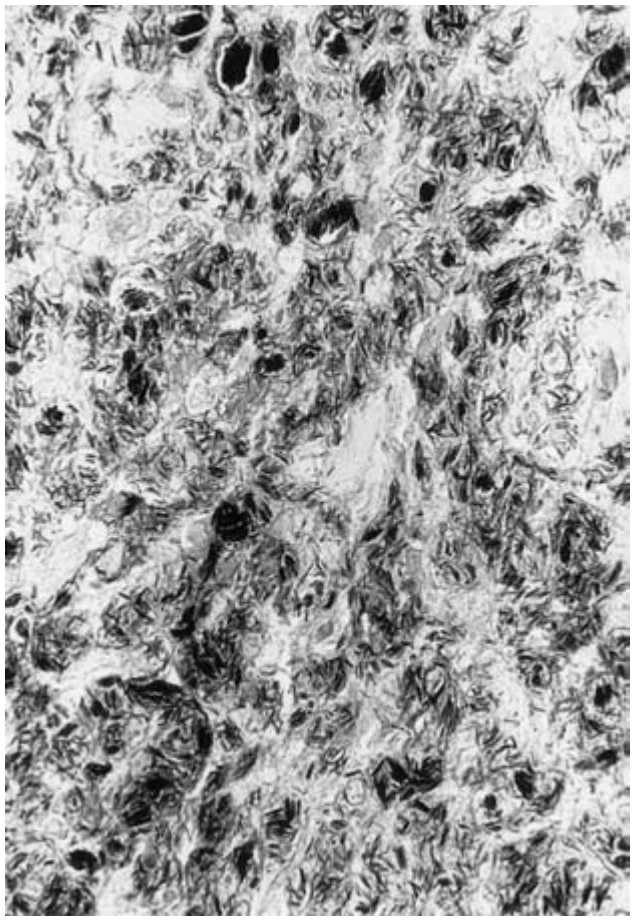


Fig. 12.14 Higher magnification of feline lepromatous leprosy. Large numbers of acid-fast rods fill the cytoplasm of macrophages and are seen densely in extracellular spaces (Ziehl–Neelsen).

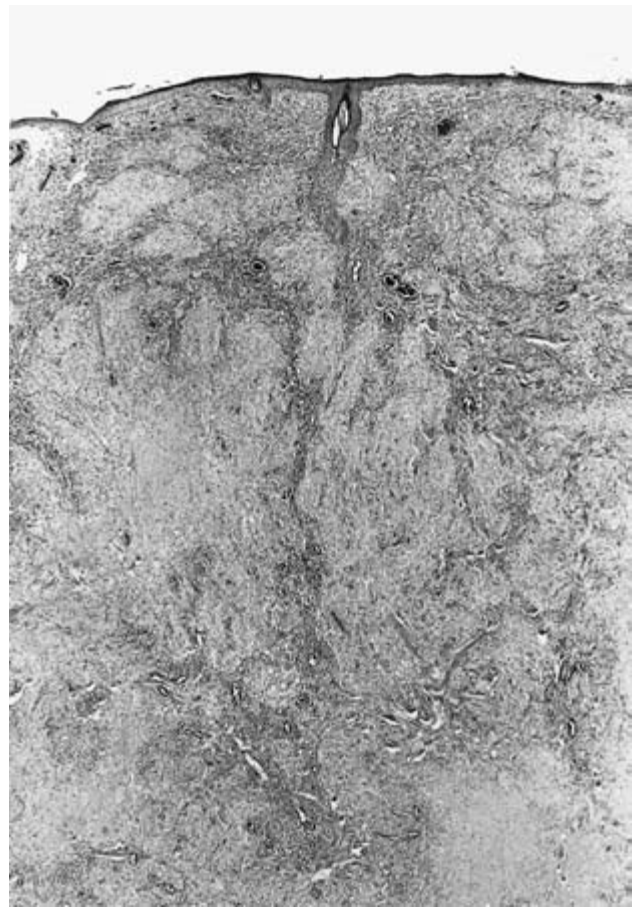


Fig. 12.15 Feline tuberculoid leprosy. Confluent pale granulomas are interspersed with acellular foci of necrosis at left and bottom right.

foci of necrosis surrounded by diffuse pyogranulomatous inflammation. Giant cells are seen occasionally. Peripherally, there may be lymphocytes in nodular arrangement, accompanied by fewer plasma cells. Small numbers of acid-fast organisms are generally confined to the necrotic foci and are not visible with HE. The polyclonal anti-*Mycobacterium bovis* (BCG) stain is superior in labeling mycobacteria (Bonenberger et al., 2001), and may be of benefit in suspected cases with scant organisms. This stain may also detect partially degraded bacteria within macrophages.

Differential diagnosis for the tuberculoid form of feline leprosy usually is not difficult due to the unique large foci of necrosis. However, morphologically similar 'sterile' pyogranulomas have been observed in cats for which organisms could not be identified by staining or PCR. Opportunistic fungal infection should be ruled out by appropriate staining; however, ghosts of fungi are often visible on HE staining, while mycobacteria of the tuberculoid form of leprosy are not.

Differential diagnoses for the lepromatous form of feline leprosy include cutaneous xanthoma, opportunistic *Mycobacterium avium* infection, some late lesions of feline progressive dendritic cell histiocytosis (see Chapter 35), and opportunistic fungal infection, all of which may feature foamy macrophages. If pale mycobacterial organisms are identified on HE staining, differentiation is not problematic. Cutaneous xanthomas usually have deposition of more obvious extracellular lipid, seen as pale lakes within tissue or cholesterol clefts. In feline *Mycobacterium avium* infection with cutaneous involvement, large numbers of organisms may be seen in tissue section, similar to lepromatous feline leprosy (Kaufman et al., 1995; Stevenson et al., 1998; Miller et al., 1999). However, unlike the mycobacterium of feline leprosy, *Mycobacterium avium* can be identified by culture. Additionally, a fibrovascular network may be present within the inflammatory infiltrate (Buergelt et al., 1982; Kaufman et al., 1995), sometimes in a sarcomatous pattern (Miller et al., 1999). Opportunistic fungal infec-

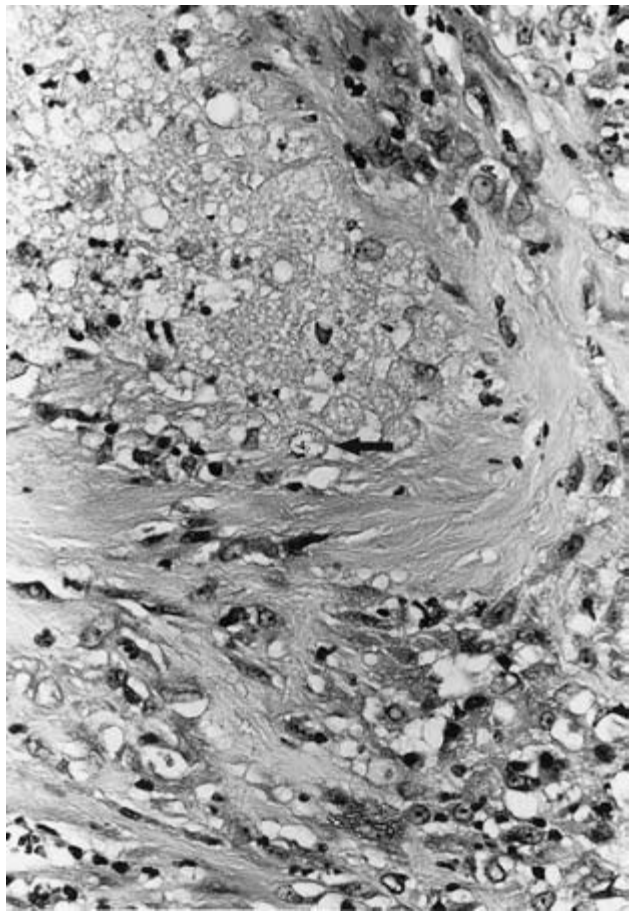


Fig. 12.16 Higher magnification of feline tuberculoid leprosy demonstrating sparse acid-fast bacilli within a necrotic focus (arrow) (Fite-Faraco).

tions often are characterized by numerous foamy macrophages, similar to feline leprosy. However, ghosts of fungal organisms are visible on close examination with HE staining and are abundant with special stains for fungi (see p. 301).

CANINE LEPROID GRANULOMA

Clinical features (Figure 12.17)

Canine leproid granuloma is an uncommon but probably underdiagnosed mycobacterial disease of the subcutis and skin caused by a novel and as yet unnamed mycobacterium that is phylogenetically related to *Mycobacterium tilburgii*, *Mycobacterium simiae*, and *Mycobacterium genavense* (Hughes et al., 2000; Foley et al., 2002). Analysis by polymerase chain reaction (PCR) and DNA sequencing showed no variability and 99% to 100% homology among organisms obtained from Australia, New Zealand, and the United States (Hughes et al., 2000; Foley et al., 2002). The organism probably is a saprophyte with ubiquitous distribution. Culture has been unsuccessful to date, indicating that the organism has fastidious *in vitro* growth requirements (Malik et al., 1998; Hughes et al., 2000; Foley et al., 2002).



Fig. 12.17 Canine leproid granuloma on the pinna of a Boxer. A solitary, well-demarcated, alopecic nodule is ulcerated. (Photograph courtesy R. Malik.)

Presumably, the organism enters the skin and subcutaneous tissues via a traumatic breach in the epidermal barrier (Malik et al., 1998). Based on colder weather seasonality, Malik et al. (1998) postulated that low ambient temperature may enhance the likelihood of growth in tissue. This theory also could explain the marked site predilection for extremities such as the pinnae and distal legs. The disease commonly is self-limiting in immunocompetent dogs (Malik et al., 1998). Spontaneous regression is common and probably leads to under-reporting. Marked breed predilections (see below) suggest the likelihood of breed-based selective immunoincompetence.

Single or multiple nodules are confined to the subcutaneous tissue and skin. Lesions vary from solitary to few to numerous. The nodules are firm and painless, and range in size from 2 mm to 5 cm (Malik et al., 2001). Larger lesions are alopecic and ulcerated (Malik et al., 2001). The dorsal surface of the pinna is a strongly predisposed site. In the largest study to date (Malik et al., 1998), the ears were involved in 64% (25/39) of dogs and the head (including the ears) was affected in 85% (33/39) of dogs; the pinnae only were affected in 54% (21/39) of these dogs. Less commonly, the distal extremities, especially the forelegs, may be affected. Lymph node enlargement, visceral organ involvement, or systemic signs have

not been noted (Malik et al., 1998). The lesions usually spontaneously regress but the clinical course may be several months in duration.

Short-coated dogs account for over 90% of those affected, with either Boxers or Boxer crossbreeds accounting for half of the cases (Malik et al., 1998). Other short-coated breeds such as the Staffordshire Terrier and Doberman Pinscher also were affected in that report. Interestingly, the German Shepherd Dog, a long-coated breed, was over-represented in a recent study (Foley et al., 2002). The Boxer, German Shepherd Dog, and Doberman Pinscher are believed by one author (P.J.I.) to be over-represented in a variety of cutaneous as well as systemic infectious diseases caused by bacteria and fungi, suggesting diminished immune surveillance. The median age at development was 5 years in Australia (Malik et al., 1998); slightly older dogs were seen in a report from North America (Foley et al., 2002). Sex predilection has not been reported.

Clinical differential diagnoses should include focal nodular neoplasms, kerion, and sterile granuloma and pyogranuloma syndrome. Localization to the pinnae and occurrence in a Boxer enhance clinical suspicion for leproid granuloma. Lesional sites and the discrete nature of the nodules make systemic and opportunistic fungal infections less likely. However, if systemic fungal infection is suspected, culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291). Differentiation is accomplished by cytologic examination with special staining of aspirates or impression smears; histopathology; and, if needed, routine and special culture techniques.

Biopsy site selection

An intact nodule should be excised surgically using wedge technique. If a solitary lesion is present, complete excision may provide the added benefit of surgical cure.

Histopathology (Figures 12.18 through 12.20)

The epidermis is moderately acanthotic and ulceration may be present. Coagulative necrosis was found beneath ulcers in four of 37 cases in a report by Charles et al. (1999). The dermis and often the panniculus contain nodular to diffuse accumulations of macrophages and neutrophils (pyogranulomatous inflammation) intermingled with prominent clusters of lymphocytes and/or plasma cells. Discrete pyogranulomas are rare. Neutrophils are in small clusters or in larger pustular accumulations. Macrophages are large and have pale cytoplasm; they are often in sheet-like or epithelioid arrangement. Small numbers of Langhans multinucleated giant cells are observed as reported (Charles et al., 1999). These giant cells may be difficult to detect due to lack of sharp cell borders within the epithelioid infiltrate. In some lesions, putatively those that are regressing, there are diffuse and more intense accumulations of lymphocytes throughout or along the outer margins of the lesion. Lymphocytic nodules may be observed. Occasionally, there is prominent fibrosis interspersed amongst multinodular inflammation.

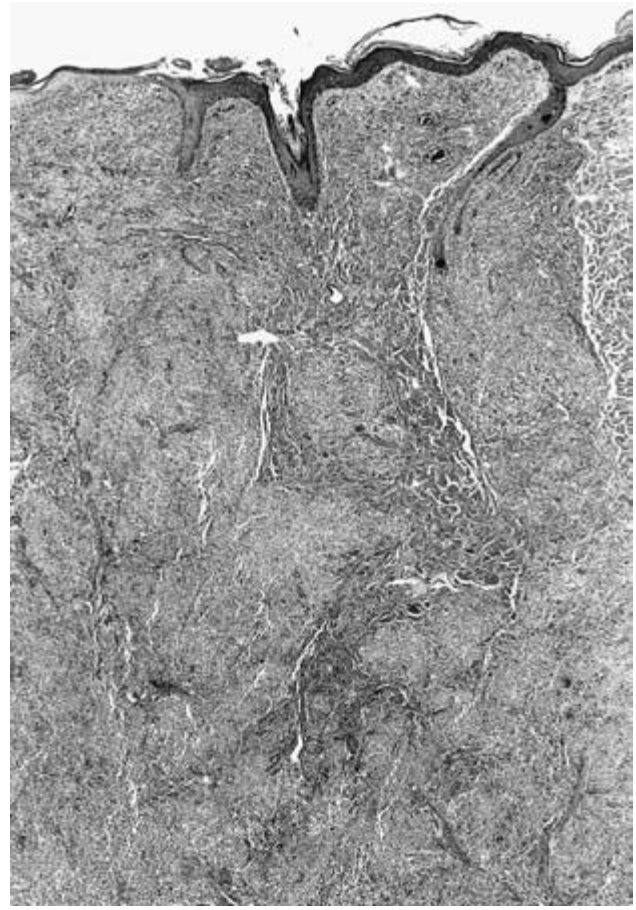


Fig. 12.18 Canine leproid granuloma demonstrating nodular to diffuse inflammation.

In the authors' experience, the acid-fast organisms of canine leproid granuloma are fairly easily identified by a modified acid-fast stain such as Fite–Faraco (Fite's stain). The bacteria can also be visualized with silver stains such as Gomori's methenamine silver (GMS). They generally are unevenly distributed, sparse overall, but can be regionally moderate. They are discovered in macrophages as clusters of pleomorphic rods, varying from short and coccoid to long, filamentous and variably beaded. Large numbers of organisms may be seen in individual macrophages. Diffusely numerous organisms were

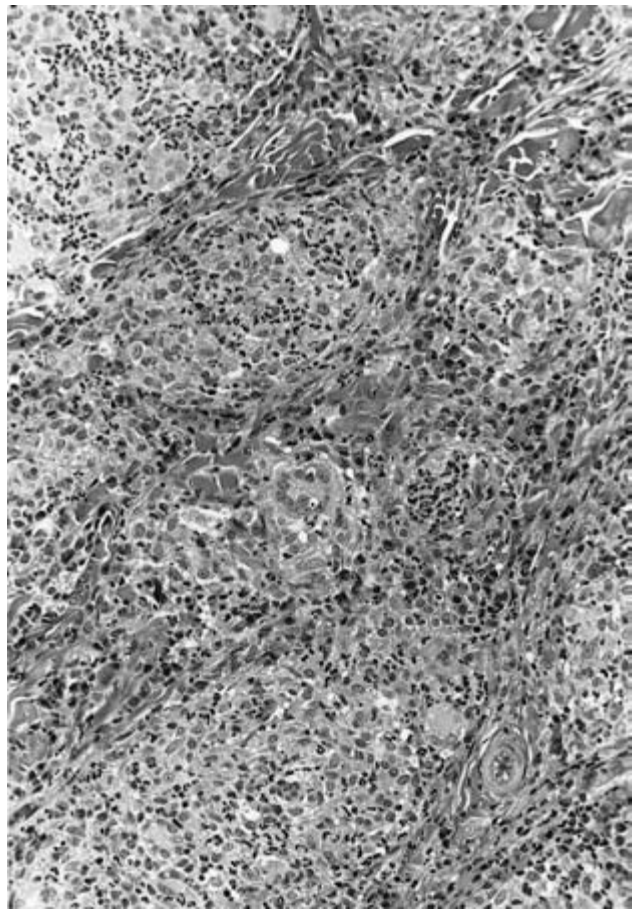


Fig. 12.19 Higher magnification of confluent pyogranulomas of canine leproid granuloma. Note giant cell at center.

reported in six of 37 animals studied (Charles et al., 1999); in that study organisms were 'very low to low' in 22 of 37 cases. The polyclonal anti-*Mycobacterium bovis* (BCG) stain is superior in labeling mycobacteria (Bonenberger et al., 2001), and may be of benefit in suspected cases with scant organisms. This stain may also detect partially degraded bacteria within macrophages.

Differential diagnoses include sterile granuloma and pyogranuloma syndrome, or other solitary histiocytic lesions such as palisading granuloma and reactive fibrohistiocytic nodules (see Chapter 35). Sterile granuloma and pyogranuloma syndrome produces multifocal lesions (less common in leproid granuloma) which tend to track along hair follicles, in contrast to the more diffuse pattern of leproid granuloma. Leproid granulomas generally include more neutrophils than reactive fibrohistiocytic nodules and palisading granulomas. Further, careful examination with acid-fast stains will reveal the organisms. Other opportunistic mycobacterial infections in dogs are uncommon; those of the rapidly growing group (Runyon Group IV) demonstrate mycobacteria in central clear spaces of pyogranulomas (see below), this pattern being distinct from canine leproid granuloma.

OPPORTUNISTIC MYCOBACTERIAL INFECTION CAUSED BY RAPIDLY GROWING MYCOBACTERIA

(Synonyms: opportunistic mycobacterial granulomas, atypical mycobacteriosis, nontuberculous mycobacterial infection)

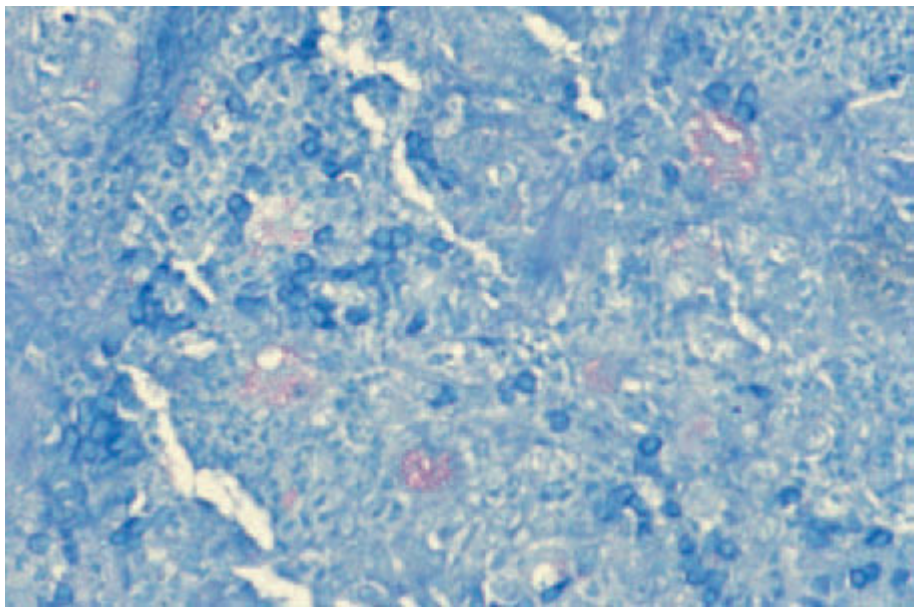


Fig. 12.20 High magnification of canine leproid granuloma demonstrating acid-fast bacteria (Fite–Faraco).

Clinical features (Figures 12.21 and 12.22)

Opportunistic infections caused by rapidly growing mycobacteria (based on *in vitro* growth rates) are uncommon in cats and rare in dogs. Causative organisms include the rapidly growing Runyon Group IV mycobacteria (*Mycobacterium fortuitum*, *Mycobacterium chelonei-abscessus*, *Mycobacterium smegmatis*, *Mycobacterium phlei*, *Mycobacterium flavescens*, *Mycobacterium thermoresistable*). These mycobacteria exist worldwide in wet environments, and commonly can be isolated from soil or bodies of fresh water. Runyon Group IV mycobacteria exhibit growth on solid media in less than 7 days. *Mycobacterium fortuitum* and *Mycobacterium chelonei-abscessus* exhibit growth in less than 3 days. In cats and dogs, *Mycobacterium fortuitum*, *Mycobacterium smegmatis*, and *Mycobacterium chelonei-abscessus* are the most frequently isolated facultative and opportunistic mycobacterial pathogens. A recent study performed in northern California indicated *Mycobacterium fortuitum* to be the most commonly isolated species (Jang & Hirsh, 2002), while *Mycobacterium smegmatis* is much more common than *Mycobacterium fortuitum* in Australia (Malik et al., 2000).



Fig. 12.21 Opportunistic mycobacterial infection in a cat caused by *Mycobacterium fortuitum*. Abscesses in the inguinal region have progressed to nonhealing craterous ulcers with thickened margins. (Photograph courtesy A.H. Werner; case material University of California, Davis.)



Fig. 12.22 Severe opportunistic mycobacterial infection in a cat caused by *Mycobacterium fortuitum*. Nonhealing ulcers have well-demarcated margins and undermine adjacent normal-appearing skin. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

Infections probably are caused by traumatic implantation of facultatively pathogenic mycobacteria. In humans, disseminated opportunistic mycobacterial infection occurs in immunocompromised individuals, while localized skin and subcutaneous infection is seen in normal individuals.

Most cats infected with Runyon Group IV mycobacteria are presumed to have acquired the infection via contaminated wounds (cat fights), other trauma, or contaminated injections. Runyon Group IV mycobacteria exhibit a marked tropism for tissues rich in lipids, leading to site predilection in the feline inguinal fat pad and disease predilection in obese individuals (Malik et al., 2000).

Feline lesions usually consist of predominantly asymptomatic cutaneous and subcutaneous abscesses. Multiple fistulas develop, but drainage is minimal. When visible, the exudate is watery. Thinning of the epidermis leads to clinically characteristic focal depressions that appear purple due to subjacent accumulations of pus (Malik et al., 2000). Abscesses progress to nonhealing ulcers with well-demarcated margins and undermined adjacent normal-appearing skin. Skin lesions are not as proliferative as those seen with many other infectious feline skin diseases, and the skin flaps at the margins of ulcers remain surprisingly thin. If prior surgery has been performed, irregular scarring may obscure more characteristic lesions.

The groin overlying the inguinal fat pad is the most commonly affected site. Lesions may be in the axillae, elsewhere on the trunk, or less commonly on the head or neck. Lesions develop slowly over weeks or months. Excessive grooming of the affected area may be noted. Regional lymphadenopathy is variable, but constitutional signs are absent or rare. One author (T.L.G.) has observed splenic dissemination in a cat that initially had chronic ventral abdominal skin lesions.

In dogs, focal or grouped cutaneous and subcutaneous nodules or larger firm swellings ulcerate and drain. The undermining of peripheral skin that is characteristic of feline opportunistic mycobacterial infection is not observed.

All affected cats were between 3 and 10 years of age, and were predominantly female (31 of 41 cats) in one large study (Malik et al., 2000). Breed predilections are

not noted and have not been reported. No predilections are known for dogs.

Feline opportunistic mycobacterial infection caused by rapidly growing mycobacteria frequently is visually distinctive due to the typical inguinal location, characteristic undermining of adjacent skin, and the purple depressions overlying accumulations of pus. Differential diagnoses in the cat should include bite wound abscesses, deep mycotic infections, and sterile nodular panniculitis. Greater local tissue swelling, pain, or signs of systemic illness are more common with bite wound abscesses and systemic mycoses. Sterile nodular panniculitis is extremely rare in the cat and must be differentiated by histopathology and culture.

Differential diagnosis in the dog may be more problematic, since the clinical presentation in this species is not visually distinctive. The nodules of canine opportunistic mycobacterial infections may mimic other bacterial or fungal infectious diseases of the skin, including actinomycosis or nocardiosis, deep folliculitis and furunculosis, cryptococcosis and other systemic fungal infections, or cutaneous infections of opportunistic fungi and algae. However, if systemic fungal infection is suspected, culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291).

Differentiation is accomplished by cytologic examination with special staining of exudates or aspirates, histopathology, and routine and special culture techniques. Direct smears of exudate and bacterial culture may be more rewarding than histopathology in identifying the etiologic agent in opportunistic mycobacterial infections. According to Malik et al. (2000), needle aspirations of affected tissue most frequently provide diagnostic specimens. Touch preparations from freshly incised biopsy specimens or smears of exudate also may be useful in identifying organisms. Acid-fast stains should be requested for all microbiological or cytological specimens submitted to the laboratory.

Biopsy site selection

Specimens should be taken by wedge technique from dermal and subcutaneous tissue at the deep advancing margins of a lesion. Care must be taken not to seed the surgical site with organisms during the biopsy process. Punch biopsy commonly is not sufficient to obtain deep tissue. Overlying skin alone may not contain characteristic inflammation and organisms, particularly if the specimen is removed from the devitalized margin. If opportunistic mycobacterial infection caused by rapidly growing mycobacteria is suspected in resectable lesions, lesions should be removed with wide margins since surgical extirpation offers the best chance of cure. After the lesion is resected, a final peripheral excision well into unaffected tissue should be performed using fresh sterile instruments.

Histopathology (Figures 12.23 through 12.25)

The epidermis is usually acanthotic or ulcerated. Typically, multinodular to diffuse pyogranulomatous dermatitis and panniculitis are present; inflammation usually extends to the deeper subcutis as well. Isolated subcutaneous nodules have been seen. A thin rim of neutrophils and a wider outer zone of epithelioid macrophages comprise pyogranulomas, which surround variably sized, central clear zones. These clear spaces correspond to residual lipid from degenerating adipocytes (lipocysts). Pyogranulomas without central spaces may be observed as well. Pyogranulomas often are confluent and are interspersed with diffuse inflammation composed of macrophages and neutrophils. Additionally, there may be

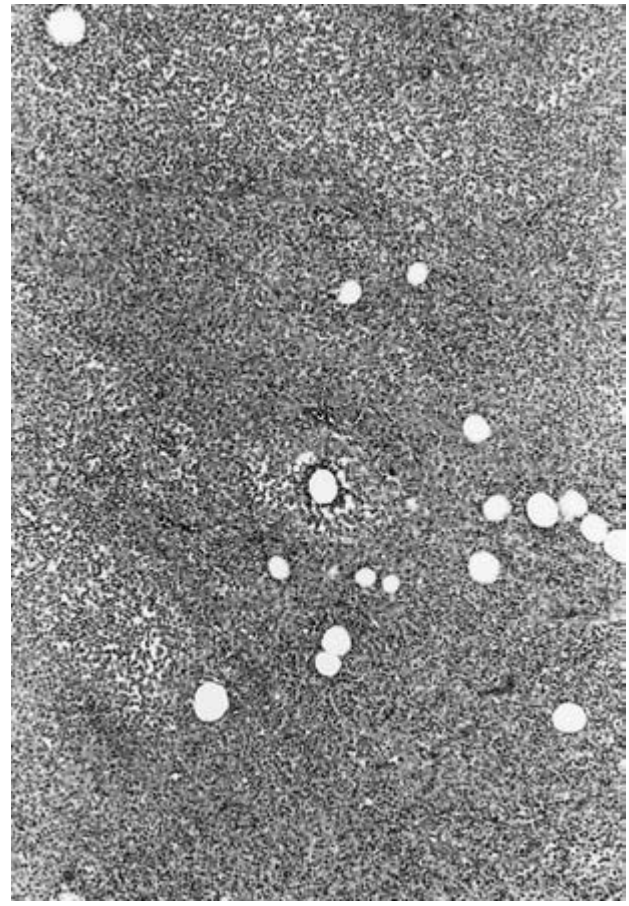


Fig. 12.23 Opportunistic mycobacterial infection caused by rapidly growing mycobacteria in a cat. Pyogranulomas surround central clear zones.

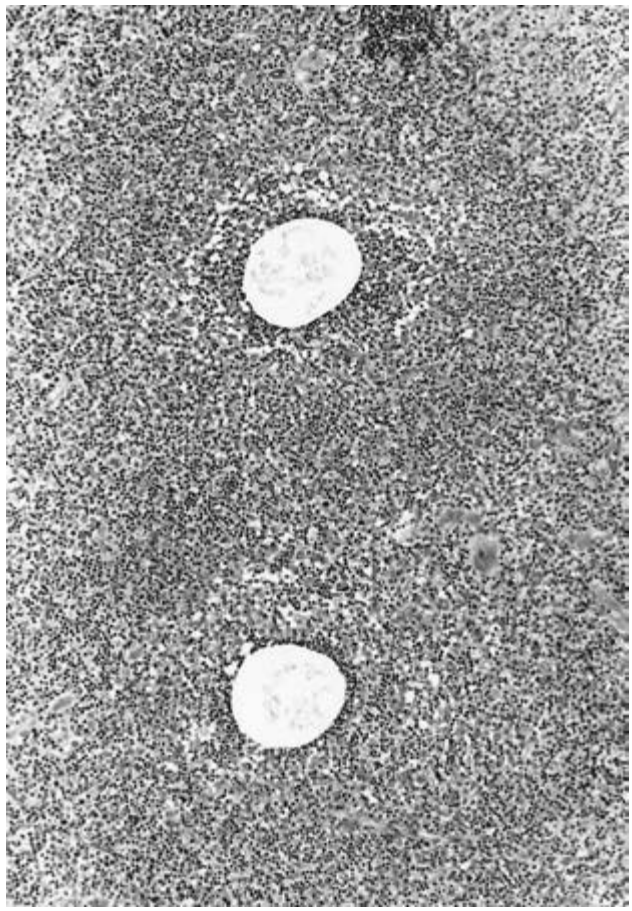


Fig. 12.24 Higher magnification of opportunistic mycobacterial infection caused by rapidly growing mycobacteria in a cat. Clear spaces contain organisms that are faintly stained with hematoxylin and eosin.

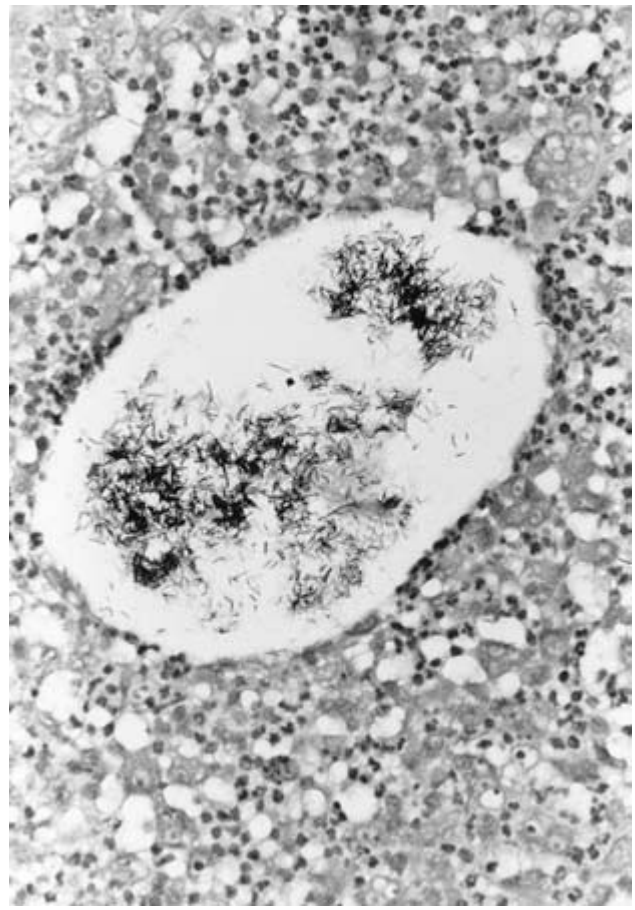


Fig. 12.25 High magnification of atypically numerous, tangled, filamentous acid-fast mycobacteria in the cat of Fig. 12.23 (Fite–Faraco).

large lakes of neutrophils. Plasma cells and lymphocytes may be numerous amongst the pyogranulomatous infiltrates. Lymphoid nodules often are observed, sometimes at the periphery of the lesion. Fibrosis may subdivide the infiltrate into lobules as well as encompass the lesion. Giant cells usually are not present; rare or scattered giant cells previously have been reported (Lewis et al., 1994; Fox et al., 1995). Giant cells may be difficult to detect due to lack of sharp cell borders within the epithelioid infiltrate.

Rapidly growing opportunistic mycobacteria are often, but not invariably, difficult to find in tissue section. When they are numerous, they may be partially visible in hematoxylin and eosin (HE) stained tissue. A Fite–Faraco modification of the acid-fast stain (Fite's stain) is useful in identification of these organisms. The staining process employs peanut oil to prevent excessive decolorization. Frozen sections of formalin-fixed specimens may enhance discovery of the bacteria, as xylene and alcohol (lipid solvents used during routine processing of tissue) are circumvented except for brief immersion following staining and before application of the coverslip. The polyclonal anti-*Mycobacterium bovis* (BCG) stain is superior in labeling mycobacteria (Bonenberger et al., 2001), and may be of benefit in suspected cases with scant organisms. The stain may also detect partially degraded bacteria within macrophages. Very small to occasionally large numbers of filamentous, sometimes tangled, and slightly beaded, acid-fast rods are found usually in the clear centers of pyogranulomas where staining may be preserved due to the presence of protective fat of the panniculus. Organisms also may be found in small numbers within macrophages.

Differential diagnoses of opportunistic mycobacterial infection caused by rapidly growing mycobacteria include foreign body reactions and other deep infections due to bacteria or fungi. Pyogranulomas surrounding clear central spaces are very suggestive of rapidly growing

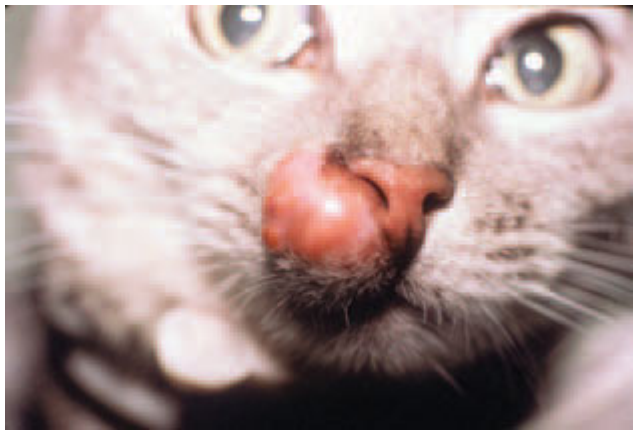


Fig. 12.26 Opportunistic mycobacterial infection caused by *Mycobacterium avium* complex. A firm, alopecic nodule is deforming the right side of the muzzle and involves haired skin and the planum nasale. (From Stewart, L.J., White, S.D., Kennedy, F.A. et al. (1993) Cutaneous *Mycobacterium avium* infection in a cat. *Vet Dermatol* **4**, 87–90. Reprinted with permission.)



Fig. 12.27 Same cat as in Fig. 12.26, 10 weeks later. Note progression to severe ulceration. (From Stewart, L.J., White, S.D., Kennedy, F.A. et al. (1993) Cutaneous *Mycobacterium avium* infection in a cat. Vet Dermatol **4**, 87–90. Reprinted with permission.)

opportunistic mycobacterial infection with HE stain, but can be featured in other deep infections, including those of higher bacteria (see p. 272). Demonstration of acid-fast organisms in these central clear spaces is highly supportive of the diagnosis, but should be confirmed by culture. These opportunistic mycobacteria may closely resemble *Nocardia* spp. in tissue. Larger clusters or longer chains of bacteria characterize nocardiosis and these organisms are generally only partially acid-fast; however, culture may be required for ultimate differentiation.

OPPORTUNISTIC MYCOBACTERIAL INFECTION CAUSED BY *MYCOBACTERIUM AVIUM* COMPLEX

(Synonyms: feline Mycobacterium avium infection, opportunistic mycobacterial infection caused by Mycobacterium avium–Mycobacterium intracellulare)

Clinical features (Figures 12.26 and 12.27)

Opportunistic infection caused by the Runyon Group III mycobacteria, *Mycobacterium avium* complex (MAC), is a rare cause of skin or visceral disease in the cat and dog. Of all the opportunistic mycobacteria, MAC organisms are most likely to produce bacteremia and systemic disease involving multiple visceral organs (Greene & Gunn-Moore, 1998). The paucity of reported cases of feline and canine infection probably reflects intrinsic species resistance to the MAC organism. *Mycobacterium avium* complex organisms are not reported to have either zoonotic potential or to be contagious from cat to cat. However, since the visceral 'tubercular' granulomas caused by MAC organisms are virtually indistinguishable from those caused by the highly pathogenic tubercle-producing mycobacteria, *Mycobacterium tuberculosis* and *Mycobacterium bovis*, differentiation is important because of public health concerns (Greene & Gunn-Moore, 1998). *Mycobacterium avium* complex organisms exhibit slow growth on specialized solid media and may require 4 to 6 weeks.

Mycobacterium avium complex organisms are saprophytic mycobacteria found in acidic soil with a high concentration of organic matter (Greene & Gunn-Moore, 1998). These environmental conditions are best met in acidic swamps and brackish coastal waters. Feces of infested birds harbor large numbers of MAC organisms (Greene & Gunn-Moore, 1998). Feline and canine infection most likely occurs as a result of contact with infected soil, contamination with bird carcasses or feces, or ingestion of contaminated meat (Greene & Gunn-Moore, 1998). Presumed portals of entry include the skin, alimentary tract, and the respiratory tract.

Single or multiple dermal or subcutaneous nodules may be seen (Buergelt et al., 1982, Stewart et al., 1993). Larger nodules may fistulate and ulcerate (Miller et al., 1999). Regional lymphadenopathy is noted. Visceral mycobacterial infection with MAC organism produces 'tubercular' granulomas and preferentially targets lymphoid tissue, but may affect virtually any visceral organ (Greene & Gunn-Moore, 1998).

Siamese cats, Basset Hounds, and Miniature Schnauzers are over-represented in case populations of animals with visceral disease due to MAC organisms, perhaps indicating selective absence of immune surveillance (Greene & Gunn-Moore, 1998). Breed predilections

are not available for opportunistic cutaneous infections caused by MAC organisms. Age or sex predilections are not reported for either cutaneous or visceral disease.

Clinical differential diagnoses for cutaneous infection with MAC organisms should primarily include nodular neoplasms, and sterile granuloma and pyogranuloma syndrome. If systemic fungal infection is suspected, culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291). Diagnosis is accomplished by cytologic examination with special staining of exudates, impression smears, or needle aspiration of nodules, and histopathology. If necessary, MAC organisms can be differentiated from tuberculosis by nucleic acid testing (Greene & Gunn-Moore, 1998).

Biopsy site selection

An intact nodule should be excised surgically using wedge technique. If a solitary lesion is present, complete excision is recommended, as it may provide the added benefit of a surgical cure.

Histopathology (Figure 12.28)

Mycobacterium avium complex infections in the skin and subcutis of cats are characterized by granulomatous or pyogranulomatous inflammation, accompanied by a variable fibroblastic reaction (Buergelt et al., 1982; Kaufman et al., 1995; Stevenson et al., 1998). In one morphologic presentation, large foamy or granular macrophages and multinucleated giant cells are accompanied by fewer neutrophils and lymphocytes (Stewart et al., 1993). Small bands of fibroblasts may subdivide the infiltrate into lobules (Buergelt et al., 1982). In the second morphologic presentation, spindle cells predominate as interlacing bundles (Miller et al., 1999). Neutrophils and histiocytic cells are interspersed among the spindle cell population. This severe and dominant fibroblastic-like reaction may mimic a sarcoma. Therefore, unusual inflamed spindle cell lesions in cats need to be stained routinely for mycobacteria. Organisms are invariably numerous in both forms of MAC infection (Stewart et al., 1993), and are found within macrophages as well as spindle cells (Miller et al., 1999).

In feline MAC infection without severe spindle cell proliferation, the finding of large numbers of organisms in foamy macrophages is similar to feline lepromatous leprosy (Kaufman et al., 1995; Stevenson et al., 1998). A fibrovascular network is present within the inflammatory infiltrate of *Mycobacterium avium* infection, in contrast to feline leprosy (Buergelt et al., 1982; Kaufman et al., 1995). Also, unlike the mycobacterium of feline leprosy, MAC organisms can be identified by culture. In the spindle cell predominant sarcomatous pattern, other inflamed sarcomas should be considered; acid-fast stains allow differentiation (Miller et al., 1999).

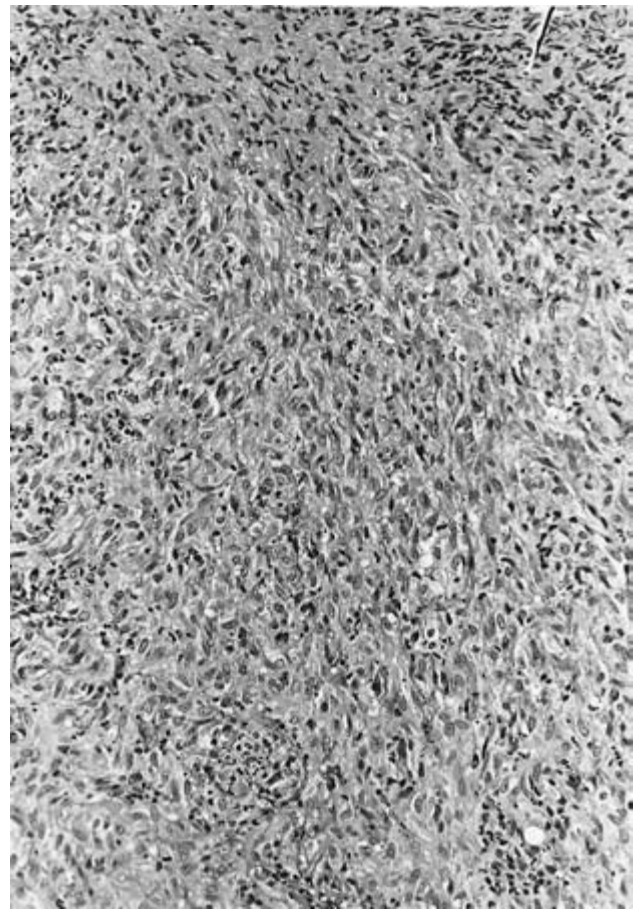


Fig. 12.28 Opportunistic mycobacterial infection caused by *Mycobacterium avium*, demonstrating prominent spindle cell proliferation amidst pale macrophages and scattered neutrophils. (Case material courtesy M.A. Miller.)

DERMATOPHYTIC PSEUDOMYCETOMA

(Synonym: dermatophytic mycetoma)

Clinical features (Figures 12.29 and 12.30)

Dermatophytic pseudomycetomas are uncommon to rare, deep cutaneous to subcutaneous fungal infections that produce tissue grains or granules. These tissue grains are composed of fungal aggregates imbedded in amorphous eosinophilic material presumed to be antigen–antibody complexes (Splendore–Hoeppli reaction), as seen in higher bacterial infections (see p. 272). The syndrome is



Fig. 12.29 Feline dermatophytic pseudomycetoma due to *Microsporum canis* in the scapular region of a Persian cat. Crusted and hyperpigmented nodules have an irregular contour.



Fig. 12.30 Feline dermatophytic pseudomycetoma due to *Microsporum canis* on the dorsal trunk of a Persian cat. Note irregularly shaped, coalescing, subcutaneous and dermal nodules. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

uncommon in cats and rare in dogs. In cats, the syndrome is seen almost exclusively in Persian cats.

The term 'pseudomycetoma' for dermatophytic granulomatous skin disease has gained acceptance over mycetoma (Ajello et al., 1980; Rinaldi et al., 1983). Although dermatophytic granulomatous skin disease fulfills most of the criteria for true mycetomas (nodular inflammation with fibrosis, fistulae draining from deep tissue, presence of tissue grains), fewer hyphal elements are present, and the lesions apparently lack the cement substance that holds true mycetoma grains together.

Microsporum canis has been isolated in all well-substantiated and histologically typical cases of dermatophytic pseudomycetomas published to date where fungal culture was performed (Medleau & Rakich, 1994; MacKay et al., 1997; Abramo et al., 2001; Bond et al., 2001). Additionally, *Trichophyton mentagrophytes* has been reported to cause dermatophytic granulomas, but these do not have the typical histologic features of dermatophytic pseudomycetoma as grains are lacking (Bergman et al., 2002).

In humans, a selective immune deficit has been proposed as a relatively common cause of chronic dermatophytosis (Jones, 1993). Persian cats are predisposed to conventional dermatophytosis (Scott et al., 2001) as well as dermatophytic pseudomycetoma. This marked breed predilection suggests that a genetically preprogrammed, selective immunodeficiency may play a role in the development of dermatophytic pseudomycetoma in this breed. Dermatophytic pseudomycetoma has been reported in two Yorkshire Terriers (MacKay et al., 1997; Abramo et al., 2001). Granulomatous skin disease caused by *Trichophyton mentagrophytes* has been reported in a Manchester Terrier (Bergman et al., 2002). One author (P.J.I.) has the strong clinical impression that both the Yorkshire Terrier and the Manchester Terrier are over-represented breeds for generalized dermatophytosis as well as for poor response to antifungal therapy, both of which may predispose them to dermatophytic pseudomycetoma.

Presumably, pseudomycetomas begin with more typical follicular dermatophyte colonization. Frequent localization of pseudomycetomas to the dorsal thorax in outdoor cats suggests traumatic implantation of organisms into the dermis and subcutis from colonized hairs. This traumatic implantation of organisms could result from fights or mating behavior. Positive dermatophyte cultures from normal-appearing areas distant from the dermatophytic pseudomycetoma indicate that affected cats may previously have been inapparent carriers. Inapparent carriage of *Microsporum canis* is common in Persian and Himalayan cats.

Firm, irregularly shaped nodules (5 to 20 mm in diameter) develop and gradually enlarge and coalesce in the dermis or the underlying subcutaneous tissue. Larger lesions may ulcerate and discharge a seropurulent to granular material. Hyperpigmentation may overlie chronic lesions. Concomitant alopecia may be a feature if the syndrome coexists with more typical feline dermatophytosis. Lesions usually are grouped but may be solitary. Lymphadenopathy may be present, but systemic signs are uncommon. One author (T.L.G.) has seen dermatophytic pseudomycetoma in a lymph node. Intra-abdominal dermatophytic granulomatous peritonitis sharing many features with pseudomycetoma has been reported in a Persian cat (Black et al., 2001). Recurrence after seemingly successful therapy is common.

Feline dermatophytic pseudomycetoma is seen almost exclusively in Persian cats, and to a lesser extent in Himalayan cats. Age and sex predilections have not been

noted. Published cases of granulomatous dermatophytic skin disease in dogs to date include a Manchester Terrier, two Yorkshire Terriers, and a Chow Chow (MacKay et al., 1997; Abramo et al., 2001; Bergman et al., 2002).

Clinical differential diagnoses should include cryptococcosis and other systemic mycoses, sporotrichosis, cutaneous infections of other opportunistic fungi, and neoplasia. The marked breed predilection for Persian cats is helpful in increasing the index of suspicion for dermatophytic pseudomycetoma. Histopathology and separate fungal culture of a tissue specimen are required for differentiation. If systemic fungal infection is suspected, culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291). Positive fungal culture from distant sites, positive fluorescence with a Wood's lamp, or a positive trichogram (microscopic hair analysis) for dermatophytosis increases the likelihood of dermatophytic pseudomycetoma.

Biopsy site selection

An entire nodule should be removed using wedge resection technique. If the lesion is solitary, as in early cases, this may afford the added benefit of a potential surgical cure. If dermatophytic pseudomycetoma is suspected clinically, a deep portion of the lesion should be submitted for dermatophyte culture, after the overlying epidermis has been removed using sterile technique. Care must be taken not to seed the surgical site with organisms during the biopsy process.

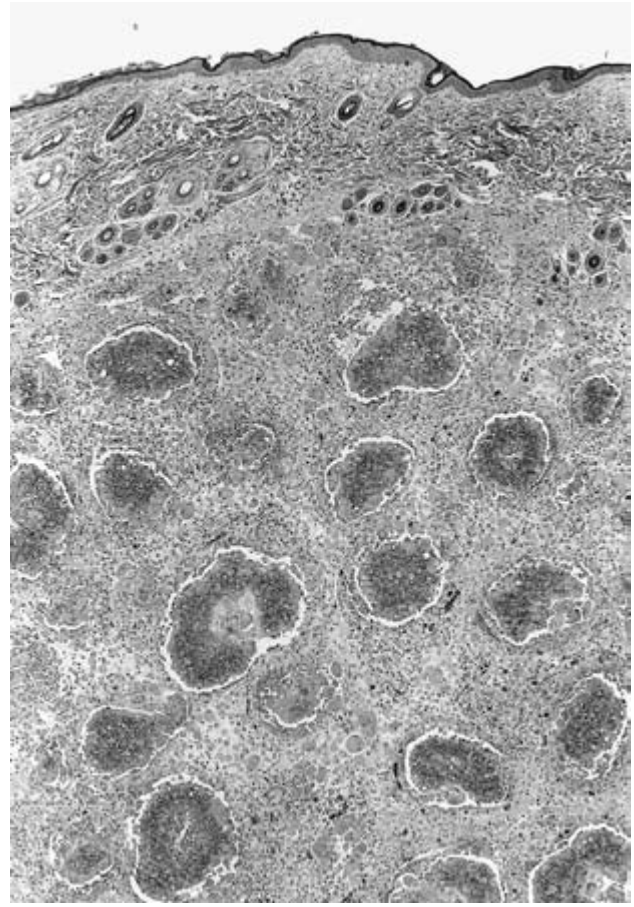


Fig. 12.31 Feline dermatophytic pseudomycetoma due to *Microsporum canis*. Granules composed of discrete colonies of dermatophytes are surrounded and interspersed by granulomatous inflammation.

Histopathology (Figure 12.31 and 12.32)

Lesions are most often encountered in cats and are reportedly identical in dogs (Abramo et al., 2001). The overlying epidermis and superficial dermis may be unremarkable, except for mild to moderate acanthosis, or minimal perivascular or periadnexal mixed inflammation. Ulceration may be present. Often there is some colonization of hair shafts by dermatophytic spores and hyphae.

Diagnostic lesions are found in the subfollicular dermis and subcutis. Large amorphous aggregates are composed of tight clusters of somewhat refractile, pleomorphic fungal hyphae. These are tangled and delicate, and contain numerous large, clear, bulbous, thick-walled dilatations, resembling spores. Smaller swellings within the hyphae create a vacuolated or bubbly appearance to these structures. The fungal aggregates are imbedded in amorphous eosinophilic material to form large tissue grains, or granules that are also visible grossly. The brightly eosinophilic material is Splendore–Hoeppli reaction, which represents an antigen–antibody reaction around infectious agents or parasites that occurs at the periphery of organized aggregates of organisms. Granules are cuffed by and intermingled with large macrophages, giant cells, and variable, sometimes numerous neutrophils. Macrophages have abundant, granular cytoplasm. In some cases, fragments of hyphae are present within individual macrophages beyond the boundaries of tissue grains or granules. Proliferating fibroblastic tissue may surround the outer aspect of the lesions but also courses amongst the granules, often creating lobules composed of multiple granules and their attendant inflammation. Lymphocytes and plasma cells may be present in small numbers at the margins of the lobules or at the outer edges of the mycetoma. Peripheral lymphocytic nodules or follicles have been observed.

Organisms are strongly positive using periodic acid–Schiff (PAS) and Gomori's methenamine silver (GMS) stains. Periodic acid–Schiff and GMS-positive

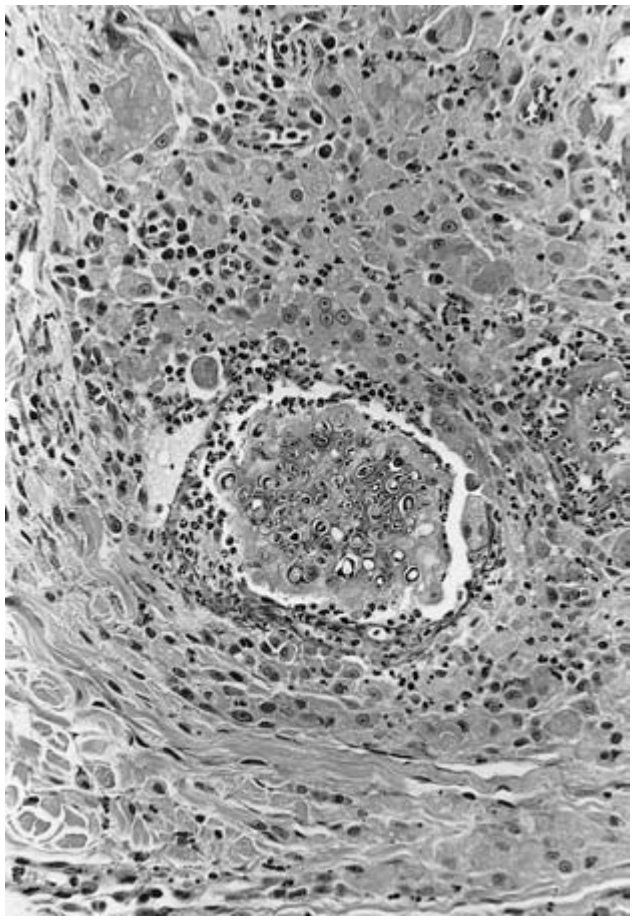


Fig. 12.32 Higher magnification of a granule of dermatophytic pseudomycetoma. Irregular hyphae with bulbous, spore-like dilatations are imbedded in Splendore–Hoeppli reaction. Note the thin rim of neutrophils surrounding the granule and large epithelioid macrophages in the outer zone of inflammation.

amorphous material may also be found within the large macrophages that encircle the granules. This material may be breakdown debris from ingestion of fungal organisms. This is suggested by the presence of intact portions of hyphae in many macrophages that lie beyond the boundaries of tissue granules. Culture confirms dermatophyte infection, generally *Microsporum canis*. Immunohistochemistry using rabbit anti-*Microsporum canis* antiserum identified this etiologic agent in two canine cases by specifically staining the fungal organisms in tissue (Abramo et al., 2001).

The reported case of granulomas caused by *Trichophyton mentagrophytes* in a dog differed histopathologically from dermatophytic pseudomycetomas. Organisms, which also heavily colonized the keratin of hair follicles and the epidermis, were diffusely organized within granulomatous inflammation of the dermis, panniculus, and subcutis. Tissue grains containing aggregates of organisms were not identified (Bergman et al., 2002).



Fig. 12.33 Cutaneous blastomycosis in a dog. Well-demarcated nodules of the muzzle have coalesced and ulcerated. (Photograph courtesy V.A. Fadok.)

The histopathologic appearance of dermatophytic pseudomycetoma is distinctive, but may need to be differentiated from other fungal infections. Most of the systemic and opportunistic fungi affecting cats and dogs are smaller and more uniform in appearance in tissue section, and do not accumulate in tissue grains or granules. In contrast, the diffuse distribution of *Trichophyton mentagrophytes* in dermatophytic granulomas is similar to opportunistic fungal infection (Bergman et al., 2002). Concurrent identification of *Trichophyton mentagrophytes* in the keratin of hair follicles and epidermis (typical of this organism) will allow diagnosis.

CUTANEOUS BLASTOMYCOSIS, HISTOPLASMOSIS, AND COCCIDIOIDOMYCOSIS

Clinical features (Figures 12.33 through 12.37)

Blastomycosis, histoplasmosis, and coccidioidomycosis are systemic mycoses that occasionally disseminate secondarily to the skin. The dog is a natural host for these three systemic mycoses. Canine blastomycosis is the most common systemic mycosis seen in small animal practice; skin lesions are seen in up to 40% of affected dogs (Legendre, 1998). Cutaneous involvement is uncommon in histoplasmosis and coccidioidomycosis (Greene, 1998; Wolf, 1998). The systemic mycoses are considered



Fig. 12.34 Multiple nodules and soft tissue swelling on the hindleg of the dog in Fig. 12.33. (Photograph courtesy V.A. Fadok.)



Fig. 12.35 Closer view of an ulcerated nodule on the hindleg of the dog in Fig. 12.33. Drainage is minimal. (Photograph courtesy V.A. Fadok.)

regional dermatoses with geographic restrictions to certain endemic areas globally (see Table 12.1). Histoplasmosis is seen in the cat as frequently as it is in the dog (Wolf, 1998). Blastomycosis and coccidioidomycosis are both rare in the cat. Cryptococcosis, another systemic mycosis caused by an encapsulated yeast-like fungus, is discussed separately as the organism is viewed as an opportunist with infection predominantly seen in



Fig. 12.36 Histoplasmosis in a cat. Soft tissue swelling and ulceration are severe. The cat is wearing an Elizabethan collar. (Photograph courtesy M. Rosenbaum.)



Fig. 12.37 Different view of the cat in Fig. 12.35. (Photograph courtesy M. Rosenbaum.)

conjunction with debilitating underlying disease or immunosuppression (see p. 295).

The organisms that cause these systemic mycoses, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides immitis*, are able to invade the normal immunocompetent host, usually via inhalation of conidia, and are thus differentiated from the opportunistic systemic mycosis, cryptococcosis, plus other opportunistic fungal infections. In most cases, cutaneous infection with these three systemic fungi should be considered a manifestation of underlying disseminated visceral disease. Very rarely, direct wound inoculation with these fungal organisms may produce solitary primary skin lesions; this may

Table 12.1 Ecology of the systemic mycoses.

Disease	Ecologic niche	Endemic areas
Blastomycosis	Moist soil enriched with organic debris, waterways, water	Mississippi–Missouri–Ohio River Valleys, mid-Atlantic states (USA), Africa, Central America
Histoplasmosis	Bird or bat excrement	Mississippi–Missouri–Ohio River Valleys, temperate and sub-tropical regions globally
Coccidioidomycosis	Desert soil, high temperature, low rainfall, dust storms	Southwestern USA, Mexico, Central and South America (lower Sonoran life zone)

be most common in coccidioidomycosis. Skin lesions seen with systemic mycoses are generally of much less consequence than the underlying, often life-threatening, visceral disease.

A commonality of skin lesions among the systemic mycoses is observed. Variability is contingent on the host species, organism, portal of entry, and anatomic site of infection. Papular to nodular lesions progress to abscessation or ulceration, and draining fistulous tracts may develop. Draining fluid may be either serosanguinous or purulent. Other lesions may be proliferative without drainage.

Ulceration with drainage of serosanguinous or purulent fluid is typical of cutaneous blastomycosis (Legendre, 1998). Well-defined subcutaneous abscesses may be present (Legendre, 1998). The planum nasale, face, and clawbeds may be preferred sites (Legendre, 1998). The hard palate and scrotum also may be preferentially affected (Grooters, 2002).

Cutaneous histoplasmosis causes dermal and subcutaneous nodules similar to blastomycosis; lesions may ulcerate and develop fistulous tracts (Wolf, 1998; Grooters, 2002).

Cutaneous coccidioidomycosis causes similar dermal and subcutaneous nodules, usually localized over sites of subjacent infected bone (Greene, 1998). Ulceration and drainage is common with coccidioidomycosis. Ulcerated nodules, subcutaneous abscesses, and draining fistulous tracts are the most frequently seen skin lesions (Grooters, 2002). Rarely, skin lesions have been seen without evidence of systemic involvement (Plotnick et al., 1997).

Noncutaneous signs of systemic mycoses include anorexia, weight loss, fever, depression, cough, dyspnea, ocular disease, and lameness. The lungs are often the primary site of infection in systemic mycoses. The reader is referred to standard texts of infectious diseases and mycology for further information (Greene, 1998).

Reported breed predilections for blastomycosis include sporting dogs and hounds, as well as larger breed dogs in general (Rudmann et al., 1992; Legendre, 1998). Bluetick Coonhounds, Walker Hounds, Pointers, and Weimaraners are reportedly at highest risk (Rudmann et al., 1992). Doberman Pinschers also are at increased risk (Legendre, 1998). Male dogs, possibly due to behavioral characteristics, are at greater risk (Legendre, 1998). The highest disease prevalence for blastomycosis is reportedly in 2-year-old dogs (Legendre, 1998).

Breed predilections for histoplasmosis include pointers, Weimaraners, and Brittanys (Wolf, 1998). Histoplasmosis is seen most commonly in young dogs and cats less than 4 years old (Wolf, 1998). Female cats appear to be over-represented, but sex predilection has not been noted in dogs (Wolf, 1998).

A greater prevalence of disseminated coccidioidomycosis following respiratory infection has been reported in Boxers and Doberman Pinschers in the older literature (Maddy, 1958). A possible predilection for male dogs has been reported (Selby et al., 1981)

Clinical differential diagnoses include cutaneous cryptococcosis, sporotrichosis, cutaneous infections of other opportunistic fungi and algae, feline leprosy syndrome, opportunistic mycobacterial infection, canine leproid granuloma, sterile granuloma and pyogranuloma syndrome, reactive histiocytosis, and neoplasia. Travel history to or residence in endemic areas is important in raising the index of suspicion. Cytology of impression smears and exudate, and/or histopathology are required for definitive diagnosis.

Fungal culture is not recommended for veterinary practices or most diagnostic laboratories because of substantial danger of infection from the mycelial forms of these fungal organisms (Legendre, 1998). Primary pulmonary blastomycosis continues to be reported occasionally in laboratory workers exposed to cultures of the mycelial form of *Blastomyces dermatitidis* (Cote et al., 1997). A veterinarian died of disseminated coccidioidomycosis after transporting necropsy material from a horse with disseminated infection; physicians postulated that transmission occurred by inhalation of aerosolized tissue-phase endospores (Kohn et al., 1992). This further emphasizes

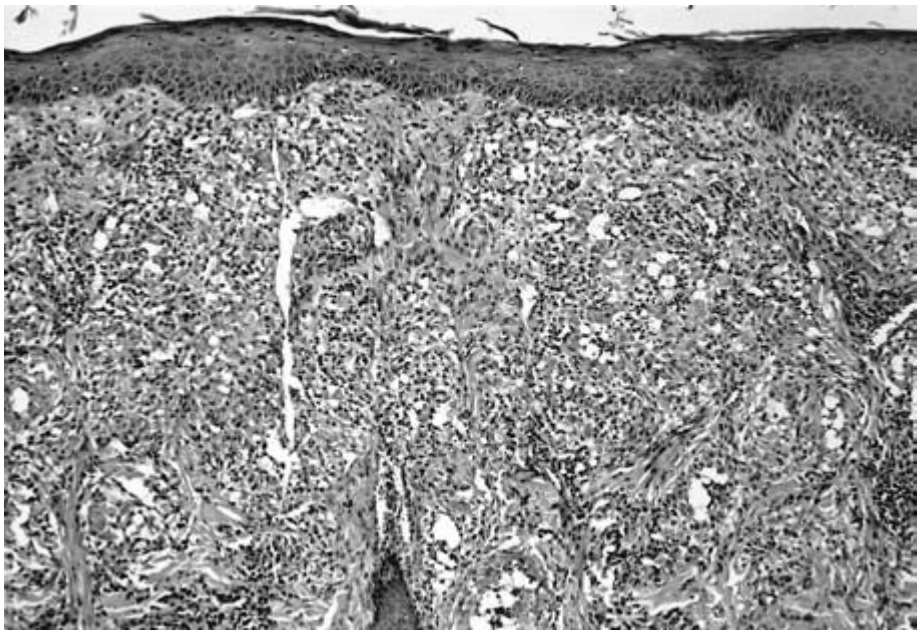


Fig. 12.38 Cutaneous coccidioidomycosis demonstrating diffuse pyogranulomatous inflammation of the dermis.

that strict caution should be exercised in the handling of all specimens from suspected or confirmed systemic fungal infection.

Biopsy site selection

Intact nodules, when present, should be surgically excised for histopathology. Impression smears for cytology should be made from freshly cut biopsy specimens and exudates. Clinicians and laboratory personnel should wear protective gloves when handling fresh specimens, if systemic mycoses are suspected. Although systemic mycoses are not considered to be contagious diseases, localized skin lesions have been reported in humans in conjunction with the direct inoculation of infective material via contaminated needles or scalpels (Legendre, 1998). Blastomycosis has been seen secondary to bites from an infected dog (Legendre, 1998). Fortunately, systemic dissemination of these accidental skin infections has not been reported.

Histopathology (Figures 12.38 through 12.40)

The epidermis may be acanthotic, or ulcerated and exudative. The dermis, panniculus, and sometimes the deeper subcutis contain a nodular to diffuse infiltration of large macrophages, admixed with variable neutrophils, lymphocytes, and plasma cells. Discrete granulomas or pyogranulomas often are present. Necrosis may be observed and there may be abundant deep and/or peripheral fibrosis. Organisms are found in tissue as yeasts, often at the center of pyogranulomas or granulomas. The yeast phase

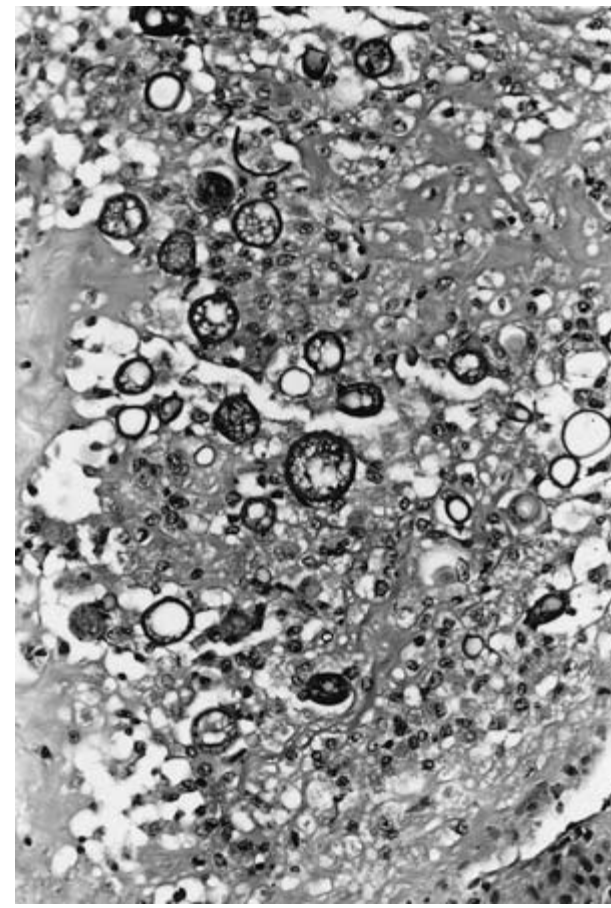


Fig. 12.39 High magnification of *Coccidioides immitis* in a dog, featuring atypically large numbers of spherules with endospores.

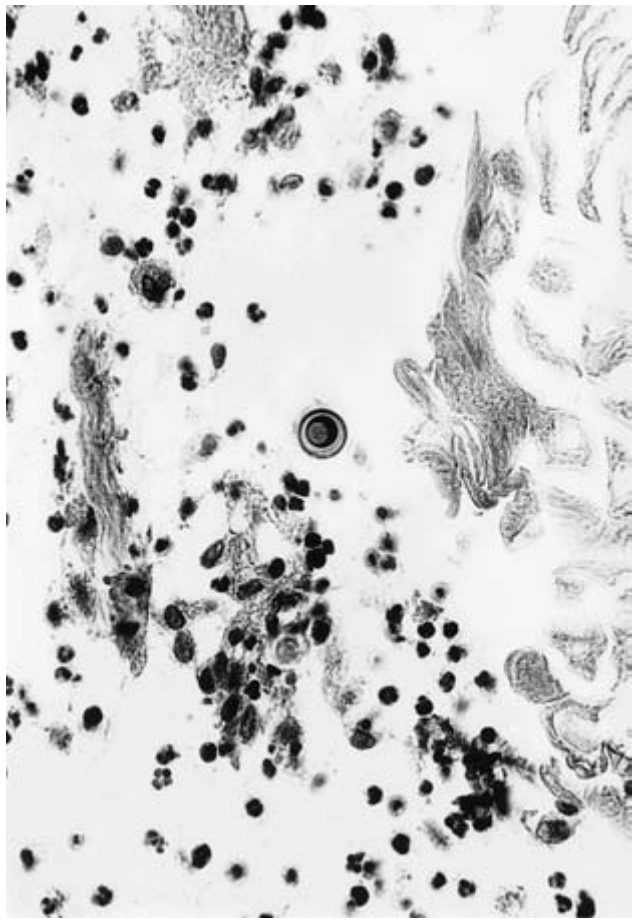


Fig. 12.40 High magnification of *Blastomyces dermatitidis* in a skin lesion from a dog.

Table 12.2 Histopathologic features of the systemic mycoses.

Organism	Morphology	Location
Blastomyces dermatitidis	Spherical; 5–20 µm; double wall; broad based budding	Free and in macrophages
Coccidioides immitis	Spherules with endospores; 20–80 µm; double wall	Free
Histoplasma capsulatum	Egg-shaped; 2–4 µm; clear halo within single wall	In macrophages

of these organisms has single or double-contoured walls; fungal stains such as periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) will selectively stain the wall. Tissue identification depends on recognition of typical morphologic features of the individual organisms (see Table 12.2). Numbers of organisms vary from scarce to moderate in coccidioidomycosis and blastomycosis, and numerous in histoplasmosis.



Fig. 12.41 Cutaneous cryptococcosis in a cat. Large ulcerated dermal nodules efface and disfigure the dorsal muzzle, planum nasale, and periorbital regions. (Photograph courtesy N. Gulbas & C. Foil.)

Differential diagnoses include foreign body reactions (if organisms are not easily seen) and other pyogranulomatous infections due to bacteria or fungi. Differential diagnosis is not difficult if organisms are identified, as the morphologic characteristics of these generally are diagnostic, particularly for coccidioidomycosis. Histoplasmosis and sporotrichosis are similar in size and distribution; typical cigar-shaped, slightly larger organisms of sporotrichosis and the increased prevalence of this infection in cats should allow separation. In dogs, sporotrichosis may be similar to blastomycosis; organisms are similarly sparse and display budding. *Blastomyces dermatitidis* is larger than *Sporothrix schenckii*.

CUTANEOUS CRYPTOCOCCOSIS

Clinical features (Figure 12.41)

Cryptococcosis is a systemic and opportunistic mycosis caused by the encapsulated yeast-like fungus, *Cryptococcus neoformans*. The causative organism is a ubiquitous saprophyte found in nitrogen-rich, alkaline debris, but the organism is isolated most commonly from soil contaminated with pigeon excrement. Two variants and five serotypes of *Cryptococcus neoformans* have been identified. Marked differences in virulence are noted. The heteropolysaccharide capsule, consisting predominantly of glucuronoxlomannan, confers virulence and resistance to desiccation (Jacobs & Medleau, 1998).

Cryptococcosis is global in distribution. However, the disease is seen most frequently in humid, subtropical

regions of the world. Although uncommon, cryptococcosis is the most frequently diagnosed systemic mycosis in the cat. Skin lesions are seen in approximately 40% of cats with cryptococcosis (Jacobs & Medleau, 1998). The respiratory tract, skin, central nervous system, and eyes are affected most commonly in the cat. Cutaneous cryptococcosis is very rare in the dog.

Inhalation of airborne organisms into the upper respiratory tract is thought to be the usual portal of entry (Jacobs et al., 1997; Jacobs & Medleau, 1998). Intranasal granulomatous disease is the most common initial infection and accounts for more than 80% of the cases of feline cryptococcosis (Grooters, 2002). Feline cutaneous cryptococcosis most often occurs as a sequela to nasal involvement. Spread to the skin of the muzzle may occur simply by local extension. Experimental direct inoculation has produced localized disease; this is not reported as occurring spontaneously (Jacobs & Medleau, 1998).

The organism generally is considered to be an opportunist, as cryptococcosis may be seen in association with coexistent debilitating or immunosuppressive diseases such as neoplasia and diabetes mellitus. However, since underlying disease commonly is not identified, predisposing factors remain elusive (Jacobs & Medleau, 1998). Cryptococcosis is seen as a sequela to iatrogenic immunosuppression due to glucocorticoids or cytotoxic chemotherapy (Jacobs & Medleau, 1998). The association between feline cryptococcosis and feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infection is controversial, with some data supporting a link and other data discounting association (Gerds-Grogan & Dayrell-Hart, 1997; Jacobs et al., 1997; Jacobs & Medleau, 1998). However, treatment outcome is affected markedly by the status of immunosuppressive viral infection (Jacobs et al., 1997).

Cats develop well-circumscribed, usually grouped, dermal, or subcutaneous, firm or fluctuant nodules. Lesions ulcerate and drain a scant to copious, serous to mucoid exudate. Less commonly, lesions may be solitary or widely disseminated. The head, neck, and ears are affected most frequently. Firm subcutaneous swellings of the dorsal muzzle are a characteristic presentation (Jacobs & Medleau, 1998). Regional lymphadenopathy is common. Visceral and nasal cavity disease can cause a variety of systemic signs including fever, inappetence, weight loss, general malaise, and neurological and ophthalmologic signs.

The rare cases of canine cryptococcosis usually preferentially affect the central nervous system and the eyes (Jacobs & Medleau, 1998). Rare canine cutaneous cryptococcosis results from disseminated systemic disease, and presents as ulcers and fistulas affecting the muzzle, oral cavity, lips, and clawbeds (Jacobs & Medleau, 1998).

Although cryptococcosis is seen in all breeds of cats, one report indicates that Siamese cats may be overrepresented (Jacobs & Medleau, 1998). Male cats accounted for 66% of cases in one recent study (Gerds-Grogan & Dayrell-Hart, 1997). Although cryptococcosis has been seen in cats of all ages, middle-aged cats may be predisposed (Gerds-Grogan & Dayrell-Hart, 1997).

The American Cocker Spaniel is reported to be predisposed in North America, and the Doberman Pinscher and Great Dane are reported to be at greater risk in Australia (Jacobs & Medleau, 1998). Young adult dogs are affected most frequently (Jacobs & Medleau, 1998). Canine sex predilections have not been reported.

Clinical differential diagnoses should include the other cutaneous systemic mycoses (blastomycosis, histoplasmosis, and coccidioidomycosis), sporotrichosis, infections caused by other opportunistic fungi and algae, feline leprosy syndrome, sterile granuloma and pyogranuloma syndrome, reactive histiocytosis, and neoplasia. Diagnosis is confirmed by impression smears of exudate or biopsy specimens, histopathology, culture, or cryptococcal antigen latex agglutination test. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291). The culture of *Cryptococcus neoformans* is not a public health hazard because only the yeast form is routinely isolated.

Biopsy site selection

Wedge or punch biopsy specimens should be taken from intact or recently ulcerated nodules. Impression smears for cytology should be made from freshly cut biopsy specimens. Newer lesions should be sampled, as extensive necrosis may complicate the histopathologic diagnosis in older lesions. In contrast to the other systemic fungi, contact with infected tissue is not a risk to clinicians or laboratory personnel, since the yeast form is not infective and does not aerosolize from tissue.

Histopathology (Figures 12.42 and 12.43)

The epidermis is normal, slightly acanthotic, or ulcerated and exudative. Nodules composed of diffuse infiltrates affect the dermis, panniculus, and sometimes the subcutis. Abundant organisms surrounded by confluent unstained capsules create a pale, foamy or 'soap bubble' low-power appearance to the tissue that is highly characteristic of cryptococcosis. Inflammation often is scant, but may be mild to moderate. Diffusely amongst the infiltrating organisms there are large prominently vacuolated, foamy macrophages, accompanied by variable numbers of neu-

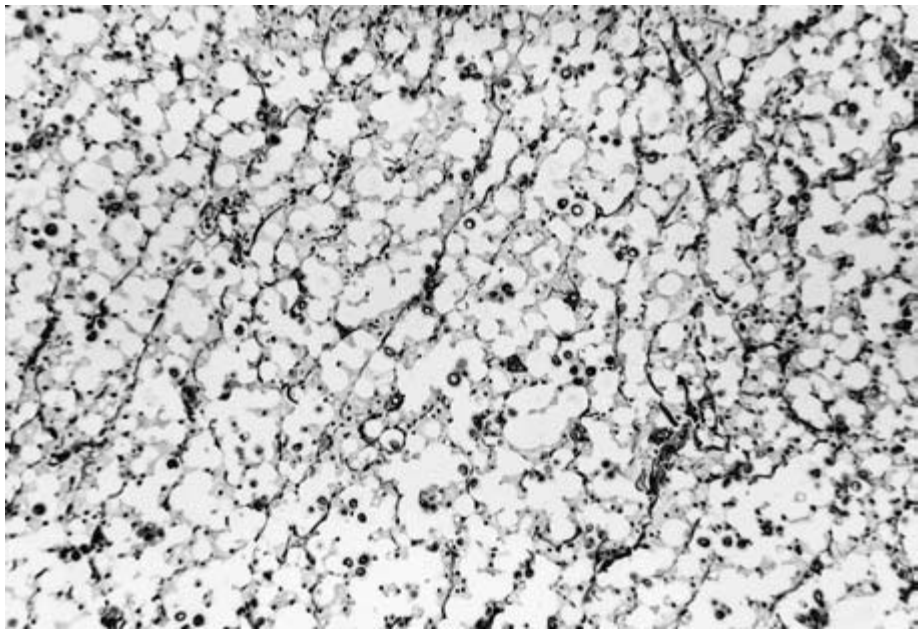


Fig. 12.42 Feline cryptococcosis demonstrating diffuse accumulation of yeast-like organisms. Scant inflammation and prominent capsulation of the organisms create a foamy or bubbly appearance.

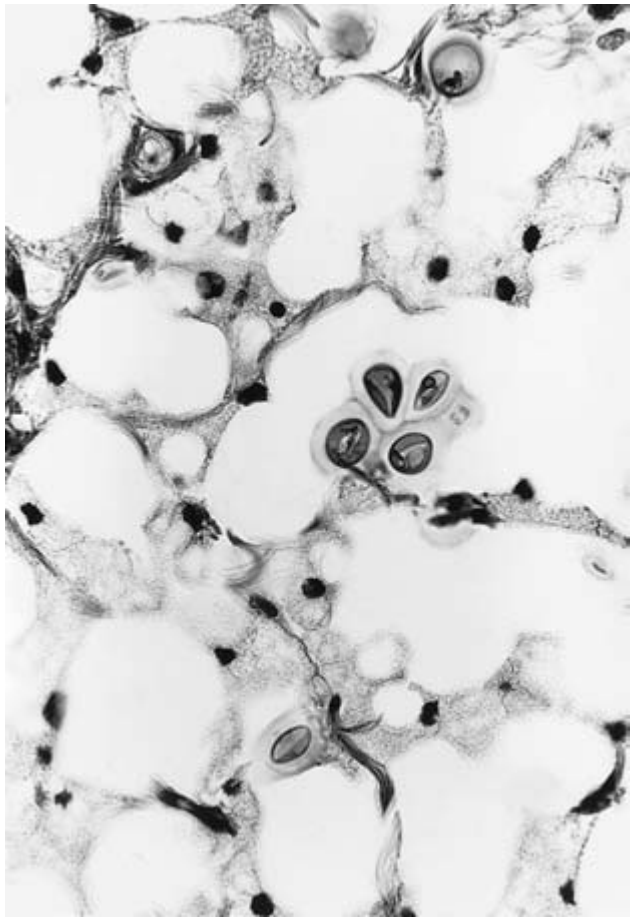


Fig. 12.43 High magnification of *Cryptococcus neoformans* in a skin lesion from a dog.

trophils. Capsular debris is the likely source of cytoplasmic engorgement. Intact yeasts may also be visible within macrophages. Discrete pyogranulomas are uncommon. Neutrophils, lymphocytes, and plasma cells may be prominent around blood vessels within the lesions. Rare cases exhibit abundant granulomatous or pyogranulomatous inflammation, often with eosinophils, and few organisms.

Refractile, round to oval organisms measure 3.5 to 20 μm, and are surrounded by a wide clear capsule that increases the overall diameter to a maximum of about 40 μm. Narrow-based budding often is visible. Mucicarmine staining will define the capsule. There may be artifactual loss or collapse of capsular material, leaving a dense, mucicarmine-positive zone immediately surrounding the central body and an outer unstained zone where the capsule existed prior to tissue processing. In rare cases, poor capsule formation may be present and smaller organisms may predominate, sometimes grouped in clear spaces.

Cryptococcosis generally is typical histopathologically. Occasionally, differentiation from blastomycosis may be required, particularly in infections caused by strains exhibiting poor capsulation. *Blastomyces dermatitidis* lacks a capsule, has broad-based rather than narrow-based budding, and usually evokes more inflammation in tissue than does *Cryptococcus neoformans*. Feline lesions characterized by large numbers of small poorly capsulated organisms grouped in clear spaces may resemble sporotrichosis. A few larger and more typically encapsulated *Cryptococcus neoformans* are generally easily identified, however.

SPOROTRICHOSIS

Clinical features (Figure 12.44)

Sporotrichosis is an uncommon, subacute or chronic cutaneous disease seen in the cat and dog that is caused by the dimorphic fungus, *Sporothrix schenckii*. The organism is worldwide in distribution and grows as a saprophytic mycelial fungus in moist organic debris, sphagnum moss, and hay (Dunstan et al., 1986a; Sykes et al., 2001). Risk factors in humans include rose gardening, topiary production, Christmas tree farming, and hay baling (Sykes et al., 2001). Access to the host is accomplished by puncture wound contamination. Specific puncture risk factors in animals include rose and barberry thorns and pruned fir trees (Rosser & Dunstan, 1998; Sykes et al., 2001).

The organism establishes opportunistic infection as yeast at body temperature. Infection of the dermis and subcutis may extend to regional lymph nodes. Animals may develop either cutaneous/cutaneolymphatic or viscerally disseminated disease (Rosser & Dunstan, 1998). Most cats with cutaneous/cutaneolymphatic disease also have disseminated disease (Rosser & Dunstan, 1998). In contrast, disseminated disease is extremely rare in the dog and is seen most commonly in conjunction with immunosuppression such as from the excessive use of corticosteroids.

Sporotrichosis in cats, unlike in other host species, is characterized by large numbers of organisms in draining fluids and in tissue. For this reason, feline sporotrichosis represents a substantial public health hazard, as infected cats may more readily transmit the disease to humans (Dunstan et al., 1986b). Extreme caution should be exercised by all handlers of infected animals or fresh tissue. If sporotrichosis is suspected, all handlers should wear gloves and limit the time of contact. Motile organisms may penetrate intact human skin (Dunstan et al., 1986b). To the authors' knowledge, canine to human transmission of sporotrichosis has not been proven; transmission is unlikely due to the paucity of organisms present in draining fluid or tissue from infections of that species.



Fig. 12.44 Sporotrichosis in a cat. An alopecic nodule on the lateral muzzle has ulcerated and fistulated, discharging a light brown serosanguinous fluid which contained large numbers of organisms on direct smear.

Skin lesions develop at the site of percutaneous inoculation. Lesions tend to be grouped and localized. Firm, alopecic, nonpainful nodules ulcerate and fistulate to discharge a light brown serosanguinous fluid. Satellite lesions may form near the primary puncture wound. Individual nodules may appear verruciform. The head and legs are the most common sites of infection. Autoinoculation may initiate new lesions when cats groom ulcerated lesions and then groom previously unaffected sites on the extremities, face, and pinnae (Rosser & Dunstan, 1998). Regional lymphadenopathy is common in the cat and affected lymph nodes may fistulate. Systemic clinical signs associated with disseminated sporotrichosis may not be obvious in cats, despite visceral involvement.

Roaming outdoor male cats are at increased risk (Rosser & Dunstan, 1998). Sporotrichosis is seen most frequently in hunting dog breeds (Rosser & Dunstan, 1998). Age and sex predilections are not reported. The authors have the strong clinical impression that Doberman Pinschers are at increased risk for the development of multicentric and severe cutaneous sporotrichosis.

Sporotrichosis must be differentiated clinically from other opportunistic fungal infections, cryptococcosis, other systemic mycoses, feline leprosy syndrome, leproid granulomas, bacterial abscesses, foreign body reactions, sterile granuloma and pyogranuloma syndrome, reactive histiocytosis, and neoplasms. Multicentric lesions, as seen in the Doberman Pinscher, may resemble deep folliculitis and furunculosis. Impression smears of biopsy specimens and exudate, and histopathology should be performed. Fungal culture from tissue specimens may be required to establish a diagnosis in dogs. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291).

Biopsy site selection

Deep punch or wedge biopsy specimens should be obtained, preferably from newer, intact, nondraining lesions. Since feline sporotrichosis has marked zoonotic potential, veterinarians or laboratory personnel handling affected cats or fresh specimens from cats should wear

gloves and wash thoroughly with fungicidal antiseptics such as povidone–iodine or chlorhexidine.

Histopathology (Figures 12.45 through 12.48)

The epidermis in both feline and canine sporotrichosis is acanthotic to ulcerated. There is variable exudation and crusting. Inflammation is diffuse throughout the superficial and deep dermis and panniculus, and may extend to the deeper subcutis. There may be large foci of necrosis. Blood vessels may be prominent within the infiltrate. Macrophages are diffusely present and are intermingled with neutrophils; the latter sometimes form small clusters. Neutrophils are sometimes more abundant and congregate in necrotic foci. Discrete pyogranulomas may be present in canine sporotrichosis. Lymphocytes and plasma cells are variably present, and may be prominently perivascular or more intense and nodular in distribution.

Feline sporotrichosis differs from canine sporotrichosis in that organisms usually are abundant and easily visible, even on routine staining with hematoxylin and eosin. Culture-verified sporotrichosis in a cat with sparse organ-

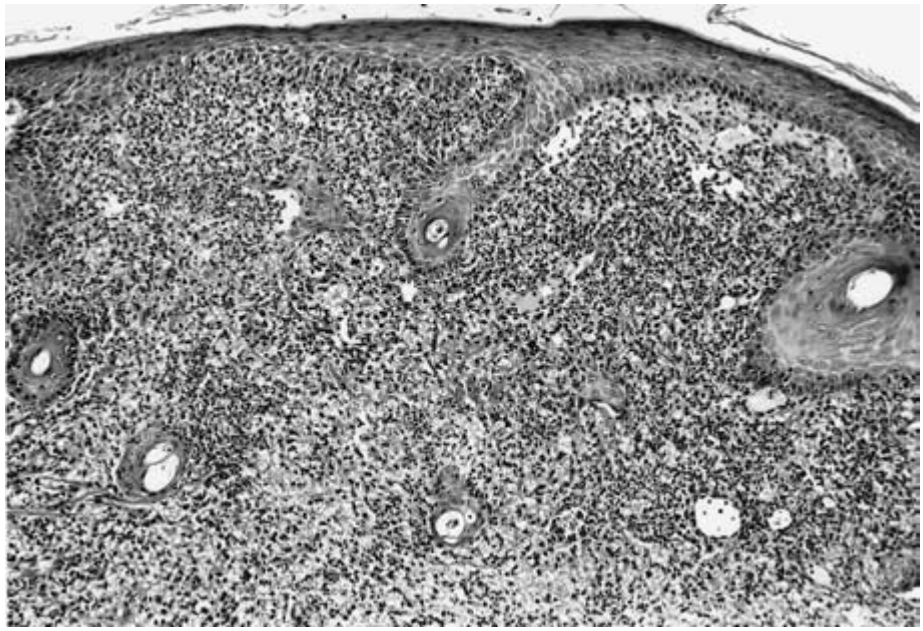


Fig. 12.45 Feline sporotrichosis. Severe diffuse pyogranulomatous inflammation is interspersed by hypocellular, gray zones which contain numerous organisms (not visible at this power).

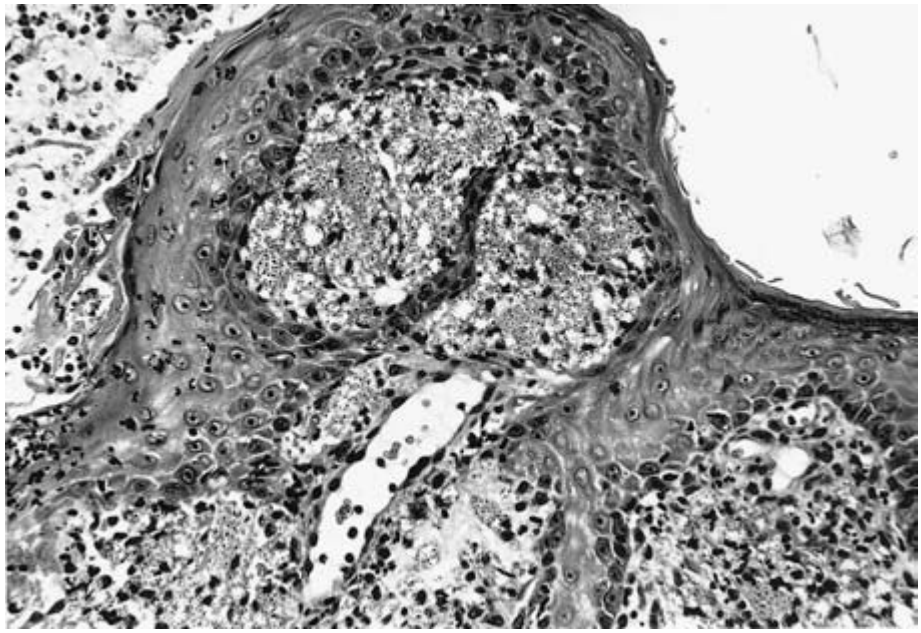


Fig. 12.46 Higher magnification of feline sporotrichosis. Note myriads of small, elongated or dot-like *Sporothrix schenckii*.

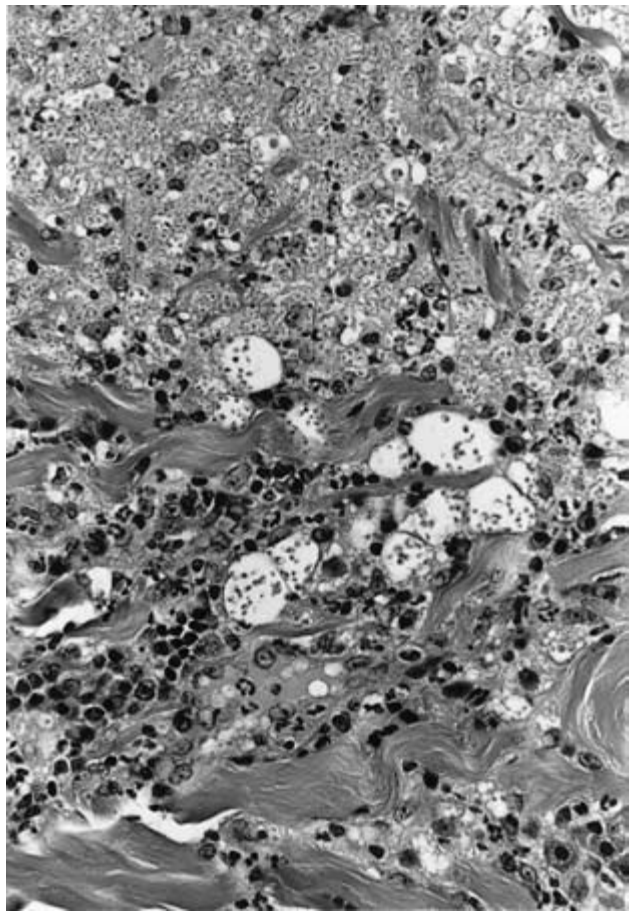


Fig. 12.47 High magnification of *Sporothrix schenckii* in a cat demonstrating oval to cigar-shaped organisms best delineated in clear spaces.

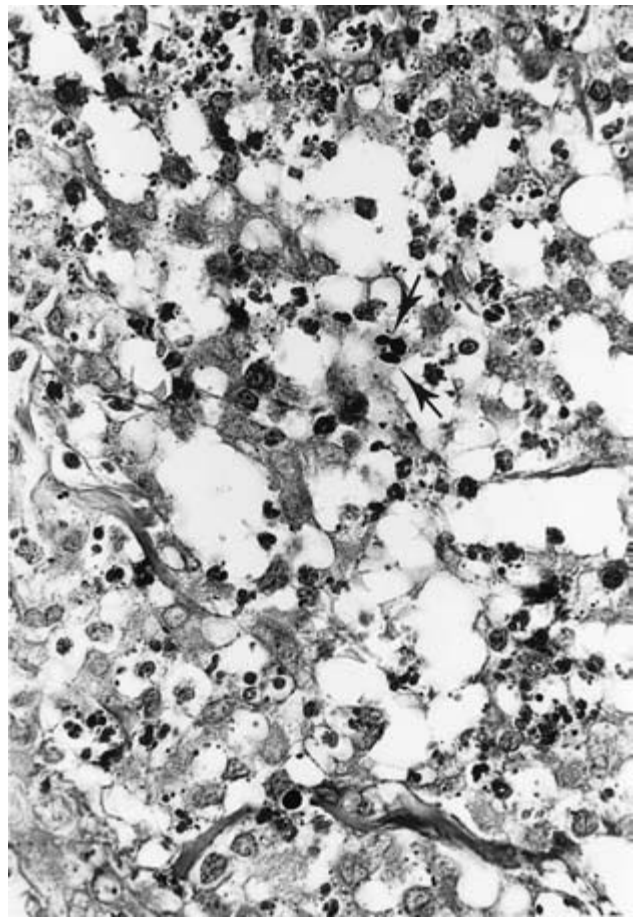


Fig. 12.48 High magnification of canine sporotrichosis. Focal oval and budding organisms (arrows) are present within pyogranulomatous infiltrate (periodic acid–Schiff).

isms in tissue has been reported (Kennis et al., 1994). Elongated, 'cigar-shaped' organisms (round in cross-section), 3 to 10 μm in length and 1 to 2 μm in diameter, usually are present in profusion, both free and within macrophages. Contraction of the cytoplasm creates clear spaces around central nuclei. Discrete organisms may be observed; more often the cytoplasmic spaces appear confluent due to poorly visible cell walls. These confluent spaces create large clear pockets inside macrophages that are crowded with organisms. The nucleus of the engorged macrophage often is not visible.

In canine sporotrichosis usually very small numbers of organisms are scattered throughout the inflammatory infiltrate. Organisms may be numerous in dogs that have received recent corticosteroid therapy. Visible organisms may be absent in some cases. *Sporothrix schenckii* is best visualized in dogs using a periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) stain. Organisms in tissue are pleomorphic, round or oval, occasionally budding yeasts which measure 3 to 8 μm in diameter. When demonstration of organisms in tissue is not successful, the diagnosis may be problematic unless cytological evaluation of smears of exudate reveals the fungus. In the experience of one author (V.K.A.) the polyclonal anti-*Mycobacterium bovis* (BCG) stain (Bonenberger et al., 2001) may help to identify organisms in suspected cases. Fluorescent antibody testing to detect organisms in biopsy specimens also has been used; however, this test may not be widely available.

Differential diagnosis is more difficult in the dog than in the cat, due to the relative paucity of organisms in canine cases. Histopathologic differential diagnoses in the dog include infections by opportunistic or systemic fungi, foreign body reactions, and sterile granuloma and pyogranuloma syndrome. Clinical differentiation and culture may be required. In the cat, organisms are highly characteristic in tissue and allow definitive diagnosis. Confusion with cryptococcosis might be encountered for organisms within clear spaces, mimicking the capsule formation of *Cryptococcus neoformans*. *Sporothrix schenckii* are gen-



Fig. 12.49 Opportunistic fungal infection (phaeohyphomycosis) in a cat due to *Alternaria* sp. Ulcerated, firm nodules are present on the planum nasale, muzzle, and pinna.



Fig. 12.50 Side view of the cat in Fig. 12.49. A large nodule is deforming the planum nasale.

erally smaller and more elongated in shape than *Cryptococcus neoformans*.

CUTANEOUS INFECTIONS OF OTHER OPPORTUNISTIC FUNGI

Clinical features (Figures 12.49 through 12.52)

Cutaneous hyalohyphomycosis, phaeohyphomycosis, mucormycosis, eumycotic mycetoma, aspergillosis, and penicilliosis are uncommon to rare opportunistic fungal

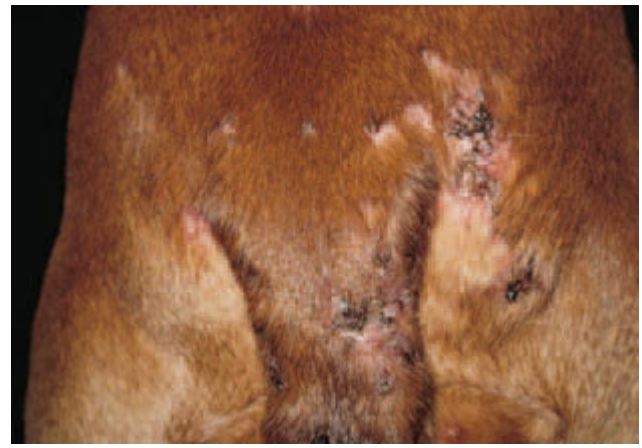


Fig. 12.51 Widespread opportunistic fungal infection (phaeohyphomycosis) in a Viszla. Multiple ulcerated plaques and nodules are present on the rump and tail.



Fig. 12.52 Closer view of the tail of the dog in Fig. 12.51. Alopecic nodules have coalesced and ulcerated.

infections seen in the dog and cat. They are grouped together for discussion because of shared histopathologic and clinical features. Definitive diagnosis of any opportunistic infection caused by saprophytic fungi requires the isolation of the organism from tissue rather than exudate, plus histologic demonstration of tissue invasion by organisms with compatible morphologic characteristics (Foil, 1998). The term 'zygomycosis' is avoided as it refers to two groups of histopathologically disparate saprophytic fungal diseases: mucormycosis, discussed here, and entomophthoromycosis (see p. 303).

Hyalohyphomycosis (previously termed paecilomycosis) refers to opportunistic fungal infections caused by ubiquitous saprophytic soil fungi that produce nonpigmented (nondematiaceous) hyphal elements in tissue. The organisms reported to cause cutaneous or disseminated hyalohyphomycosis include *Paecilomyces* spp., *Pseudoallescheria* spp., *Acremonium* spp., *Fusarium* spp., and *Geotrichum* spp. (Foil, 1998).

Phaeohyphomycosis describes opportunistic fungal infections caused by a number of ubiquitous molds that are either saprophytes or plant pathogens, and that

produce pigmented (dematiaceous) hyphal elements in mammalian tissue. The organisms that cause cutaneous or disseminated phaeohyphomycosis include *Alternaria* spp., *Bipolaris* spp., *Cladosporium* spp., *Curvularia* spp., *Drechslera* spp., *Exophiala* spp., *Moniliella* spp., *Ochroconis* spp., *Phialemonium* spp., *Phialophora* spp., *Pseudomicrodochium* spp., *Scolecobasidium* spp., *Staphylotrichum* spp., *Stemphyllium* spp., *Fonsecaea* spp., and *Cladophyalophora* spp. (Foil, 1998; Fondati et al., 2001; Abramo et al., 2002).

Mucormycosis refers to opportunistic fungal infections caused by organisms of the order Mucorales. The organisms that cause disseminated disease leading to skin infection include *Mucor* spp., *Rhizopus* spp., *Rhizomucor* spp., *Absidia* spp., and *Saksenaea* spp. (Foil, 1998; Grooters, 2002). Organisms of the order Mucorales are ubiquitous saprophytic fungi widely distributed in nature. They are common contaminants in fungal cultures obtained from animal skin and hair.

Eumycotic mycetomas are opportunistic fungal infections that form variably pigmented tissue grains or granules composed of dense aggregates of organisms plus host-derived material. Similar to the tissue grains seen with actinomycosis (see p. 272), and dermatophytic and bacterial pseudomycetomas, these tissue grains are composed of fungal aggregates imbedded in amorphous eosinophilic material presumed to be antigen–antibody complexes formed as a result of the Splendore–Hoeppli reaction. White-grain (eumycotic) mycetomas are caused by *Pseudoallescheria boydii* and *Acremonium hyalinum* and black-grain (eumycotic) mycetomas are caused by *Curvularia geniculata*, *Madurella grisea*, and *Phaeococcus* spp. (Foil, 1998).

Aspergillosis and penicilliosis are opportunistic fungal infections caused by ubiquitous saprophytic fungi that have predominantly nasal, pulmonary, or disseminated involvement (Day, 1998; Sharp, 1998). Nasal disease is caused predominantly by *Aspergillus* spp., which can extend to involve adjacent skin and mucocutaneous junctions.

Skin infections develop either secondary to disseminated disease or as a result of trauma to the skin. A defective immunologic response probably is present in most animals with systemic opportunistic infection. Skin disease secondary to systemic infection occurs with aspergillosis and white-grain eumycotic mycetomas. Skin infection in hyalohyphomycosis can be primary, or secondary to systemic infection. Primary cutaneous or subcutaneous infection most commonly characterizes phaeohyphomycosis and mucormycosis. Black-grain eumycotic mycetomas usually develop at the site of a superficial wound.

Similar to the systemic mycoses (see p. 291) there is a commonality of clinical lesions seen with opportunistic fungal diseases. Grouped papules or nodules, located either in the dermis or subcutis, coalesce and enlarge by local extension. Ulceration results in chronic nonhealing abscesses, draining fistulous tracts, or, less commonly, coalescing shallow ulcers. Eumycotic mycetomas additionally are characterized by tissue grains or granules. For undetermined reasons, feline phaeohyphomycosis most commonly affects the planum nasale in cats (Abramo et al., 2002).

Most reported cases of mucormycosis have gastrointestinal or respiratory tract infection; mucormycosis is highly suggestive of a defective immune response (Foil, 1998). In comparison to other infections caused by saprophytic fungi, mucormycosis usually is characterized by acute, rapidly-progressive disease (Grooters, 2002).

Variation in associated clinical signs caused by opportunistic fungal infection is substantial, and is contingent on the host species, organism, and the site of entry. The reader is referred to standard texts of infectious diseases and mycology for further information.

Few data are available on breed, age, or sex predilections; this may reflect the comparative infrequency of these diseases. Since acquired immunologic incompetence is more common in older animals, older animals may be at greater risk for opportunistic fungal infection. German Shepherd Dogs appear to be predisposed to aspergillosis (Day, 1998; Sharp, 1998). In addition, nine of ten dogs described with various opportunistic fungal diseases were German Shepherd Dogs, indicating likelihood of increased susceptibility (Watt et al., 1995).

Clinically, cutaneous infections of opportunistic fungi must be differentiated from neoplasms, cryptococcosis and other systemic mycoses, feline leprosy syndrome, opportunistic mycobacterial infection, sterile granuloma and pyogranuloma syndrome, reactive histiocytosis, and foreign body reactions. Impression smears from biopsy specimens and exudate may demonstrate the offending agent. Fungal culture from tissue and histopathology are required to establish a diagnosis. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291).

Biopsy site selection

Both intact and ulcerated nodules should be excised using sterile wedge technique or punch biopsy. The subjacent panniculus should be included in the specimen. If opportunistic fungal infection is suspected for a solitary lesion, wide surgical extirpation is recommended, and offers the additional advantage of a potential cure. If only fistulated nodules or chronic abscesses are present, care should be taken to obtain a deep, representative sample. Clinicians and laboratory personnel should wear protective gloves when handling infected tissue. These organisms can cause opportunistic infections in humans by direct inoculation, similar to the systemic fungi (see p. 291).

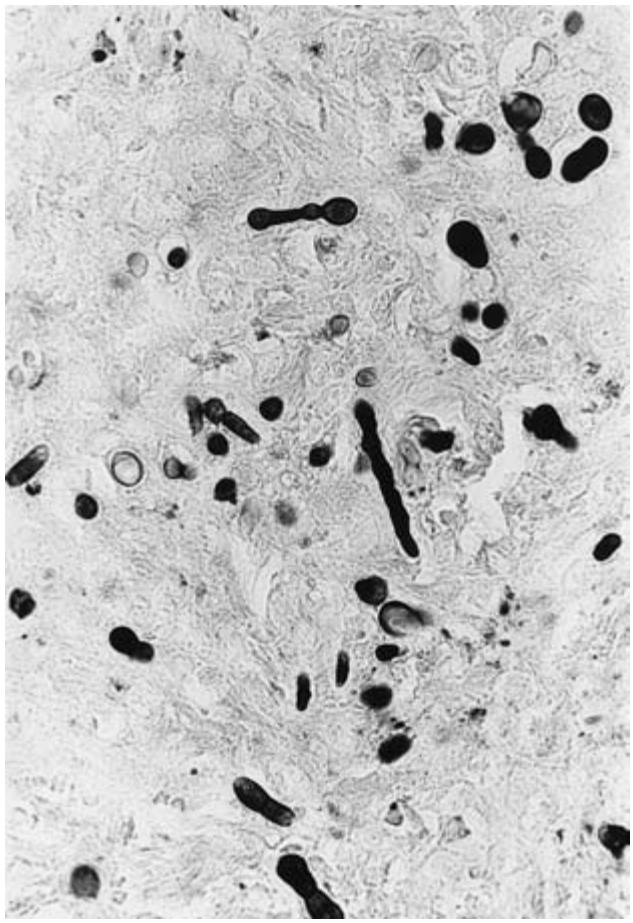


Fig. 12.53 Opportunistic fungal infection in a cat. Irregular, septate hyphae have bulbous swellings (Gomori's methenamine silver).

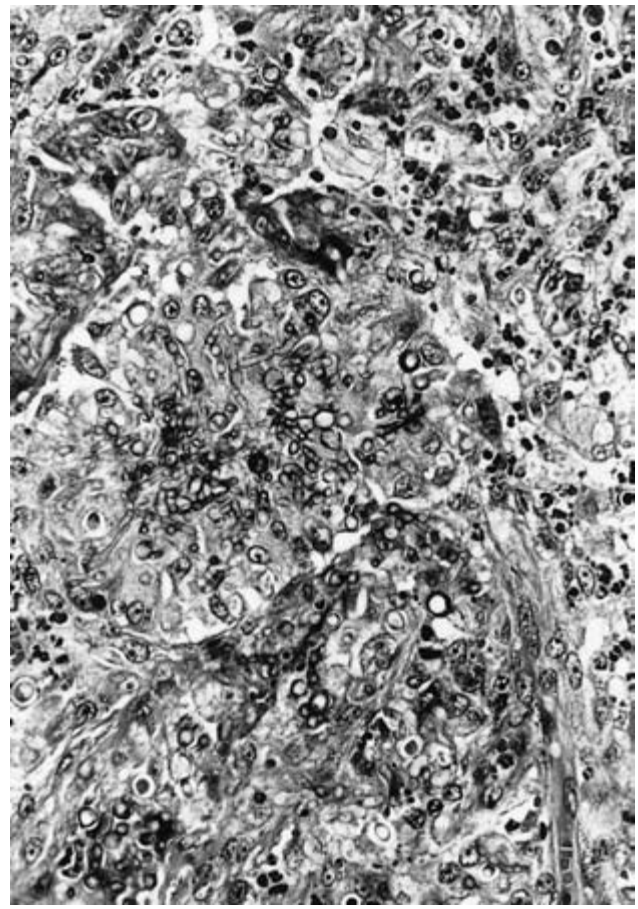


Fig. 12.54 Phaeohyphomycosis in a cat. Pigmented hyphae are clearly evident with hematoxylin and eosin.

Histopathology (Figures 12.53 and 12.54)

The epidermis is acanthotic and may be ulcerated. In opportunistic fungal infection, the dermis and usually the underlying panniculus are diffusely infiltrated with large epithelioid or foamy macrophages. Variable numbers of neutrophils and lymphocytes are present, and multinucleated giant cells may be found.

Basophilic fungal organisms may be identified on hematoxylin and eosin (HE) stained sections. Most often, examination reveals predominantly clear 'ghosts' of fungi within or among macrophages. These fungal ghosts help to create the vacuolated or foamy appearance of the cytoplasm. Periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) staining will delineate these organisms; the number identified with special stains is always more profuse than suggested by HE examination. In phaeohyphomycosis, organisms are pigmented in HE stained sections and do not require additional staining for identification. Many of the opportunistic fungi have branching, septate hyphae, sometimes with spore-like swellings. Morphology will vary depending on the species of fungus present; the reader is referred to standard textbooks of medical mycology. Histopathology cannot speciate these organisms; fungal culture is required.

Opportunistic fungal infections as a group are usually diagnosed with little difficulty due to the presence of organisms or their ghosts on HE examination. Differential etiologic diagnosis principally involves definitive identification of the causative agent, and is not possible with histopathology alone. Fungal culture is required. In cats, the opportunistic fungal infections that are characterized by infiltration of foamy macrophages may resemble cutaneous xanthoma or feline lepromatous leprosy. Again, the observation of fungal structures allows differentiation.

CUTANEOUS PYTHIOSIS, LAGENIDIOSIS, AND ENTOMOPHTHOROMYCOSIS

Clinical features (Figures 12.55 through 12.58)

Cutaneous pythiosis, lagenidiosis, and entomophthoromycosis are markedly regional opportunistic skin infections seen in the dog and cat. These infections are



Fig. 12.55 Cutaneous pythiosis affecting the leg of a dog. Coalescing nodules on the left foreleg are necrotic and ulcerated. (Photograph courtesy A.M. Grooters.)



Fig. 12.57 Cutaneous lagenidiosis affecting the lower leg and foot of a dog. These areas are irregularly swollen. Nodules have become necrotic and ulcerated, and drain a serosanguinous material. (Photograph courtesy A.M. Grooters.)



Fig. 12.56 Cutaneous pythiosis affecting the foot of a dog. Little of the normal anatomy of the foot is recognizable. (Photograph courtesy A.M. Grooters.)

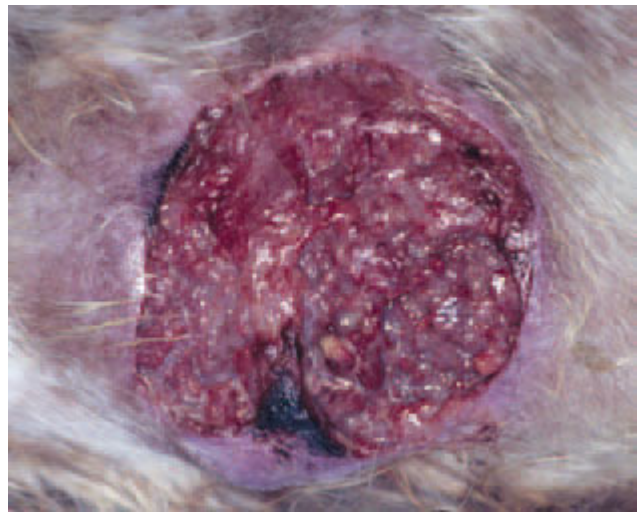


Fig. 12.58 Close view of cutaneous lagenidiosis on the chest of a dog. A large slightly crateriform ulcer with a well-demarcated rim exhibits multiple draining fistulous tracts. (Photograph courtesy A.M. Grooters.)

not seen in most parts of North America, but are seen rarely in localized enzootic areas. They are caused by saprophytic water molds and fungi. All three diseases have the potential to cause cutaneous or systemic granulomatous disease, and are grouped here because they share strong histopathologic and clinical similarities. Definitive diagnosis of any opportunistic infection caused

by saprophytic organisms requires the isolation of the organism from tissue rather than exudate, plus histologic demonstration of tissue invasion by organisms with compatible morphologic characteristics (Foil, 1998).

Cutaneous pythiosis is a rare, ulcerative, pyogranulomatous skin disease in the dog and cat caused by *Pythium insidiosum* (Duncan et al., 1992; Foil, 1998; Dykstra et al., 1999; Grooters, 2002). P*ythium insidiosum* is a fungus-like, aquatic, dimorphic, flagellate water mold protoctistid oomycete. The natural habitat of *Pythium insidiosum* is warm stagnant water with a high content of organic debris (Foil, 1998). Animals that develop pythiosis probably have previously existing trauma and acquire the organism when swimming or wading in infested water. Pythiosis is seen primarily in warm humid climates such as along the gulf coast of the United States, and in multiple Pacific Rim countries (Foil, 1998). Pythiosis affects predominantly the gastrointestinal tract and the skin in the dog and cat, with gastrointestinal disease seen most frequently (Foil, 1998).

Cutaneous lagenidiosis is a rare disease with marked similarities to pythiosis, reported recently only in dogs (Grooters, 2002; Grooters et al., 2003). Lagenidiosis is caused by an as yet unnamed species of *Lagenidium*, which is another fungus-like, aquatic, dimorphic, flagellate water mold protoctistid oomycete (Grooters, 2002; Grooters et al., 2003). *Lagenidium* spp. probably occupy a similar ecologic niche and cause skin disease via wound contamination (Grooters et al., 2003). Skin disease and granulomatous lymphadenitis usually occur together. Lagenidiosis may be a more clinically aggressive disease than pythiosis, as affected dogs have lesions at distant sites including the great vessels, lungs, esophagus, trachea, and mediastinum (Grooters, 2002; Grooters et al., 2003).

Cutaneous entomophthoromycosis is a rare, ulcerative, pyogranulomatous, fungal skin disease (Hillier et al., 1994; Foil, 1998; Greene et al., 2002). Entomophthoromycosis is caused by ubiquitous saprophytic soil fungi in the order Entomophthorales and genera *Conidiobolus* or *Basidiobolus* (Hillier et al., 1994; Foil, 1998; Greene et al., 2002). Entomophthorales are soil saprophytes seen predominantly in humid tropical and subtropical regions. In the past, entomophthoromycosis has been grouped with mucormycosis (see p. 301) as zygomycosis. In the opinion of the authors, the term zygomycosis should be avoided as it refers to two groups of histopathologically disparate saprophytic fungal diseases. The portal of entry for cutaneous disease is likely to be either wound contamination, or by extension from gastrointestinal or respiratory disease (Foil, 1998; Grooters, 2002). Entomophthoromycosis can either be restricted to the skin or can disseminate viscerally (Foil, 1998).

The clinical features of the cutaneous form of all three diseases are very similar in both dogs and cats. Most initial lesions consist of poorly circumscribed dermal nodules. Progression is moderate to rapid as the lesions expand peripherally and subcutaneously, leading to the formation of satellite nodules. Nodules become necrotic, ulcerate, and develop fistulous tracts which drain purulent or serosanguinous exudate.

Canine cutaneous pythiosis occurs most commonly on the extremities, muzzle, inguinal region, and lumbosacral area (Grooters, 2002). Dorsal lumbosacral pythiosis may be seen secondary to self-trauma associated with flea allergy dermatitis. Pruritus may be marked with pythiosis, and commonly initiates severe self-trauma. Viscerally disseminated canine pythiosis has been noted rarely (Foil, 1998). Feline cutaneous pythiosis is reported to affect the inguinal region, tailhead, periorbital region, ventral neck, perineum, and medial thighs (Grooters, 2002).

Canine lagenidiosis has a distribution pattern similar to pythiosis (Grooters, 2002; Grooters et al., 2003). In contrast to pythiosis and entomophthoromycosis, lagenidiosis commonly is characterized by the development of lesions at distant visceral sites such as the lungs, esophagus, trachea, and mediastinum, plus lymph nodes (Grooters, 2002; Grooters et al., 2003).

Entomophthoromycosis may cause more widely distributed draining nodules in the dog (Hillier et al., 1994; Grooters, 2002). Lesions of the hard palate also have been reported (Bauer et al., 1997; Grooters, 2002). Entomophthoromycosis seems to be a less locally aggressive disease clinically than either pythiosis or lagenidiosis.

Active, young adult large-breed dogs may be at increased risk for all three diseases. German Shepherd Dogs may be predisposed to cutaneous pythiosis (Foil, 1998). Other signalment predilection data are not available.

Clinically, pythiosis, lagenidiosis, and entomophthoromycosis may resemble deep folliculitis and furunculosis, opportunistic mycobacterial infection, actinomycosis, nocardiosis, cryptococcosis and other systemic mycoses, infections of other opportunistic fungi, neoplasms, or canine acral lick dermatitis (if involving a distal extremity). Histopathology is the most efficient method of ruling out the diseases listed above. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out, since attempted culture may be dangerous (see p. 291). Nested polymerase chain reaction (PCR) assays to detect oomycotic DNA, and immunoblot analyses are the tests of choice to differentiate these three diseases from each other (Grooters, 2002; Grooters & Gee, 2002; Znajda et al., 2002). It is likely that some previous cases diagnosed as pythiosis prior to the development of newer testing



Fig. 12.59 Cutaneous pythiosis in a dog. Darkly staining lakes of degranulated, eosinophilic debris are accompanied by hemorrhage and inflammation.

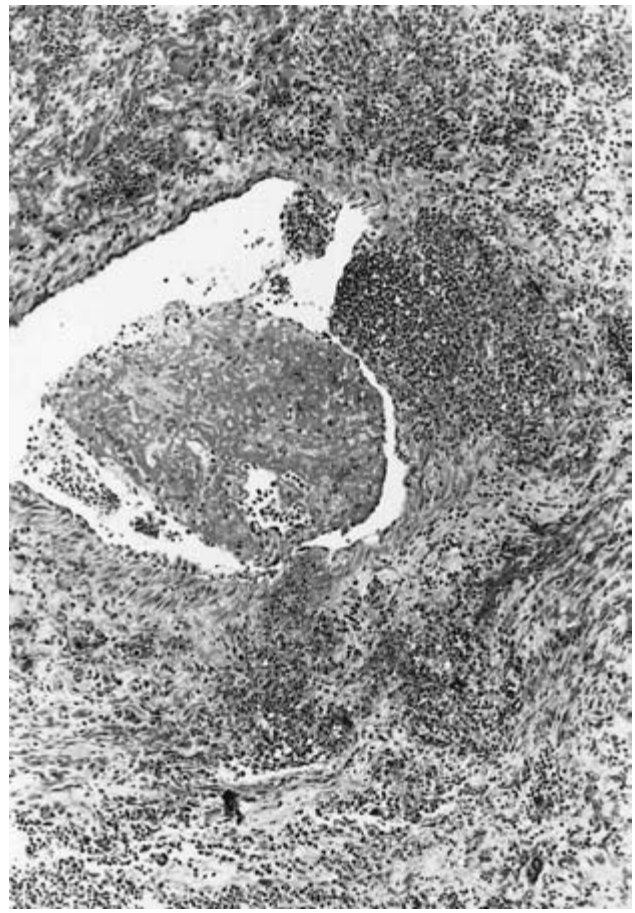


Fig. 12.60 Cutaneous pythiosis in a dog demonstrating a large inflamed and thrombosed blood vessel. (Case material courtesy A.M. Grooters.)

procedures may have been lagenidiosis or entomophthoromycosis (Grooters, 2002; Grooters et al., 2003).

Biopsy site selection

Both intact and ulcerated nodules should be excised using sterile wedge technique or punch biopsy. The subjacent panniculus should be included in the specimen. If these diseases are suspected for a solitary lesion, wide surgical extirpation is recommended and offers the additional advantage of a potential cure. The zoonotic potential of pythiosis, lagenidiosis, and entomophthoromycosis is not known, but probably is minimal in healthy individuals with competent immune systems. However, reasonable caution such as the wearing of gloves is recommended.

Histopathology (Figures 12.59 through 12.70)

For pythiosis, acanthosis or severe ulceration of the epidermis is seen. The dermis, panniculus, and often the deeper subcutis are diffusely and severely inflamed. Necrosis is present, and may be extensive. Pyogranulomatous inflammation may be multifocal to diffuse, and is punctuated by indiscrete and irregular, large foci of degenerating, degranulating eosinophils. Intact eosinophils, neutrophils, macrophages, and rare multinucleated giant cells surround these eosinophilic foci. Mucin may border these foci as well, and there is encircling or intervening fibrosis. In hematoxylin and eosin (HE) stained sections, organisms may be seen as clear ghosts within eosinophilic degenerate foci or in other areas of necrosis and inflammation, but generally are not visible without special staining. *Pythium insidiosum*-infected tissue tends to be rich in hyphae, often clustered within areas of necrosis or inflammation (Grooters, A., personal communication, 2003). Occasional vascular necrosis and thrombosis are present, and may be attended by hyphae within devitalized vessel walls. Edema and hemorrhage are variable.

The inflammatory reaction pattern of *Lagenidium* sp. is very similar to that of pythiosis. Giant cells may be

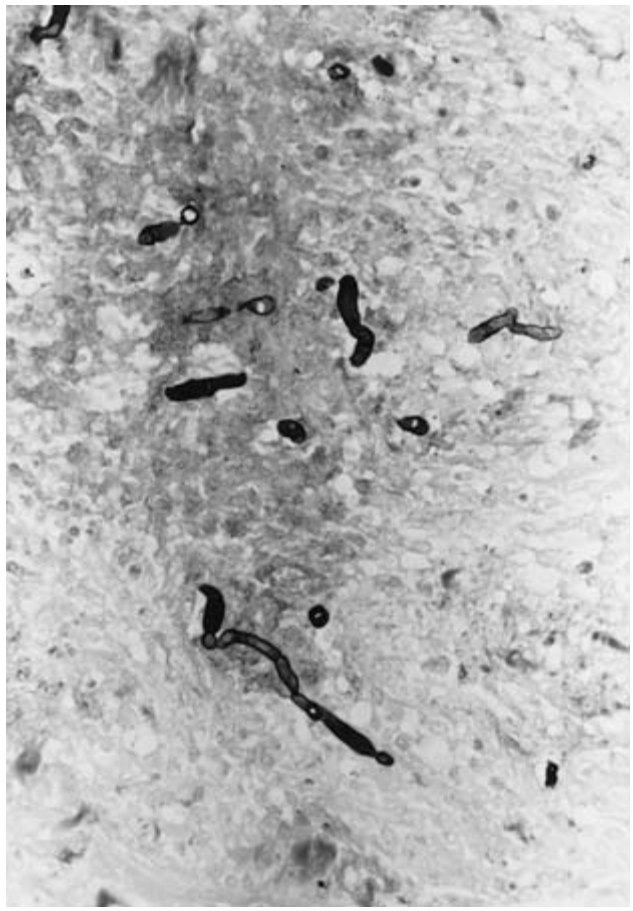


Fig. 12.61 *Pythium insidiosum* from the dog of Fig. 12.60. Large silver-positive irregularly branching hyphae are evident; septations are poorly visible (Gomori's methenamine silver). (Case material courtesy A.M. Grooters.)

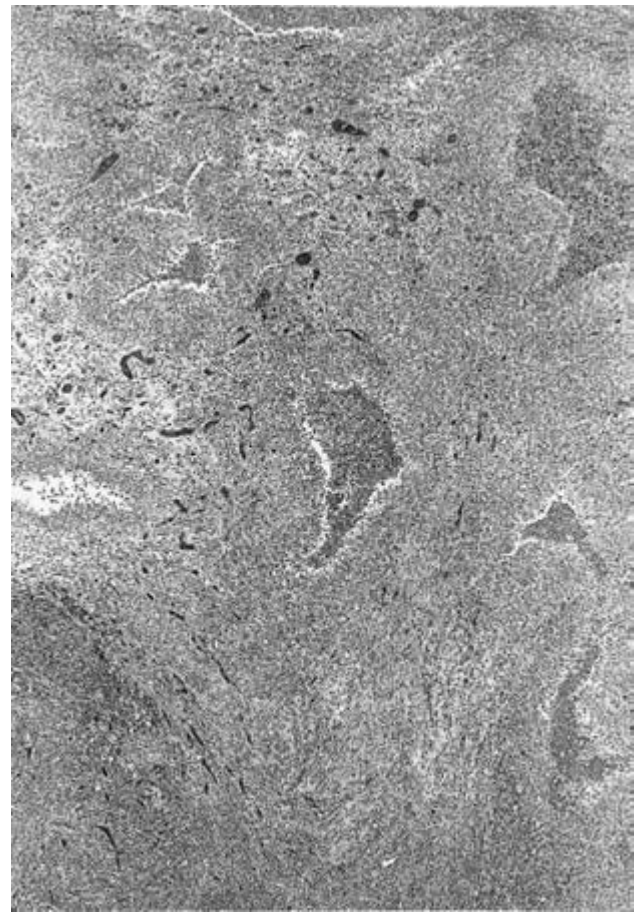


Fig. 12.62 Entomophthoromycosis due to *Conidiobolus* sp. infection in a dog, demonstrating diffuse pyogranulomatous inflammation. (Case material courtesy R. Bauer & A.M. Grooters.)

numerous (Grooters et al., 2003), in contrast to pythiosis. Eosinophilic inflammation is often intense, but may be outshone by pyogranulomatous infiltrates in some cases (Grooters et al., 2003). Organisms are usually numerous. Vascular invasion by fungi and thrombosis may be prominent, as in pythiosis.

Microscopic lesions of cutaneous entomophthoromycosis also are very similar histologically to pythiosis (Hillier et al., 1994; Foil, 1998). Organisms tend to be less abundant, in contrast to pythiosis (Grooters, A., personal communication, 2003). Pyogranulomatous inflammation with prominent eosinophils and degenerate foci with eosinophilic degranulation were reported in a dog with skin and subcutaneous infection with *Conidiobolus* sp.; fungi were within eosinophilic degenerate foci, as seen in pythiosis (Hillier et al., 1994). *Basidiobolus ranarum* infection in a dog was associated with diffuse mixed inflammation with giant cells, necrosis, and fibrosis (Greene et al., 2002).

All four organisms have broad, irregularly branching, poorly septate hyphae with nonparallel walls. *Pythium insidiosum* usually are not visible in HE-stained sections other than as occasional ghosts. Periodic acid–Schiff (PAS) stain also usually will not detect *Pythium insidiosum* very clearly in tissue; this stain is superior in detecting living organisms, and *Pythium insidiosum* often is devitalized in specimens obtained for histopathology. Gomori's methenamine silver (GMS) will stain the wall of living or dead fungi and must be utilized in any suspected case of pythiosis, or the diagnosis may be overlooked. *Pythium insidiosum* has broad, occasionally septate, irregularly branching hyphae, which range from 2.5 to 8.9 μm in diameter (Foil, 1998).

Conidiobolus spp., and *Basidiobolus* spp. are similarly difficult to visualize on HE examination, in comparison to *Lagenidium* sp. (Grooters et al., 2003). *Conidiobolus* sp. in one reported dog were identified as 'non-branching and clearly septate' (Hillier et al., 1994), but were



Fig. 12.63 High magnification of *Conidiobolus* sp. infection in the dog of Fig. 12.62. Eosinophilic sleeves of Splendore–Hoeppli material bring ghosts of hyphae into relief. (Case material courtesy R. Bauer & A.M. Grooters.)

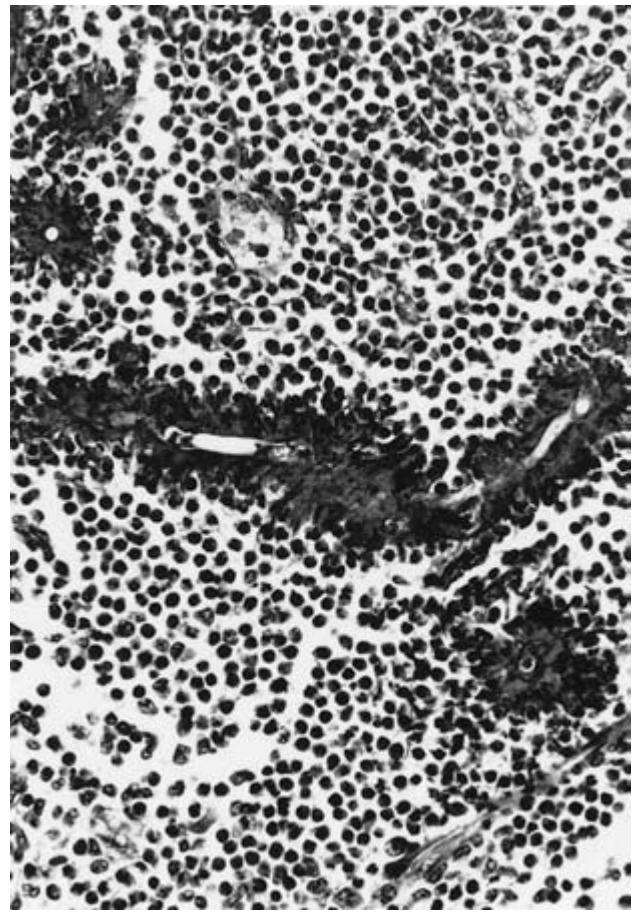


Fig. 12.64 Higher magnification of Fig. 12.63. (Case material courtesy R. Bauer & A.M. Grooters)

described as 'rarely septate and rarely branched' in a dog with oral infection (Bauer et al., 1997). Hyphal width varied from 5 to 11 μm in the dog with skin and subcutaneous infection (Hillier et al., 1994), and averaged 8 μm in the dog with oral infection (Bauer et al., 1997). *Basidiobolus ranarum* hyphae were 7 to 20 μm in diameter, deeply basophilic, thin-walled, rarely branching, and occasionally septate; spore-like bulbous enlargements at the tips of hyphae were described (Greene et al., 2002).

As reported, in contrast to *Pythium insidiosum*, *Lagenidium* sp. hyphae are usually recognizable on HE stained sections and may be within giant cells or in extracellular location (Grooters et al., 2003). Hyphal diameter ranges from 7 to 25 μm, with an average of 12 μm, and they are thus larger than *Pythium insidiosum* as well as *Conidiobolus* spp. and *Basidiobolus* spp. Scant to thin eosinophilic sleeves of Splendore-Hoeppli reaction may surround hyphae of *Lagenidium* sp. Some hyphae may appear round or bulbous, with occasional right angle branching observed (Grooters et al., 2003).

The entomophthoromycotic organisms, *Conidiobolus* spp. and *Basidiobolus* spp. may be more likely to have prominent encircling Splendore–Hoeppli material ('eosinophilic sleeves') than *Pythium insidiosum* (Foil, 1998) or *Lagenidium* sp. (Grooters et al., 2003); this material tends to bring hyphal ghosts into relief against the brightly eosinophilic deposits. However, eosinophilic sleeves were not reported in the dog with skin and subcutaneous *Conidiobolus* sp. infection (Hillier et al., 1994), nor described in the dog with *Basidiobolus ranarum* infection (Greene et al., 2002). They were identified in the dog with oral *Conidiobolus* sp. infection (Bauer et al., 1997), and observed by the authors in a case of oropharyngeal infection in a dog (case material courtesy A. Grooters, 2003). Different species of *Conidiobolus* may be involved in cutaneous versus oral infection.

Immunohistochemistry, originally developed for equine cases (Brown et al., 1988), has been utilized to identify

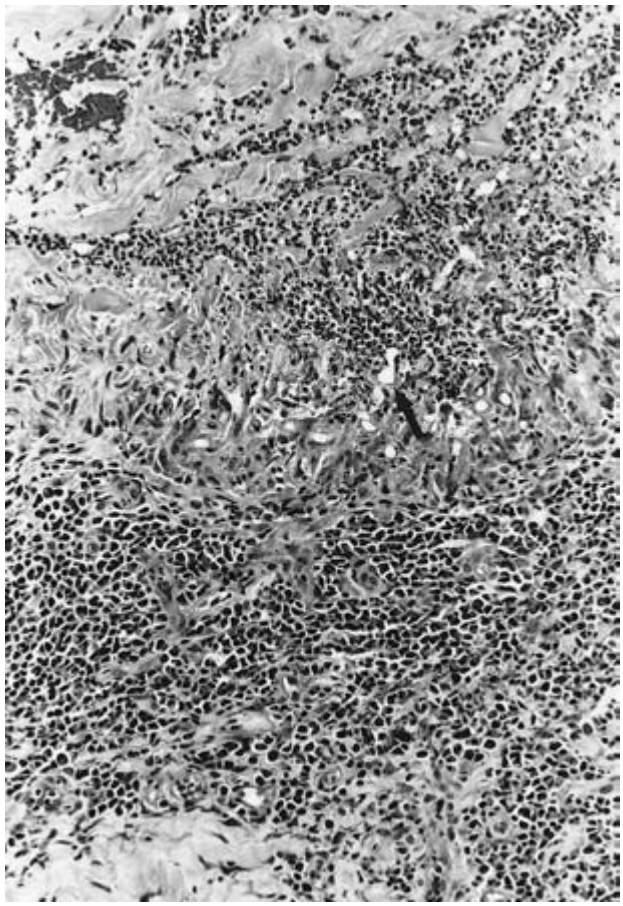


Fig. 12.65 Entomophthoromycosis due to *Basidiobolus ranarum* infection in a dog. Pale irregular hyphal ghosts are seen amidst intense inflammation. (Case material courtesy C.W. Brockus & K. Latimer.)

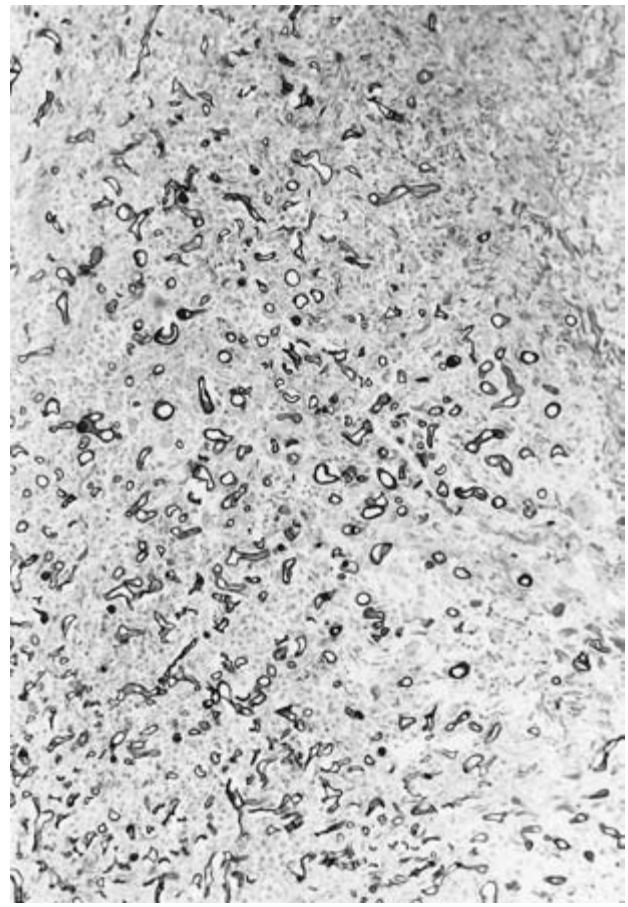


Fig. 12.66 *Basidiobolus ranarum* infection in the dog of Fig. 12.65. Numerous silver-positive organisms are present (Gomori's methenamine silver). (Case material courtesy C.W. Brockus & K. Latimer.)

pythiosis in tissue (Duncan et al., 1992). However, weak staining of *Lagenidium* hyphae has been documented, and is likely due to antigenic similarities. Testing by polymerase chain reaction (PCR) has successfully identified both *Pythium insidiosum* and *Lagenidium* sp. in tissue (Znajda et al., 2002), and is considered most reliable in their ultimate differentiation. Immunohistochemistry will allow definitive identification of *Pythium insidiosum* and permit its differentiation from the morphologically similar *Conidiobolus* spp. and *Basidiobolus* spp. (Hillier et al., 1994), as well as *Lagenidium* sp.

Differential diagnoses in the dog include deep bacterial or fungal infections, or foreign body reactions, particularly those characterized by severe necrosis. In cats, lesions may resemble eosinophilic granuloma, but inflammation is much deeper. Necrotizing inflammation due to deep arthropod trauma (spider bites) also may be considered (see Chapter 14). Demonstration of the organisms of this group within eosinophilic degenerate foci will allow differentiation from other infectious diseases, but not from each other. Identification of the specific etiologic organism by immunohistochemistry, testing by PCR, or culture of clinical specimens is required for definitive diagnosis.

CUTANEOUS PROTOTHECOSIS

Clinical features (Figure 12.71)

Protothecosis is an uncommon to very rare disseminated visceral or cutaneous/subcutaneous opportunistic infection caused by the ubiquitous saprophytic achlorophyllous algae of the genus *Prototheca*. Reproduction is by endosporulation. Primary cutaneous and subcutaneous protothecosis is a very rare skin disease in both the dog and the cat and is caused by *Prototheca wickerhamii*.

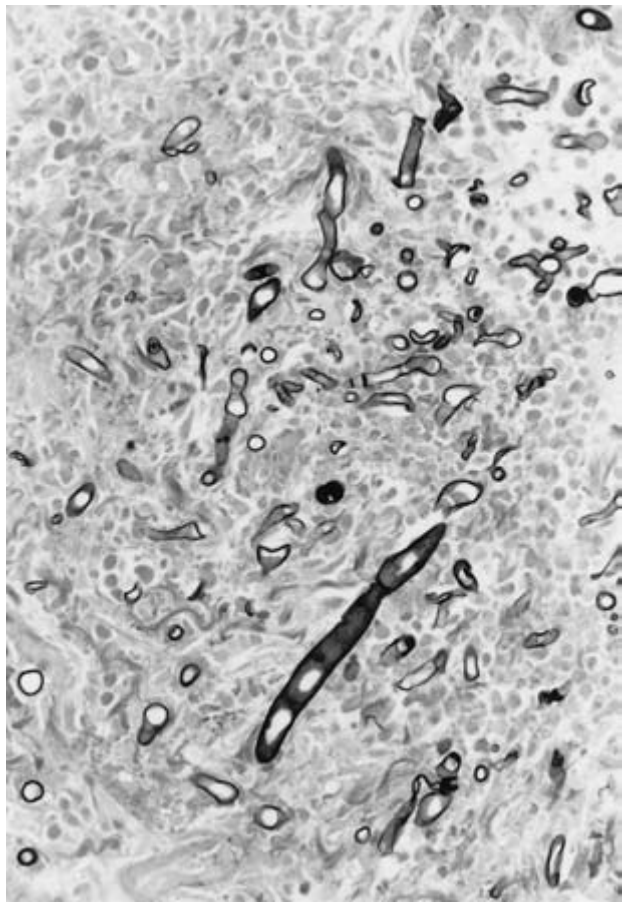


Fig. 12.67 Higher magnification of *Basidiobolus ranarum* infection in the dog of Fig. 12.65, demonstrating irregular, poorly branching and occasionally septate hyphae (Gomori's methenamine silver). (Case material courtesy C.W. Brockus & K. Latimer.)



Fig. 12.68 Lagenidiosis in a German Shepherd Dog demonstrating diffuse inflammation with giant cells (arrow). (Case material courtesy A.M. Grooters.)

Cutaneous protothecosis in humans is caused by the same organism (Chao et al., 2002). Only three cases of primary canine cutaneous protothecosis have been reported (Ginel et al., 1997). Feline primary cutaneous and subcutaneous protothecosis is uncommon, but is the most frequently seen form of protothecosis in that species (Greene, 1998).

Canine disseminated visceral protothecosis is uncommon, but is the most frequent form of protothecosis observed (Greene, 1998). Disseminated visceral protothecosis is very rare in the cat. *Prototheca zopfii* is most frequently isolated from canine disseminated visceral protothecosis (Greene, 1998). Although secondary skin lesions may be seen with disseminated visceral protothecosis, they are not a prominent feature. Thus, the rest of this discussion will center on primary cutaneous and subcutaneous protothecosis.

Protothecosis in animals and humans is worldwide in distribution. Most North American cases are diagnosed in the southeastern United States. *Prototheca* spp. are isolated most commonly from sewage and animal waste. Contamination of water systems, soil, and food probably initiates infection via contact with injured skin or mucosa (Greene, 1998).

Depressed cell-mediated immunity commonly is incriminated in canine disseminated visceral disease, and is suspected in canine cutaneous and subcutaneous prothecosis (Greene, 1998). In comparison, primary cutaneous protothecosis in cats seems to occur in healthy animals with no evidence of a compromised immune system (Greene, 1998). Primary or acquired lack of cell mediated immunity predisposes to protothecosis in humans; defects in neutrophil function also have been documented (Chao et al., 2002).

Crusted nodules with fistulation are the most common clinical features of canine primary cutaneous protothecosis. Affected sites include the external nares, pinnae, distal legs, and scrotum (Ginel et al., 1997). One author (P.J.I.) has seen primary cutaneous protothecosis involving a

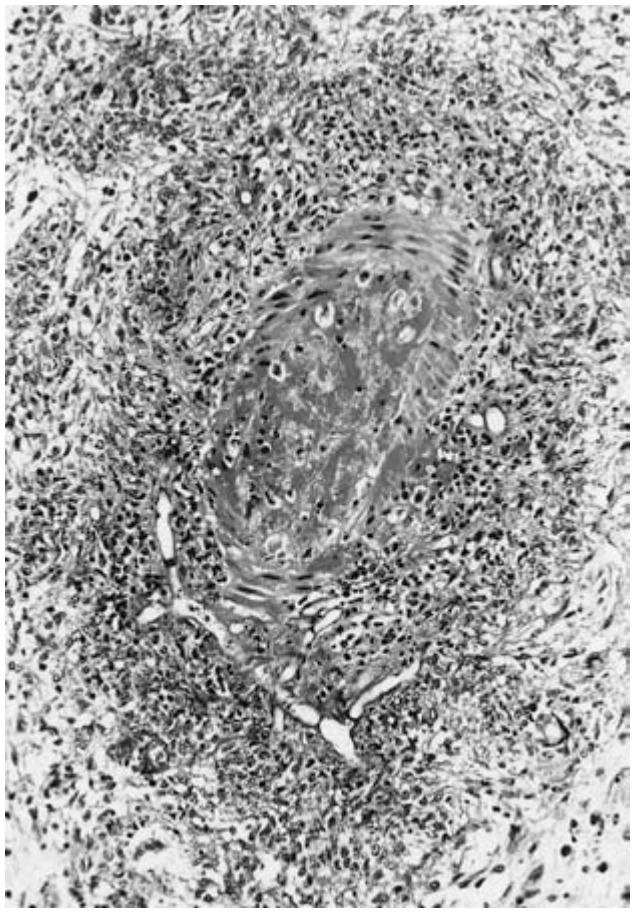


Fig. 12.69 Lagenidiosis in the dog of Fig. 12.68 demonstrating large thrombosed vessel. Note prominent adjacent hyphal ghosts, characteristic of this infection. (Case material courtesy A.M. Grooters.)

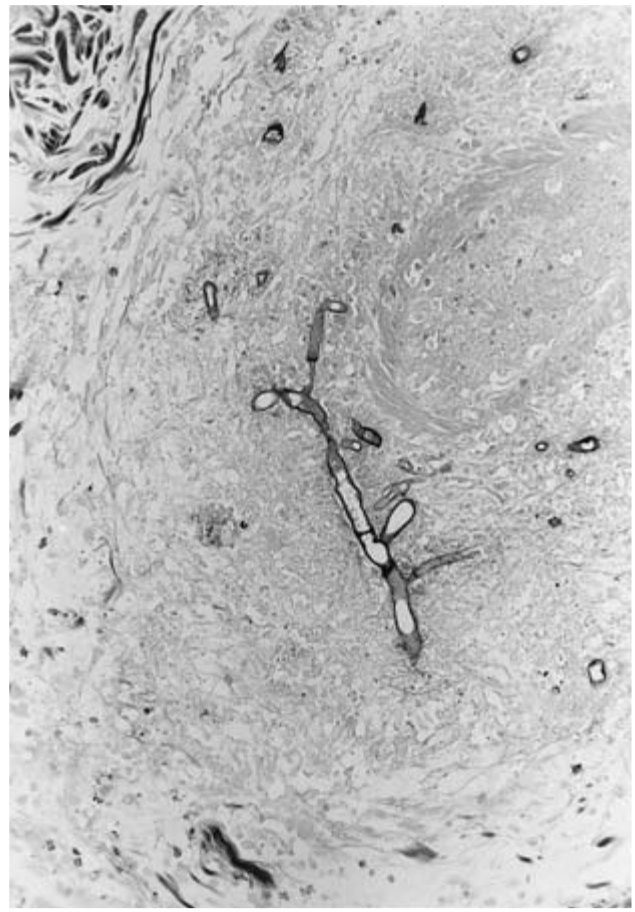


Fig. 12.70 Silver staining of the same field as in Fig. 12.69. Irregular branching and partially septate hyphae are prominent (Gomori's methenamine silver). (Case material courtesy A.M. Grooters.)

lateral alar wing of the planum nasale. Depigmentation was a prominent additional feature.

Feline cutaneous protothecosis is characterized by gradually enlarging, firm nodules. Lesions are noted most commonly on the legs and paws, although nodules have been reported to affect the planum nasale, muzzle, pinnae, and base of the tail (Greene, 1998).

Breed predilections are not available for canine cutaneous protothecosis. Collies may be predisposed to disseminated visceral protothecosis (Greene, 1998). The only case of canine protothecosis seen by one author (P.J.I.) also was in a Collie. Female dogs seem to be preferentially affected with visceral disease; age predilections have not been noted (Greene, 1998). Signalment predilections have not been identified in cats.

Protothecosis must be differentiated from opportunistic fungal infections, feline leprosy syndrome, cryptococcosis, other systemic fungal diseases, sterile granuloma and pyogranuloma syndrome, reactive histiocytosis, foreign body reactions, and neoplasia. Impression smears from exudates and biopsy specimens may demonstrate organisms. Histopathology and culture from sterile biopsy specimens are required for definitive diagnosis. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see p. 291).

Biopsy site selection

Nonulcerated nodules should be removed in their entirety using wedge resection technique or larger punch biopsies. If only ulcerated nodules are present, care should be taken to obtain a deep representative sample. Clinicians and laboratory personnel should wear protective gloves when handling infected tissue, since systemic fungal infections clinically may mimic protothecosis. Animal protothecosis



Fig. 12.71 Cutaneous protothecosis in a Collie. A mass deforming the left alar wing of the planum nasale has ulcerated.

is not a health risk for humans with competent immune systems as the organisms are ubiquitous.

Histopathology (Figures 12.72 and 12.73)

The epidermis is acanthotic and ulcerated. Variable diffuse inflammation affects the dermis, panniculus, and often the deeper subcutis, and is accompanied by heavy colonization by irregular organisms. There is often severe necrosis resulting in degeneration and fragmentation of organisms. Inflammation may be minimal. Large macrophages are accompanied by fewer neutrophils, lymphocytes, and plasma cells. Neutrophils may form small clusters, but discrete pyogranuloma formation is uncommon. There is often fibrosis throughout the lesions.

Organisms are found within and among macrophages. Viable *Prototheca* spp. in tissue are round to oval, have thin highly refractile walls and a light to darkly basophilic internal structure, and measure 8 to 30 µm in diameter. Periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) staining will delineate these organisms. They are often degenerated, resulting in loss of internal structure but retention of the refractile wall that is collapsed, folded, shrunken, or irregular. Careful examination will reveal four to eight characteristic daughter cells, or endospores, that create a subdivided or 'cut pie' appearance to the organism. In one reported case, lesions recently treated with ketoconazole showed relatively more intense inflammation and fewer organisms than untreated lesions (Perez et al., 1997).

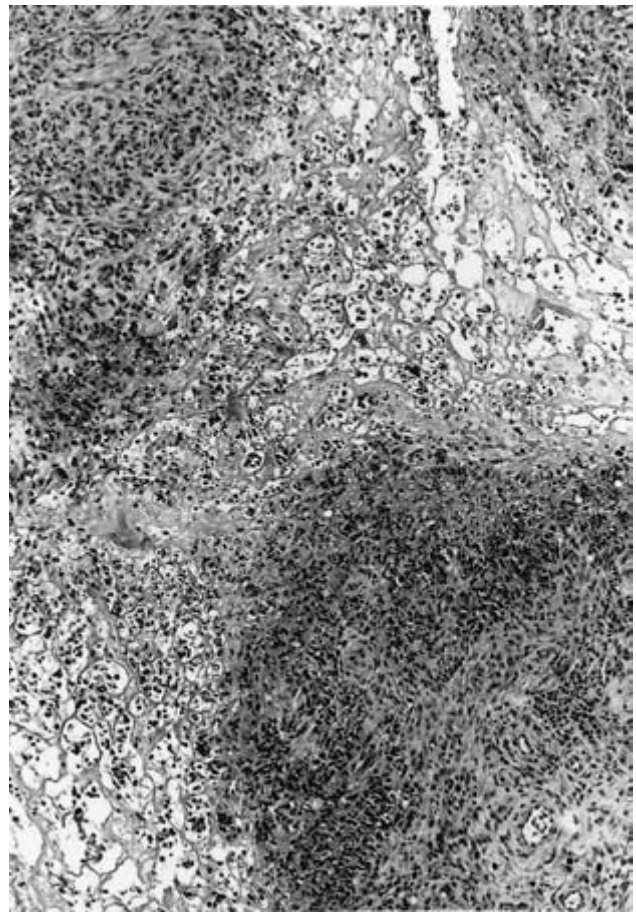


Fig. 12.72 Cutaneous protothecosis in a dog demonstrating extensive inflammation and necrosis. Clear spaces contain numerous degenerate organisms.

Cutaneous protothecosis produces a characteristic histopathologic picture, as the organisms are numerous, unique, and easily identified. Refractile organisms containing pie wedge-shaped endospores are diagnostic.

CUTANEOUS LEISHMANIASIS

(Synonym: leishmaniosis)

Clinical features (Figures 12.74 and 12.75)

Leishmaniasis is a chronic cutaneous and visceral, insect-transmitted, infectious protozoan disease with worldwide distribution (Slappendel, 1988). Clinically apparent leishmaniasis is uncommon in the dog and rare in the cat, even in enzootic areas. It is very rare outside endemic areas. The disease is caused by obligatory intracellular, diphasic

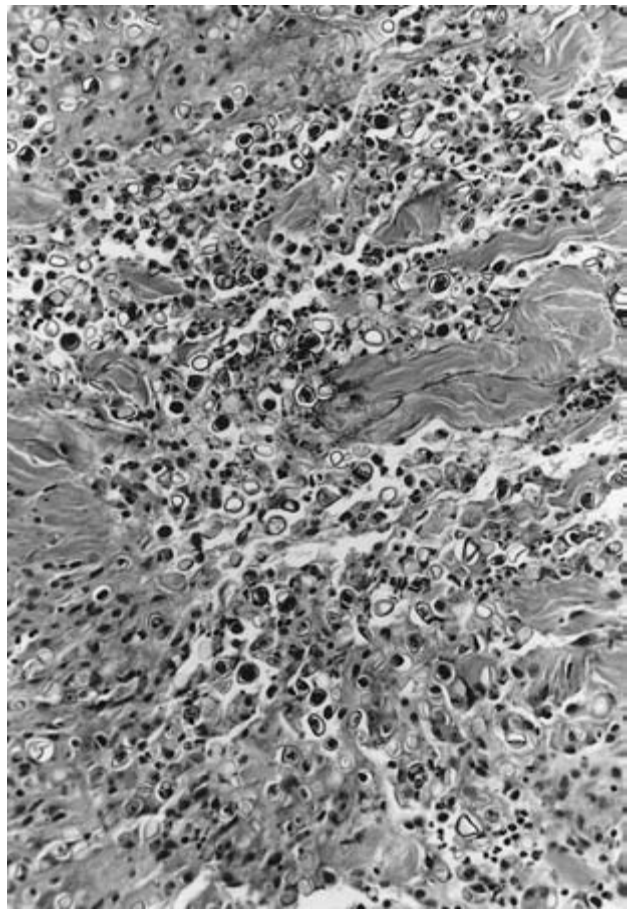


Fig. 12.73 Cutaneous protothecosis in a dog. Numerous irregular organisms are present throughout the field; many lack internal structure and are likely nonviable.



Fig. 12.74 Cutaneous leishmaniasis in a dog. As is typical, scaling is more severe on the muzzle, periorbital region, and the pinnae. (Photograph courtesy Z. Alhaidari.)

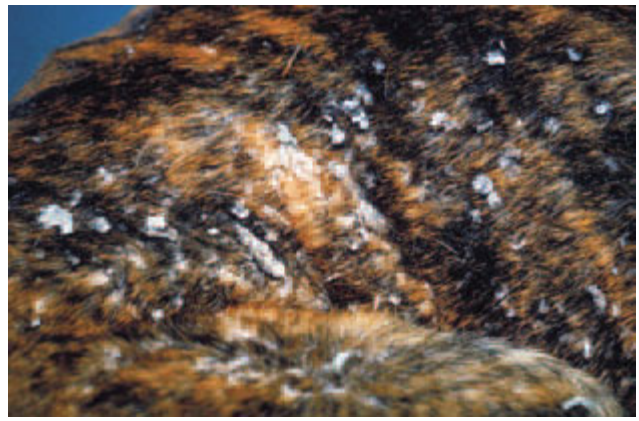


Fig. 12.75 Cutaneous leishmaniasis in a dog. Distinctive silvery-white, asbestos-like adherent scales are distributed in the haircoat. (Photograph courtesy Z. Alhaidari.)

protozoa of the genus *Leishmania* which usually are transmitted by sandflies. Canine cutaneous and visceral disease is most often caused by *Leishmania infantum*, the organism primarily responsible for causing visceral leishmaniasis in humans (Marsella & de Gopegui, 1998; Slappendel & Ferrer, 1998). The insect vectors in North America are the blood-sucking sandflies of the genus *Lutzomyia*, while the European vectors are *Phlebotomus* spp. Dogs, wild canids, and rodents are the natural reservoirs.

Differences between leishmaniasis in dogs and leishmaniasis in humans have created confusion in classification. In humans, leishmaniasis commonly is subdivided into cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (Klaus et al., 2003). Canine leishmaniasis usually is classified as 'visceral leishmaniasis' since the causative organism, *Leishmania infantum*, causes visceral leishmaniasis in people (Slappendel & Ferrer, 1998). However, the syndrome seen in dogs almost always combines cutaneous and visceral disease.

Although *Leishmania* spp. are worldwide in distribution, canine leishmaniasis is diagnosed most commonly near the Mediterranean basin, particularly in southern France, Portugal, Spain, Greece, and Italy (Denerolle, 1996; Ciaramella et al., 1997; Koutinas et al., 1999). Canine leishmaniasis still is rare in North America; enzootic foci are located in Oklahoma, Texas, and Ohio. However, with increased pet mobility, autochthonous cases are being seen in nonendemic areas worldwide after pets return from or are imported from distant locales. Canine 'visceral' leishmaniasis has now been reported in 21 states in the USA; incidence is low but seems to be increasing (Grosjean et al., 2003). Seroprevalence is still very low in the USA as only two of 957 serum samples collected in a recent study were positive for antibodies against *Leishmania* spp. (Grosjean et al., 2003).

The pathogenesis of leishmaniasis is complex as the host immune response plays a key role in the evolution of infection, morbidity, and mortality. Using modern immunologic testing and DNA probe methodology, it is now known that the prevalence of canine infection is greater than 50% in endemic areas (Ferrer, 2002). However, most infected dogs do not develop clinical disease; disease prevalence ranges only from 3% to 10% (Ferrer, 2002). Antibody-mediated immune response is nonprotective and is, in fact, detrimental, as massive antibody production leads to organ damage from circulating immune complexes (Slappendel & Ferrer, 1998). Conversely, cell-mediated immune response is protective and genetically predetermined (Ferrer, 2002). Underlying occult immunosuppressive disease may trigger overt clinical leishmaniasis. Leishmaniasis is seen, presumably secondary to suppressed cell-mediated immune surveillance, in conjunction with visceral neoplasia, autoimmune disease, other infectious diseases, and immunosuppressive drug therapy (Ferrer, 2002).

Typical clinical features include a nonpruritic, generalized, exfoliative dermatitis with alopecia. Silvery-white, asbestos-like adherent scales are a distinctive feature. Nodules and multifocal ulceration may occur in concert with exfoliation as the disease progresses. More generalized nodular skin disease is seen much less commonly. In general, the phenotype of generalized exfoliative dermatitis with alopecia probably results from a more effective immune response than the less common phenotype of generalized nodular skin disease, which is seen with more severe immunosuppression (Slappendel & Ferrer, 1998).

Three recent large retrospective studies have increased our knowledge of the range of clinical disease (Denerolle, 1996; Ciaramella et al., 1997; Koutinas et al., 1999). All three groups concur that generalized, dry exfoliative dermatitis is the prime clinical sign; ulcers, nodules, and both sterile and bacterial pustules also occur frequently (Denerolle, 1996; Ciaramella et al., 1997; Koutinas et al., 1999). Onychogryphosis (misshapen, dysplastic brittle claws), a highly distinctive change, occurs in 20% to 30% of affected dogs (Ciaramella et al., 1997; Koutinas et al., 1999). Lingual ulcers have been reported (Font et al., 1996; Blavier et al., 2001). The muzzle, periorbital region, and pinnae commonly are preferentially and more severely affected. Facial bilateral symmetry may be marked. Periorbital rings of alopecia (lunettes) and scaling are common. Depigmentation of the planum nasale and muzzle may be seen. Keratinous proliferation of the pawpads rarely may occur. Generalized peripheral lymphadenopathy is common. Systemic signs include weight loss, inappetence, emaciation, fever, malaise, muscle atrophy, exercise intolerance, coagulopathies, polyarthritis, and immune-complex renal failure.

Perhaps due to likelihood of exposure to the vector, cutaneous leishmaniasis is more common in active young adult dogs, usually 3 to 7 years of age (Ciaramella et al., 1997; Koutinas et al., 1999). Multiple sources indicate that male dogs are at slightly increased risk (Slappendel, 1988; Ciaramella et al, 1997; Slappendel & Ferrer, 1998; Koutinas et al., 1999). Canine breed predilections have not been reported in countries where canine leishmaniasis is relatively common. However, one report noted a surprising number of cases in German Shepherd Dogs, although hospital population-corrected data were not given (Ciaramella et al., 1997).

The link between leishmaniasis and Foxhounds in North America is significant and worrisome. Visceral leishmaniasis has been identified in Foxhounds in hunting kennels and in Foxhounds used as blood donors at a university teaching hospital (Owens et al., 2001; Gaskin et al., 2002). The identification of leishmaniasis in Foxhounds but not in co-housed Beagles and Bassett Hounds in the former study suggests striking breed predilection for susceptibility to infection. This link is of concern as Foxhounds commonly are used as canine blood donors. It is likely that Foxhounds exhibit diminished immune surveillance against *Leishmania*, thus allowing infection to occur more frequently.

Clinical differential diagnoses for canine cutaneous leishmaniasis characterized by exfoliative dermatitis with alopecia should include autoimmune skin diseases with frequent facial involvement (discoid lupus erythematosus, systemic lupus erythematosus, pemphigus foliaceus, pemphigus erythematosus), epitheliotropic lymphoma, dermatophytosis, and zinc-responsive dermatosis. Sebaceous adenitis is an additional differential diagnosis. Vesicles or pustules characterize pemphigus; involvement of the pawpads is common in pemphigus foliaceus, but rare in leishmaniasis. Systemic or discoid lupus erythematosus may closely mimic leishmaniasis, particularly when depigmentation is present, but scaling usually is a less striking feature. Antinuclear antibody (ANA) positivity must not be used as the sole criteria for diagnosing systemic lupus erythematosus, since leishmaniasis may initiate false positive ANA tests in almost 50% of cases (Ciaramella, et al., 1997). Zinc-responsive dermatosis exhibits more frequent mucocutaneous involvement. Leishmaniasis presenting as nodules with exfoliation may mimic epitheliotropic lymphoma. Skin biopsy is mandatory for the differentiation of these diseases. Other useful diagnostic procedures include serology, testing by polymerase chain reaction (PCR), culture, and the identification of *Leishmania* amastigotes by cytology.

Biopsy site selection

Biopsy specimens should be taken from multiple areas of adherent scale. Nodules, if present, should be sampled. Chronic lesions are more likely to yield diagnostic results. Cytology of bone marrow or lymph node aspi-

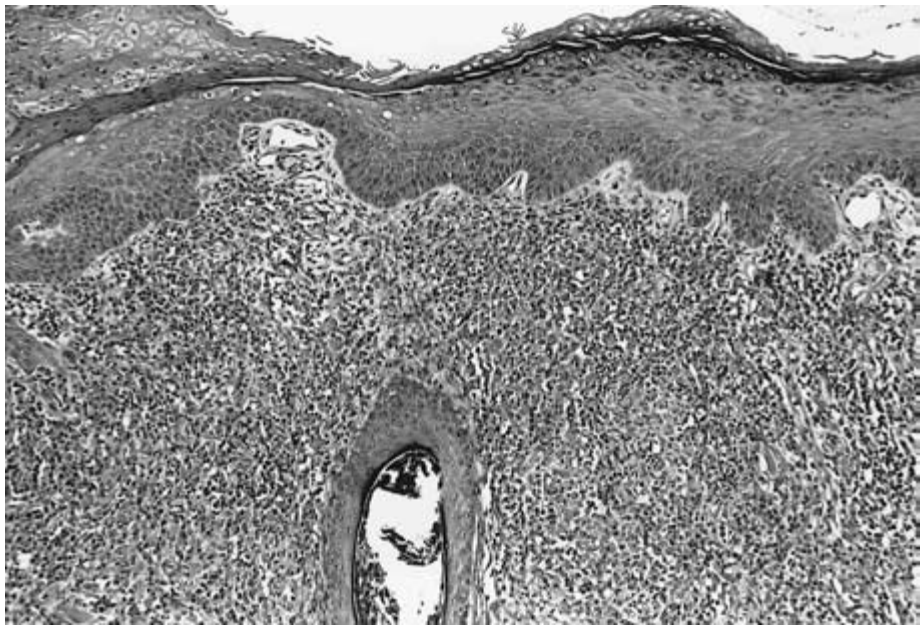


Fig. 12.76 Cutaneous leishmaniasis in a dog. The dermis is diffusely and severely inflamed.

rates, or biopsy of lymph node may aid in establishing the diagnosis.

Histopathology (Figures 12.76 and 12.77)

Moderate acanthosis and moderate to severe orthokeratotic or parakeratotic hyperkeratosis with crusting characterize the epidermis. Ulceration may occur. Dermal patterns of inflammation are highly variable (Koutinas et al., 1992), and inflammation may extend to the panniculus. Most commonly, there are perivascular infiltrations of pale granular or foamy macrophages and fewer lymphocytes and plasma cells. Discrete granulomas may be present. Neutrophils are uncommon, but occasionally may be present as small clusters. Neutrophils, lymphocytes, and plasma cells may be more abundant in ulcerated lesions; this finding also has been reported by Ferrer et al. (1988). Intense perivascular inflammation may be oriented nodularly around adnexal appendages (perifolliculitis), diffusely in the superficial dermis as a lichenoid band, or may be interstitial to diffuse. Sebaceous glands may be swept up and obliterated by the inflammation, which may explain the development of hyperkeratosis. This 'sebaceous adenitis' pattern of leishmaniasis also has been reported by Denerolle (1996). Less commonly, large discrete nodules are composed of diffuse inflammation, as described above (Ferrer et al., 1990). Intraepidermal pustulation and pustular folliculitis are reported (Ferrer et al., 1988; Koutinas et al., 1992), and necrotizing vasculitis has been described (Ferrer et al., 1990; Pumarola et al., 1991).

Variable numbers of amastigotes, which are round to oval, 1 to 2 μm in width, and 2 to 4 μm in length, may be

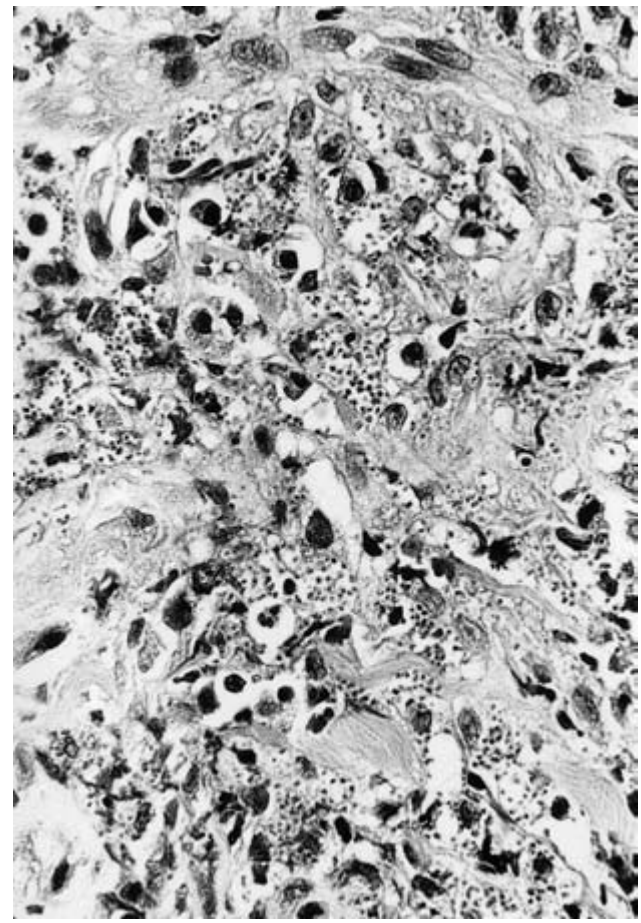


Fig. 12.77 High magnification of cutaneous leishmaniasis in a dog demonstrating numerous, small intracytoplasmic *Leishmania* sp. within macrophages.

present either within macrophages or extracellularly. Organisms are visible with hematoxylin and eosin but are accentuated with Giemsa staining; they are negative with periodic–acid Schiff (PAS) staining and Gomori's methenamine silver (GMS) (Morgan et al., 1997). A round basophilic nucleus and typical rod-shaped kinetoplast are clustered near one end of the amastigote. Organisms have been identified within fibroblasts (Ferrer et al., 1988; Hervás Rodríguez et al., 1996). Organisms may be scant and were discovered in only 50% of dogs examined in one study (Koutinas et al., 1992). The ulcerated lesions of leishmaniasis are associated with scant organisms (Ferrer et al., 1988). Immunohistochemistry for *Leishmania* spp. has been used in the definitive diagnosis of amastigote-poor lesions (Ferrer et al., 1988; Font et al., 1996), but is not routinely available in most parts of the world.

Periadnexal inflammation in cutaneous leishmaniasis may be confused with periadnexally-oriented granulomatous lesions of sterile granuloma and pyogranuloma syndrome (see Chapter 13) or with the granulomatous forms of sebaceous adenitis as seen in Vizslas (see Chapter 17). To complicate the picture, 12 of 21 European cases of sterile granuloma and pyogranuloma syndrome were positive for *Leishmania* sp. using PCR testing and immunohistochemistry; this indicated infection with the organism was present (Cornegliani et al., 2002). Superficially diffuse lichenoid and periadnexal inflammation may mimic the inflammatory pattern of Vogt–Koyanagi–Harada-like syndrome (see Chapter 11). Differential diagnosis is not difficult when typical organisms are identified in tissue; however, organisms may be difficult to find in skin biopsy specimens. When clinical and historical suspicion is high, lymph node biopsy and bone marrow aspirates may be needed to establish proof of leishmaniasis. If available, immunohistochemistry may be invaluable in these cases.

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Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis, Second Edition
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Chapter 13

Noninfectious nodular and diffuse granulomatous and pyogranulomatous diseases of the dermis

Nodular and diffuse granulomatous and pyogranulomatous diseases of the dermis are characterized by multifocal nodular inflammation that tends toward confluence or a diffuse pattern. Granulomatous inflammation is composed principally of macrophages, with or without giant cells, which are often but not exclusively organized as discrete granulomas. Pyogranulomatous inflammation has a prominent component of neutrophils that may be diffusely intermingled with macrophages; pyogranulomas are formed by central accumulations of neutrophils that are surrounded by macrophages. By convention, the presence of discrete granulomas or pyogranulomas is not a requisite for a 'granulomatous' or 'pyogranulomatous' pattern.

A third morphologic category, typified by reactive histiocytosis, is characterized by nodular to diffuse infiltrations of dermal dendritic cells that accumulate in tumor-like configurations. Histiocyte is the general term for a CD45+, CD18+ mononuclear leukocyte that originates from a CD34+ precursor cell in the bone marrow. Upon differentiation, guided by a variety of cytokines and stem cell factors, the precursor cells develop into separate lineages with different phenotypes, tissue distributions, and functions (see Chapter 35). Macrophages are primarily involved with phagocytosis and intracellular digestion of foreign antigens. Dendritic antigen presenting cells are poorly phagocytic; they specialize in processing and presenting antigens.

Diseases included in this chapter are not the result of readily identifiable infectious agents, but occur due to foreign body penetration, metabolic aberrations, or idiopathic factors. Differentiation from infectious processes of similar appearance may be required through the use of special stains and culture. However, some of these 'sterile' processes may be due to antigenic fragments of infectious agents or other antigens that elicit an inappropriate and prolonged inflammatory reaction; these are beginning to be identified by analysis by polymerase chain reaction (PCR) and DNA sequencing or other techniques. Future studies may uncover a wide range of potential immunostimulatory antigens that underlie these diseases in animals.

STERILE GRANULOMA AND PYOGRANULOMA SYNDROME

(Synonyms: sterile pyogranuloma and granuloma syndrome, SPGS)

Clinical features (Figures 13.1 and 13.2)

Sterile granuloma and pyogranuloma syndrome (SGPS) is a somewhat heterogenous group of nodular skin lesions united by similar histopathologic features. The syndrome is uncommon in dogs and rare in cats. The histiocytic nature of the inflammation, coupled with the often dramatic response to glucocorticoids or other immunosuppressive agents, suggests the likelihood of immune dysfunction, perhaps associated with persistent antigenic drive. It has long been speculated by the authors and others that infectious agents present in small numbers, or incomplete clearing of antigens associated with infectious agents, could initiate this process in domestic animals and humans. These theories gained credence when mycobacterial DNA was identified in cutaneous sarcoidosis in humans, which is a 'sterile' histiocytic proliferative disorder (Li et al., 1999). Recently, the presence of *Leishmania* spp. DNA has been documented by immunohistochemistry and testing by polymerase chain reaction (PCR) and DNA sequencing in 20 of 35 specimens in lesions of canine SGPS in Spain and Italy (Cornegliani et al., 2003); however, one would expect these results to reflect the limited geographic distribution of *Leishmania* spp. infection in the dog. In that study, testing by PCR for mycobacteria was negative. Detection of other fragmented or incomplete infectious agents in SGPS may be forthcoming, as sensitive techniques become more widely available.



Fig. 13.1 Sterile granuloma and pyogranuloma syndrome in a cat. Well-demarcated, coalescing, hairless nodules are present on the muzzle.



Fig. 13.2 Sterile granuloma and pyogranuloma syndrome in a Great Dane. Multiple alopecic nodules are present on the lateral thorax. Several nodules have had surrounding hair clipped to enhance visibility.

It is not surprising that the clinical features and biologic behavior of SGPS vary in both the dog and the cat, as there may be multiple initiators of this syndrome. Clinical appearance in dogs may differ, even with the breed affected. As more information is gained, subtypes may emerge that are based on breed affected, distribution of lesions, response to therapy, specific histopathologic features, and antigenic trigger based on molecular investigation.

The most typical skin lesions recognized in the dog consist of multiple, firm, well-demarcated, variably alopecic dermal plaques or nodules. These usually measure between 0.5 and 2 cm in diameter. The lesions are clinically asymptomatic. Lesions most commonly affect the head, particularly the dorsal and lateral muzzle, pinnae, and periorbital skin. Lesions also may occur on the neck, trunk, and, occasionally, on the extremities. Larger lesions may ulcerate and become secondarily infected. Lesions may remain indolent, regress spontaneously, or wax and wane.

A single case of cutaneous erythrophagocytosis in a 13-year-old dog was manifested clinically by multifocal alopecia and hyperpigmentation; the dog was otherwise asymptomatic and the lesions resolved spontaneously (Galvin, C., personal communication, 2003). Although this lesion may be associated with T cell lymphoma in humans, viral association has also been observed (Magro, C.M., personal communication, 2003).

Firm, well demarcated to coalescing, hairless nodules, 2 to 10 mm in diameter, have been observed in cats. Lesions are often restricted to the muzzle, but also may affect the pinnae, extremities, or regions adjacent to the pawpads. Feline SGPS may be pruritic and initiate self-trauma (Scott et al., 1990).

Sterile granuloma and pyogranuloma syndrome may be seen more frequently in the Great Dane, Boxer, Golden Retriever, Collie, and Weimaraner (Panich et al., 1991; Scott et al., 2001). The English Bulldog and Dachshund also may be at increased risk. However, SGPS may affect any breed. Age or sex predilections have not been noted in dogs. Breed, age, or sex predilections have not been documented for cats.

Clinical differential diagnoses of SGPS include neoplasia, other sterile granulomatous or pyogranulomatous diseases (reactive histiocytosis, cutaneous xanthoma, canine sarcoidosis), and granulomatous and pyogranulomatous disorders caused by infectious agents (see Chapter 12). Clinical features cannot be relied upon to differentiate among most of these diseases. Differentiation from cutaneous lymphoma, multiple canine cutaneous histiocytomas, feline progressive dendritic cell histiocytosis (see Chapter 35), and multiple mast cell tumors is especially important. Provisional differential diagnosis can be accomplished by routine histopathology and special stains for infectious agents. Impression smears obtained from fresh biopsy specimens also should be stained to search for organisms. Fungal culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may present a health hazard (Legendre, 1998) (see Chapter 12). After systemic fungi of zoonotic significance are ruled out, vigorous efforts to culture bacteria, fungi, molds, or algae from aseptically obtained biopsy specimens should be made contingent on biopsy results, since some organisms may be difficult to identify histopathologically. Immunohistochemistry and PCR testing may be used to further assess for specific infectious agents, as available. Additional support of the diagnosis of SGPS is obtained

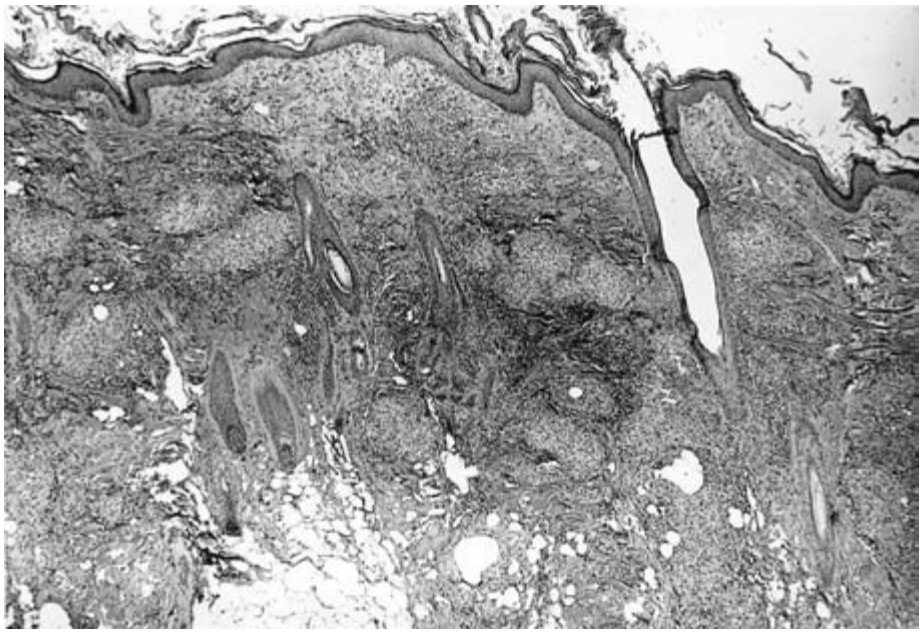


Fig. 13.3 Sterile granuloma and pyogranuloma syndrome in a dog. Pale and discrete granulomas and pyogranulomas are disseminated throughout the dermis.

retrospectively if the syndrome responds to glucocorticoid therapy.

Biopsy site selection

Multiple biopsy specimens should be obtained from intact lesions. Early nonulcerated lesions may provide more characteristic findings.

Histopathology (Figures 13.3 and 13.4)

The common element of 'sterile' granulomatous or pyogranulomatous inflammation currently unites the histopathologically variable diseases within this group. The hallmark feature is an inflammatory reaction that mimics one due to infectious agents (see Chapter 12). Epidermal features of SGPS include a normal to moderately acanthotic epidermis with occasional ulceration. Granulomatous and pyogranulomatous inflammation with discrete to confluent granulomas and/or pyogranulomas extends from the dermis to the panniculus and often to the deeper subcutis. Early inflammation may be most prominent perivascularly, and may be strikingly oriented along adnexa where blood vessels are dense, creating a periadnexal, sometimes sausage-shaped or nodular pattern. Pyogranulomas contain central neutrophils and peripheral cuffs of macrophages. Granulomas, which are less common, have sparse neutrophils. Lymphocytes and plasma cells are seen in small numbers and both surround granulomas or pyogranulomas and partially infiltrate them. There may be mild vacuolation of macrophages.

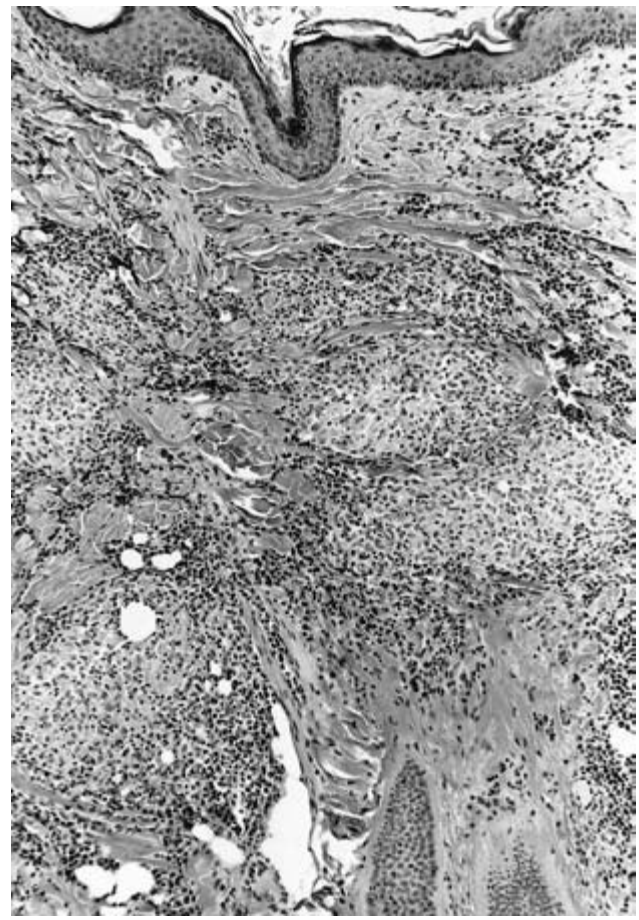


Fig. 13.4 Higher magnification of Fig. 13.3. Granulomas are surrounded by darkly staining lymphocytes and fewer neutrophils.

The inflammatory infiltrate is devoid of foreign material or infectious agents that can be detected by currently utilized routine techniques, including polarization and special staining. Special stains are always indicated due to the resemblance of this syndrome to infectious diseases. A recent study in Europe demonstrated *Leishmania* sp. by immunohistochemistry and PCR testing (Cornegliani et al., 2003).

In the single case of cutaneous erythrophagocytosis in a dog (see above) the dermis and panniculus were diffusely infiltrated with histiocytic cells that frequently contained intracytoplasmic, entire, or fragmented erythrocytes. There were fewer neutrophils intermingled. Mature lymphocytes were oriented primarily around hair follicles and within the panniculus. Diffuse edema was noted.

Variation in the microscopic pattern may depend on the species and breed in which the disorder is expressed or on what potential antigen is implicated. Further clinical and molecular subdivision of this complex is required so that the pathologist may determine which morphologic variations may be used to obtain more specific diagnoses.

Sterile granuloma and pyogranuloma syndrome has been confused with reactive histiocytosis, including in previously published reports. Reactive histiocytosis presents as diffuse sheet-like infiltrations of large histiocytes, often with vasoinvasion, rather than as confluent granulomas or pyogranulomas. In histiocytosis, a 'bottom heavy' infiltrate predominates from the middle dermis to a variable depth in the subcutis. Furthermore, immunohistochemistry will identify the histiocytes of cutaneous histiocytosis as dendritic cells, whereas macrophages are the predominant large mononuclear cell of sterile granuloma and pyogranuloma syndrome. However, late stage lesions of reactive histiocytosis may have increased numbers of macrophages (distinguished by immunohistochemistry), as well as significant infiltrations of neutrophils secondary to ischemic necrosis. Differentiation may be problematic in these cases.

Other differential diagnoses principally include granulomatous and pyogranulomatous inflammation due to infectious agents such as opportunistic myobacterial infection or fungal infections in dogs and cats, and feline leprosy syndrome in cats. In contrast to SGPS, infectious granulomatous diseases may be composed of histiocytes with severely vacuolated and/or granular cytoplasm with hematoxylin and eosin staining, often due to a high density of unstained or poorly stained infectious agents (opportunistic fungi, lepromatous leprosy type mycobacteria). Special staining allows differentiation from infectious diseases in most cases.

Discrete perifollicular and subcutaneous pyogranulomas should be differentiated from juvenile sterile granulomatous dermatitis and lymphadenitis, particularly when identified in puppies. Some lesions of juvenile sterile granulomatous dermatitis and lymphadenitis are more pustular to suppurative, which should allow differentiation from SGPS; however, clinical differentiation may be required in some cases. Early lesions of SGPS that are localized around hair follicles may resemble the nodular form of sebaceous adenitis, as seen most often in Vizslas (see Chapter 17). Clinical differentiation may be required.

REACTIVE HISTIOCYTOSIS

Clinical features (Figures 13.5 through 13.9)

Reactive histiocytosis is a relatively uncommon, poorly understood disorder characterized by the reactive proli-

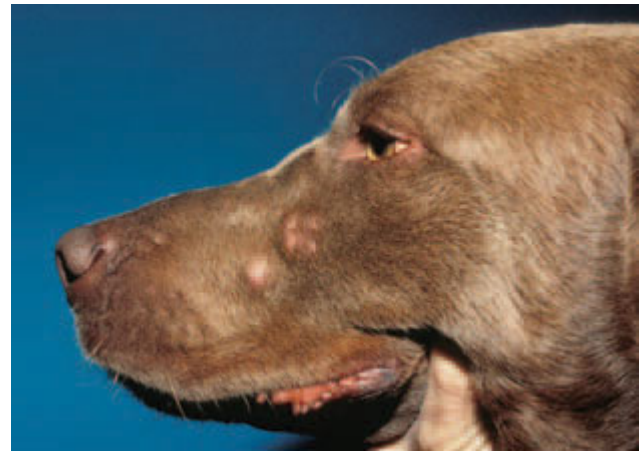


Fig. 13.5 Cutaneous reactive histiocytosis in a Chesapeake Bay Retriever. Multiple, partially alopecic nodules are present on the face. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)



Fig. 13.6 Cutaneous reactive histiocytosis in a Shetland Sheepdog. An alopecic nodule on the dorsal digit has ulcerated. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

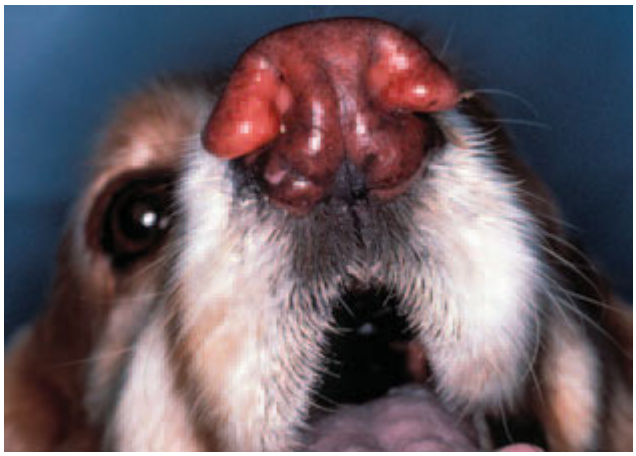


Fig. 13.7 Cutaneous reactive histiocytosis in Labrador Retriever-crossbreed. Diffuse infiltration of the planum nasale has resulted in a 'clown nose' appearance.



Fig. 13.8 Systemic reactive histiocytosis in a Bernese Mountain Dog. Multiple dermal nodules are present on the muzzle and in the conjunctiva.



Fig. 13.9 Systemic reactive histiocytosis in the Bernese Mountain Dog. Chronic ulcers on the ventral abdomen have characteristic peripheral thickening, creating a crateriform appearance.

feration of activated, perivascular interstitial dendritic antigen presenting cells, also referred to as dermal dendritic cells (see introduction, p. 320) (Affolter & Moore, 2000). Canine reactive histiocytosis includes two separate forms, cutaneous and systemic, which both primarily target the skin and subcutaneous tissue (Moore, 1984; Mays & Bergeron, 1986; Affolter & Moore, 2000). Lesions of cutaneous histiocytosis are limited to the skin, while systemic histiocytosis affects the skin and other organ systems, including lymph nodes, eyelids, sclera, nasal cavity, lungs, spleen, and bone marrow (Moore, 1984; Affolter & Moore, 2000).

The etiology and pathogenesis of reactive histiocytosis are unknown. Lesions are consistent with a reactive inflammatory process in response to persistent antigen. The nature of the antigen or antigens remains unknown, as evaluation for infectious agents has been consistently negative. Clinical course and response to immunosuppressive therapy suggest immunoregulatory dysfunction. Marked breed predilections indicate an at least partial genetic basis for systemic histiocytosis. Breed predilections have not been verified for cutaneous histiocytosis (Affolter & Moore, 2000). Reactive histiocytosis has not been conclusively documented in cats to date.

Skin lesions of canine reactive histiocytosis are characterized by usually multiple, nonpruritic and nonpainful, haired or partially alopecic, cutaneous nodules and plaques. They are predominantly located on the head, neck, perineum, scrotum, and extremities. Occasionally, nodules occur in a linear fashion, indicating the possibility of arrangement along lymphatics or blood vessels. As further indication of vascular involvement, larger nodules often ulcerate centrally, cavitate, and become necrotic. Secondary bacterial infection subsequent to deep ulceration is common. A visually distinctive subgroup of cutaneous histiocytosis with lesions limited to the nasal mucosa and planum nasale presents as marked enlargement of the planum nasale resembling a 'clown nose'.

Clinical features of systemic histiocytosis in dogs are contingent on the organ systems affected. Nodular or diffuse swelling of the mucous membranes of the nares and nasal cavity is associated with respiratory stertor. The eyes are often affected; bilateral conjunctivitis and scleritis are common, but intrabulbar and retrobulbar lesions also may occur. Ocular lesions have occasionally incorrectly been referred to as nodular fasciitis (Bellhorn & Henkind, 1967; Gwinn et al., 1977). Lymphadenopathy may be observed, and scrotal lesions may be accompanied by orchitis. Additional clinical evaluation for the presence of pulmonary, splenic, or bone marrow involvement is

warranted. In most instances, complete blood counts and serum blood chemistry results are within normal ranges.

Canine reactive histiocytosis presents with a waxing and waning clinical course. Spontaneous regressions occur, especially early in the disease process; some lesions may disappear while new lesions develop concurrently. The majority of cases follow a slowly progressive course.

The epidemiology of canine reactive histiocytosis is controversial. Some data indicate that cutaneous histiocytosis is seen with equal frequency throughout the entire dog population (Affolter & Moore, 2000); others indicate a breed predilection for Collies and Shetland Sheepdogs (Scott et al., 2001). Bernese Mountain Dogs, Rottweilers, Golden Retrievers, Labrador Retrievers, and Irish Wolfhounds appear over-represented in systemic histiocytosis, indicating probable genetic predilection (Moore, 1984; Affolter and Moore, 2000). The age of dogs with reactive histiocytosis ranges from 2 to 11 years; well-defined age predilections have not been reported.

Clinical differential diagnoses for reactive histiocytosis include neoplasia, other sterile granulomatous or pyogranulomatous diseases (sterile granuloma and pyogranuloma syndrome, cutaneous xanthoma, canine sarcoidosis), and granulomatous and pyogranulomatous disorders caused by infectious agents (see Chapter 12). Clinical features cannot be relied upon to differentiate most of these diseases. Differentiation from cutaneous lymphoma, multiple canine cutaneous histiocytomas, and multiple mast cell tumors is especially important. As with other noninfectious histiocytic skin diseases, provisional differential diagnosis can be accomplished by routine histopathology and special stains to identify infectious agents. Impression smears obtained from fresh biopsy specimens may also be stained to search for organisms. Culture for infectious organisms may be indicated contingent on histopathology. Fungal culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may present a health hazard (see Chapter 12). Immunohistochemistry and testing by polymerase chain reaction (PCR) for specific infectious agents may be useful, as available. Immunohistochemistry is key to the documentation of reactive histiocytosis and the separation from other histiocytic processes (see below).

Biopsy site selection

Early lesions with intact surface epithelium are preferred for histologic evaluation. Lesions with prominent areas of necrosis and surface ulceration may become secondarily infected and severely inflamed, which may obfuscate the diagnosis. Bisection of each biopsy specimen, with subsequent formalin-fixation of one half and snap-freezing of the second half, permits morphologic evaluation of paraffin-embedded tissues and immunophenotypic evaluation of frozen tissue of paired samples. These specimens should be shipped separately as formalin fumes will spoil the integrity of frozen fresh tissue.

Histopathology (Figures 13.10 through 13.12)

Skin lesions of cutaneous and systemic histiocytosis present with identical morphologic features. A nodular to diffuse infiltrate predominates from the middle dermis through the superficial subcutis, often referred to as a 'bottom-heavy' infiltrate. The infiltrate is markedly angiocentric and may be vasoinvasive. Nodular lesions are often observed involving the mid-dermal vascular plexus which is concentrated around adnexal structures. The infiltrate may track along adnexa to the superficial dermis in a linear or tubular configuration. These nodular to linear forms coalesce to form a diffuse pattern in advanced lesions. Vasoinvasion is associated with degen-

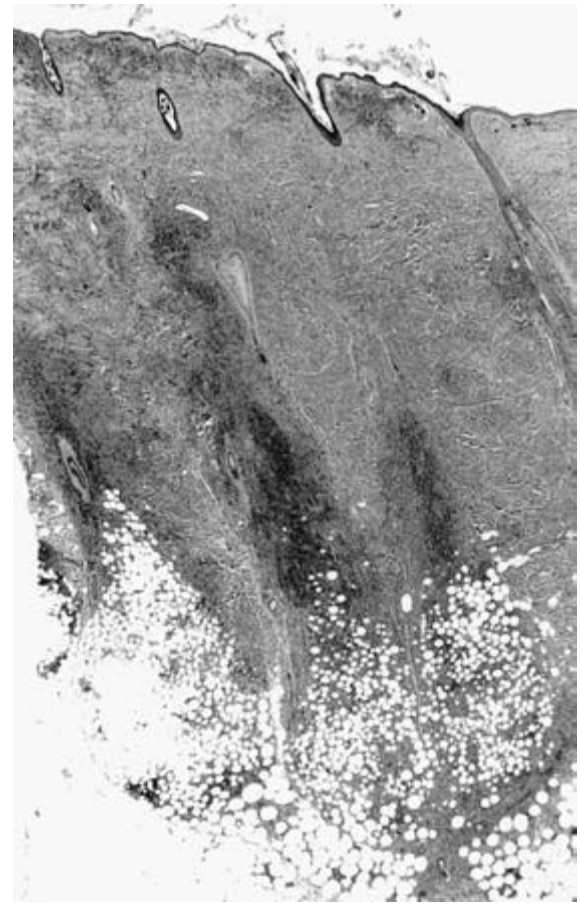


Fig. 13.10 Cutaneous reactive histiocytosis. Note the bottom-heavy infiltrate extending to the underlying subcutis; dark areas are lymphocytic infiltrates.

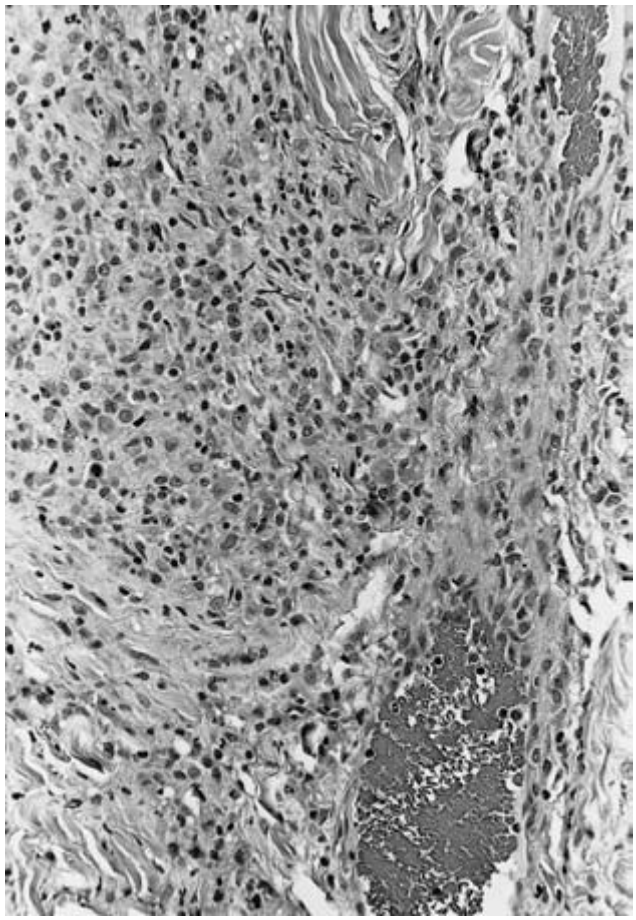


Fig. 13.11 Higher magnification of reactive histiocytosis. Large, pale histiocytes are accompanied by fewer lymphocytes and occasional neutrophils.

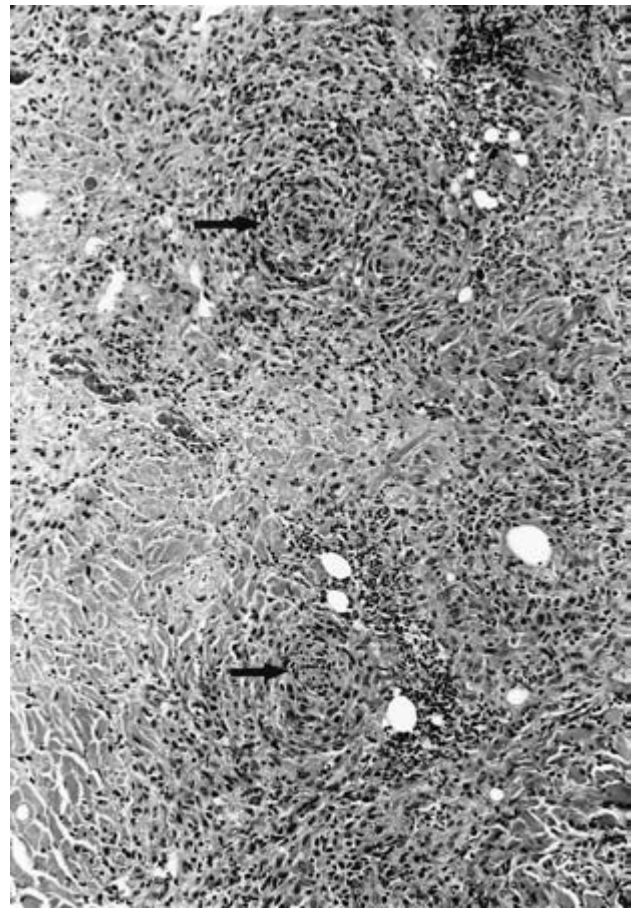


Fig. 13.12 Reactive histiocytosis demonstrating marked vascular invasion (arrows). Note pale areas of necrosis containing fragmented cellular debris.

eration of vascular walls and vascular obstruction or obliteration, which results in multifocal areas of ischemic tissue necrosis. Large, punched-out acellular areas of necrosis are noted with involvement of larger vessels.

The infiltrate is composed of mainly histiocytes, small lymphocytes, and neutrophils. The histiocytes have large, round to oval, indented or folded and twisted, vesicular nuclei. Their abundant, pale eosinophilic cytoplasm has variable numbers of small cytoplasmic vacuoles. Small lymphocytes may contribute up to 50% of the infiltrating cell population. The number of neutrophils varies and increases with necrosis. Eosinophils are occasionally seen and plasma cells are rare. Histologic lesions in other organ systems present as angiocentric nodules, as described; ischemic necrosis as a result of vascular invasion is common.

Sterile granuloma and pyogranuloma syndrome has been confused with reactive histiocytosis, including in previously published reports. Reactive histiocytosis presents as diffuse sheet-like infiltrations of large histiocytes, often with vasoinvasion, rather than as confluent granulomas or pyogranulomas. Furthermore, immunohistochemistry will identify the histiocytes of cutaneous histiocytosis as dendritic cells; whereas macrophages are the predominant large mononuclear cell of sterile granuloma and pyogranuloma syndrome. However, late stage lesions of reactive histiocytosis may have increased numbers of macrophages (distinguished by immunohistochemistry), as well as significant infiltrations of neutrophils secondary to ischemic necrosis. Differentiation may be problematic in these cases.

Differentiation between reactive histiocytosis and multiple canine cutaneous histiocytomas in regression is crucial, as immunosuppressive therapy is not warranted in the latter condition. Immunohistochemistry may be required (see below). In general, regressing histiocytomas tend to maintain their 'top heavy' configuration (see Chapter 35). The reactive lymphoid infiltrate is predominantly at the base of the tumor, and intraepidermal histiocytes may be observed. In contrast to histiocytomas, lesions of reactive histiocytosis are characterized by primarily deep dermal to subcutaneous infiltrates, intraepi-

dermal histiocytic cells are not seen, and the pleocellular infiltrate is markedly angiocentric.

Further differential diagnoses for early periadnexal lesions of reactive histiocytosis include nodular forms of sebaceous adenitis, as seen most often in Vizslas (see Chapter 17), and juvenile sterile granulomatous dermatitis and lymphadenitis (juvenile cellulitis). Reactive histiocytosis also can mimic a variety of inflammatory disease processes, including infectious diseases. In contrast to reactive histiocytosis, the inflammation of nodular sebaceous adenitis is less extensive and is centered on sebaceous glands and sebaceous gland ducts. Discrete perifollicular and subcutaneous pyogranulomas are suggestive of juvenile sterile granulomatous dermatitis and lymphadenitis, particularly in puppies. In contrast to reactive histiocytosis, infectious granulomatous diseases may be composed of histiocytes with severely vacuolated and/or granular cytoplasm on hematoxylin and eosin staining, often due to a high density of unstained or poorly stained infectious agents (opportunistic fungi, lepromatous leprosy type mycobacteria). Special stains will confirm the presence of infectious agents in many of these cases.

A limited panel of antibodies currently is available for immunophenotyping histiocytic cells in formalin-fixed, paraffin-embedded tissues (see Table 35.1). Immunophenotypic differentiation between macrophages and dendritic cells, and among dendritic cell types, requires fresh-frozen tissue samples. The proliferating histiocytic cells of reactive histiocytosis consistently express CD45, CD18, CD1c, CD11c, MHC II, CD90, and CD4, but lack expression of E-cadherin; this phenotype is characteristic of activated perivascular interstitial dendritic antigen presenting cells (dermal dendritic cells; Affolter & Moore, 2000). The majority of the lymphocytic population consists of CD3+, CD8+ T cells, which express the T cell receptor alpha, beta (TCR αβ).

In contrast to reactive histiocytosis, regressing histiocytomas are composed of CD1+, CD11c+, MHC II+, CD4–, CD90–, E-cadherin+ Langerhans cells. Infectious granulomatous lesions are characterized by numerous CD45+, CD18+, CD1–, CD11c–, CD11b+ macrophages, and fewer admixed CD1+, CD11c+, MHCII+ dendritic cells.

JUVENILE STERILE GRANULOMATOUS DERMATITIS AND LYMPHADENITIS

(Synonyms: juvenile cellulitis, juvenile pyoderma, puppy strangles)

Clinical features (Figures 13.13 and 13.14)

Juvenile sterile granulomatous dermatitis and lymphadenitis is an uncommon, fulminant canine disease seen almost exclusively in puppies. Dramatic response to immunosuppressive dosages of glucocorticoids supports the likelihood of an underlying immune dysfunction. Suppression of *in vitro* lymphocyte blastogenesis secondary to a serum factor has been documented by one author (P.J.I.) and others (Scott et al., 2001). Bacterial involvement, when present, is secondary; bacterial culture, special stains, and electron microscopy do not reveal causative microorganisms (Reimann et al., 1989). The likelihood of heritability is supported by increased occurrence in certain breeds and a genetic study of an affected family of Dachshunds (Prieur & Hargis, 1982).

Commonly, the initial clinical feature noted by owners is acute swelling of the face, especially affecting the eyelids, lips, and muzzle (Scott et al., 2001). The swelling is markedly bilaterally symmetric. Extreme submandibular



Fig. 13.13 Juvenile sterile granulomatous dermatitis and lymphadenitis in a Labrador Retriever. Pustules and nodules accompanied by edema and crusting have developed rapidly on the muzzle in a partially bilaterally symmetric pattern.



Fig. 13.14 Closer view of the dog in Fig. 13.13. Perioral lesions are draining copious purulent hemorrhagic material.

lymphadenopathy develops in concert with the facial swelling, but is less likely to be recognized by owners. Swelling is rapidly joined by bilaterally symmetric erythema, papules, nodules, and transient pustules and vesicles, usually within 24 hours. Epidermal fragility may be marked. Crusting results from rupture of the pustules and vesicles. Lesions may fistulate and drain copious purulent material. The muzzle, periorbital region, chin, and pinnae are affected most commonly. Bilaterally symmetric alopecia involves the rostral muzzle surrounding the planum nasale and the periorbital region, and may be visually striking. The medial surfaces of the pinnae commonly are edematous and covered by pustules, as a highly purulent otitis externa develops. Occasionally, the prepuce and perianal area may be affected. Once lesions fistulate, secondary bacterial infection is common. Cicatricial alopecia may occur if treatment is delayed. Lethargy and general malaise are common. Fever, anorexia, and joint pain are less consistent findings, and sterile suppurative arthritis may occur (White et al., 1989).

Juvenile sterile granulomatous dermatitis and lymphadenitis usually is seen in dogs older than 3 weeks but less than 4 months of age. Single or multiple puppies in a litter may be affected. On rare occasion, clinically and histopathologically identical disease has been noted in adult dogs by the authors and others (Jeffers et al., 1995). Breed predilections probably exist for Golden Retrievers, Dachshunds, Gordon Setters, Labrador Retrievers, and Lhasa Apsos. However, juvenile sterile granulomatous dermatitis and lymphadenitis also has been seen in many other breeds, including Brittanys, English Pointers, Chesapeake Bay Retrievers, Weimaraners, Miniature Poodles, Rottweilers, and mixed breed dogs. Sex predilections have not been noted.

Juvenile sterile granulomatous dermatitis and lymphadenitis is characteristic, especially in puppies. In very early cases, juvenile sterile granulomatous dermatitis and lymphadenitis must be differentiated from angioedema (Scott et al., 2001). After 24 to 48 hours, the syndrome must be differentiated from fulminating generalized demodicosis, severe pyoderma secondary to immunodeficiency, and drug eruption. Multiple skin scrapings to rule out demodicosis, and smears from intact pustules or vesicles to rule out primary bacterial infection should be performed. Histopathology of early lesions is necessary for definitive diagnosis.

Biopsy site selection

Multiple punch biopsy specimens (4 or 6 mm in diameter) should be taken from early, nontraumatized intact pustules, vesicles, or nodules. Wedge biopsy technique or 8 mm biopsy punches are not recommended since the devitalized tissue is quite friable and sutures may not maintain tissue integrity if the biopsy creates defects larger than 6 mm in diameter.

Histopathology (Figures 13.15 through 13.17)

The epidermis may be normal, acanthotic, or ulcerated in severe lesions. Superficial exudation may be severe. The dermis is most often characterized by multiple discrete or confluent granulomas and pyogranulomas, comprising nodular clusters of large epithelioid macrophages with

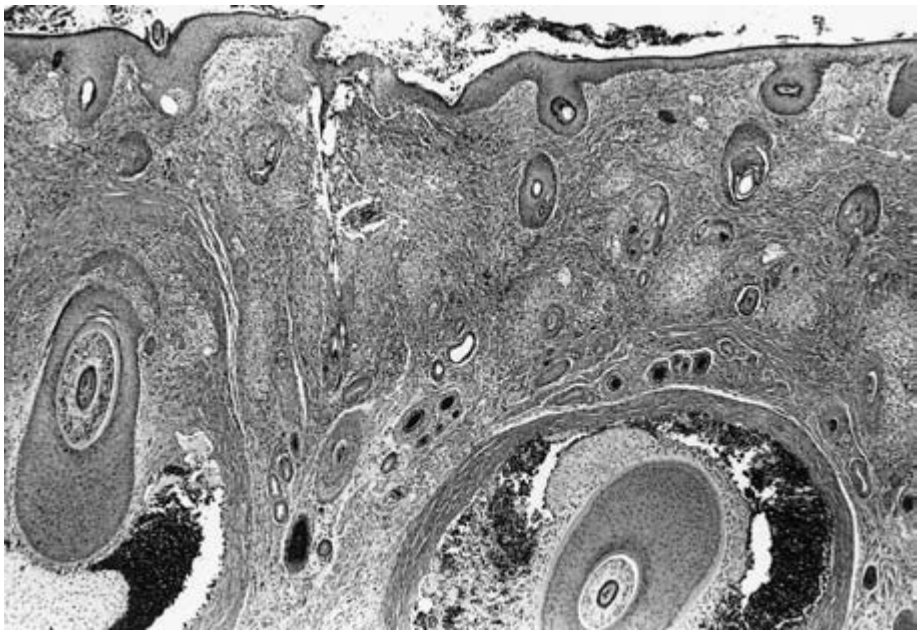


Fig. 13.15 Juvenile sterile granulomatous dermatitis and lymphadenitis revealing diffuse pale-staining granulomas and pyogranulomas in the periadnexal dermis of the muzzle.



Fig. 13.16 Higher magnification of juvenile sterile granulomatous dermatitis and lymphadenitis. The large granuloma at right surrounds the deep aspect of a follicle.



Fig. 13.17 Juvenile sterile granulomatous dermatitis and lymphadenitis demonstrating involvement of the panniculus. Inflammation is diffuse and contains a prominent component of neutrophils.

variably sized cores of neutrophils. Pyogranulomas are often oriented around follicles, at least in part, and in some lesions, may be more discretely perifollicular at the level of the isthmus. Inflammation does not invade follicular walls, but often obliterates sebaceous glands. Pyogranulomas often extend to the panniculus and subcutis.

In some lesions, inflammation is predominantly pustular and suppurative, and large lakes of neutrophils may be present in the superficial dermis, in and around ruptured follicles, and in the subjacent subcutis. Follicular degeneration may be accompanied by dermal edema and hemorrhage. It is not known whether these lesions represent secondary bacterial pyoderma, or if they simply reflect the inflammatory spectrum of this disease. Since pustules also are often observed as transient clinical lesions (see above), it is more likely that pustules represent a primary manifestation of this syndrome.

Chronic lesions may be scarred, particularly within the subcutis, which may display prominent interlobular fibrosis. Affected lymph nodes have obliterative pyogranulomatous inflammation with variable fibrosis (Reimann et al., 1989).

Differential diagnoses include other infectious and noninfectious granulomatous and pyogranulomatous diseases, including sterile granuloma and pyogranuloma syndrome. Discrete perifollicular and subcutaneous pyogranulomas, without evidence of infectious agents with special stains, are suggestive of juvenile sterile granulomatous dermatitis and lymphadenitis, particularly in puppies. Without knowledge of clinical features and age affected, differentiation from sterile granuloma and pyogranuloma syndrome may be impossible. However, pustular and suppurative lesions are more suggestive of juvenile sterile granulomatous dermatitis and lymphadenitis. The subcutaneous pyogranulomas of juvenile sterile granulomatous dermatitis and lymphadenitis closely resemble those of idiopathic sterile nodular panniculitis (see Chapter 21). It is of interest that the Dachshund is at increased risk for both diseases.



Fig. 13.18 Feline cutaneous xanthoma localized to the preauricular and periorbital regions. The bilaterally symmetric dark plaques contain hemorrhage; these lesions are friable and bruise readily. (Photograph courtesy C.B. Vitale; case material University of California, Davis.)



Fig. 13.19 Closer view of the cat in Fig. 13.18. Erythematous nodules and plaques may be seen among darker areas of dermal hemorrhage. (Photograph courtesy C.B. Vitale; case material University of California, Davis.)

CUTANEOUS XANTHOMA

(Synonym: xanthomatosis)

Clinical features (Figures 13.18 through 13.20)

Cutaneous xanthomas are benign, typically multifocal granulomatous skin lesions containing lipoprotein-derived deposits. Cutaneous xanthomas are rare in the cat and very rare in the dog. In all species, formation of xanthomas reflects abnormal plasma concentrations of cholesterol, triglycerides, or lipoproteins, termed 'dys-



Fig. 13.20 Severe multicentric cutaneous xanthomas in a cat. Larger masses, resembling neoplasms, are ulcerated and exudative.

lipoproteinemias'. Lipoproteins are lipid–protein conjugates that transport lipids, including cholesterol and triglycerides, in the blood. Lipoproteins are classified by both size and density, which is contingent on both the type and ratio of constitutive proteins and fats. Lipoproteins are divided into five major classes including chylomicrons (largest, least dense), very low density lipoproteins (VLDLs), intermediate density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) (smallest and most dense). An elevation of serum lipid levels is termed hyperlipidemia or hyperlipoproteinemia. The infiltration and deposition of lipoproteins into tissue secondary to elevated serum lipid levels produces xanthomas. The exact mechanisms are not known; trauma may predispose to their formation (Jones et al., 1985; Vitale et al., 1998).

Xanthomatosis in humans is a histiocytic disease characterized by the deposition of lipids in the skin, tendons, and subcutaneous tissue (Grundy, 1999). Different species of lipoproteins produce clinically different subgroups of xanthomas in humans (Grundy, 1999). Xanthomas in humans are associated with fasting hyperlipoproteinemia caused by either defects in lipid metabolism such as a deficiency in lipoprotein lipase (LPL), or reduction in LPL activity due to insulin deficiency, as seen in diabetes mellitus. Gross hyperlipidemia or hyperlipoproteinemia may or may not be present. Lipid deposits may create xanthomas in a variety of different organs including the skin. In contrast, cutaneous xanthomas are usually absent in cats with familial hyperlipoproteinemia due to LPL deficiency (Jones et al., 1986; Johnstone et al., 1990).

Most feline cutaneous xanthomas are linked to the feeding of a high fat diet and fasting hyperlipoproteinemia (Vitale et al., 1998; Vogelnest, 2001). Presumably, these cats have an underlying abnormality in lipid meta-

bolism, and therefore cannot tolerate fat-laden food; however, the specific metabolic defect has not been elucidated. Affected cats have substantially elevated fasting triglycerides, cholesterol, or LDLs (Vitale et al., 1998). Feline cutaneous xanthomas can develop secondary to naturally occurring and megesterol acetate-induced diabetes mellitus with hypertriglyceridemia (Chastain & Graham, 1978; Jones et al., 1985). This is presumably due to decreased LPL activity from insulin deficiency as in humans, and was documented in one cat (Jones et al., 1985). However, the occurrence of cutaneous xanthoma in cats with diabetes mellitus is at odds with the relative absence of xanthomas in cats with familial LPL deficiency (see above). Other metabolic factors may be operant in diabetic cats with cutaneous xanthomas. One cat developed cutaneous xanthomatosis and atherosclerosis in conjunction with prolonged use of corticosteroids; the authors speculated that a primary hyperlipoproteinemia may have been complicated by long-term corticosteroid usage (Wisselink et al., 1994).

Dietary-related cutaneous xanthomas have been reported in a dog secondary to an experimental high cholesterol diet (Reedy, 1986). Cutaneous xanthomas have also been reported in a dog with diabetes mellitus-associated hypertriglyceridemia (Chastain & Graham, 1978). A dog with cutaneous xanthomas due to hypertriglyceridemia (without diabetes mellitus) has been observed by one author (T.L.G.).

Multiple, pale, yellow to white papules, plaques, or nodules with erythematous borders are the most common clinical presentation of feline xanthomas. Rarely, larger masses may ulcerate and discharge inspissated, amorphous, necrotic material. Erythematous, yellowish to brownish-red or purple plaques are seen most commonly in the preauricular location and may extend periorbitally. Preauricular xanthomas are friable and bruise readily; the dark color change represents hemorrhage in various stages of resolution. Bilateral symmetry is typical. Feline xanthomas occur most commonly in the preauricular and periorbital region, and to a lesser extent elsewhere on the head, pinnae, or neck (Vitale et al., 1998). Lesions also have been seen affecting the legs, with more severe lesions occurring over bony prominences and in the pawpads. Very rarely, feline xanthomas, seen in conjunction with inherited hyperchylomicronemia, may cause peripheral neuropathy believed to be due to nerve compression from lipid deposits (Jones et al., 1986). Similar cutaneous lesions at or near the eyelid margins usually are chalazions and not cutaneous xanthomas.

Yellow papular skin lesions in one dog were noted on the face, ears, and ventrum (Chastain & Graham, 1978). Lesions in a second dog were on the face, neck, feet, elbows, and tips of the ears and tail (Reedy, 1986). Breed, age, or sex predilections for cutaneous xanthomas have not been established.

Clinical differential diagnoses should include other noninfectious granulomas and pyogranulomas as well as neoplasms. Infectious granulomas may need to be considered for large, necrotic xanthomas. Preauricular xanthomas in cats are clinically distinctive. Histopathology is required for definitive diagnosis. A preliminary chemical screening panel should be performed to evaluate for diabetes mellitus, or elevated lipids. Fasting 24-hour lipid profiles and apoprotein electrophoresis should be performed to determine the origin of xanthomas. Triglycerides, cholesterol, HDLs, LDLs, and VLDLs should be measured or calculated, as well as LPL activity (Vitale et al., 1998).

Biopsy site selection

Punch or wedge biopsy specimens should be taken from plaques or nodules prior to ulceration, since secondary inflammation or necrosis may impede evaluation. If possible, pawpad lesions should be avoided, since healing may be prolonged if the underlying reason for dyslipoproteinemia is not medically manageable.

Histopathology (Figures 13.21 through 13.24)

The epidermis may be normal to moderately acanthotic. Ulceration is rare. There is diffuse granulomatous inflammation composed of large macrophages containing abundant, foamy cytoplasm. Foamy macrophages may diffusely percolate between collagen fibers, or may be in diffuse sheets that obliterate normal architecture. In some cases, macrophages and giant cells are individualized in tissue and are separated by clear spaces. In other cases, macrophages are compactly organized and may abut residual collagen fibers in a slightly palisaded arrangement. Giant cells are seen and may be massive (containing up to 20 nuclei) and numerous. Eosinophils are observed and may be abundant. Neutrophils are sporadic and usually are present in small numbers. Lymphocytes and plasma cells are variable and may be focally numerous. There may be prominent hemorrhage, particularly in preauricular lesions. Superficial dermal fibrosis is present in some putatively chronic or traumatized lesions.

There are often small to occasionally large lakes of extracellular, amorphous and pale-staining lipid deposits. Acicular cholesterol clefts may be present. Demonstration of extracellular lipid is not present in all lesions, however, and should not be relied upon for definitive diagnosis. Oil red O staining of frozen tissue confirms lipid within macrophages and giant cells and in extracellular lakes

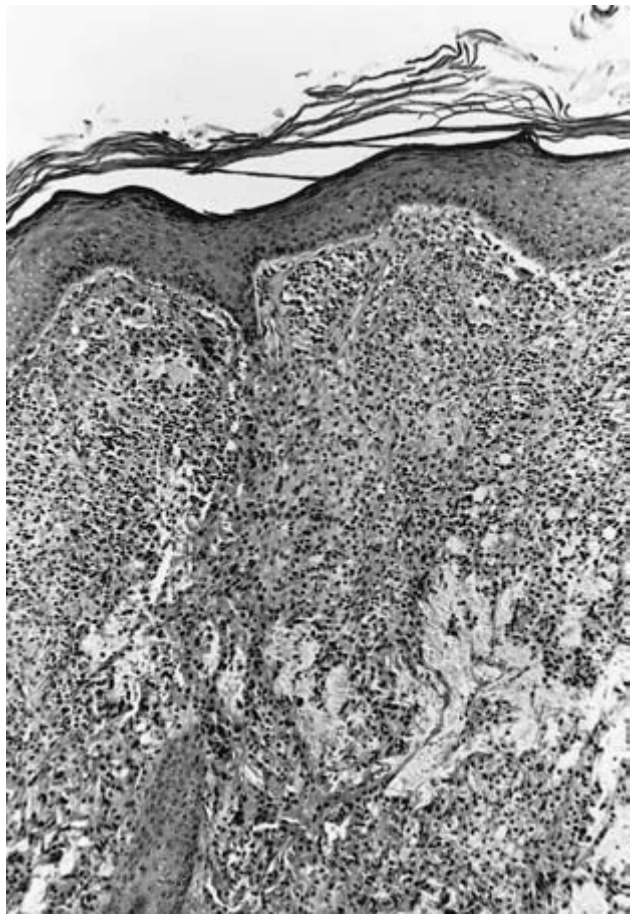


Fig. 13.21 Cutaneous xanthoma in a cat with diabetes mellitus. Diffuse pyogranulomatous inflammation is interspersed with large, pale, acellular lakes of lipid.

(Chastain & Graham, 1978). A hypertriglyceridemic (nondiabetic) dog with cutaneous xanthomas, observed by one author (T.L.G.), had small basophilic foci of saponified-like mineral deposits amongst the extracellular lipid.

In some feline cutaneous xanthomas the inflammation is more discretely nodular or tumor-like. It is composed of large foamy macrophages intermingled with prominent lymphoid nodules and accumulations of eosinophils. Giant cells may be massive. Extracellular lakes and acicular deposits may be present or absent.

The rare multifocal cutaneous xanthomas in dogs are distinctive and unique. Solitary reactive fibrohisticytic nodules in dogs may contain lipidized histiocytic cells, and thus appear xanthomatous (see Chapter 35). However, these usually have a spindle cell component, and lack extracellular lipid. Palisading granulomas may appear somewhat similar histologically, but are more distinctly aligned along collagen fibers and do not contain lipidized cytoplasm; these are also generally solitary.

Principal differential diagnoses for cutaneous xanthomas in cats must include cutaneous infection by opportunistic fungi or lepromatous feline leprosy, both of which may have diffuse infiltrations of pale or foamy macrophages. Demonstration of organisms will allow differentiation; the prominence of eosinophils in some cutaneous xanthomas tends to discount these infectious causes as well. Cutaneous xanthomas may have extracellular deposits of lipid or cholesterol clefts, whereas infectious granulomas do not. Tumor-like, nodular xanthomas are vaguely reminiscent of mast cell neoplasms; a Giemsa stain for mast cell metachromatic granules is negative.

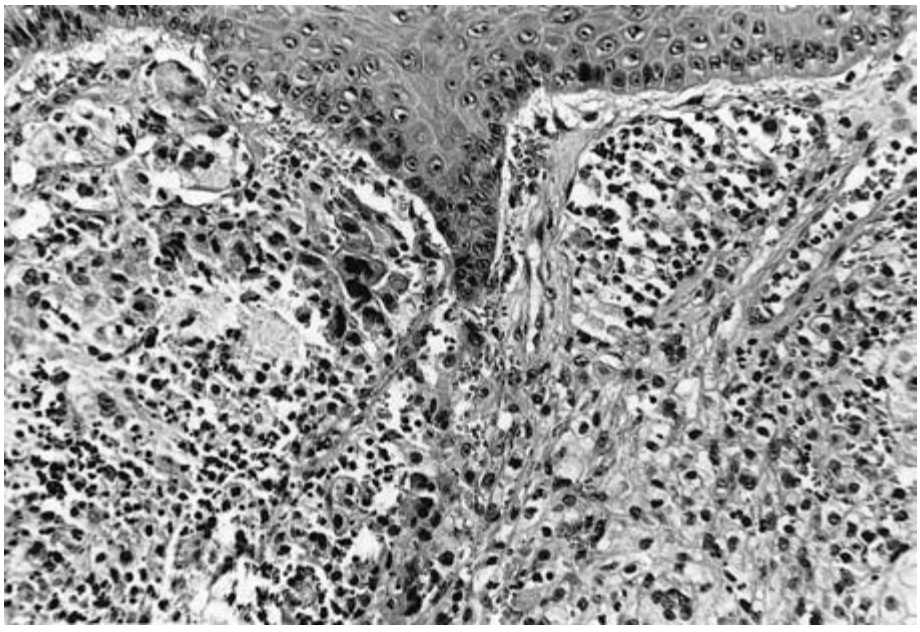


Fig. 13.22 Higher magnification of Fig. 13.21. Note diffuse distribution of neutrophils, foamy macrophages, and giant cells.



Fig. 13.23 Preauricular xanthoma in a cat. Compactly organized macrophages are partially aligned along collagen fibers.

Feline progressive dendritic cell histiocytosis in cats may resemble cutaneous xanthoma since foamy macrophage infiltration may occur in long standing lesions, as confirmed by immunohistochemistry (see Chapter 35). Extracellular lipid deposits are not found in feline progressive dendritic cell histiocytosis. An absence of dietary or blood lipid abnormalities suggests progressive dendritic cell histiocytosis for generalized xanthomatous lesions.

Focal or multifocal lesions of the eyelid margins may closely resemble xanthomas, particularly in cats. These eyelid lesions are due to rupture of regional meibomian glands (chalazions) and include more neutrophils, resulting in a more pyogranulomatous appearance than most cutaneous xanthomas. Clinical differentiation may be required.

CANINE SARCOIDOSIS

Clinical features (Figure 13.25)

Canine sarcoidosis is a very rare, idiopathic, predominantly nodular skin disease characterized histologically by 'naked' granulomas (Scott & Noxon, 1990). These granulomas lack the lymphocytic component that characterizes other granulomatous and pyogranulomatous skin diseases. The histopathologic features of canine sarcoidosis mirror those of sarcoidosis in humans (Scott & Noxon, 1990). Despite the confusing nomenclature, canine sarcoidosis is not related to 'sarcoid' in the cat (see Chapter 27).

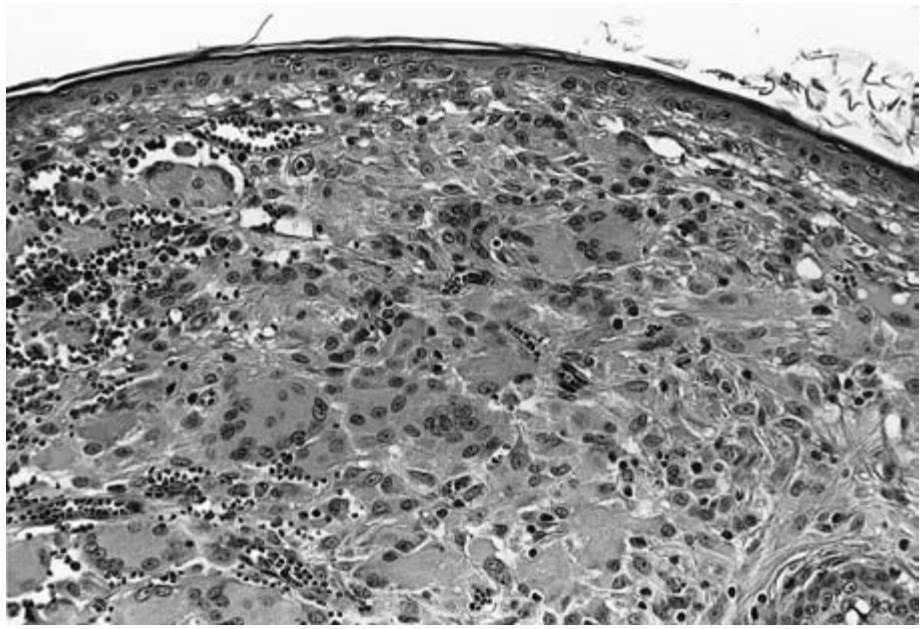


Fig. 13.24 Preauricular xanthoma in a cat. Large histiocytic cells and numerous giant cells diffusely fill the dermis. Note hemorrhage.

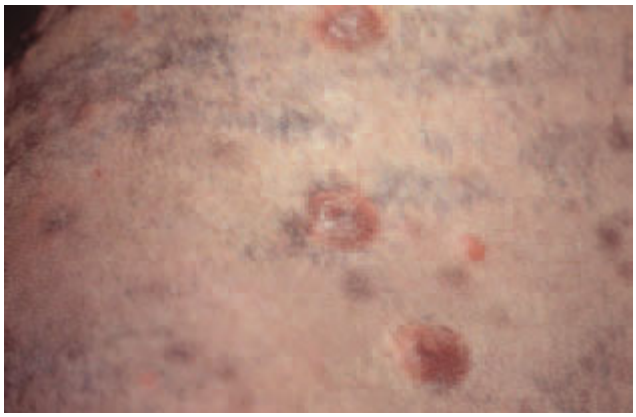


Fig. 13.25 Canine sarcoidosis. Erythematous papules, plaques, and nodules are present on the trunk of a dog. (Photograph courtesy D.W. Scott.)

Sarcoidosis in humans is a multisystemic granulomatous disorder of uncertain and likely complex etiology commonly affecting the lungs, lymph nodes, skin, and eyes (Braverman, 2003). To date, only cutaneous involvement has been seen with canine sarcoidosis. Modern techniques indicate that T cells of the CD4+ helper–inducer phenotype (TH1) are increased in the lungs in human sarcoidosis and a peripheral T cell lymphopenia is present (Braverman, 2003).

As in other sterile granulomatous and pyogranulomatous skin diseases, persistent antigenic drive directed against unknown antigens, or incomplete clearing of antigens associated with infectious agents is suspected. Recently, DNA from *Mycobacterium tuberculosis* and unidentified nontuberculous mycobacteria was identified in cutaneous sarcoidosis in humans (Li et al., 1999; Braverman, 2003). In canine sterile granuloma and pyogranuloma syndrome, another sterile granulomatous skin disease, *Leishmania* spp. DNA has been documented via immunohistochemistry and PCR in 20 of 35 dogs; mycobacterial DNA was not discovered (Cornegliani et al., 2003). To the authors' knowledge, tissue from canine sarcoidosis has not yet been examined by molecular and immunohistochemical techniques.

Described clinical features are derived from a very small case sample, which includes three dogs in the published report (Scott & Noxon, 1990) and one additional dog observed by one author (T.L.G.). Clinical lesions include erythematous papules, plaques, and nodules. Neither pruritus nor pain has been linked to this syndrome. Affected sites include the trunk, neck, face, and ears.

Case numbers are too small to infer signalment predilections. All affected dogs have been between 4 and 7 years of age. Of possible interest is that one of three dogs in the sole published report (Scott & Noxon, 1990) and one dog seen by one author (T.L.G.) were Shetland Sheepdogs.

Clinical differential diagnoses should include neoplasia, other sterile granulomatous or pyogranulomatous diseases (sterile granuloma and pyogranuloma syndrome, reactive histiocytosis, cutaneous xanthoma), in addition to granulomatous and pyogranulomatous disorders caused by infectious agents (see Chapter 12). Cytology of impression smears from cut biopsy specimens may be useful. Clinical features cannot be relied upon to differentiate most of these conditions. As with other noninfectious histiocytic skin diseases, provisional differential diagnosis can be accomplished by routine histopathology and special stains to rule out infectious agents, as well as culture, if indicated.

Biopsy site selection

Multiple biopsy specimens should be obtained from intact lesions. A range of lesions, including papules and nodules, should be sampled.

Histopathology (Figures 13.26 and 13.27)

Lesions of canine sarcoidosis, resembling the granulomas in human cutaneous sarcoidosis, are characterized by multifocal 'naked' granulomas. These are granulomas that are composed predominantly of epithelioid macrophages without a peripheral cuff of lymphocytes. Peripheral palisading, as in palisading granuloma (see 337) is absent. Granulomas are oriented within the superficial to deep dermis; subcutaneous involvement has been reported (Scott & Noxon, 1990). Individual granulomas are generally contiguous, but not often confluent. Pale, slightly vacuolated macrophages comprise the granulomas; cell borders are difficult to discern. Small accumulations of lymphocytes intervene. Neutrophils are rare. The epidermis is normal to mildly acanthotic.

Differential diagnosis principally includes sterile granuloma and pyogranuloma syndrome. Although pyogranulomas are not a feature of sarcoidosis, separation of these two entities may be artificial as both likely represent 'sterile' inflammation derived from circulating macrophages in response to undetected antigen.

FOREIGN BODY REACTIONS

(Synonym: foreign body granuloma)

Clinical features (Figures 13.28 and 13.29)

Cutaneous and subcutaneous foreign body reactions are common in dogs and uncommon in cats. The lesser frequency in cats probably is attributable to more effective

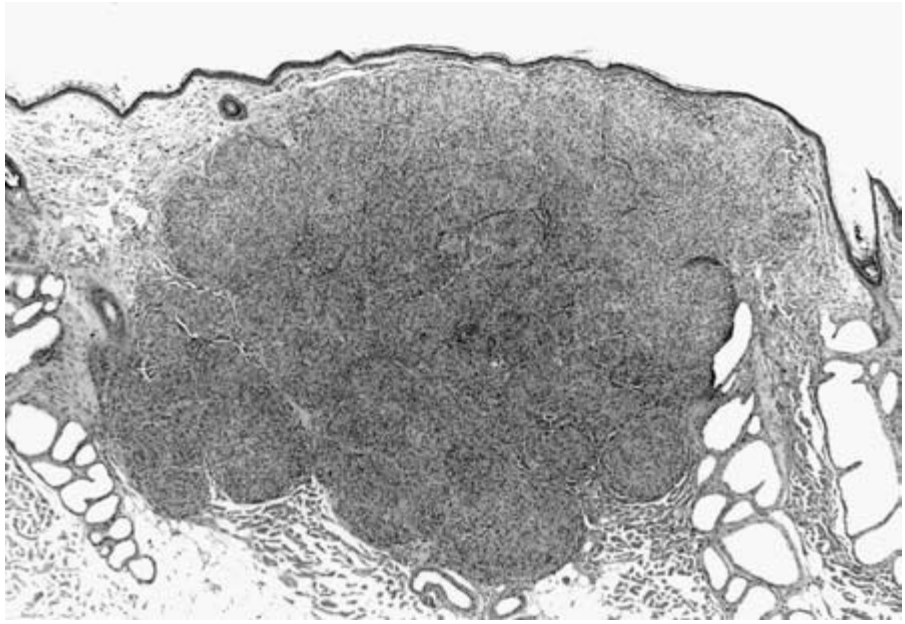


Fig. 13.26 Sarcoidosis in a Shetland Sheepdog. Confluent granulomas form a discrete nodule in the dermis.

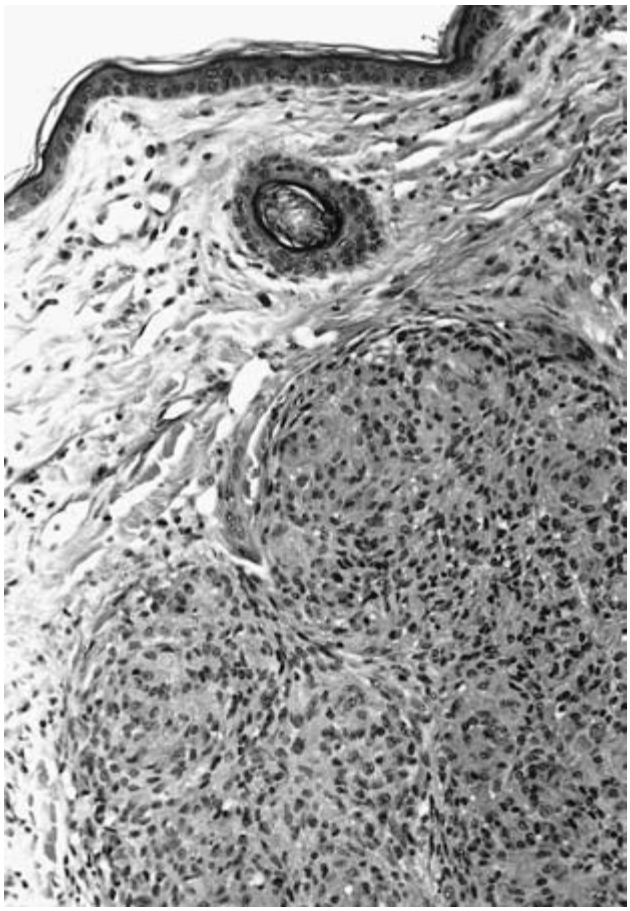


Fig. 13.27 Higher magnification of Fig. 13.26. 'Naked' granulomas are composed of epithelioid macrophages.



Fig. 13.28 Interdigital foreign body reaction in a dog caused by grass awns. A firm nodule in the dorsal interdigital web has fistulated and another grass awn has begun penetration of the fistula.

and meticulous self-grooming. Penetrating foreign bodies commonly pass through the epidermis and lodge in the dermis, panniculus, or the subcutis. Pyogranulomatous or granulomatous inflammation results from host response directed against the foreign material plus contaminant infectious agents carried into the wound. These organisms include bacteria that commonly cause secondary infection (such as *Staphylococcus intermedius*), actinomycetes or *Nocardia* spp., opportunistic mycobacteria, saprophytic fungi that may act as opportunists, organisms that cause subcutaneous or systemic fungi, dermatophytes, saprophytic water molds (*Pythium insidiosum* and *Lagenidium*

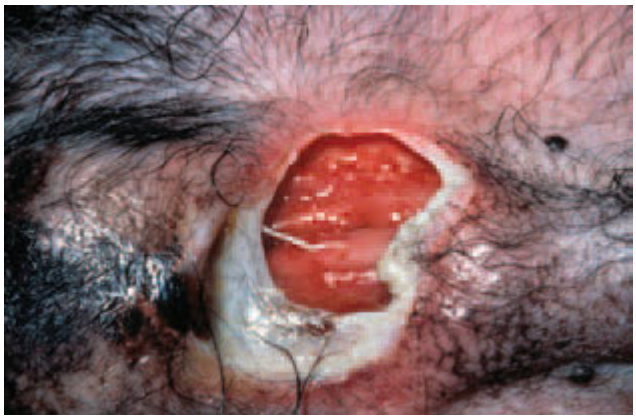


Fig. 13.29 Severe foreign body reaction due to a grass awn in the sheath of the prepuce of a Miniature Poodle. The lesion has fistulated and sloughed necrotic inflamed tissue, discharging the grass awn, and resulting in a deep cavity.

spp.), and saprophytic achlorophyllous algae (*Prototheca* spp). Specific infectious diseases caused by the above-mentioned organisms are discussed separately (see Chapter 12).

Common penetrating foreign bodies such as wood slivers, suture material, road gravel, fiberglass fibers, and air gun pellets share worldwide distribution. Various species of grass awns (foxtails), cactus spines, burdock burrs, seeds, and porcupine quills have regional distribution (Georgi et al., 1982; Brennan & Ihrke, 1983; Scott et al., 2001). Foreign bodies of plant origin are the most commonly implanted (Brennan & Ihrke, 1983). In addition, endogenous foreign bodies such as free hair shafts commonly incite foreign body reactions.

The foxtail, *Hordeum jubatum*, is the most common foreign body seen in North America. Other barbed awns from the genera *Hordeum*, *Stipa*, and *Setaria* are distributed worldwide. Grass awns usually penetrate the skin or a body orifice after being retained in the haircoat of the animal. Distinctive sharply barbed anterior florets on the surface of the grass awn prevent retrograde migration; anterograde motion is encouraged by muscular movement (Brennan & Ihrke, 1983). Secondary bacterial infection with *Staphylococcus intermedius* or actinomycetes (see Chapter 12) is a common sequela.

Clinically, the initial site of penetration may not be obvious until inflammation progresses. Localized erythema and swelling are often the initial signs. As the foreign body migrates inward, firm nodules or abscesses form, fistulate, and drain seropurulent or serosanguinous exudate. Nonbarbed foreign bodies and some grass awns may be shed by this process. Nodular areas of scar tissue surround the fistulas as the lesions progress. Deep folliculitis and furunculosis aggravate the process as hair follicles rupture and release hair and keratin into the dermis, leading to additional foreign body response. Rapidly penetrating foreign bodies may also carry hair and environmental debris into deep tissues. Multiple lesions are common.

The external ear canal is the most common orificial portal of grass awn entry (Brennan & Ihrke, 1983). The dorsal interdigital webs are the most common cutaneous location of grass awn penetration, although penetration can occur at any site. Lesions associated with other foreign bodies usually do not exhibit distinct site predilections.

Young dogs of hunting and working breeds are at greater risk, probably indicating that an active outdoor lifestyle enhances the opportunity for exposure in these breeds (Brennan & Ihrke, 1983). Grass awns are trapped more readily in the hair coats of long-coated breeds. Sex predilections have not been noted. Grass awn foreign bodies exhibit a seasonal incidence in late summer and autumn during dry weather.

Puncture wounds without retention of foreign material may mimic foreign body reactions. Other clinical differential diagnoses should include deep folliculitis and furunculosis without foreign bodies (particularly interdigital pyoderma or interdigital pyoderma secondary to demodicosis), deep fungal infection, ruptured follicular cysts, or neoplasms. Cytology of impression smears or exudate may be useful. Deep pyoderma without associated foreign body penetration usually is more disseminated in distribution. Fistulous tracts associated with grass awns commonly are deeper (as determined by probing) and more well-defined than the cavitating or necrotizing lesions caused by deep pyoderma or ruptured follicular cysts that fistulate. Site and clinical features aid identification, but clinical or histologic identification of foreign material is required for definitive diagnosis.

Biopsy site selection

Solitary lesions should be removed in their entirety, if surgically feasible. If multiple lesions are present, representative specimens should be taken from multiple sites. Ideally, both closed and open lesions should be sampled. Deep wedge resection is recommended since the foreign bodies may be located in the subcutis.

Histopathology (Figure 13.30)

The epidermis is often severely acanthotic and exudative. There may be ulceration present, and inflammation may fistulate through the epidermal defect. The dermis, subcutis, and occasionally underlying skeletal muscle, are diffusely and severely inflamed, and often fibrotic. Large



Fig. 13.30 Foreign body reaction in a dog. A cross-section of plant material is surrounded by fibrinosuppurative exudate which extends into a fistulous tract above.

central or multicentric foci of frank suppuration or pyogranulomatous inflammation are observed. Eosinophils are variable and may be prominent. Necrosis may be severe and can be accompanied by cavitation due to liquefaction and loss of devitalized tissue. At the periphery, there are mixed mononuclear cells which usually include many plasma cells. Granulation tissue proliferation and mature areas of fibrosis often subtend and surround the inflammatory core or cores. Fistula formation is frequent and is characterized by linear or curvilinear spaces, lined with neutrophils and surrounded by fibrosis. Fibrosis may predominate in chronic lesions.

Foreign material, usually of plant origin, occasionally may be found superficially or deeply within fistulas or suppurative foci, but its presence is not required to suggest the diagnosis. Plant foreign bodies usually appear in tissue section as polygonal or linear structures, which have very pale eosinophilic or amphophilic staining properties. The plant fragment may contain yellow or brown pigment. Plant cell walls have a honeycomb-like configuration when viewed in cross-section, and individual plant cells have little internal structure. Colonies of bacteria are often present within the plant material. Free hair and keratin may be present and may aggravate the inflammatory process.

Differential diagnoses include penetrating wounds without foreign body retention, deep folliculitis and furunculosis with ruptured hair follicles, or ruptured follicular cysts. Puncture wounds without penetration of foreign material may produce a similar lesion, particularly if bacteria or follicular tissue are introduced. Ruptured furuncles or follicular cysts may also lead to a similar pattern of inflammation, since keratin and hair essentially act as endogenous foreign bodies when released from hair follicles.

PALISADING GRANULOMA

Clinical features

Palisading granulomas are solitary nodules seen occasionally in dogs. Distinctive, discrete, granulomas center on putatively degenerate or devitalized collagen fibers. Blunt trauma may be an initiator of palisading granuloma.

Palisading granulomas usually present clinically as solitary dermal nodules located over pressure points such as the zygomatic arch or hip, or sites possibly prone to localized blunt trauma such as the lips or tongue. A palisading granuloma also has been seen by one author (T.L.G.) on the pinna in conjunction with an underlying arteriovenous malformation, suggesting that local ischemia may play a role in the development of these lesions.

A distinctive presentation of palisading granuloma, microscopically resembling Churg Strauss granuloma of humans, has been observed in a dog that presented with oval, alopecic plaques on the dorsum of the muzzle (Gallant, W.P., personal communication, 2003). There was mild scaling and crusting. The lesions were asymptomatic. This type of granuloma has been associated with systemic immunoreactive or autoimmune diseases in people (Lee et al., 1999). The affected dog had inappropriate secretion of antidiuretic hormone (ADH) but no other systemic disease process was discovered.

Dogs of any age, sex, or breed may be affected. However, most of the dogs noted with this syndrome have been larger breed dogs that are perhaps more likely to incur trauma during vigorous activity.

Clinical differential diagnoses include solitary dermal neoplasms or solitary infectious granulomas such as canine leproid granuloma (see Chapter 12). Other sterile or infectious granulomatous diseases are less likely differential diagnoses, as they rarely present as solitary lesions. Histopathology is diagnostic.

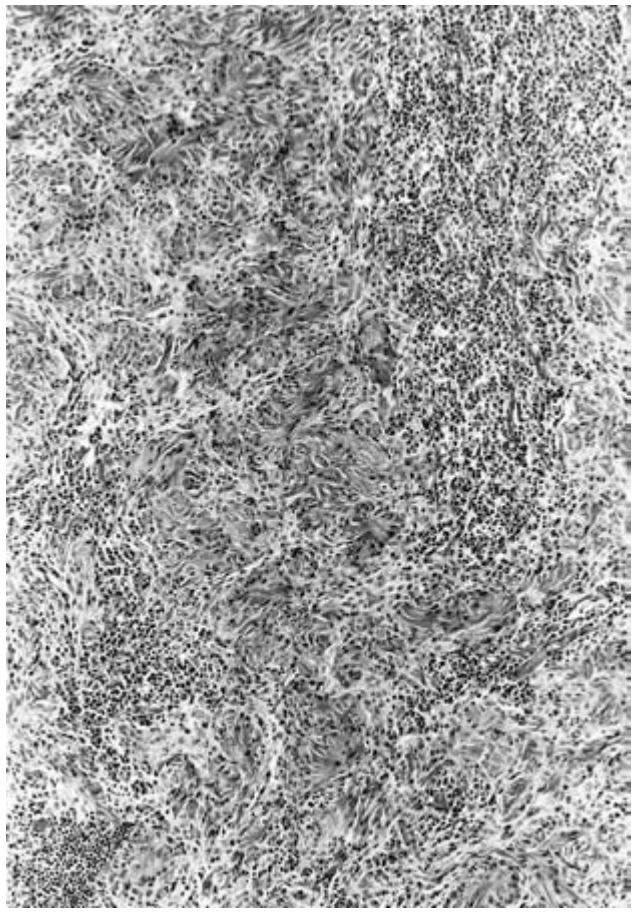


Fig. 13.31 Palisading granuloma in a dog. Prominent palisading along collagen fibers by macrophages is producing a 'starburst' pattern.

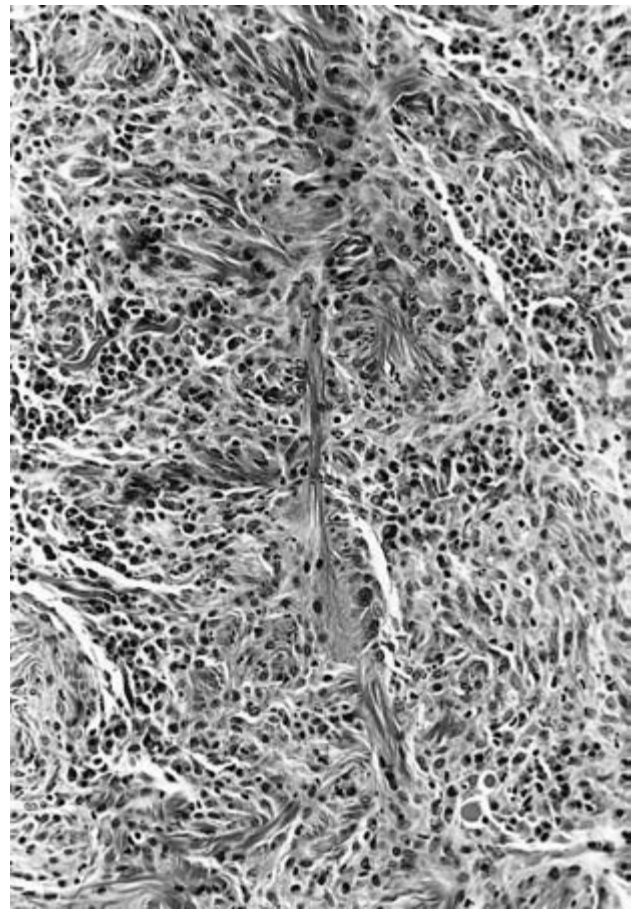


Fig. 13.32 Higher magnification of palisading granuloma in the dog of Fig. 13.31. Macrophages are aligned in a radiating palisaded pattern along collagen fibers; fewer neutrophils, lymphocytes, and plasma cells are intermingled.

Biopsy site selection

Nodules should be removed by excisional biopsy. This provides the added benefit of a surgical cure, since lesions usually are solitary.

Histopathology (Figures 13.31 through 13.35)

The epidermis is normal to moderately acanthotic. Nodular lesions are of variable depth, and affect the dermis and/or the panniculus and deeper subcutis. The nodules are composed of diffuse granulomatous inflammation that replaces normal architecture. Individual granulomas are discrete to confluent, and are round to often elongated and tubular. At the centers of these granulomas are collagen fibers with altered tinctorial quality and appearance. These fibers are brightly eosinophilic and may appear fragmented or smudged. Occasionally they may be mineralized (basophilic). Central collagen may be surrounded by zones of eosinophilic, paler, amorphous material. A few neutrophils are intermingled in the central collagenous foci or the outer amorphous layer; some larger foci of frank pustulation occur. Large numbers of pale epithelioid macrophages encircle the centers, and are partially linearly aligned in a palisading pattern along fibers. This palisading arrangement is striking in some lesions, creating a radiating, or 'starburst' pattern. Lymphocytes and plasma cells variably separate the granulomas. These may be abundant and more diffuse in some lesions, resulting in wide partitioning of individual granulomas, or partial obliteration by the lymphoplasmacytic inflammation. Large foci of acellular necrosis, suggesting ischemia, also may obliterate portions of the lesion. There may be mucin amongst granulomas in some cases.

Masson's trichrome stain often colors collagen fibers at the centers of granulomas bright red, in contrast to normal blue or blue-green. Staining is inconsistent, however, and red cores can be demonstrated in normal collagen fibers as well; thus, the use of this stain is con-

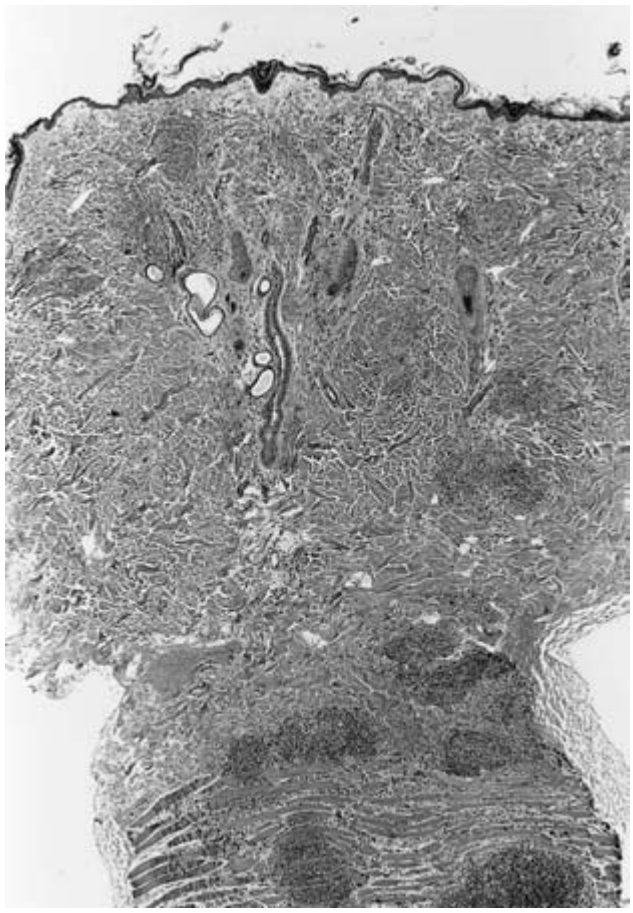


Fig. 13.33 Churg Strauss granuloma in a dog. Dark foci throughout the dermis and panniculus comprise inflammation organized around collagen.

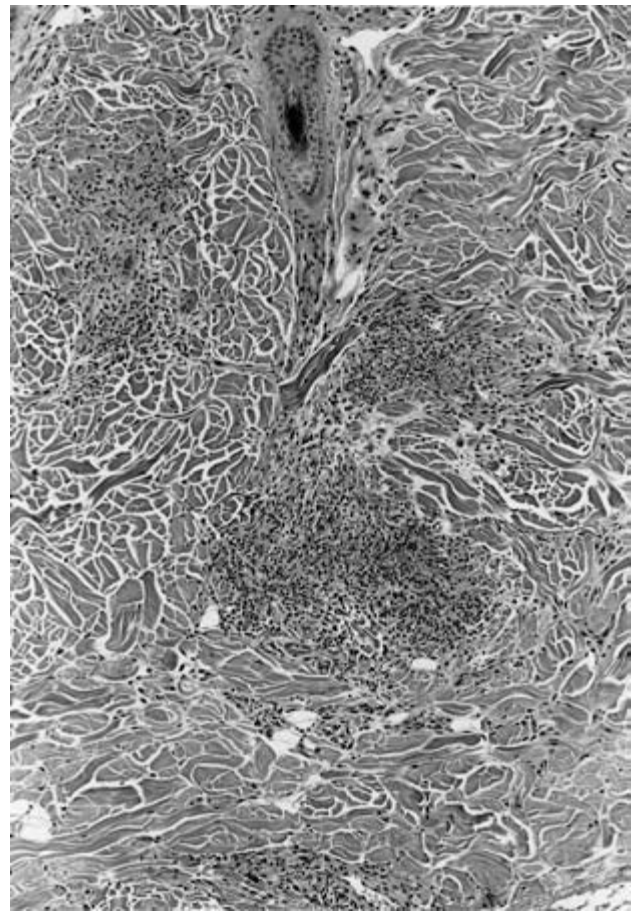


Fig. 13.34 Higher magnification of Fig. 13.33.

sidered diagnostically unreliable. Red staining of collagen, although not highly specific, may be a sign of degeneration or abnormal development; it has been reported in thermal trauma of collagen (Chvapil et al., 1984) and in some cats with cutaneous asthenia or skin fragility (see Chapter 15) (Fernandez et al., 1998).

In the single dog with palisading granulomas resembling Churg Strauss granuloma of humans (see above), multiple small, often necrotic appearing granulomas were present. These were characterized by central foci of degenerate neutrophils with prominent leukocytoclasia organized around collagen. A few eosinophils were intermingled. Peripheral palisading of histiocytic cells was accompanied by fewer lymphocytes. Early foci were characterized by leukocytoclastic debris and/or histiocytic cells aligned along individual collagen fibers. The granulomas extended to the panniculus and underlying skeletal muscle. Mild multifocal interstitial inflammation of skin and muscle featured lymphocytes, histiocytes, neutrophils and fewer eosinophils.

Lesions that are similar to palisading granuloma have been seen on the chin of cats. Macrophages and fewer giant cells are aligned linearly amongst collagen fibers. Central discrete foci of collagen and amorphous material are not seen. Plasma cells and lymphocytes may be numerous. Eosinophils are seen sporadically and in small numbers. It is likely that these lesions represent late stage eosinophilic granulomas from which eosinophils have faded, rather than true palisading granuloma. Similarly, palisading lesions around collagen have been observed within noneosinophilic foci of canine eosinophilic granulomas that are putatively due to arthropod insult (see Chapter 14). If the unifying feature of palisading granuloma is previous damage to collagen that elicits a secondary granulomatous response, then palisading in the context of some eosinophilic granulomas may be pathogenically similar.

The principal differential diagnoses for palisading granulomas are sterile granuloma and pyogranuloma syndrome, cutaneous sarcoidosis, and reactive fibrohistiocytic nodules (see Chapter 35). The two former conditions

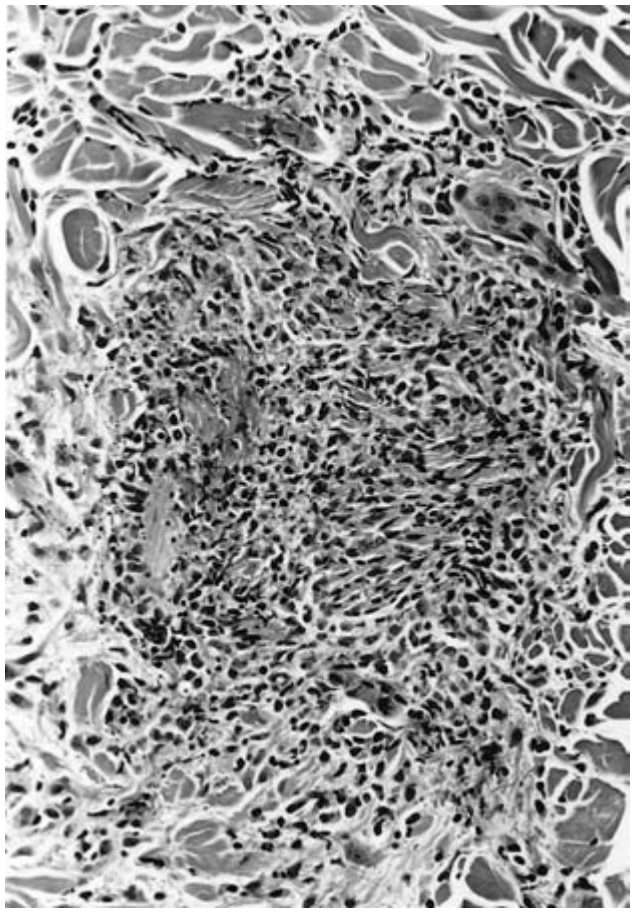


Fig. 13.35 High magnification of Churg Strauss granuloma in the dog of Fig. 13.33. Neutrophils and lymphocytes are palisading along collagen fibers at left; note dark fragments of leukocytoclastic neutrophilic debris, best visualized at left.

present with multiple lesions, rather than the solitary lesions that typify palisading granuloma. Fibrohistiocytic nodules are similarly solitary. Pyogranulomatous inflammation is a more consistent feature of the sterile granuloma and pyogranuloma syndrome than of palisading granuloma. Palisading granulomas feature typical palisading linear alignment of macrophages along central foci of collagen, a feature that is absent in the other three lesions.

Very small palisading granulomas may develop around individual collagen fibers in lesions of cell poor vasculitis (see Chapter 10); differentiation is not problematic due to the occurrence of the latter in the context of ischemic dermatopathy. The leukocytoclastic degenerate foci of the Churg Strauss-like variant of palisading granuloma somewhat resemble those of familial cutaneous vasculopathy of German Shepherd Dogs (see Chapter 14). Inflammation is generally more diffuse and severe in the latter; clinical differentiation may be required.

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Chapter 14

Nodular and diffuse diseases of the dermis with prominent eosinophils, neutrophils, or plasma cells

This group of diseases is characterized by prominent eosinophils, neutrophils, or plasma cells in a diffuse dermal pattern. The inflammation tends to obscure normal dermal architecture and may compress or replace adnexal appendages. Degranulation of eosinophils to form flame figures around collagen fibers often accompanies eosinophilic inflammation of this type. Several of these diseases are suspected of having an allergic or immunologic basis, and some may be triggered by exposure to arthropod bites or stings.

ARTHROPOD BITE REACTIONS

(Synonym: insect bite granuloma)

Clinical features (Figure 14.1)

Arthropod bite reaction occurs in the dog and cat as a sequel to the bite or sting of various arthropods (Walder & Howard, 1982). Arthropod bite reactions rarely are reported in animals due to the difficulty in establishing cause and effect. Consequently, the true frequency is unknown. Ticks are the most commonly documented cause in dogs; this may be the result of the propensity of the tick to remain attached to the host after the initial insult, thus aiding in causal identification. Besides ticks, other aggressively biting and stinging arthropods probably produce similar reactions in dogs and cats. Fly-strike on the ears of dogs is very common. Black flies (Scott et al., 2001) and buffalo gnats (both *Simuliidae* spp.) are under-recognized regional causes of skin lesions and pruritus in dogs. In humans, hundreds of species of arthropods, encompassing five of nine classes (Arachnida, Chilopoda, Diplopoda, Crustacea, Insecta) can cause bite reactions of varying severity (Wilson & King, 1999; Wilson et al., 2003). Canine eosinophilic granuloma and eosinophilic furunculosis of the face are likely additional manifestations of arthropod insult in dogs and are discussed separately below and in Chapter 17.

Type III and IV hypersensitivity reactions are the most commonly proposed pathogenesis of arthropod bite reactions in humans (Doros, 1988; Wilson & King, 1999). Urticaria and angioedema probably represent type I reactions.

Focal erythema and swelling are the usual initial clinical signs of many arthropod bites. These initial lesions may be the sole clinical signs in many cases and may not progress to chronic granuloma formation. Early lesions vary from 5 to 20 mm in diameter and usually are circular.

The clinically typical arthropod bite reaction is a firm, palpable dermal nodule that forms as a chronic sequela to often surprisingly minimal acute lesions. Lesions may be pruritic, painful, or asymptomatic. Less commonly, acute erythematous lesions may eventuate rapidly in necrosis with ulceration, alopecia, and crusting. Scarring with striae, permanent alopecia, and either hyperpigmentation or hypopigmentation may efface the normal surface architecture of the affected cutaneous site. Most commonly, arthropod bite granulomas are solitary. Site predilections mirror the biting habits of the various arthropods. For example, tick bite reactions are seen most frequently on the muzzle, periorbital region, ears, and interdigital webs.

Fly strike caused by stable flies (*Stomoxys calcitrans*) is a very common regional skin disease in outdoor dogs (Scott et al., 2001). Severe erythema, ulceration, and hemorrhagic crusts are the most common lesions. Dog breeds with erect ears (such as the German Shepherd Dog) are attacked predominantly on the tips of the pinnae; breeds with folded ears (such as the Shetland Sheepdog) commonly are attacked at the folds of the pinnae. Lesions also occur on the face and occasionally elsewhere. Pruritus and pain are common. The disease is seasonal.

Black flies and buffalo gnats can initiate highly distinctive erythematous, macular targetoid lesions. These are characterized by central hemorrhage and necrosis and circumferential blanching, surrounded by an additional ring

of erythema that may not blanch with diascopy (direct pressure with a glass slide). Lesions may vary from a few to dozens. Urticaria may be a feature of more severely hypersensitive dogs after multiple episodes. One author (P.J.I.) has seen angioedema due to buffalo gnat bites. The glabrous abdomen, axilla, pawpad margins, philtrum, and perioral and periorbital regions may be predisposed due to a relative lack of hair at these sites in many dogs. Pruritus varies from moderate to severe. Severity of reaction seems to increase with additional exposure. Skin disease initiated by black flies and buffalo gnats is markedly seasonal, commonly occurring in the spring.

Breed, age, or sex predilections have not been noted. Dogs and cats with greater opportunity for outdoor access, particularly in rural or semirural areas, are likely to be more frequently affected. Animals lacking dense, protective haircoats may be at greater risk.

Clinical differential diagnoses for early arthropod bite reactions (swelling and erythema) are legion, but should include drug eruption, kerion dermatophytosis, and trauma. The various causes of angioedema may need to be considered if that is the principal presenting sign (see Chapter 10). The later stage, or true arthropod bite granuloma, must be differentiated from infectious and noninfectious granulomatous or pyogranulomatous diseases, including foreign body reactions, as well as neoplasms. Differentiation of arthropod bites from many of these other inflammatory lesions is aided by the fact that arthropod bite granulomas often are solitary. Clinical history and histopathology may be required for differentiation. Lesions caused by black flies or buffalo gnats are visually very distinctive and usually confined to less well haired body regions.



Fig. 14.1 Chronic arthropod bite reaction caused by a tick in a Labrador Retriever. The well-demarcated nodule has a small central ulcer.

Biopsy site selection

Solitary nodules should be removed in their entirety. If multiple lesions are present, punch or wedge specimens should be taken from representative lesions.

Histopathology (Figures 14.2 through 14.4)

The epidermis is necrotic, ulcerated, and exudative in acute lesions. Acanthosis or ulceration occurs in chronic lesions.



Fig. 14.2 Acute arthropod bite reaction in a cat. Note prominent wedge-shaped necrosis and superficial exudate.

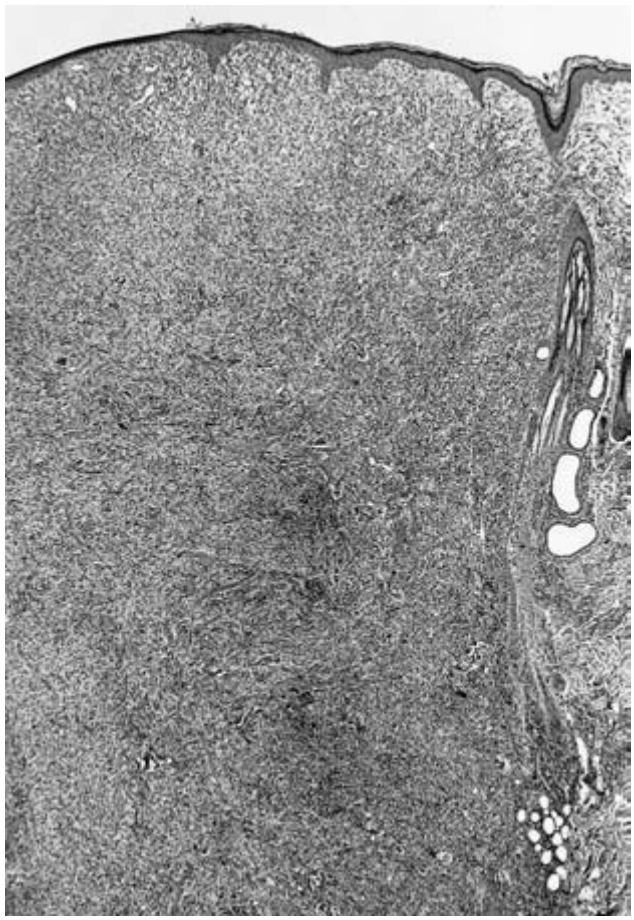


Fig. 14.3 Chronic arthropod bite reaction (insect bite granuloma) in a dog. Mixed inflammation fills the dermis and subcutis.

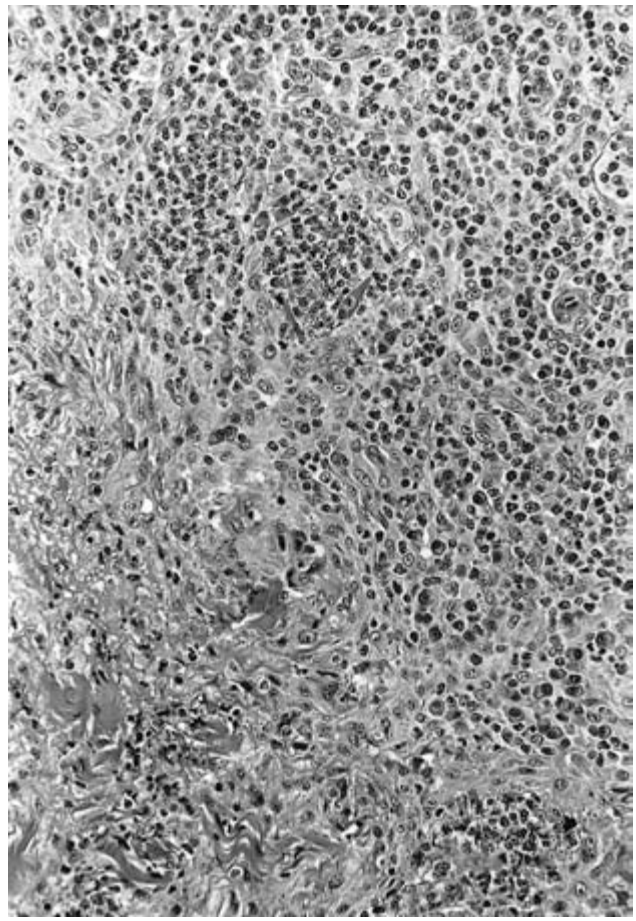


Fig. 14.4 Higher magnification of arthropod bite granuloma in the dog of Fig. 14.3, revealing dense population of mixed mononuclear cells and fewer eosinophils. Eosinophils are organizing around collagen fibers at lower left.

Early arthropod bite reactions, as typified by tick bites, are focally severe but poorly circumscribed. At the site of arthropod trauma there is extensive necrosis and inflammation that may occasionally occur in the classic triangular or 'wedge-shaped' configuration with the apex near the subcutis. Inflammation is perivascular to diffuse surrounding the necrotic foci, and includes numerous eosinophils, macrophages, and lymphocytes. Edema, mucin, and hemorrhage may be prominent. Milder lesions from cases of confirmed tick or other arthropod exposure may be characterized by superficial and deep, perivascular to diffuse infiltrates of eosinophils and lymphocytes, accompanied by variable edema and/or mucin.

Chronic arthropod bite 'granulomas' tend to have sharper margins, and are composed of dense infiltrates of macrophages, lymphocytes, mast cells, eosinophils, and plasma cells. The inflammation is predominantly in the dermis and sometimes the superficial subcutis, and obscures normal architecture. Nodular accumulations of lymphocytes, resembling lymphoid follicles, may be prominent but are not invariably present. Fibrovascular tissue often is intermingled with inflammatory cells amongst the lymphoid follicles. In some cases, discrete granulomas composed of large macrophages may be observed within the larger lesion. Eosinophils may be numerous and may degranulate around scattered collagen fibers. Localized arthropod bite reactions in dogs also may be manifested by more flagrant eosinophilic granulomas with eosinophil degranulation (see p. 358).

'Fly strike' lesions have moderate irregular acanthosis with compact orthokeratotic or parakeratotic hyperkeratosis. There is variable erosion and serocellular or sanguinocellular crusting. The dermis has fibrosis that varies from mild to marked. Superficial hair follicles are hyperplastic, but more severe or chronic lesions can have adnexal atrophy and dropout due to advanced dermal fibrosis. The dermal infiltrate is deep, moderate to severe, interstitial and perivascular, and comprises plasma cells and eosinophils primarily. Smaller numbers of pigmented macrophages, neutrophils, and lymphocytes are present.

Differential diagnoses are few for acute arthropod bite reactions, particularly if typical wedge-shaped configuration is seen. The intense eosinophilic and neutrophilic inflammation with necrosis of the acute reaction resembles other recognized arthropod insults, including spider bites and fire ant bites (see pp. 347 and 349). Milder insect bite reactions resemble allergic reactions of many types, including urticarial allergic eruption (see Chapter 9). Chronic fly strike lesions also suggest allergic dermatitis with self-trauma; knowledge of site affected is diagnostic, however. The presence of a deep component of perivascular eosinophilic inflammation suggests insect or other arthropod exposure, at least in dogs. The difficulty in confirming histologic reactions in response to insects comes from the poor correlation with clinical exposure in most cases.

Discrete chronic granulomas may resemble sterile granuloma and pyogranuloma syndrome, reactive fibrohistiocytic nodule (see Chapter 35), or palisading granuloma. Arthropod insult may be suggested by inflammation that includes lymphocytes, often in follicular arrangement, and eosinophils; there is a relative absence of prominent pyogranulomas and palisading is not a feature. Reactive fibrohistiocytic nodules and palisading granulomas generally do not feature many eosinophils, in contrast to most arthropod bite reactions.

FELINE MOSQUITO BITE HYPERSENSITIVITY

(Synonym: feline insect bite hypersensitivity)

Clinical features (Figures 14.5 and 14.6)

See Chapter 6.

Biopsy site selection

See Chapter 6.

Histopathology (Figures 14.7 through 14.9)

There is moderate to severe acanthosis with variable but frequently severe erosion, ulceration, and exudation (see Chapter 6). The superficial and the deep dermis are usually severely and diffusely inflamed, and inflammation may extend to the panniculus. Eosinophils predominate and are accompanied by lymphocytes, mast cells, macrophages, and neutrophils in variable numbers. Edema and sometimes hemorrhage are present.

Small to moderately sized foci of eosinophil degranulation may form flame figures around collagen fibers, as seen in eosinophilic granuloma. There may be similar degranulating eosinophils in the follicular wall (eosinophilic mural folliculitis) or within and surrounding blood vessels. In some cases, eosinophilic follicular lesions are striking and are manifested by free hair shafts surrounded by amorphous eosinophilic debris and, more peripherally, by macrophages. Degranulating eosinophils may develop along the length of the follicle, creating an eosinophilic follicular 'cast' surrounding the residual hair. Hairs may drop out of these foci, leaving hair-shaped clear spaces at their center.

Differential diagnoses for the eosinophilic dermatitis of mosquito bite hypersensitivity in cats include food allergy, eosinophilic plaque, indolent ulcer, eosinophilic granuloma, and the eosinophilic form of herpesvirus ulcerative

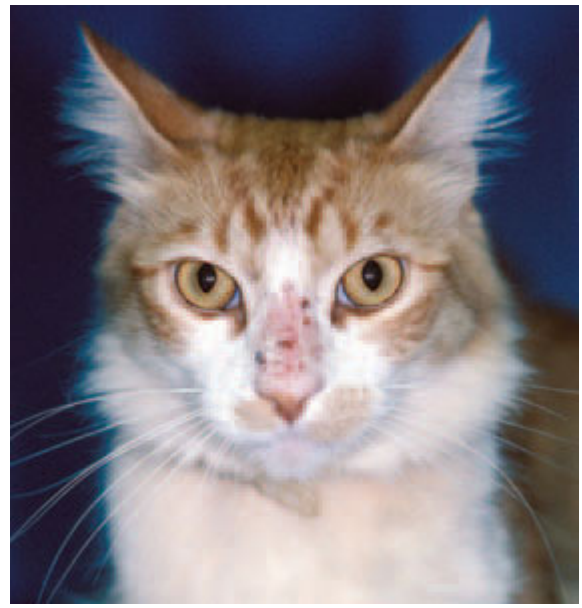


Fig. 14.5 Mild feline mosquito bite hypersensitivity. Lesions are confined to the dorsal muzzle and do not affect the pinnae.



Fig. 14.6 Closer view of the cat in Fig. 14.5. Mild erythema, partial alopecia, and adherent crusts are present.

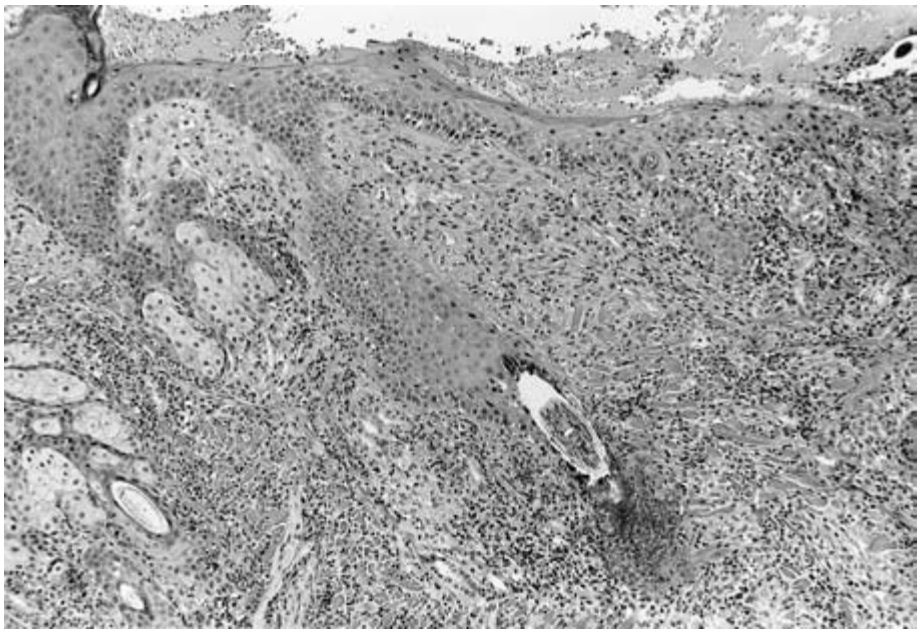


Fig. 14.7 Feline mosquito bite hypersensitivity. Diffuse inflammation is punctuated by degranulating eosinophilic mural folliculitis.

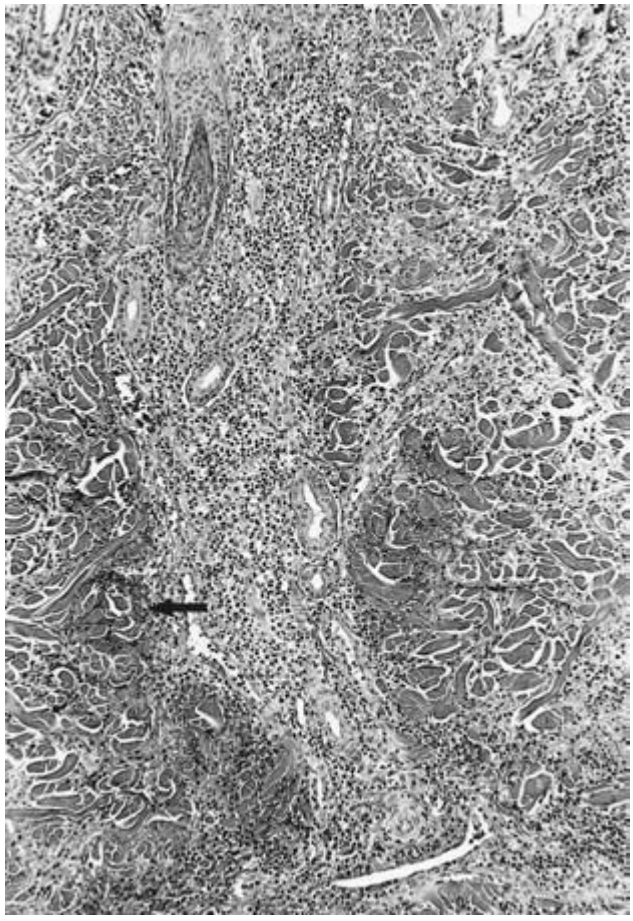


Fig. 14.8 Feline mosquito bite hypersensitivity. Several foci of eosinophil degranulation around collagen fibers (flame figures) (arrow) are intermingled with diffuse eosinophilic inflammation.

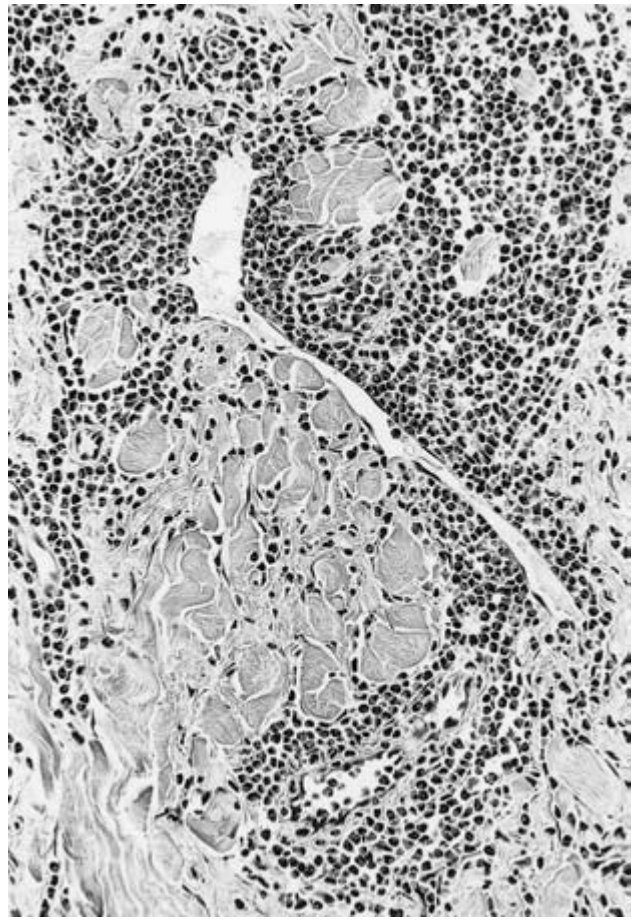


Fig. 14.9 Higher magnification of feline mosquito bite hypersensitivity. Large numbers of eosinophils are accumulating around vessels of the deep dermis.

dermatitis. Food allergy, eosinophilic plaque, and indolent ulcer may have similar deep, eosinophil-rich inflammation. Eosinophilic plaque usually does not demonstrate eosinophilic degranulation. Although small flame figures may be seen in indolent ulcers, eosinophilic degranulation generally occurs in or just beneath the ulcer bed. Both food allergy and mosquito bite hypersensitivity may show eosinophilic mural folliculitis as well as dermal flame figure formation; however, these lesions are more common and generally more prominent in mosquito bite hypersensitivity. Flame figures around collagen fibers are much larger in feline eosinophilic granuloma than in mosquito bite hypersensitivity. Additionally, eosinophilic mural folliculitis, as seen in mosquito bite hypersensitivity, is not a typical feature of eosinophilic granuloma. The eosinophilic form of feline herpesvirus ulcerative dermatitis may be nearly indistinguishable from mosquito bite hypersensitivity (see p. 351) if inclusion bodies cannot be found. In general, however, herpesvirus ulcerative dermatitis is more necrotizing. These cases may require immunohistochemical analysis or testing by polymerase chain reaction (PCR) for the detection of viral infection. Knowledge of seasonality and response to therapy may be required for ultimate differentiation.

It is important to stress that severe eosinophilic inflammation of any kind can evoke secondary degranulation and flame figure formation. Clinical features often are required to differentiate among histopathologically similar eosinophilic diseases of the cat.

SPIDER BITES

Clinical features (Figure 14.10)

Spider bites cause a wide spectrum of skin lesions in the dog and cat, ranging from local swelling to life-threatening tissue necrosis. Spider bites rarely are reported in veterinary medicine. This may be because spider bites are confirmed infrequently due to the secretive behavior of spiders. In human medicine, the diagnosis of spider bites also is considered challenging unless the spider is seen or captured (Wong et al., 1987; Carbonaro et al., 1995; Wilson et al., 2003). Woodpiles and undisturbed areas of older buildings are favorite habitats of spiders.



Fig. 14.10 Putative spider bite in a dog. Note drip-like configuration of necrotic lesion which characterizes a heavy molecular weight necrotoxin. (Photograph courtesy C.S. Foil.)

Species of the genus *Latrodectus* (widow spiders) produce primarily systemic effects via neurotoxins such as alpha-latrotoxin (Wilson et al., 2003). Species of the genus *Loxosceles* (recluse spiders) mainly produce local tissue damage via protein necrotoxins with sphingomyelinase D activity (Wilson et al., 2003). The necrotoxin produced by the brown recluse spider causes the most severe tissue damage. Other North American spiders capable of producing necrotic skin lesions include the running spiders (*Chiracanthium* spp.), black jumping spiders (*Phidippus* spp.), golden orb weavers (*Argiope* spp.), wolf spiders (*Lycosa* spp.), green lynx spiders (*Peucetia viridans*), and funnel-web spiders (*Atarx* spp.) (Wong et al., 1987). The spiders most often implicated in spider bites in North America include the brown recluse (*Loxosceles reclusa*), the black widow (*Latrodectus mactans*), the red widow (*Latrodectus bishopi*), and the common brown spider (*Loxosceles unicolor*) (Wong et al., 1987). Regional differences in species distribution are profound (Wong et al., 1987).

The brown recluse spider produces inapparent puncture marks followed by a central papule with surrounding erythema; blister formation and skin necrosis occur within 6 to 12 hours in humans (Wilson & King, 1999). A similar sequence of events probably occurs in domestic animals. Tissue damage is extensive and results in a dark, necrotic, indolent, nonhealing ulcer with sloughing. Gravitational drip configurations may be striking, and are due to the high molecular weight of the necrotoxin. The muzzle and forelegs most commonly are affected, probably due to the inquisitive behavior of the animal victim. Necrotic spider bite lesions of distal extremities present a problem of more extensive sloughing due to decreased collateral circulation of this anatomic region. The black widow spider produces minimal skin damage, usually limited to localized erythema.

Pain or pruritus rarely is present. In humans, systemic effects can include disseminated intravascular coagulopathy, renal failure, and death (Carbonaro et al., 1995; Wilson et al., 2003). Systemic signs occur within 1 to 8 hours after envenomation in all species.

Breed, age, or sex predilections are not available. However, active and inquisitive young animals with access to spider habitats should be at increased risk. Brown recluse spider bites occur primarily between spring and autumn since this spider hibernates in the winter.



Fig. 14.11 Putative spider bite in a dog. Note diffuse necrosis with prominent amorphous superficial dermal fibrin.

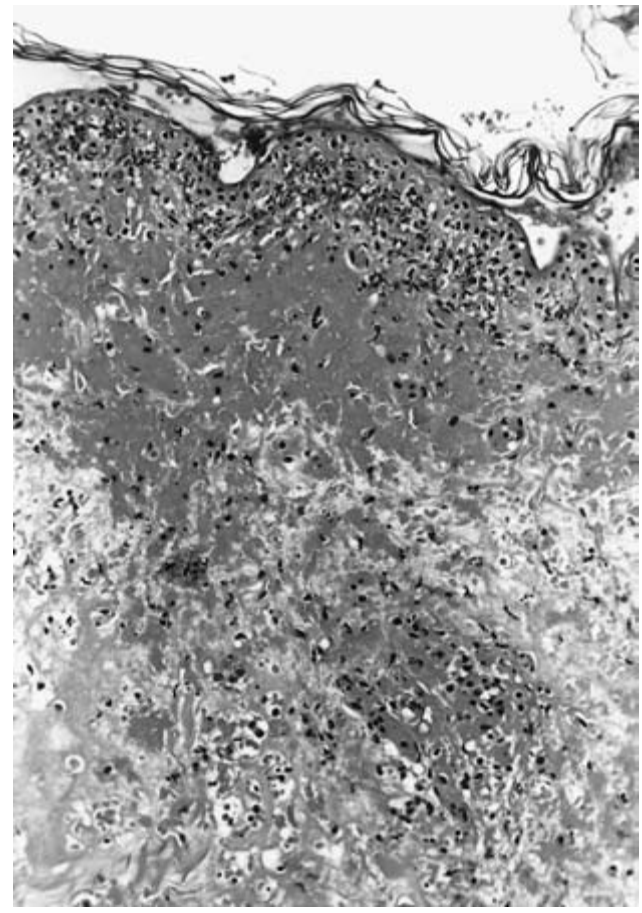


Fig. 14.12 Higher magnification of Fig. 14.11. The epidermis and dermis are necrotic and there is marked fibrin accumulation mixed with neutrophils.

Clinical differential diagnoses for necrotizing spider bites should include lesions caused by other venomous arthropods such as tropical centipedes, in addition to poisonous snake bites, and localized cutaneous vasculitis of any cause. The iatrogenic perivascular deposition of potentially irritating intravenous medications can produce similar lesions. Differentiation depends upon a history of exposure and the clinical course.

Biopsy site selection

Wedge specimens should be taken from the borders of necrotic ulcers. Specimens sampled should be small (less than 6 mm) since the inflammation and necrosis produced by the venom inhibit healing of the biopsy site. Care must be taken not to diminish the remaining vascular supply when sampling distal extremities.

Histopathology (Figures 14.11 through 14.14)

The epidermis is often necrotic and usually is ulcerated; superficial exudate may be prominent. Inflammation is diffuse and extends into the subcutis. Necrosis of the dermis may be severe and deep, and usually is accompanied by edema, fibrin, and/or hemorrhage, and sometimes cavitation. If present, localized vasculopathy is characterized by swelling of endothelial cells, necrosis, and thrombosis, and may involve large deep vessels in some cases. Inflammatory cells are mixed and include large numbers of neutrophils and macrophages. Eosinophils may not be prominent in comparison to other arthropod bite reactions.

Differential diagnoses include deep vessel vasculitis with secondary necrosis, and severe foreign body reactions. Deep vessel neutrophilic immunologic or septic vasculitis may appear similar if significant tissue damage is present, requiring clinical differentiation (multicentric distribution for vasculitis but focal for spider bite). Severe foreign body reactions generally do not have a vascular component; however, vascular changes may not always be evident in random specimens from spider bite reactions. A highly virulent bacterial infection could potentially cause tissue necrosis mimicking spider envenomation.

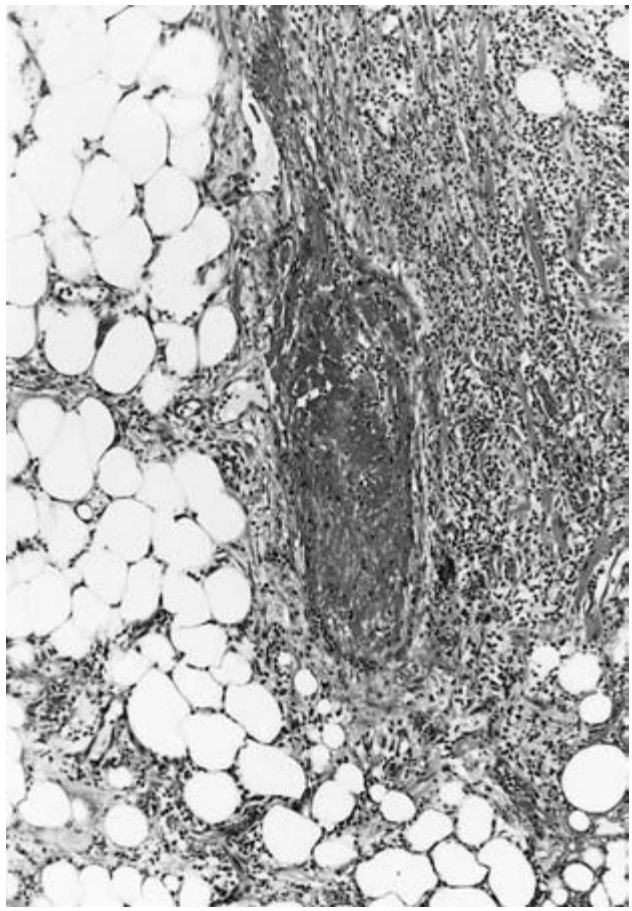


Fig. 14.13 Large deep vessel thrombosis in a dog with putative spider bite. Neutrophilic inflammation is intense.

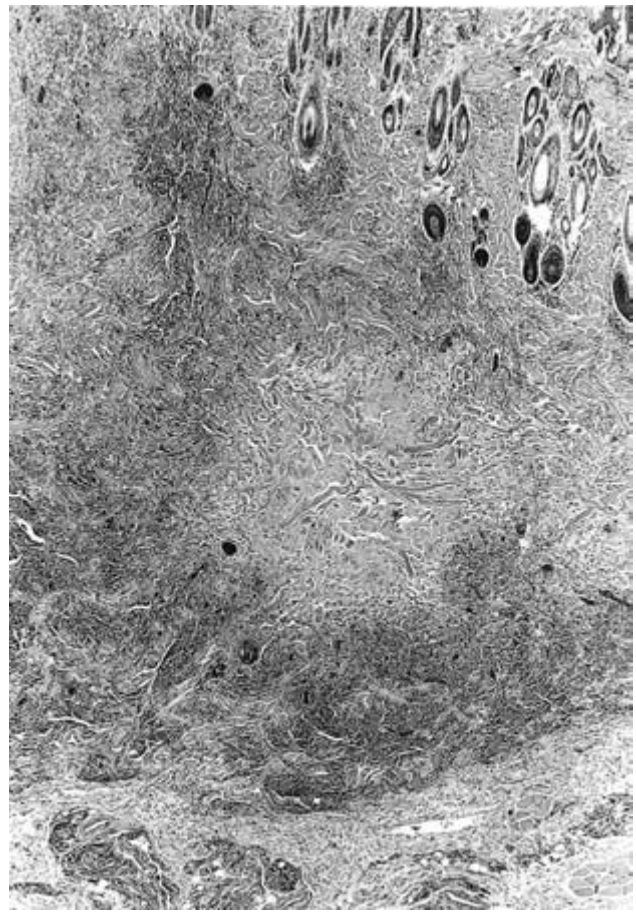


Fig. 14.14 Putative spider bite in a cat. Note pale acellular zone of necrosis ringed by intense inflammation.

Correlation with the clinical features of a nonhealing severe ulcer on the face or distal extremity is essential for the diagnosis of spider bites, as histopathologic findings are not specifically diagnostic.

FIRE ANT BITES

Clinical features (Figure 14.15)

The imported fire ant *Solenopsis invicta* is an increasing cause of skin disease in enlarging endemic regions of the world. The fire ant was introduced into the southeastern United States during the 1930s or 1940s, probably from Argentina, since when it has established a niche in at least ten southeastern states both in rural and urban areas (Rakich et al., 1993). Experimental localized, highly inflammatory canine skin disease has been documented in the dog (Rakich et al., 1993).

One of the major components of the venom of fire ants is solenopsin D, a nonproteinaceous hemolytic factor, identified as a dialkylpiperidine alkaloid derivative (Wilson & King, 1999). Protein components include a phospholipase and hyaluronidase (Rakich et al., 1993). The allergens in fire ant venom that lead to severe immediate hypersensitivity and anaphylaxis are not yet well characterized. Fire ants and vespids (wasp family) share at least one common allergen (King & Spangfort, 2000).

Hypersensitivity to the bite of the fire ant is an increasingly important cause of morbidity and mortality in humans in newly endemic regions of the southeastern United States (Tankersley et al., 2002). In addition to the intense cutaneous inflammatory reaction at the site of bites, fire ants have become the major cause of hymenopteran hypersensitivity, including systemic anaphylaxis (Freeman, 1997; Wilson & King, 1999). Anecdotal reports have come from South America of anaphylaxis in dogs attributed to fire ants. Fire ants also have been documented as a cause of inoculation of sporotrichosis in humans (Miller & Keeling, 2002).

Erythema and swelling are the earliest signs of experimental fire ant bites in the dog and occur within 5 to 10 minutes (Rakich et al., 1993). Transient sterile pustules or vesicles may be seen. Based on multiple photographs of dogs that were attacked in endemic areas, observed by

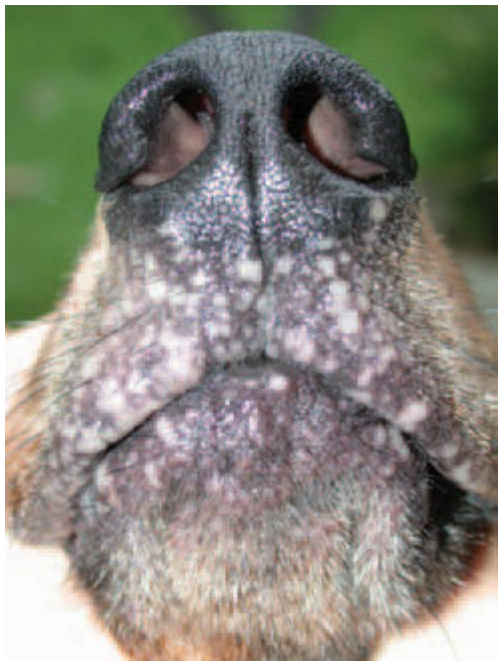


Fig. 14.15 Fire ant bites. Distinctive white vesicles or pustules are noted in a bilaterally symmetric pattern on the rostral muzzle, indicating points of attack. (Photograph courtesy C. Nett.)

one author (P.J.I.), the pustules and vesicles have a distinctive white coloration. The initial lesion measures less than 1 cm in diameter and enlarges to a maximum of 1.5 to 2 cm within 6 hours (Rakich et al., 1993). Lesions subside within 24 to 48 hours. The most common site of attack is the rostral muzzle, and lesions are distributed in a remarkably bilaterally symmetric pattern. Dogs also may be bitten on their feet.

Surprisingly, considering that fire ant bites are very painful in humans, pain or pruritus were not noted following experimental bites in four dogs (Rakich et al., 1993). Some pruritus was noted with delayed reactions (Rakich et al., 1993). However, in clinical cases, discomfiture manifested by jumping back, running away, head shaking and rubbing of the muzzle with the paws has been noted (Nett, C., personal communication, 2004).

Signalment predilections are not reported. However, active and inquisitive young animals should be at increased risk. Fire ant attack on the rostral muzzle is visually distinctive. Clinical differential diagnoses should include the stings or bites of other arthropods. Historical information such as geographic location and identification of fire ants in the environment aids in diagnosis.

Biopsy site selection

Biopsy specimens should be taken within the confines of the erythematous inflammatory reaction, from pustules or vesicles, or from the outer aspect of necrotic ulcers. Until more information is available on the healing process after multiple bites, specimens sampled should be small (less than 6 mm) since necrosis may retard healing.



Fig. 14.16 Fire ant bite in a dog, demonstrating darkly staining dermal foci of obliterative inflammation. (Case material courtesy P.M. Rakich.)

Histopathology (Figures 14.16 and 14.17)

Discrete foci of necrosis may have accompanying full thickness ulceration and severe surface exudation. The necrotic foci extend into the deep dermis and contain degenerating eosinophils and fewer neutrophils. Identification of cells within necrotic foci is difficult due to frequent advanced degeneration. Intact cells are present interstitially in the adjacent non-necrotic dermis, and include eosinophils, neutrophils, and a few lymphocytes and plasma cells. There may be mild vascular necrosis.

As reported in experimental cases of fire ant stings in dogs (Rakich et al., 1993), full thickness dermal coagulative necrosis develops 6 hours after stinging. These necrotic lesions are vertically oriented and involve dermal collagen and adnexa. Extension of necrosis to the subcutis is identified in lesions sampled 24 to 48 hours after biting.

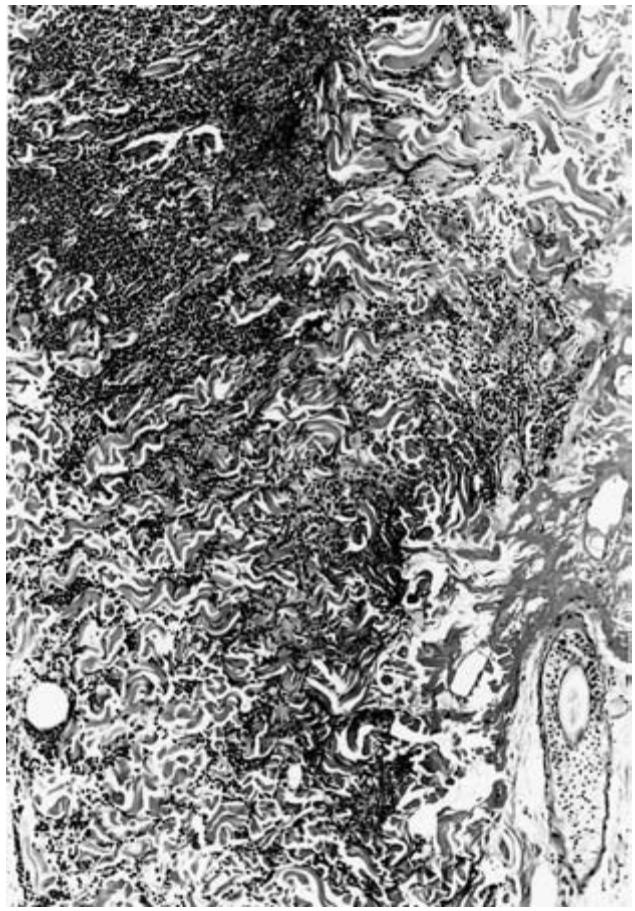


Fig. 14.17 Higher magnification of Fig. 14.16. Degenerating granulocytes predominate in inflammatory foci.

Intense inflammation bordering necrotic areas is composed largely of eosinophils, which are predominantly degenerated. The surrounding dermis is edematous and contains perivascular eosinophils and fewer neutrophils, lymphocytes, and macrophages. Interestingly, the epidermis usually is only mildly acanthotic; these reactions are likely too rapid to be associated with marked epidermal change. The epidermis is sometimes necrotic in later lesions.

Differential diagnoses are few. The severe necrosis is reminiscent of spider bite reactions, but spider bite reactions are generally deeper and locally more extensive. Fire ant bites are smaller and more compact in orientation.

FELINE HERPESVIRUS ULCERATIVE DERMATITIS

Clinical features

See Chapter 6.

Biopsy site selection

See Chapter 6.

Histopathology (Figure 14.18)

Epidermal and superficial follicular epithelial lesions include severe ulceration, necrosis, and exudation; necrosis may extend to sebaceous glands (see Chapter 6). Intranuclear inclusions are best found in intact epithelium

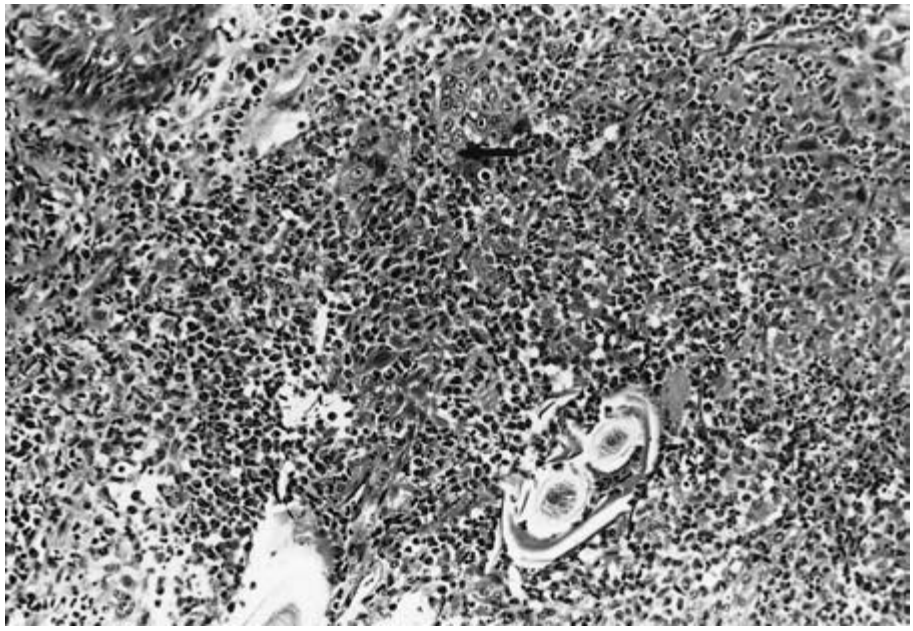


Fig. 14.18 Feline herpesvirus ulcerative dermatitis featuring diffuse eosinophilic inflammation and follicular epithelial necrosis and obliteration. Note scattered inclusions (arrow).

adjacent to necrotic foci. Since herpesvirus inclusion bodies may be difficult to identify with routine histopathology, immunohistochemistry or testing by polymerase chain reaction (PCR) may be of benefit, if available (Hargis et al., 1999; Suchy et al, 2000).

The dermis is intensely and diffusely inflamed, usually with eosinophils predominating. Eosinophils are intermingled with lymphocytes, neutrophils, plasma cells, and macrophages. Mast cells may be prominent. There may be foci of eosinophil degranulation around collagen fibers (flame figures) or, more commonly, within follicular walls (eosinophilic mural folliculitis). Linear foci of degranulated eosinophils organized within degenerated follicular walls (eosinophilic 'casts') surround central hairs, which sometimes drop out to leave clear hair-shaped spaces. Suppurative luminal folliculitis may occur.

Some lesions are predominantly neutrophilic and are nearly devoid of eosinophils. Increasing numbers of neutrophil-predominant lesions (with typical intranuclear inclusions) have been recognized recently by the authors. Neutrophils may be accompanied by numerous plasma cells. The cause of this histologic bimorphism is unclear.

Differential diagnoses for eosinophil-rich herpesvirus ulcerative dermatitis, in which inclusion bodies are not found, include eosinophilic plaque, eosinophilic feline indolent ulcer, eosinophilic granuloma, and mosquito bite hypersensitivity. Eosinophilic plaque features more profound spongiosis and mucinosis of intact epidermis and superficial hair follicles. Indolent ulcer generally does not feature prominent eosinophilic degranulation, except in or just beneath the ulcer bed. Foci of eosinophil degranulation (flame figures) are generally more abundant and individually larger in feline eosinophilic granuloma than in herpesvirus ulcerative dermatitis. Also, eosinophilic degranulation within hair follicles is more prominent in herpesvirus ulcerative dermatitis than in eosinophilic granuloma. Mosquito bite hypersensitivity may be indistinguishable if inclusion bodies cannot be identified; however, in general, herpesvirus ulcerative dermatitis is more necrotizing. These cases may require clinical differentiation, or detection of viral infection by immunohistochemical analysis or testing by PCR. Knowledge of season affected and response to therapy may be of additional benefit.

It is important to stress that severe eosinophilic inflammation of any kind can evoke secondary degranulation and flame figure formation. Clinical features often are required to differentiate among histopathologically similar eosinophilic diseases of the cat.

Differential diagnoses for neutrophilic herpesvirus ulcerative dermatitis are few, as the extent of necrosis and ulceration of this entity is unusual in the context of neutrophilic inflammation. This pattern of inflammation could be indicative of chronic severe bacterial infection or trauma with secondary infection. Inclusion bodies allow definitive diagnosis; if these are absent, correlation with clinical findings and results of immunohistochemistry, or testing by PCR may be required.

FELINE EOSINOPHILIC PLAQUE

Clinical features (Figures 14.19 and 14.20)

See Chapter 5.

Biopsy site selection

See Chapter 5.



Fig. 14.19 Feline eosinophilic plaque. Early lesions on the medial thigh are characterized by small eroded and ulcerated plaques that are coalescing. (Photograph courtesy T. Olivry; case material University of California, Davis.)



Fig. 14.20 Feline eosinophilic plaque. Two well-developed eosinophilic plaques are contiguous (Photograph courtesy C.B. Vitale; case material University of California, Davis.)

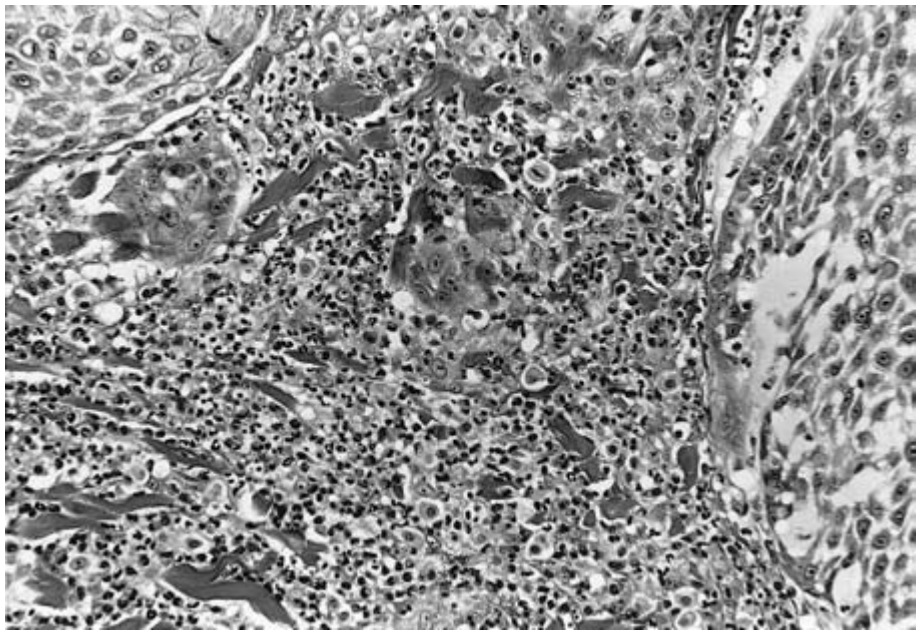


Fig. 14.21 Feline eosinophilic plaque demonstrating diffuse eosinophils and fewer mast cells. Adjacent epithelium is spongiotic and mucinotic.

Histopathology (Figure 14.21)

Epidermal lesions have been described (see Chapters 5 and 6), and most characteristically include widespread spongiosis and mucinosis of the epidermis and follicular infundibular epithelium, often with severe ulceration. In the dermis, typical eosinophilic plaque is characterized by perivascular to diffuse, moderate to severe infiltrations of eosinophils. Inflammation often extends to the deep dermis, and may be present in the panniculus in severe lesions. Lymphocytes, mast cells, and macrophages are present in smaller numbers. Neutrophils also may be prominent beneath areas of severe erosion or ulceration.

Differential diagnoses for eosinophilic plaque include severe allergic miliary dermatitis, mosquito bite hypersensitivity, food allergy, eosinophilic feline herpesvirus ulcerative dermatitis in which inclusions are not found, and eosinophilic indolent ulcer. Epidermal lesions of spongiosis and mucinosis are more severe in eosinophilic plaque than in these other eosinophilic diseases. The lesions of eosinophilic plaque histopathologically resemble those of severe allergic miliary dermatitis, but are more intensely and deeply inflamed. Since eosinophilic plaque and miliary dermatitis both may be manifestations of allergic skin disease in the cat (and can exist concurrently), histopathologic separation of these may not be critical diagnostically. Lesions of mosquito bite hypersensitivity, occasionally food allergy, and herpesvirus ulcerative dermatitis may show flame figure formation or eosinophilic mural folliculitis. Eosinophilic indolent ulcer may have eosinophilic degranulation beneath the ulcer bed, or more sparsely in deeper tissue. Eosinophil degranulation and flame figure formation are not characteristic of eosinophilic plaque.



Fig. 14.22 Feline indolent ulcer. Early lesions are present bilaterally near the upper canine teeth.

FELINE INDOLENT ULCER

(Synonyms: feline eosinophilic ulcer, rodent ulcer)

Clinical features (Figures 14.22 and 14.23)

See Chapter 6.

Biopsy site selection

See Chapter 6.



Fig. 14.23 Feline indolent ulcer. A chronic lesion involves the upper lip, philtrum, and planum nasale. (Photograph courtesy R. Mueller; case material University of California, Davis.)

Histopathology (Figure 14.24)

Sequential sampling of feline indolent ulcers from a related group of specific pathogen free cats showed variation in the histopathologic appearance over time; this variation also has been reported (Power & Ihrke, 1995). Epidermal lesions consist of variable ulceration with subjacent necrosis (see Chapter 6). These deep necrotic ulcers contain masses of degenerating eosinophils and neutrophils, and are imbedded superficially with colonies of bacteria.

Acute indolent ulcer of the pathogen free cats contains predominantly eosinophils, mast cells, and macrophages in the dermis. Neutrophils are seen in the acute phase and remain at all stages in concert with ulceration. Eosinophils and macrophages persist as the lesion ages, and plasma cells and lymphocytes, frequently in nodular clusters, first become evident at 5 to 7 days. Lesions of several months' duration may contain predominantly eosinophils and macrophages; plasma cells and lymphocytes are variable. Fibrovascular tissue proliferates with chronicity, and capillaries are prominent amongst inflammatory cells. Mature fibrous connective tissue is conspicuous in lesions of 4 to 6 months' duration. Inflammation extends deeply at all stages of indolent ulcer and often involves the muscle of the lip. Acutely affected muscle fibers may be swollen and myocyte nuclei pyknotic or fragmented.

Random specimens from cats affected with classical upper lip ulcers are similar to chronic lesions of specific pathogen free cats. In the authors' experience, field cases, including those of several years' duration, demonstrate diffuse, severe, and deep, predominantly eosinophilic inflammation, with fewer neutrophils, and variable fibrosis. Inflammation and fibrosis usually obliterate normal architecture. There may be eosinophilic degranulation just beneath ulcers or less commonly in deeper areas of the lesion. Superficial eosinophilic degranulation may create a brightly eosinophilic band in the ulcer bed. Deep eosinophilic flame figures, as in eosinophilic granuloma (see p. 355), are usually not prominent. Plasma cells and macrophages are variable.

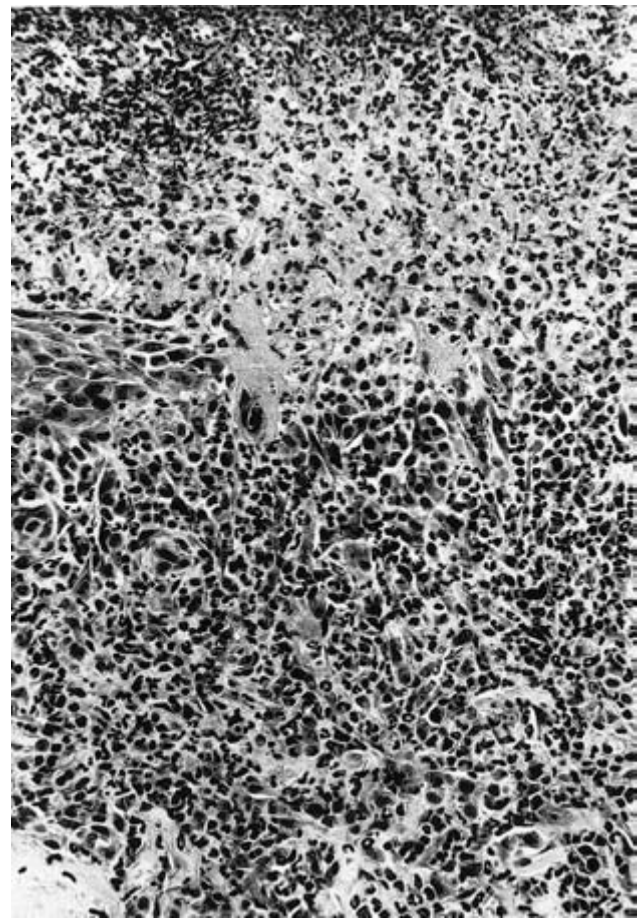


Fig. 14.24 Feline indolent ulcer. Ulcer with exudate at top is subtended by severe subjacent eosinophilic inflammation.

Neutrophil-predominant ulcers were reported in cats with indolent ulcer occurring in association with experimentally induced flea allergy dermatitis (Colombini et al., 2001). They have been described previously in naturally occurring cases (Scott, 1975). Neutrophilic indolent ulcers are extremely rare in the authors' experience; only a single case has been observed.

Differential diagnoses for eosinophilic indolent ulcer include eosinophilic herpesvirus ulcerative dermatitis in which inclusions are not found, mosquito bite hypersensitivity, or severely ulcerated eosinophilic plaque. Indolent ulcers tend to have eosinophilic degranulation predominantly within or just beneath the ulcer bed, rather than the deeper, often folliculocentric foci (eosinophilic mural folliculitis) seen in mosquito bite hypersensitivity and



Fig. 14.25 Feline eosinophilic granuloma ('linear granuloma' subgroup) on the caudal hindleg. The affected area has been clipped to enhance visualization of the crusted, erythematous and yellowish-pink, linear plaque. (Photograph courtesy H.T. Power; case material, University of California, Davis.)



Fig. 14.26 Feline oral eosinophilic granuloma. A well-demarcated erythematous plaque containing white, caseous, necrotic foci is present on the soft palate. Note somewhat symmetric, linear ulcers of the hard palate.

herpesvirus ulcerative dermatitis. Eosinophilic plaque features prominent epidermal and follicular spongiosis and mucinosis that are generally absent in indolent ulcers. Neutrophilic indolent ulcers may resemble pyotraumatic dermatitis, which is very rare in cats. Clinical differentiation may be required.

FELINE EOSINOPHILIC GRANULOMA

(Synonyms: feline collagenolytic granuloma, feline linear granuloma)

Clinical features (Figures 14.25 through 14.27)

Feline eosinophilic granuloma is a common, clinically heterogeneous syndrome affecting skin, mucocutaneous junctions, and oral mucosa; clinical presentations are unified by a similar histopathologic pattern. Underlying hypersensitivity (atopic dermatitis, food allergy, flea allergy) often is suggested, but rarely is documented definitively. Eosinophilic granulomas were studied in an inbred, specific pathogen free colony of cats without exposure to ectoparasites or endoparasites, and without indications of either concomitant atopic dermatitis or food allergy as documented by intradermal skin testing and elimination diets (Power, 1990). This suggests that some cats with eosinophilic granulomas may have an inherited disorder of eosinophil proliferation or dysfunction (Power &Ihrke, 1995). Major basic protein, a product of eosinophils identified in eosinophilic diseases of humans such as Wells' syndrome (Nutman et al., 1988), probably is involved in the pathogenesis of eosinophilic granuloma in animals.

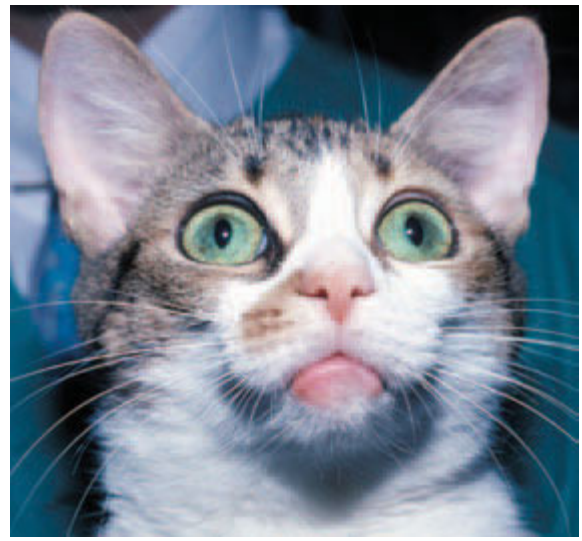


Fig. 14.27 Feline eosinophilic granuloma. This subgroup is characterized by a protruding, alopecic thickening of the rostral portion of the lower lip and adjacent haired skin, which gives the cat a 'pouting' appearance. (Photograph courtesy H.T. Power; case material, University of California, Davis.)

The clinical presentations of feline eosinophilic granulomas may be subdivided based on clinical characteristics and site predilections. Peripheral lymphadenopathy may be present with any form of feline eosinophilic granuloma. Concomitant indolent ulcers or eosinophilic plaques may be observed (see Chapter 6).

The most common cutaneous presentation is that of 'linear granuloma'. In this form, distinctive, hairless, well circumscribed, firm, pink-yellow or salmon-colored, ele-

vated plaques develop in a strikingly linear pattern on the caudal thighs, lateral thighs, forelegs, or less commonly the neck or thorax. Occasionally, similar firm plaques and nodules, but without a linear pattern, may occur on the pinnae. A second cutaneous pattern is characterized by asymptomatic pink-yellow swelling of the lower lip ('pouting cat') or chin ('chin edema', 'fat chin'). Lesions are asymptomatic. Much less commonly, eosinophilic granulomas of the pawpads present with crusting and ulceration accompanied by interdigital alopecia, erythema, crusting, and inflammation. The syndrome may involve multiple pawpads concurrently or sequentially. Digital as well as metacarpal or metatarsal pads may be affected. Lesions on weight-bearing pads may cause lameness. Eroded cutaneous eosinophilic granulomas may have characteristic pinpoint, white to pink foci, corresponding to foci of eosinophil degranulation seen microscopically. Mucocutaneous eosinophilic granulomas are considerably less common, occur predominantly at the junctures of facial mucous membranes, and may be papular or nodular.

Oral eosinophilic granulomas are uncommon, and are characterized by a more severe and aggressive clinical course. Solitary or multiple, firm, white-pink to yellow-orange nodules affect the tongue, tonsilar region, frenulum, or soft palate. Ulceration is common and gritty, pinpoint, white foci may be seen grossly; as in the skin, these correspond to foci of eosinophil degranulation. Necrosis and secondary infection lead to a foul odor. Oral eosinophilic granulomas usually are painful and interfere with prehension and swallowing.

Female cats may be predisposed to eosinophilic granuloma. Age or breed predilections have not been documented; however, cats under 2 years of age appear to have increased incidence of eosinophilic granuloma of the pawpads.

Clinical differential diagnoses vary considerably among the various clinical forms of feline eosinophilic granuloma. Cutaneous linear granulomas and cutaneous eosinophilic granulomas involving the lower lip and chin are visually distinctive. Oral eosinophilic granulomas must be differentiated from neoplasms (squamous cell carcinoma, fibrosarcoma, and tonsilar lymphoma), proliferative plasma cell stomatitis, foreign body reactions, or proliferative traumatic lesions (inflamed granulation tissue). Lesions of the pawpads may resemble plasma cell pododermatitis (see p. 363). Histopathology is required for definitive diagnosis.

Biopsy site selection

A deep punch or wedge specimen should be obtained to establish a diagnosis. A maximum punch size of 4 mm should be used for chin lesions as healing may be prolonged at this site.

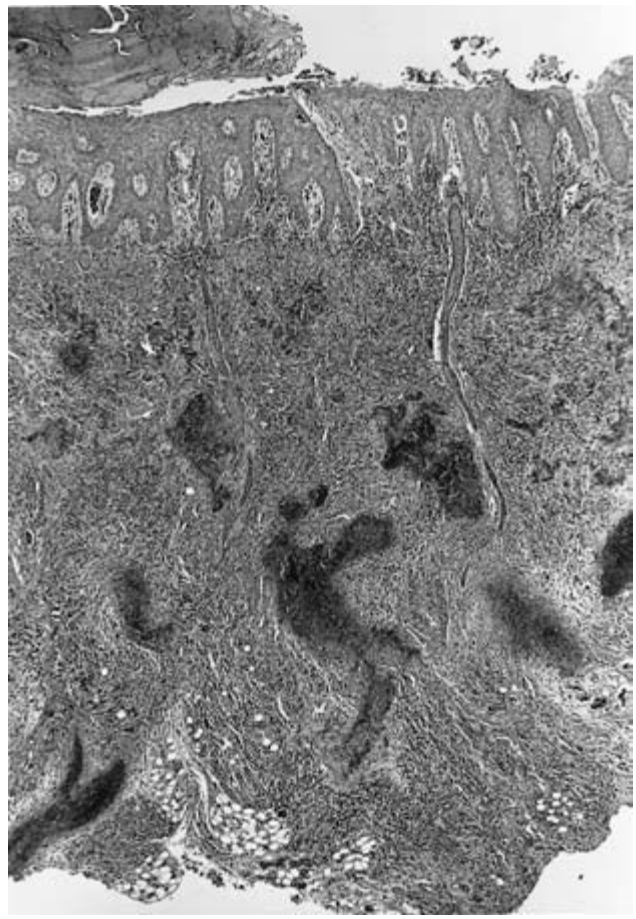


Fig. 14.28 Feline eosinophilic granuloma of the pawpad. Diffusely inflamed tissue contains large, lake-like, darkly staining zones of eosinophil degranulation.

Histopathology (Figures 14.28 through 14.30)

The epidermis is normal to moderately acanthotic, and occasionally may be eroded, ulcerated, and exudative. The dermis is diffusely inflamed and contains generally large, irregular, acellular foci of eosinophilic degranulation around collagen fibers (flame figures). True collagen fiber degeneration, or 'collagenolysis', as evidenced by Masson's trichrome staining, is not a consistent or predictable finding in feline eosinophilic granulomas (Fernandez et al., 2000; Fondati et al., 2001). Random abnormally staining collagen fibers, characterized by red cores (versus normal blue staining), are just as likely to be found in other areas of the biopsy as within the eosinophilic degranulated foci (Fernandez et al., 2000). Furthermore, electron microscopy of flame figures demonstrates degenerating and degranulating eosinophils around otherwise normal-appearing collagen fibers (Bardagi et al., 2003).

Flame figures may be girdled by macrophages and giant cells, often in palisading array. The intervening dermis is

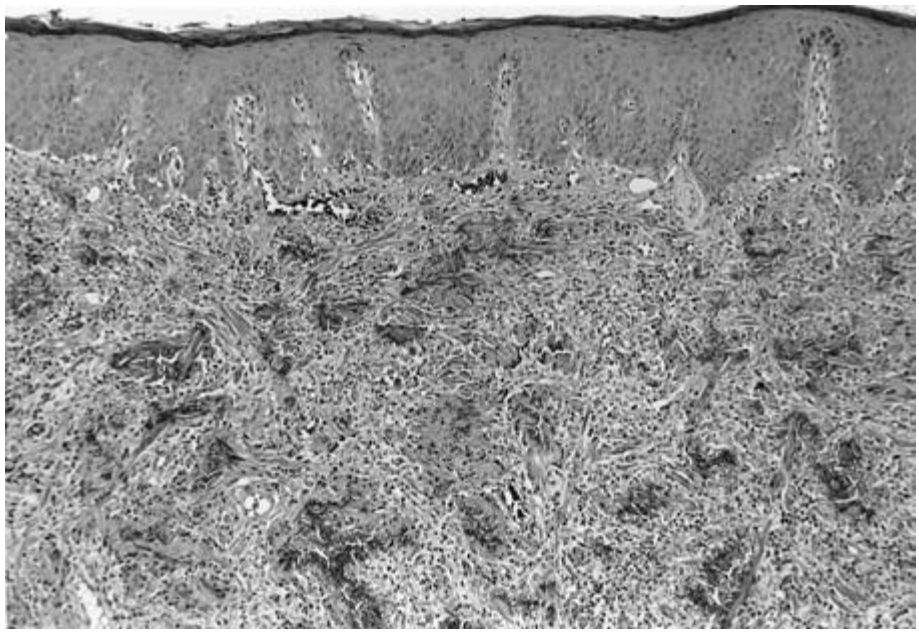


Fig. 14.29 Feline eosinophilic granuloma. Diffuse inflammation is punctuated by discrete granulomas containing dark areas of eosinophilic degranulation.

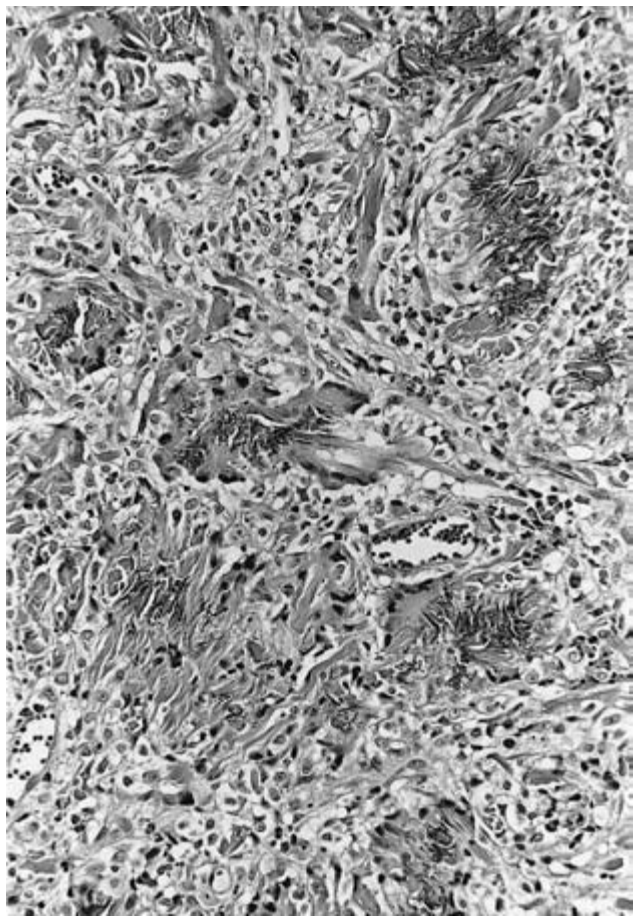


Fig. 14.30 Higher magnification of feline eosinophilic granuloma demonstrating multinucleated giant cells around foci of eosinophilic degranulation. Note the somewhat palisaded pattern of granulomatous inflammation along collagen fibers.

diffusely inflamed with eosinophils, macrophages, mast cells, and fewer lymphocytes. Dermal mucin and/or edema may be observed. Eosinophils are not as prominent in chronic lesions, and macrophages and giant cells may predominate around discrete foci of collagen, or interpolate diffusely among collagen fibers. Eosinophil-poor lesions resembling palisading granuloma (see Chapter 13) may occur at sites for which eosinophilic granulomas are expected, and likely represent late stage lesions from which eosinophils have faded.

Oral eosinophilic granulomas are similar, except that lesions are more frequently and severely ulcerated. Eosinophil degranulation may be limited in some cases to the craterous ulcer beds. Occasionally, particularly in oral lesions, deeply imbedded hair shafts are seen. It has been suggested that hair foreign bodies may have an inciting role in these cases; the authors believe that hairs may aggravate eosinophil degranulation, but factors initiating the influx of eosinophils are likely pre-existent.

Differential diagnoses are few, particularly in lesions that have large and numerous flame figures. Eosinophilic degranulation is seen in indolent ulcers, but usually is most prominent just beneath ulcers. Small foci of eosinophilic degranulation around collagen fibers may be seen in feline mosquito bite hypersensitivity and in some cases of feline food allergy, as well as in feline herpesvirus ulcerative dermatitis. Eosinophilic degranulation within hair follicles (eosinophilic mural folliculitis) is more prominent in herpesvirus ulcerative dermatitis and often mosquito bite hypersensitivity, than in eosinophilic granuloma. Identification of intranuclear inclusion bodies also will allow separation of herpesvirus ulcerative dermatitis.

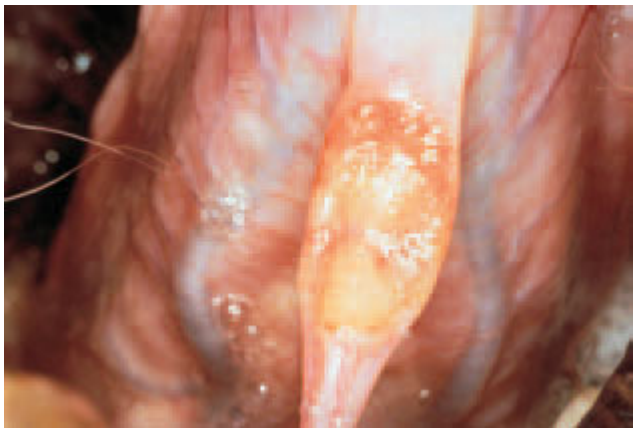


Fig. 14.31 Canine eosinophilic granuloma on the frenulum of the tongue of a dog. The nodule is ulcerated and has a yellowish-pink appearance. (Photograph courtesy D.-N. Carlotti.)



Fig. 14.32 Canine eosinophilic granuloma on the tongue of a dog. (Photograph courtesy B.R. Madewell.)

It is important to stress that severe eosinophilic inflammation of any kind can evoke secondary degranulation and flame figure formation. Clinical features often are required to differentiate among histopathologically similar eosinophilic diseases of the cat.

CANINE EOSINOPHILIC GRANULOMA

(Synonym: canine collagenolytic granuloma)

Clinical features (Figures 14.31 through 14.33)

Canine eosinophilic granuloma is a relatively rare, heterogeneous skin disease; clinical presentations are unified by a similar histopathologic pattern. It is characterized by nodules or plaques affecting the skin, oral mucosa, or external ear canal. Clinical and histopathologic features both suggest a hypersensitivity reaction. The elaboration of major basic protein, a product of eosinophils identified in eosinophilic diseases of humans such as Wells' syndrome (Nutman et al., 1988) probably is involved in the pathogenesis of eosinophilic granuloma in animals.



Fig. 14.33 Canine eosinophilic granuloma on the face of a Doberman Pinscher. An arthropod bite was suspected to have caused this lesion.

Canine eosinophilic granulomas probably are of multifactorial allergic etiology. Hypersensitivity is supported by tissue eosinophilia, occasional blood eosinophilia, marked response to corticosteroids, and occasional seasonal recurrence (Scott et al., 2001). The authors suspect that many eosinophilic granulomas of the canine skin are the result of arthropod insult. This observation is based upon their often solitary or limited number, lesional distribution to relatively glabrous and/or cranial regions, and lack of recurrence following excision. One author (T.L.G.) has seen axillary eosinophilic granuloma develop concomitantly with eosinophilic furunculosis of the face (see Chapter 17), a syndrome induced by arthropod stings or bites.

An arthropod-initiated reaction is less likely to trigger eosinophilic granulomas of the mouth. Marked breed predilections for oral eosinophilic granulomas suggest a genetic predilection (Madewell et al., 1980; Joffe & Allen, 1995; Bredal et al., 1996). It is possible that familial forms of oral eosinophilic granuloma in dogs represent an idiopathic, genetically driven eosinophil dysfunction, as seen in some cats (see p. 355). It also is conceivable that some oral eosinophilic granulomas in nongenetically susceptible breeds might be linked to biting at bees, wasps, hornets, or other arthropods. Unknown antecedent events such as trauma or foreign body embedment also might explain oral lesions. The rare polypoid plaques reported in the external ear canal are unexplained (Poulet et al., 1991).

Cutaneous eosinophilic granulomas present as solitary or grouped erythematous plaques, nodules, or papules.

Larger plaques or nodules may ulcerate. Commonly affected sites include the pinnae, muzzle, neck, axillae, flank, prepuce, and scrotum. Pain or pruritus usually is not noted. On rare occasion, asymptomatic domed papules and nodules of the tips of the pinnae, clinically reminiscent of granuloma annulare in humans, have been observed by the authors. The rare eosinophilic granulomas of the external ear canal present as pale, polypoid granular masses attached to the ear epithelium by a slender stalk (Poulet et al., 1991); one author (T.L.G.) has observed more sessile masses that replaced much of the pinna.

The clinical features of oral eosinophilic granuloma include well-demarcated, yellow to green-brown, vegetative, granulomatous plaques or nodules that develop predominantly on the lateral or ventral surface of the tongue or the commisures of the mouth. Ulceration is common. Ulcers with a slightly elevated border may be present on the soft or hard palate, either coexistent with lingual lesions or alone. Lingual lesions have a friable surface and bleed readily. The oral cavity commonly has a necrotic, fetid odor. Pain is marked; affected dogs usually are partially anorectic and reluctant to prehend and chew dry Dog food. Discomfort and odor are not noted in dogs with lesions confined to the palate.

Siberian Huskies and Cavalier King Charles Spaniels are markedly predisposed to oral eosinophilic granulomas (Madewell et al., 1980; Joffe & Allen, 1995; Bredal et al., 1996). A recent report in two unrelated German Shepherd Dogs may indicate an additional breed predilection (Vercelli & Cornegliani, 2002). A mixed breed dog and a Bullmastiff also were reported (Walsh, 1983). Male Siberian Huskies less than 3 years of age are at increased risk for lingual eosinophilic granulomas (Madewell et al., 1980; Scott et al., 2001). Breed predilections have not been noted for cutaneous or pinnal eosinophilic granulomas.

Clinical differential diagnoses for cutaneous eosinophilic granulomas include foreign body reactions, infectious and noninfectious granulomatous or pyogranulomatous diseases (see Chapters 12 and 13), and neoplasms. Oral eosinophilic granulomas are visually distinctive, have marked breed predilections, and hence have few differential diagnoses. Histopathology is required for diagnosis. Canine cutaneous eosinophilic granulomas are not clinically distinctive, and consequently this is most often an unexpected histopathologic diagnosis.

Biopsy site selection

The clinician should not attempt to completely excise proliferative lingual lesions in at risk breeds, since large specimens are not necessary for diagnosis. Deformation may result, and the lesions are readily responsive to glucocorticoids. Solitary cutaneous nodules should be removed in their entirety.

Histopathology (Figures 14.34 and 14.35)

For cutaneous eosinophilic granulomas, the epidermis is variably acanthotic and may be necrotic or ulcerated in some cases. Superficial to deep, perivascular to diffuse accumulations of numerous eosinophils are accompanied by variable edema and/or mucin. Degranulating



Fig. 14.34 Canine eosinophilic granuloma. Darkly staining degranulating eosinophils are accumulating along collagen fibers. Large pale macrophages surround these foci to form granulomas in a slightly palisaded pattern.

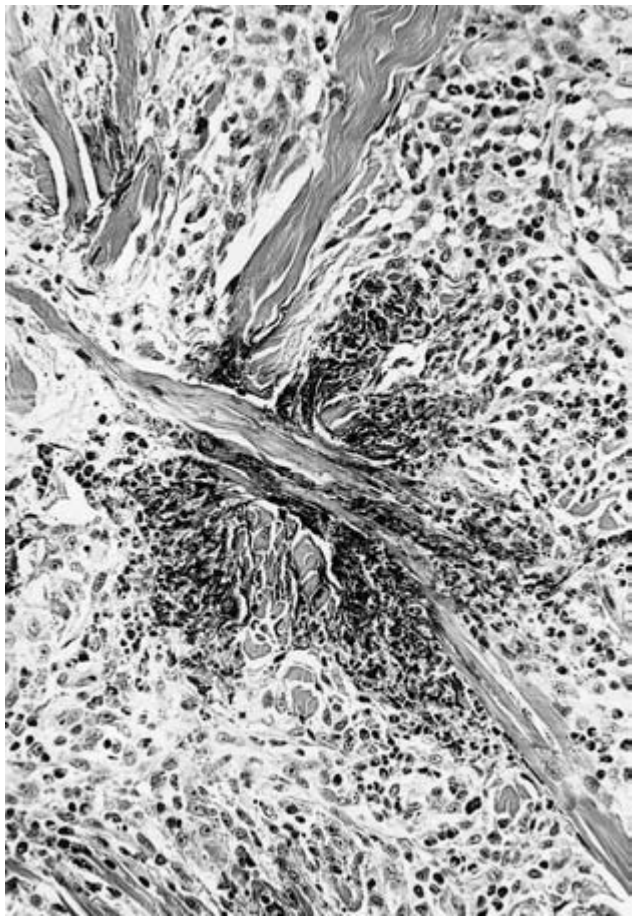


Fig. 14.35 Higher magnification of canine eosinophilic granuloma. Eosinophils are degranulating along collagen fibers.

eosinophils often orient around individual collagen fibers to form flame figures of variable size and prominence. These flame figures may have peripheral radiating projections, and are surrounded by intact eosinophils, as well as macrophages, and occasional giant cells to form granulomas. Granulomas may be slightly palisaded in their arrangement along collagen fibers. Similar inflammation courses among the flame figures, accompanied by mast cells, lymphocytes, and plasma cells. Fibrosis may be prominent in chronic lesions. As in cats with eosinophilic granuloma, true collagen degeneration or lysis likely is not present (see p. 355).

Oral eosinophilic granulomas are more frequently ulcerated, often severely. Eosinophils are diffusely oriented within an edematous submucosa, and are intermingled with lymphocytes, macrophages, and plasma cells. There may be variable fibrovascular proliferation with endothelial swelling. In Cavalier King Charles Spaniels, degranulating eosinophils may be absent or confined to the ulcer beds; mild deep flame figure formation has been reported (Bredal et al., 1996). In Siberian Huskies, flame figures are prominent and are seen throughout the submucosa or muscle of the tongue.



Fig. 14.36 Canine eosinophilic dermatitis in a Labrador Retriever due to an adverse drug reaction to diethylcarbamazine. Erythematous coalescing plaques are present on the face and muzzle. (From Vitale, C., Ihrke, P.J. & Gross, T.L. (1995) Putative diethylcarbamazine-induced urticaria with eosinophilic dermatitis in a dog. *Vet Dermatol* **5**, 197–203. Reprinted with permission.)

Severe eosinophilic dermatitis with flame figure formation has been observed on the pinnae of dogs by the authors and others (Poulet et al., 1991). These polypoid eosinophilic lesions are composed of severely inflamed granulation tissue containing flame figures. Lymphocytes, plasma cells, and macrophages are numerous. Mast cells are prominent; one author (T.L.G.) has observed progressive lesions on the ear of a dog that eventuated in diffuse mast cell infiltration resembling mast cell neoplasia.

Canine eosinophilic granuloma is distinctive. Canine eosinophilic dermatitis also features variable flame figure formation (see below); clinical differentiation may be required. Eosinophilic furunculosis of the face, suspected to be arthropod-related, also may have foci of eosinophil degranulation and collagen degeneration; however, typical furunculosis allows differentiation (see Chapter 17).

CANINE EOSINOPHILIC DERMATITIS

(Synonym: eosinophilic dermatitis with edema; eosinophilic cellulitis)

Clinical features (Figures 14.36 and 14.37)

Canine eosinophilic dermatitis is a relatively rare reaction pattern of probable multifactorial allergic etiology united by a similar histopathologic pattern. Most affected dogs present with erythematous, coalescing macules and plaques with edema, involving the pinnae and the ventral

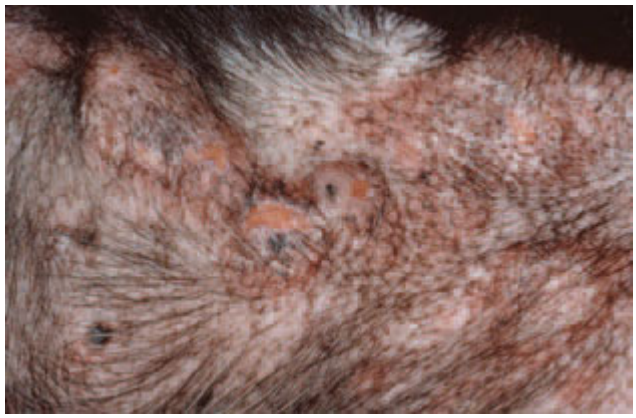


Fig. 14.37 Closer view of the ventral abdomen of the dog in Fig. 14.36. Note eroded, erythematous plaques with urticaria. (From Vitale, C., Ihrke, P.J. & Gross, T.L. (1995) Putative diethylcarbamazine-induced urticaria with eosinophilic dermatitis in a dog. *Vet Dermatol* **5**, 197–203. Reprinted with permission.)

abdomen and thorax. Clinical and histopathologic features both suggest hypersensitivity. The histopathology more closely resembles eosinophilic cellulitis of humans (Wells' syndrome) than the clinical manifestations. Wells' syndrome is most often associated with various hypersensitivities (Leiferman, 1999). The elaboration of major basic protein, a product of eosinophils identified in multiple eosinophilic diseases of humans including Wells' syndrome (Nutman et al., 1988), probably is involved in the pathogenesis of this distinctive canine dermatitis.

Multiple factors support allergic hypersensitivity as the trigger. This syndrome has an increased occurrence in late summer and early autumn, plus late winter to early spring (Holm et al., 1999). This marked seasonality could indicate an arthropod or other seasonal allergic etiology for some cases. Lesions in one dog were initiated by a drug reaction to diethylcarbamazine (Vitale et al., 1994).

The predominant clinical features of canine eosinophilic dermatitis include targetoid erythematous macules or wheals that eventuate in arciform and serpiginous macules and plaques (Vitale et al., 1994; Holm et al., 1999). Some lesions appear purpuric as they do not blanch with diascopy (direct pressure with a glass slide) (Holm et al., 1999). Lesions are generalized, but may preferentially affect the ventral abdomen and thorax, face, and pinnae. Edema may have either a facial or a generalized distribution and may be pitting. Pruritus usually is moderate. Lymphadenopathy is common. Peripheral eosinophilia, which is common in Wells' syndrome in people, was not noted in the seven of nine dogs in which complete blood counts were performed in one study (Holm et al., 1999), while peripheral eosinophilia and basophilia were present in one dog (Vitale et al., 1994).

A distinctive severe syndrome with close clinical and histopathologic similarities to Wells' syndrome in humans was observed in a Beagle. The dog presented with multiple, discrete dermal and subcutaneous nodules of the head, accompanied by diffuse swelling (Power, H.T., personal communication, 2003).

Breed predilection for Labrador Retrievers is suspected since four of ten dogs were Labrador Retrievers and one was a retriever crossbreed (Vitale et al., 1994; Holm et al., 1999). Age and sex predilections have not been noted.

Canine eosinophilic dermatitis is visually distinctive. Arciform and serpiginous wheals, macules, and plaques with edema are highly unusual lesions in the dog. Clinical differential diagnoses include erythema multiforme and canine sterile neutrophilic dermatosis (see p. 366). Histopathology is required for diagnosis.

Biopsy site selection

Multiple specimens should be obtained early from targetoid macules, wheals, or plaques. If present, less well-defined areas of edema also should be sampled, making sure that specimens are of full thickness and include the deep dermis.

Histopathology (Figures 14.38 through 14.40)

The epidermis is mildly to moderately acanthotic, variably spongiotic, and sometimes ulcerated. There is moderate to severe, superficial and deep, eosinophilic dermatitis in a perivascular to diffuse distribution. Fewer neutrophils, macrophages, lymphocytes, and plasma cells may be present. Perivascular mast cells have been reported (Holm et al., 1999). Edema is variable and there may be mucin deposition. Eosinophils are frequently degranulating around collagen fibers to form flame figures. Flame figures were not present in all affected dogs of a previous report (Holm et al., 1999). There may be occasional vascular intramural eosinophils and/or fibrin thrombi (Vitale et al., 1994), suggesting some vascular involvement; however, lesions are not severe or widespread enough to suggest a primary vasculitis. Variable hemorrhage is observed. The lesions resemble eosinophilic cellulitis of humans (Wells' syndrome).

In the severely affected Beagle described above there was predominant subcutaneous involvement, more closely representing true eosinophilic 'cellulitis'. Inflammation in that case extended to the deep skeletal muscle. Mucin deposition and edema were prominent and flame figures were numerous and striking.

Eosinophilic dermatitis probably represents a reaction pattern of variable causation, including drug and arthropod reactions, and likely is not a single entity. Histologically, distinguishing eosinophilic dermatitis from

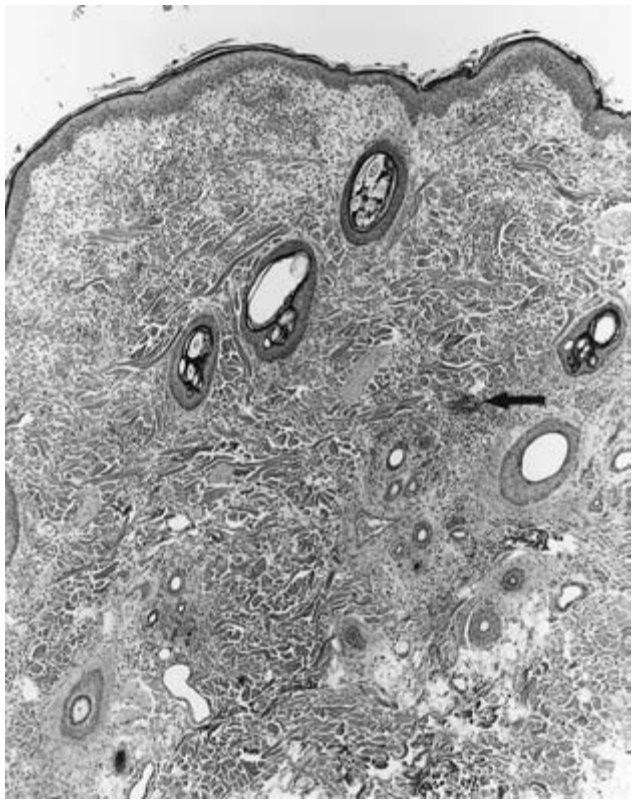


Fig. 14.38 Canine eosinophilic dermatitis demonstrating diffuse inflammation and superficial edema. The small dark focus at right is a flame figure (arrow).

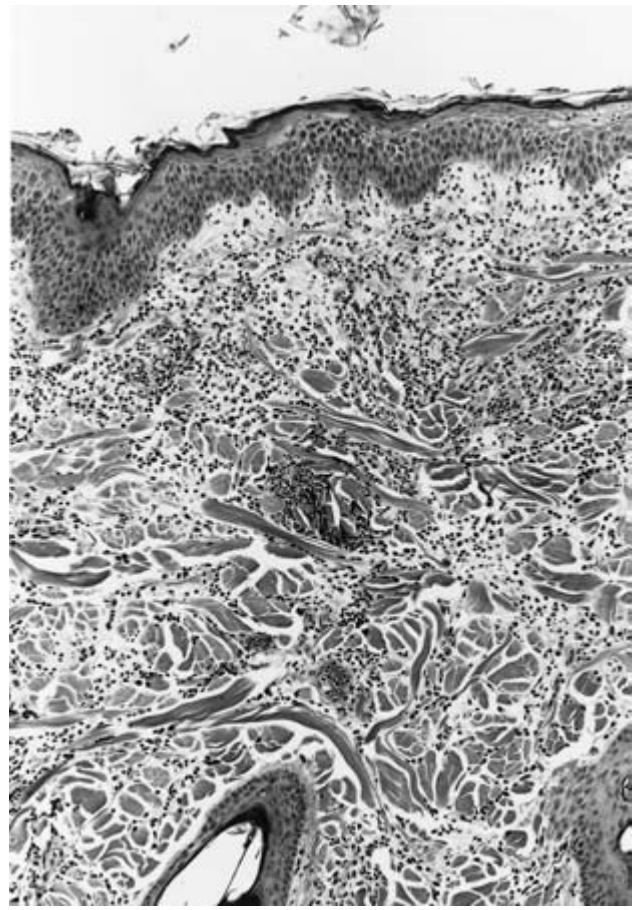


Fig. 14.39 Higher magnification of eosinophilic inflammation and edema of canine eosinophilic dermatitis. Note central flame figure.

eosinophilic granuloma may be difficult; clinical differentiation may be required as eosinophilic granulomas usually are papular to nodular.

FELINE HYPEREOSINOPHILIC SYNDROME

Clinical features (Figure 14.41)

Feline hypereosinophilic syndrome is a rare, multisystemic disease that is characterized by the sustained production and tissue infiltration of mature eosinophils. The bone marrow, lymph nodes, gastrointestinal tract, liver, and spleen are the most commonly affected organs (Muir et al., 1993; Huibregtse & Turner, 1994). Skin involvement is rare (Scott et al., 1985; Harvey, 1990). Disseminated eosinophilic disease was recently reported in a dog with involvement of the heart, lungs, liver, spleen, lymph nodes, and skeletal muscles; skin was not affected (Aroch et al., 2001).

The cause or causes of feline hypereosinophilic syndrome are unknown. Bone marrow hyperplasia and the overproduction of mature eosinophils are triggered, leading to peripheral eosinophilia and the invasion of multiple organs (Huibregtse & Turner, 1994). Eosinophilic leukemia is characterized by persistent eosinophilia, bone marrow hyperplasia of eosinophilic precursors, and organ infiltration; however, the overproduction and infiltration include more frequent and higher proportions of immature eosinophils than in hypereosinophilic syndrome (Huibregtse & Turner, 1994). Clear division between these two diseases may not always be possible (Huibregtse & Turner, 1994). To the authors' knowledge, cutaneous involvement with eosinophilic leukemia has not been reported.

The most common clinical signs are associated with infiltration of the gastrointestinal tract and include weight loss, anorexia, diarrhea, and vomiting (Huibregtse & Turner, 1994). Rare skin lesions include generalized erythematous macules and papules, wheals, and edema (Scott et al., 1985; Harvey, 1990). Pruritus is marked and initiates excoriations (Scott et al., 1985; Harvey, 1990).

Middle-aged domestic shorthaired cats are most commonly affected (Huibregtse & Turner, 1994). The skin

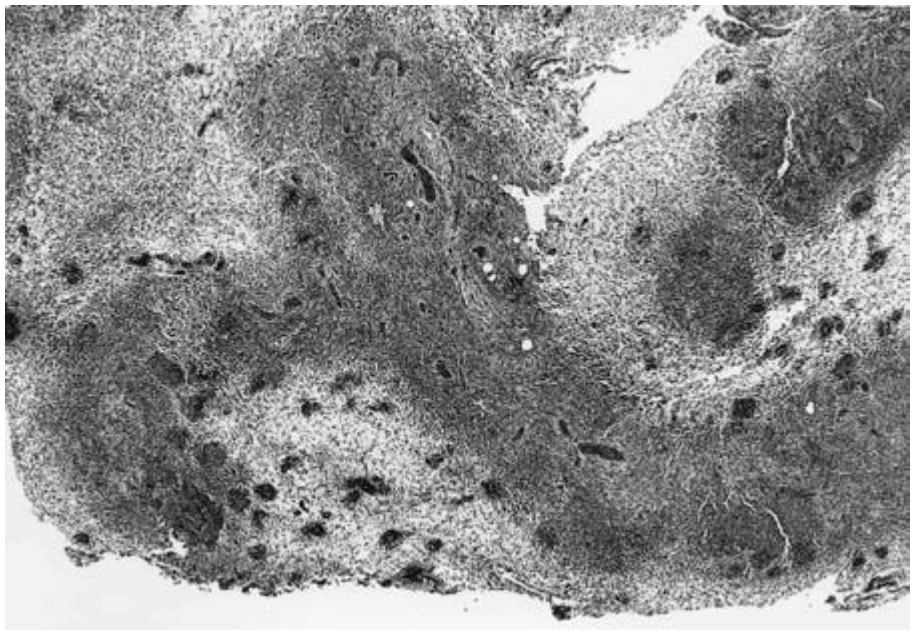


Fig. 14.40 Intense and deep eosinophilic inflammation of subcutis (eosinophilic 'cellulitis') with numerous darkly staining flame figures in a Beagle.



Fig. 14.41 Feline hypereosinophilic syndrome. A crusted maculopapular rash is present. (Photograph courtesy H.T. Power.)

lesions seen with feline hypereosinophilic syndrome must be differentiated from other feline eosinophilic dermatoses. Definitive diagnosis requires the exclusion of other causes of cutaneous eosinophilic lesions (flea allergy dermatitis, other ectoparasitic skin diseases, food allergy, and endoparasitic infections), the presence of peripheral eosinophilia, evidence of infiltration of other organs, and the ruling out of eosinophilic leukemia (Huibregtse et al., 1994).

Biopsy site selection

Multiple biopsy specimens should be obtained from macules, papules, and wheals. If putative edema is present, these lesions also should be sampled.

Histopathology

As reported, the dermis contains predominantly eosinophils (Scott et al., 1985; Harvey, 1990; Muir et al., 1993). The distribution is perivascular to diffuse and superficial to deep. Mature mast cells are intermingled. There is accompanying superficial crusting, likely as a result of self-trauma. Visceral eosinophilic infiltration is invariably present; skin lesions are rare.

The appearance of the rare cutaneous lesions of feline hypereosinophilic syndrome is similar to other eosinophil-predominant dermatoses. Thus, definitive diagnosis will always require correlation with appropriate clinical findings, including eosinophilia and eosinophilic infiltration of other organs.

PLASMA CELL PODODERMATITIS

Clinical features (Figure 14.42)

Plasma cell pododermatitis is a disease exclusively affecting the pawpads. It is rare in cats, and very rare in dogs. All published cases to date have been in cats; the authors have seen several dogs with similar clinical and histopathologic features.

The etiology of plasma cell pododermatitis is unknown, but the marked plasma cell infiltrate, consistent hypergammaglobulinemia, and response to immunomodulating therapy suggest an immune-mediated basis (Gruffydd-Jones et al., 1980; Scott et al., 2001). Recurrence in warm weather may support an allergic origin (Gruffydd-Jones et al., 1980). The status of feline retrovirus infection is controversial. While most reports indicate that affected



Fig. 14.42 Plasma cell pododermatitis in a cat affecting predominantly the metacarpal pad. The affected pad is noticeably swollen, purplish-red, and exfoliating. The white, silvery, crosshatched appearance results from the exfoliation.

cats are feline leukemia virus (FeLV) negative and feline immunodeficiency virus (FIV) negative, others report an incidence of FIV positivity as high as 50% (Guaguère & Declercq, 2000; Scott et al., 2001).

The highly characteristic clinical feature is soft, spongy swelling affecting multiple pawpads. The swelling is uniform such that normal pad symmetry usually is not disturbed. The central larger metacarpal and metatarsal pads are most consistently involved. An increased prominence of normal surface architecture, probably due to stretching, results in a white, scaly, silvery, crosshatched appearance with striae. Although multiple pads usually are affected, the syndrome may affect a single pad. Somewhat surprisingly, lesions usually are asymptomatic. If ulceration of more severely affected pawpads occurs, hemorrhage may follow and lameness may be noted. Highly characteristic 'deflated', spongy pawpads that resemble partially empty balloons may develop with chronicity. These end-stage lesions retain the peculiar surface silvery crosshatched appearance. A minority of cats have coexistent plasma cell stomatitis, immune-mediated glomerulonephritis, or renal amyloidosis (Scott et al., 2001). Skin lesions in dogs mirror those of cats; associated diseases have not been observed.

Breed, age, or sex predilections have not been noted in cats with feline plasma cell pododermatitis. Not enough dogs have been seen with this condition to note potential signalment predilections.

Differential diagnosis of plasma cell pododermatitis generally is not problematic as the disease is visually distinctive. Rarely, eosinophilic granulomas of the pawpads may appear similar. However, in eosinophilic granulomas, crusting and ulceration of the pawpads are accompanied by interdigital alopecia, erythema, and inflammation. If only one pawpad is affected, neoplasia or foreign body granulomas must be ruled out. Exfoliative cytology from aspiration should reveal plasma cells, and hypergammaglobulinemia should be demonstrable on immunoelectrophoresis. Histopathology is necessary to confirm the diagnosis.

Biopsy site selection

A wedge specimen or 6 mm punch biopsy should be obtained from a pawpad near the pad margin. Smaller punch biopsy specimens often are unsuitable as they do not provide a sample of adequate depth. If multiple pads are affected, a moderately rather than severely affected pad should be selected, since severely affected pads may not heal well after biopsy.

Histopathology (Figures 14.43 and 14.44)

The epidermis is acanthotic with variable erosion, ulceration, and exudation. The dermis and often the underlying adipose tissue of the pawpad are diffusely infiltrated with plasma cells, obscuring normal architecture. Milder lesions may show dermal inflammation only. Russell body-containing plasma cells (Mott cells) are often conspicuous. Fewer lymphocytes and macrophages are present and randomly distributed among the plasma cells. Neutrophils vary, but may comprise up to 50% of the infiltrate; their presence is not dependent upon ulceration. Eosinophils are observed in small numbers in rare cases. Edema of the dermis, deep perivascular tissue, or interlobular septa of the fat pad may be seen. In some cases, mucin is observed. Blood vessels are often prominently dilated and congested, and hemorrhage may be present. Chronic lesions may feature fibrosis which may course among lobules of inflamed tissue. Feline and canine lesions are identical.

Differential diagnosis is not difficult, as the site of the biopsy generally is known. Anatomic location, type, and deep distribution of the inflammation are typical. If inflammation is mild and dermal only, differentiation from chronic dermatitis of any origin may be difficult.

FAMILIAL CUTANEOUS VASCULOPATHY OF GERMAN SHEPHERD DOGS

Clinical features

See Chapter 10.

Biopsy site selection

See Chapter 10.

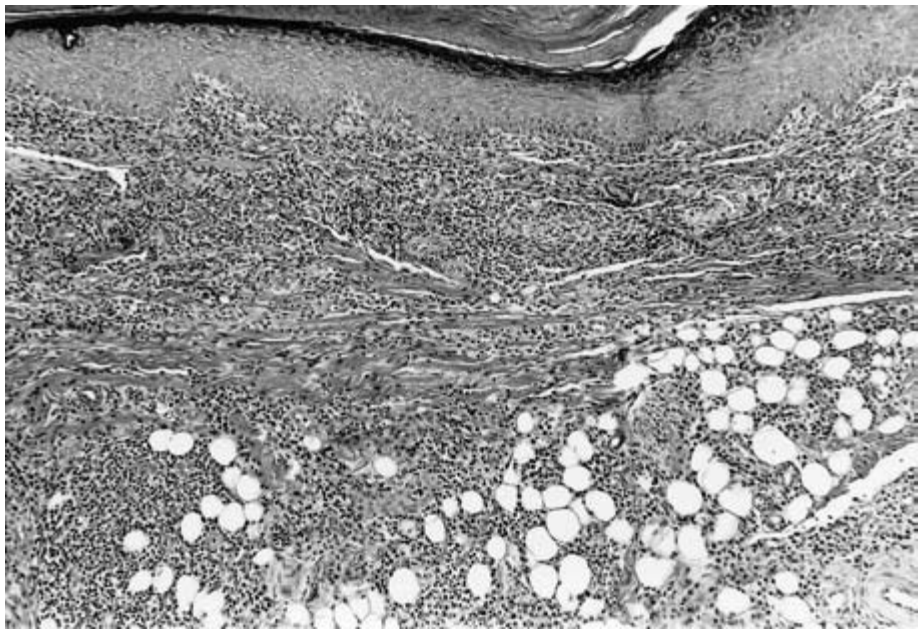


Fig. 14.43 Plasma cell pododermatitis in a cat. Diffuse inflammation is partially replacing the adipose tissue of the pawpad.

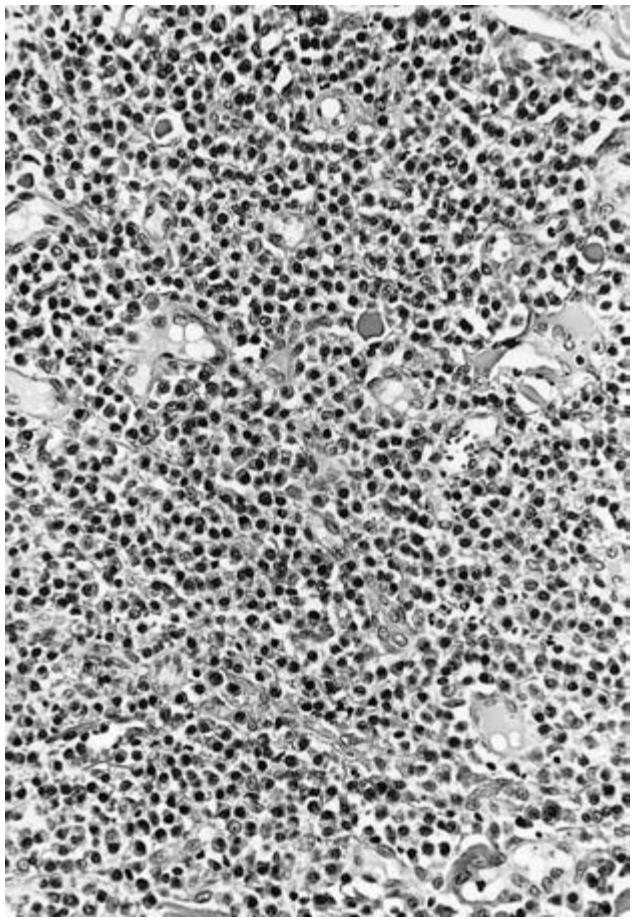


Fig. 14.44 Higher magnification of plasma cell pododermatitis in a cat. Note the predominance of plasma cells in the diffuse inflammatory infiltrate.

Histopathology (Figures 14.45 and 14.46)

Parakeratosis and mild serocellular crusting accompany moderate acanthosis and variable ulceration. Mild interface dermatitis has been described in depigmented lesions (Weir et al., 1994). Vascular lesions are subtle in some cases, and may be best seen in arterioles of the deep dermis and panniculus; these are cell poor in type, and are described in Chapter 10.

There is nodular to diffuse, superficial and deep dermatitis and panniculitis, composed of lymphocytes, macrophages, and fewer neutrophils. Mucin and/or edema are intermingled throughout. Blood vessels may be dilated. A diagnostic feature is aggregation of inflammatory cells around collagen fibers. Lymphocytes, macrophages, and neutrophils form small to large, degenerate foci around collagen. Nuclear degeneration creates a basophilic cast to these foci on low power examination; in particular, nuclear debris from neutrophils (leukocytoclastic debris) is abundant. Collagen-focused inflammation is as seen in other cases of cell poor vasculitis that feature interstitial dermatitis and panniculitis (see Chapter 10), but is more flagrant and neutrophilic in this condition.

Differential diagnoses for familial cutaneous vasculopathy of German Shepherd Dogs are few if the typical degenerate foci around collagen are found within skin of the pawpad. The leukocytoclastic foci somewhat resemble those of the Churg Strauss-like variant of palisading granuloma, observed in a single dog (see Chapter 13), but occur in a setting of more intense mixed inflammation as well as a different clinical context. The granulomas of cutaneous vasculopathy of German Shepherd Dogs are

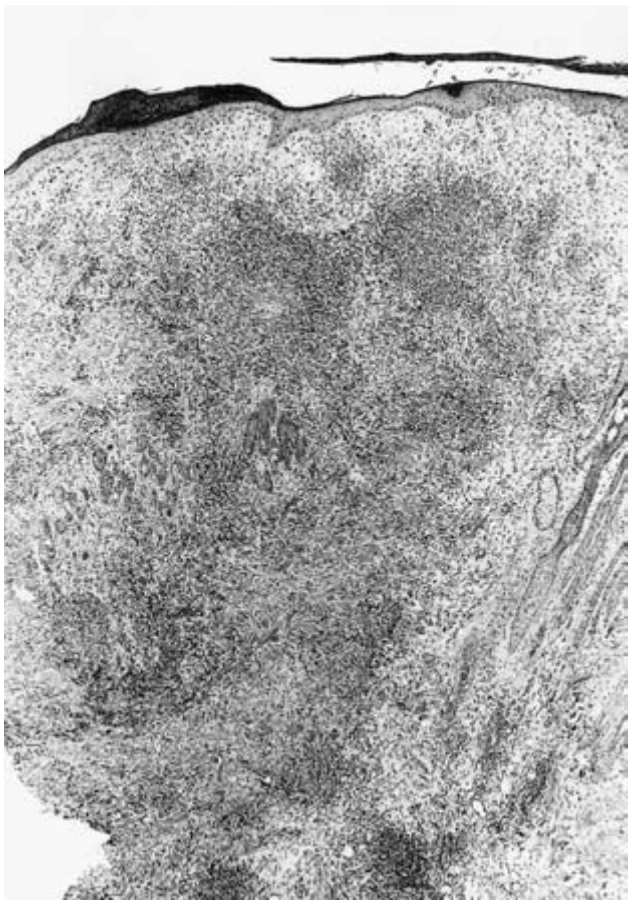


Fig. 14.45 Familial cutaneous vasculopathy in a Miniature Schnauzer. Note deep, nodular to diffuse inflammation.

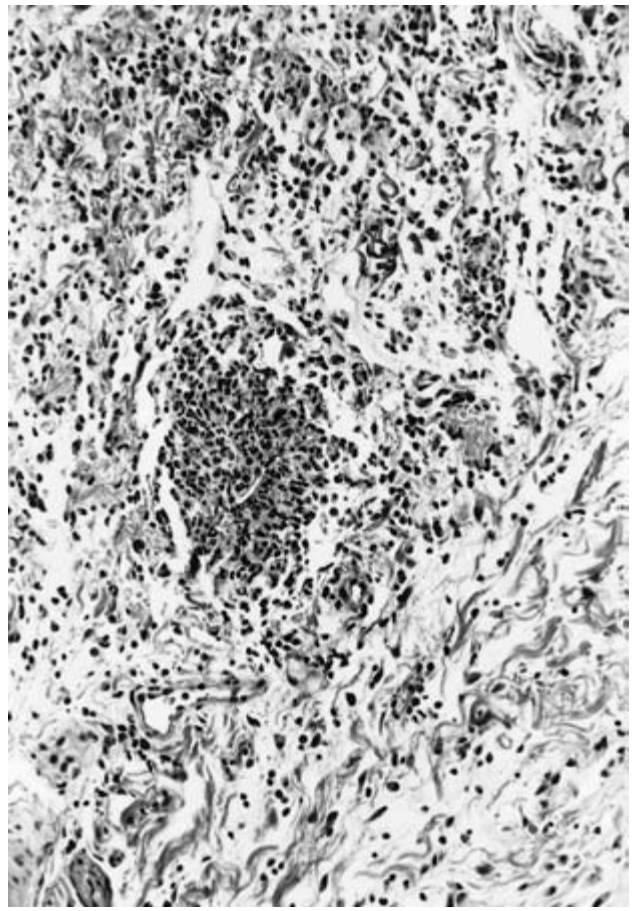


Fig. 14.46 Higher magnification of familial cutaneous vasculopathy in a Fox Terrier. Note characteristic degenerate neutrophilic inflammatory focus around a small central collagen fiber.

superficially similar to those of eosinophilic granulomas, but do not feature eosinophils. The degenerate foci of familial cutaneous vasculopathy are basophilic on low power examination, in contrast to the eosinophilic cast of flame figures of eosinophilic granulomas. If diffuse inflammation only is found, the lesions might be confused with the rare plasma cell pododermatitis of dogs (see p. 363). Clinical differentiation may be required.

CANINE STERILE NEUTROPHILIC DERMATOSIS (SWEET'S SYNDROME)

Clinical features (Figures 14.47 through 14.49)

Canine sterile neutrophilic dermatosis is a rare disease, observed to date only in dogs. There is marked clinical and histopathologic resemblance to acute febrile neutrophilic dermatosis (Sweet's syndrome) in humans. As in human Sweet's syndrome, dogs display clinical features of extracutaneous disease, including fever, arthritis, pneu-



Fig. 14.47 Canine sterile neutrophilic dermatosis (Sweet's syndrome) in a dog. In this view macular erythema predominates; papules are subtly evident. (Photograph courtesy C.B. Vitale.)



Fig. 14.48 Closer view of the dog in Fig. 14.47. Erythematous papules are visible; intact pustules were noted with a hand lens. (Photograph courtesy C.B. Vitale.)



Fig. 14.49 View of the clipped tail of the dog in Fig. 14.47. Multiple small erythematous pustules are evident. (Photograph courtesy C.B. Vitale.)

monia, and circulating neutrophilia; all signs may not be present in individual cases.

The etiology of Sweet's syndrome is not known in humans (Fitzgerald et al., 1996; Honigsmann et al., 2003). It has been postulated that it may represent an unusual hypersensitivity reaction to bacterial, viral, or tumor antigen (Honigsmann et al., 2003). Skin disease is preceded by febrile upper respiratory infection, tonsillitis, or influenza-like clinical signs in the majority of human patients (Honigsmann et al., 2003). Up to 20% of cases in humans are seen in conjunction with malignancy, especially hematologic malignancy (Fitzgerald et al., 1996; Honigsmann et al., 2003), but this association has not been observed in dogs. Drug and vaccine-induced Sweet's syndrome also is reported in humans (Fitzgerald et al., 1996; Honigsmann et al., 2003). A putative association with the nonsteroidal anti-inflammatory drug carprofen has been made in several dogs (Vitale et al., 1999). However, it is possible that the drug was administered in response to malaise or lameness that actually represented early signs of prodromal disease.

Clinical features include severe macular erythema with multiple erythematous papules, and circular or irregular plaques. Minute pustules may occur on the surface of larger lesions (Vitale, C.B., personal communication, 2003). These pustules may represent the characteristic 'illusion of vesiculation' noted in humans (Honigsmann et al., 2003). Lesions commonly coalesce. The head, neck, trunk, or extremities may be affected. Oral lesions may occur alone or in conjunction with skin lesions; this is similar to some human patients.

Extracutaneous clinical features include fever and leukocytosis. Absolute neutrophilia in the range 15 000 to 25 000 is common. General malaise may precede canine sterile neutrophilic dermatosis. Lameness and depression have been noted to precede skin lesions in dogs (Vitale, C.B., personal communication, 2003). Neutrophilic polyarthritis may be present. Respiratory signs, seen in some dogs, correlate with neutrophilic pneumonia. The presence of pyrexia and depression, neutrophilic leukocytosis, as well neutrophilic cutaneous and pulmonary lesions are similar to sterile pustular erythroderma of Miniature Schnauzers, suggesting that that syndrome may be a related phenomenon (see p. 369 and Chapter 1).

Breed, age or sex predilection have not been noted in the small number of dogs seen with this syndrome. Marked signalment predilections (women, Japanese ethnicity) do occur in humans (Fitzgerald et al., 1996; Honigsmann et al., 2003).

Clinical differential diagnoses include a wide variety of erythematous dermatoses characterized by papules, pustules, and plaques. These include erythema multiforme, canine eosinophilic dermatitis, toxic shock syndrome, and sterile pustular erythroderma of Miniature Schnauzers. Complete blood counts and chemistry screening profiles should be performed to evaluate for the presence of neutrophilia. Histopathology in conjunction with supportive clinical features is confirmatory.

Biopsy site selection

Multiple papules, pustules, plaques, or nodules should be sampled. Care should be exercised when taking the biopsy, as these lesions may be fragile.

Histopathology (Figures 14.50 and 14.51)

The epidermis is generally mildly acanthotic only. Occasionally, neutrophilic infiltration of the epidermis forms small superficial pustules, as described in humans (Cohen & Kurzrock, 2003). Ulceration and exudation may occur.



Fig. 14.50 Canine sterile neutrophilic dermatosis featuring diffuse neutrophilic dermatitis. Note mild neutrophilic infiltration of overlying epidermis.

The dermis contains a moderate to severe neutrophil-rich infiltrate in which variable eosinophils may be intermingled. The distribution is superficial to deep and perivascular to diffuse, often with clustering along follicles. Lymphocytes and macrophages may be present. Edema is generally prominent. Leukocytoclasia (fragmentation of granulocytic nuclei as they exit vessels, typified by perivascular fragments or dust) is uncommon and generally very mild, but dermal hemorrhage often is observed. There may be vascular transmural migration of neutrophils, but without vascular necrosis or fibrin thrombosis. Vascular damage of this condition is secondary to toxic metabolites released by activated neutrophils, as described in humans (Malone et al., 2002), and has been termed an 'innocent bystander epiphenomenon' (Cohen, 2002).

As in humans with Sweet's syndrome, interstitial neutrophilic infiltration of the lung with alveolitis may be present. Sterile neutrophilic arthritis/synovitis has been documented.

Differential diagnoses include sterile pustular erythroderma of Miniature Schnauzers and infectious dermatitides. Infectious neutrophilic inflammation tends to target follicles or form discrete dermal or follicular pustules. In contrast, the neutrophils of sterile neutrophilic dermatosis tend to be perivascular to diffuse. The lesions of sterile pustular erythroderma of Miniature Schnauzers more consistently feature severe epidermal pustulation and crusting (see Chapter 1) and usually are more eosinophilic.

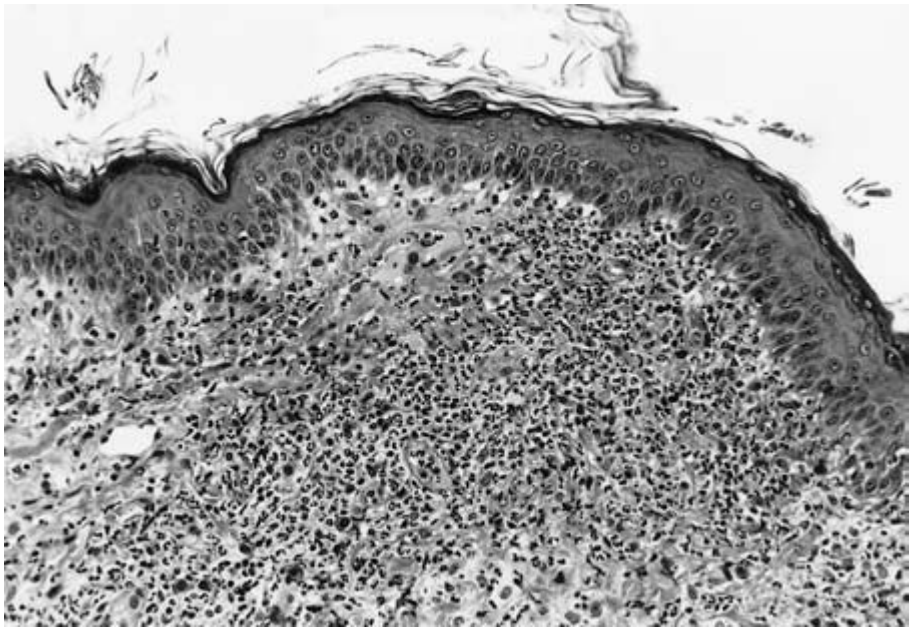


Fig. 14.51 Higher magnification of canine sterile neutrophilic dermatosis. Neutrophils are abundant in the superficial dermis.



Fig. 14.52 Sterile pustular erythroderma in a Miniature Schnauzer. Diffuse neutrophilic inflammation is accompanied by edema.

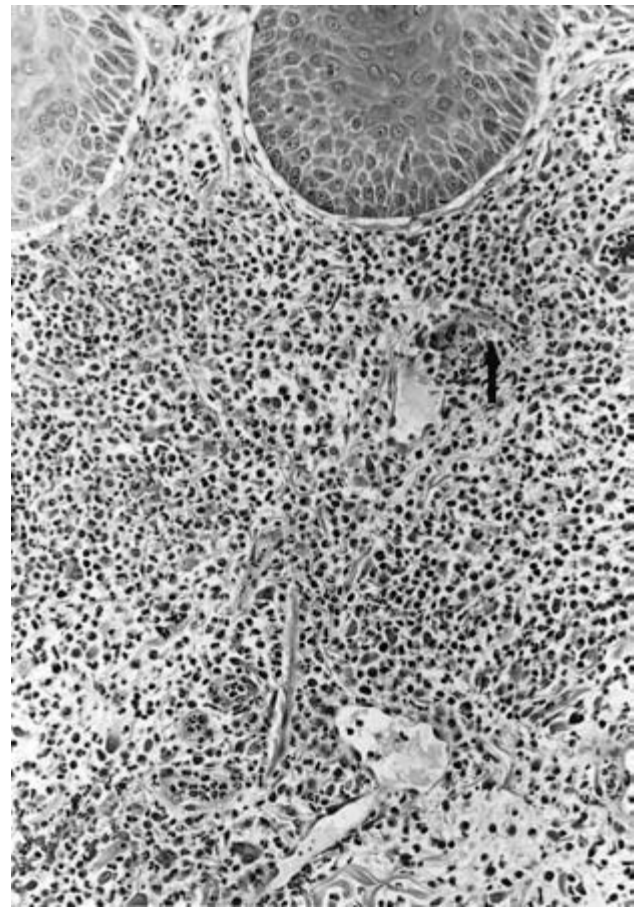


Fig. 14.53 Higher magnification of sterile pustular erythroderma. Neutrophils are diffusely abundant; note leukocytoclasia (arrow).

STERILE PUSTULAR ERYTHRODERMA OF MINIATURE SCHNAUZERS

(Synonyms: superficial suppurative necrolytic dermatitis of Miniature Schnauzers, Schnauzer syndrome)

Clinical features

See Chapter 1.

Biopsy site selection

See Chapter 1.

Histopathology (Figures 14.52 and 14.53)

Epidermal lesions include acanthosis, spongiosis, and broad pustules that are often present in late stage, fully formed lesions (see Chapter 1). The dermis is edematous and often contains a neutrophil- and/or eosinophil-rich infiltrate. Macrophages are intermingled, and plasma cells and lymphocytes may be present. The distribution is perivascular to interstitial and is often most concentrated in the superficial dermis where confluence in severe lesions creates a band-like effect. Inflammation is usually moderate to severe, but may be mild, particularly in cases with prominent epidermal lesions.

Eosinophils are often numerous. In cases where sequential biopsy is performed, lesions from earlier in the course of the disease contain predominantly neutrophils; eosinophils are prominent and may outnumber neutrophils in later-stage lesions. Eosinophils infiltrate the epidermis and also may contribute to epidermal pustulation. Rare foci of eosinophilic degranulation around collagen (flame figures) may be observed.

Early lesions may show neutrophilic leukocytoclasia (fragmentation of granulocytic nuclei as they exit affected vessels, typified by nuclear fragments or dust in perivascular distribution). There may be vasculopathic/vasculitic changes of endothelial swelling, mild mural neutrophilic inflammation, and perivascular hemorrhage. Vascular necrosis and fibrin thrombosis are not observed. Vascular

damage is secondary to toxic metabolites released by activated neutrophils, as described in humans (Malone et al., 2002), and has been termed an 'innocent bystander epiphenomenon' (Cohen, 2002).

As in some dogs with sterile neutrophilic dermatosis (see p. 366), pulmonary interstitial neutrophilic infiltrates may occur. Myocardial and hepatic necrosis has been observed; hepatic lesions support terminal disseminated intravascular coagulation.

Dermal lesions closely resemble those of canine sterile neutrophilic dermatosis. Epidermal pustular inflammation generally is more striking in sterile pustular erythroderma of Miniature Schnauzers than in sterile neutrophilic dermatosis, and eosinophils are more prominent. Clinical differentiation may be required. In lesions of sterile pustular erythroderma in which eosinophils predominate, canine eosinophilic dermatitis may be considered (see p. 360), particularly if flame figures are seen. However, eosinophil degranulation is generally a more striking feature of eosinophilic dermatitis, and commonly is not present in eosinophilic lesions of toxic pustular erythroderma.

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Chapter 15

Degenerative, dysplastic and depositional diseases of dermal connective tissue

Degenerative diseases are characterized by an acquired breakdown, atrophy, or other alteration in structural integrity of dermal connective tissue. The dysplastic diseases are those in which the structure of the dermal tissue is altered through hereditary abnormalities. Degenerative and dysplastic dermal changes usually result in skin fragility and dermal splitting, but can also result in extrusion of the affected collagen, as in perforating collagenosis.

Depositional diseases are characterized by production or deposition of substances not normally found in the dermis, such as mineral or amyloid, or production of substances in excess of normal, such as mucin. Differentiation amongst these conditions is accomplished by the identification of specific histomorphologic features of these substances, which often is aided by the use of special stains.

CALCINOSIS CUTIS

Clinical features (Figures 15.1 and 15.2)

Calcinosis cutis is an uncommon physiological process characterized by inappropriate mineral deposition in the dermis, epidermis, or subcutis. Tissue mineralization is defined as the deposition of insoluble, inorganic mineral salts. This process requires deposition of a cation (usually calcium) and an anion, typically phosphate or carbonate (Walsh & Fairley, 1999); when calcium is the predominant cation, the more specific term 'calcification' may be applied. Usually, cutaneous mineral is deposited upon the collagen or elastin matrix of the dermis.

Calcinosis cutis, as broadly used in human medicine, encompasses all forms of calcification including the four major categories of dystrophic, metastatic, idiopathic, and iatrogenic calcification (Touart & Sau, 1998; Walsh & Fairley, 1999). Although this classification scheme is theoretically useful, individual syndromes of cutaneous mineralization may have etiopathogenic overlap. The term 'calcinosis cutis' most commonly is used in veterinary medicine to denote the specific type of dystrophic calcification occurring with natural or iatrogenic hyperglucocorticoidism. Calcinosis cutis is most commonly seen with iatrogenic hyperglucocorticoidism. The term 'calcinosis circumscripta' is used predominantly for focal or multifocal, more 'tumoral' disease (see p. 378).

The mechanism of calcium salt deposition in skin is highly complex and poorly understood. *In vivo* solutions of calcium phosphate are composed of a number of salts differing in their calcium to phosphate ratio. Normally, calcium and phosphate ions exist in solution in extracellular fluid in a metastable equilibrium. Phase transformation from ions in solution to the solid phase may be induced by changes in collagen fibrils. Phosphate ions may initiate the transformation by the formation of crystal nuclei upon organic matrices. Abnormally elevated mitochondrial calcium phosphate levels apparently result in crystal deposition and cell death (Touart & Sau, 1998).

In dystrophic calcification it has been hypothesized that tissue damage allows increased intracellular calcium influx (Touart & Sau, 1998). In metastatic calcification, elevated serum levels of calcium or phosphate initiate the precipitation of crystals in soft tissue (Touart & Sau, 1998). Metastatic calcification is most commonly associated with disorders of calcium and phosphorus homeostasis leading to an elevated solubility product obtained by multiplying the serum calcium level by the serum phosphorus level (Ca × P) (Bertazzolo et al., 2003). Both dystrophic and metastatic factors may coexist in certain syndromes, such as calcification due to renal failure (see calcinosis circumscripta, p. 378). Calcification is idiopathic in the absence of antecedent trauma and in the absence of abnormal serum calcium levels (Touart & Sau, 1998). Iatrogenic calcification is due to direct exposure to calcium-containing substances.

In humans, dystrophic calcification occurs secondary to connective tissue disorders, panniculitis, various inherited disorders, benign and malignant neoplasms, infections (especially parasitic), and focal trauma (Walsh & Fairley, 1999). In dogs, dystrophic calcification most commonly occurs in conjunction with hyperglucocorticoidism as calcinosis cutis, or in response to focal trauma as calcinosis



Fig. 15.1 Calcinosis cutis in an aged Shih Tzu with naturally occurring hyperglucocorticoidism. Somewhat bilaterally symmetric, ulcerated plaques are present in the flexural surfaces of the ventral abdomen.



Fig. 15.2 Chronic calcinosis cutis in an aged Boston Terrier with naturally occurring hyperglucocorticoidism. A well-demarcated plaque is seen in a flexural surface of the ventral abdomen. Whitish-brown foci correspond to areas of transepidermal elimination of mineralized debris.

circumscripta (see p. 378). Metastatic calcification occurs most commonly in both humans and dogs in the setting of chronic renal failure, and in dogs and cats is manifested as calcinosis circumscripta.

Idiopathic calcification in humans most frequently involves the genitals, or surrounds major joints in adolescents (tumoral calcinosis) (Walsh & Fairley, 1999). In domestic animals, idiopathic calcification predominantly occurs as idiopathic calcinosis circumscripta. Rarely, widespread idiopathic calcinosis cutis has been seen in puppies, most frequently as a sequela to severe systemic illness. The etiopathogenesis is unknown, and lesions usually regress spontaneously. Unexplained severe calcinosis cutis also has been reported in conjunction with amphotericin B therapy in three dogs with blastomycosis (Gortel et al., 1999).

Iatrogenic calcification in humans, dogs, and cats is seen as a rare complication of intravenous or subcutaneous calcium chloride or calcium gluconate therapy for hypoparathyroidism (Walsh & Fairley, 1999; Ruopp, 2001; Schaer et al., 2001). Calcinosis cutis of the thinly haired skin of the ventrum of dogs has been reported in association with the percutaneous penetration of calcium chloride powder and calcium-containing bone meal present in landscaping products (Schick et al., 1987; Paradis & Scott, 1989).

Ossification, or the formation of bone by the deposition of calcium and phosphorus as hydroxyapatite crystals in a proteinaceous matrix, occurs rarely in the skin in all species studied. The term 'osteoma cutis' has been used to describe the dermal deposition of metaplastic bone. All cases of osteoma cutis seen by the authors have occurred in conjunction with multifocal calcinosis cutis caused by iatrogenic or endogenous hyperglucocorticoidism; most cases involved multiple injections of long-acting glucocorticoids. However, osteoma cutis in the absence of calcinosis cutis is reported (Frazier et al., 1998).

Clinically, chalky, white-to-pink material with a feathery or blurry margin can be seen through the intact epidermis of early nonulcerated lesions and is most easily observed with a hand lens. Firm, gritty yellowish-tan to dark red plaques evolve from coalescing erythematous papules. Ulceration and crusting occur as gritty mineral salts are extruded from older lesions (transepidermal or transfollicular elimination). On palpation, this grittiness may resemble sand. The lesions may be aggravated by self-trauma. Calcinosis cutis may be either focal or widespread. Skin regions subject to repetitive flexure are predisposed; calcinosis cutis occurs most commonly in the flexural surfaces of the groin, back of the neck, and axillae.

Contrary to popular belief, chronic lesions may be pruritic, especially if transepidermal elimination of calcium occurs. Dogs with accompanying hyperglucocorticoidism usually show other characteristic clinical features of this syndrome (see Chapter 19). Calcinosis cutis may be clinically inapparent in very early cases. The range of severity and percentage of the body affected may vary markedly; in general, more severe calcinosis cutis occurs secondary to iatrogenic hyperglucocorticoidism, especially with the use of long-acting injectable glucocorticoids. Interestingly, long term ventral application of high potency topical corticosteroids has not been associated with calcinosis cutis (see p. 392).

Calcinosis cutis in association with the percutaneous penetration of calcium products is characterized by papular to nodular, indurated, ulcerated, and exudative

lesions; sites affected reflect those of contact and absorption (Schick et al., 1987; Paradis & Scott, 1989). Calcinosis cutis secondary to administration of calcium gluconate solution in a hyperphosphatemic dog with primary hypoparathyroidism presented as severe ventral disease affecting the groin, despite administration of the calcium gluconate in the thoracolumbar region (Schaer et al., 2001).

Calcinosis cutis seen in conjunction with naturally occurring canine hyperglucocorticoidism will exhibit the age and breed predilections of hyperglucocorticoidism (see Chapter 19); sex predilections are not reported. Calcinosis cutis secondary to iatrogenic hyperglucocorticoidism may be more common in English Bulldogs. Idiopathic calcinosis cutis following severe illness has been seen only in puppies; breed or sex trends have not been observed. Calcinosis cutis due to contact absorption of calcium-containing material may be more likely in young active dogs, due to their propensity for mischief.

Calcinosis cutis secondary to hyperglucocorticoidism is visually distinctive. Differential diagnoses are few. Erythematous papules seen in early cases may resemble superficial pyoderma. Exceptionally severe ulcerated lesions may resemble deep bacterial or fungal infection. Calcinosis cutis secondary to percutaneous absorption reflects sites of contact and also may resemble severe, deep bacterial or fungal infections.

Biopsy site selection

Areas of affected skin without concurrent self-trauma or ulceration are preferred sites for biopsy. Since the mineral deposits may impede clean incision by the skin biopsy punch, specimens obtained with smaller punches (4 mm) may be damaged during sampling. Consequently, larger biopsy punches (6 or 8 mm) or wedge specimens are recommended. Pressure points should not be sampled, as healing may be prolonged in these locations.

Histopathology (Figures 15.3 through 15.7)

Although there may be etiopathogenic overlap, for descriptive purposes calcinosis cutis is histologically differentiated from calcinosis circumscripta (see p. 378). Calcinosis cutis is characterized by diffuse involvement of the dermal collagen and adnexal appendages; diffuse calcinosis may extend to deeper tissues with some etiologies. In contrast, calcinosis circumscripta is 'tumoral' and forms focal or multifocal large masses of mineral that often totally efface soft tissue, including the subcutis.

In calcinosis cutis, the epidermis often is severely acanthotic and may be ulcerated or exudative depending on the degree of accompanying self-trauma, transepidermal elimination of mineral, or pyoderma. The dermis is characterized by variable mineralization of collagen fibers. There may be superficial dermal edema. Superficial follicles are markedly hyperplastic, and sometimes tortuous; there may be infundibular hyperkeratosis. Telogen-type atrophy may be apparent if there is concurrent hyperglucocorticoidism (see Chapter 19), but is usually more evident in adjacent noncalcified dermis.

Affected collagen ranges from slightly hypereosinophilic and mildly fragmented to deeply basophilic

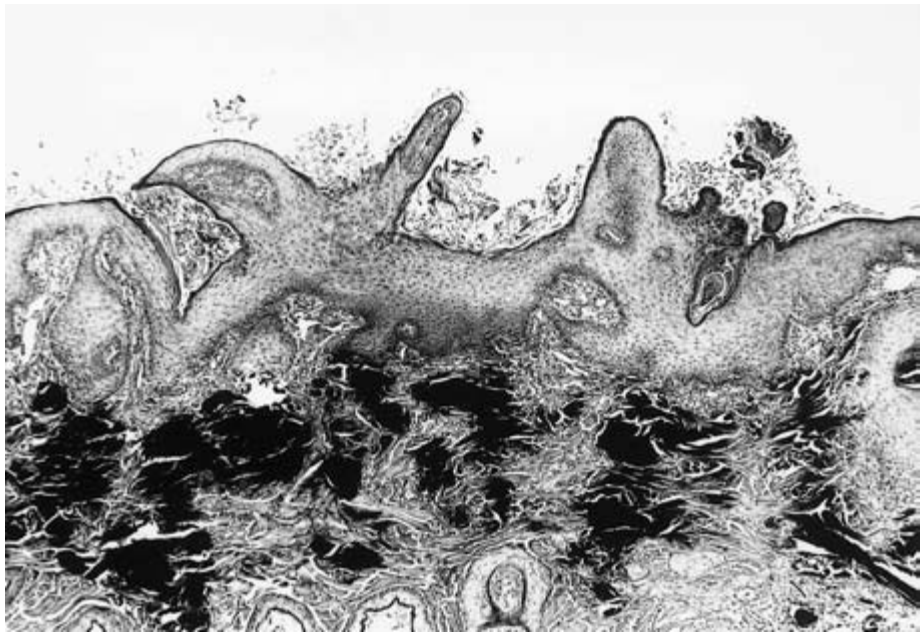


Fig. 15.3 Severe calcinosis cutis demonstrating replacement of dermal collagen fibers by darkly staining mineral.

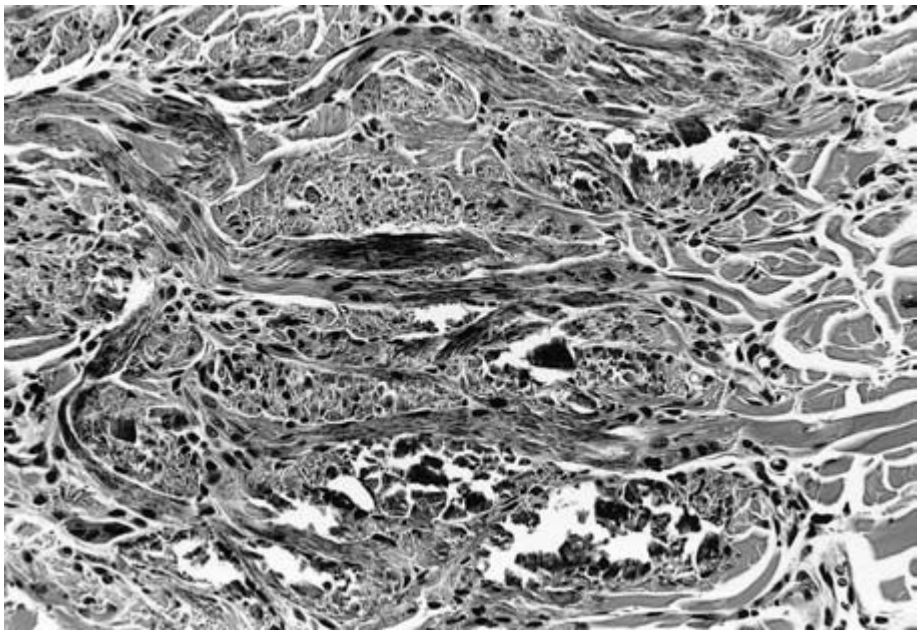


Fig. 15.4 Higher magnification of calcinosis cutis. Collagen fibers appear fractured due to early mineralization.



Fig. 15.5 Transepithelial elimination of mineral in calcinosis cutis. Mineral is being extruded through the epidermis and follicular infundibula.

and severely disrupted. Macrophages accumulating along slightly fragmented collagen fibers may be the earliest histopathologic feature of calcinosis cutis. Von Kossa stain reveals deposition of mineral (dark brown to black) in subtle early lesions. Frank deposition of small to large foci of dark blue mineral in the superficial and middle dermis is a more common finding; severe mineralization effaces normal dermal collagen. There may be mineralization of the external root sheaths of hair follicles as well. Rarely, hyperglucocorticoidism may result in widespread and prominent mineralization of the external root sheath, without dermal calcinosis. Macrophages and giant cells accumulate between affected fibers and around larger confluent foci of mineralization; neutrophils may be intermingled. Lymphocytes and plasma cells may be present. Severe dermal fibrosis may develop in chronic lesions.

Osteoma cutis (metaplastic bone) is a late stage feature and may predominate in some cases. Random samples from individual cases may show osteoma cutis only, while others feature ossification and mineralization concurrently. Osteoma cutis in the absence of apparent calcinosis cutis has been reported (Frazier et al., 1998). Dermal ossification occurs as irregular spicules of osteoid or lamellar bone. These often surround and engulf foci of calcinosis,



Fig. 15.6 Osteoma cutis featuring discrete dark islands of bone in the dermis.

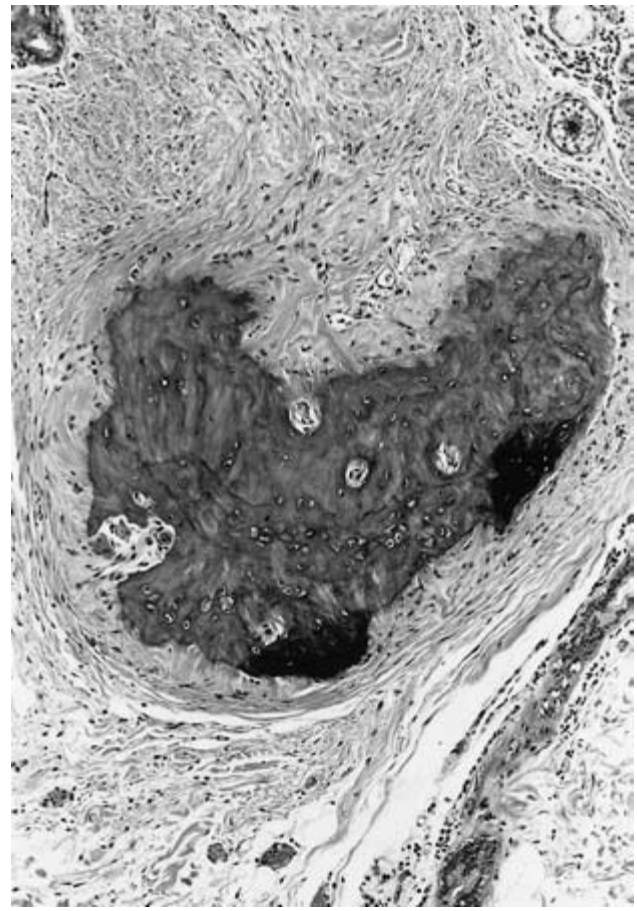


Fig. 15.7 Higher magnification of Fig. 15.6. Note fibrosis around island of bone.

or may have calcinosis at the periphery. There may be marrow-like spaces containing spindle cells. Haversian bone and bone marrow have been reported (Frazier et al., 1998). Osteoblasts and osteoclasts surround ossified foci. There is variable fibrosis surrounding and separating bone. Inflammation is mixed and variable; lesions with bone only are associated with little if any inflammatory reaction, as bone deposition is nonreactive.

Transepidermal or transfollicular (transepithelial) elimination of mineral is characterized by extrusion of mineral through the epidermis or into the lumen of hair follicles, and is a common feature of calcinosis cutis. In typical transepithelial elimination, foci of mineral are within the epidermis or follicular infundibular epithelium, and break through to the epidermal surface or the follicular lumen. An unusual and probably late-stage variant is the accumulation of mineral primarily within luminal follicular keratin, accompanied by perifollicular fibrosis. Transepithelial elimination is accompanied by neutrophilic pustular inflammation in some lesions, and ulcers may occur.

Calcinosis cutis due to percutaneous penetration of calcium chloride-containing substances may be characterized additionally by severe epidermal and dermal necrosis, likely as a direct caustic effect of the contactant. In calcinosis cutis due to injection of calcium gluconate for the treatment of hypoparathyroidism, mineralization and degeneration of blood vessels may result in secondary severe tissue necrosis. Widespread calcinosis cutis of this type has been reported in a dog that had been treated with calcium gluconate solution for hypoparathyroidism in the setting of hyperphosphatemia (Schaer et al., 2001). Calcinosis due to injectables may affect deeper tissues including skeletal muscle fibers.

Differential diagnosis of calcinosis cutis is not difficult if mineralization is obvious in tissue. Von Kossa staining may aid in the rare subtle or early lesions. Mild mineralization of the external root sheath of hair follicles may occasionally be encountered in older normal dogs, classically in Miniature Poodles but in other breeds as well.

CALCINOSIS CIRCUMSCRIPTA

(Synonym: tumoral calcinosis)

Clinical features (Figures 15.8 and 15.9)

Calcinosis circumscripta is a clinically distinctive subgroup of calcinosis cutis characterized by the focal deposition of mineral salts in tumor-like nodules, usually in the subcutaneous tissue. The syndrome is uncommon in dogs and very rare in cats. Lesions classified as calcinosis circumscripta in the dog span all etiologic classifications for calcinosis cutis and include dystrophic, metastatic, idiopathic, and iatrogenic mineralization. Many cases of calcinosis circumscripta are deemed idiopathic in the dog and cat, but may in fact be dystrophic due to focal trauma, as lesions occur over pressure points, or at sites of previous trauma, such as that incurred during ear cropping. There may be overlap of etiopathogeneses. For example, the tendency for trauma-induced calcinosis circumscripta may be enhanced by the active calcium and phosphate metabolism of large, rapidly growing dogs. Dystrophic factors may play a role in metastatic calcification seen in cats with renal failure, as lesions occur in the pads where there is repeated trauma (Bertazzolo et al., 2003). The mechanism of calcium salt deposition in tissue is incompletely understood (see calcinosis cutis, p. 373).



Fig. 15.8 Calcinosis circumscripta on the tongue of a dog characterized by a raised and irregular yellowish-pink nodule. (Photograph courtesy J.-P. Magnol.)



Fig. 15.9 Calcinosis circumscripta involving a lateral digit of a German Shepherd Dog. An ulcer is present in the center of the lesion. (Photograph courtesy S.D. White.)

In dogs, focal trauma is probably responsible for most dystrophic cases of calcinosis circumscripta. Metastatic calcification occurs in humans, dogs, and cats as a sequela to chronic renal failure in the setting of a high solubility product (Ca × P) (see p. 373) and may be tumoral in dogs and cats (Scott & Buerger, 1988; Gross, 1997; Jackson & Barber, 1998; Touart & Sau, 1998; Walsh & Fairley, 1999; Bertazzolo et al., 2003). Most reported pad lesions of calcinosis circumscripta are due to renal failure (Scott & Buerger, 1988; Gross, 1997; Jackson & Barber, 1998; Bertazzolo et al., 2003). Idiopathic calcinosis circumscripta of the pawpads also may occur (Stampley & Bellah, 1990; Alhaidari, 1995; Joffe, 1996). Iatrogenic nodular mineralization is reported in conjunction with the injection of progestational compounds in both the dog and cat (Ginel et al., 1992; O'Brien & Wilkie, 2001).

Calcification seen in conjunction with benign or malignant neoplasms and severe infections (especially parasitic) is grouped under calcinosis circumscripta in humans (Walsh & Fairley, 1999). Mineralization occurs in these contexts in animals as well, but is considered a secondary feature and is not classified separately.

Clinically, calcinosis circumscripta usually presents as firm, well-circumscribed, domed nodules in the subcutaneous tissue. The overlying skin may be freely moveable or fixed, and may be ulcerated in larger lesions with more superficial extension or with repeated trauma, such as pad lesions. The consistency of the nodules varies from firm to fluctuant. Gritty, chalky, or pasty material may extrude from ulcerated lesions. Inflammation is minimal in intact lesions. Erythema, swelling, and bacterial infection may occur secondary to ulceration and drainage. Most lesions are solitary, due to their suspected traumatic origin. Calcinosis due to renal failure often affects multiple pawpads; discovery of multiple pad involvement should prompt investigation for underlying renal disease. Most lesions of calcinosis circumscripta are not painful, except for those of the pawpads, which can be severely so. Concurrent disease usually is not a feature of dystrophic or idiopathic calcinosis circumscripta in domestic animals; however, calcinosis circumscripta has been reported in conjunction with hypertrophic osteodystrophy and polyarthritis in young dogs (Scott & Buerger, 1988).

Site predilection is diagnostically and prognostically important in calcinosis circumscripta. Calcinosis circumscripta is seen most commonly at sites of potential trauma

such as pressure points or other bony prominences such as the spine. It has also been observed in the tongue, and at the site of prior ear cropping. One author (T.L.G.) observed multiple lesions on the pinnae of a dog which occurred at the sites of previous cat bites. Cheek lesions have been described in Boston Terriers (Scott & Buerger, 1988). Metastatic calcification secondary to renal failure in dogs and cats localizes to the pawpads (Scott & Buerger, 1988; Gross, 1997; Jackson & Barber, 1998; Bertazzolo et al., 2003). Iatrogenic calcinosis circumscripta due to injection will be located at common sites of injection, especially the dorsal scapular area and elsewhere on the dorsal or lateral thorax.

Dystrophic and idiopathic calcinosis circumscripta occur most frequently in young, rapidly-growing large breed dogs. In one large study, 93% were large breed dogs; 48% were German Shepherd Dogs (Scott & Buerger, 1988). Brachycephalic dogs such as Boston Terriers and Boxers also are predisposed (Scott & Buerger, 1988). In over half of the dogs in one study, lesions developed at less than 1 year of age (Scott & Buerger, 1988). Metastatic calcification as a sequela to chronic renal failure would be expected to occur predominantly in older dogs, but also has been described in a young dog with congenital renal dysplasia and renal failure (Gross, 1997). Sex predilections have not been noted.

The clinical differential diagnoses of calcinosis circumscripta are other nodular lesions, including those in which mineralization may be a secondary feature. The latter include some cysts, neoplasms, and some nodular inflammatory lesions such as those due to parasites or foreign body penetration. Obvious inflammation usually is not a feature of calcinosis circumscripta. Sectioning of calcinosis circumscripta after surgical removal will show the characteristic pasty or chalky foci of calcinosis. Fibroadnexal hamartoma (see Chapter 23) can closely mimic calcinosis circumscripta due to its elevated dome shape, frequent pressure-point location on the legs, and pasty keratin content.

Biopsy site selection

Solitary lesions should be resected completely using wedge technique, if this is an appropriate surgical procedure for the site. Removal of lesions from pressure points may be problematical because of poor postoperative healing.

Histopathology (Figures 15.10 through 15.12)

The epidermis or mucosal epithelium is normal to slightly acanthotic, or severely ulcerated and hyperplastic. In classical calcinosis circumscripta (as typified by focal lesions in young otherwise healthy dogs), the deep dermis and subcutis contain large irregular foci of basophilic granular mineral which replace normal tissue. Smaller but similar mineral deposits are randomly scattered amongst the large foci. Appearance of the mineral varies from lightly basophilic and slightly granular to deeply basophilic and dense. Mineralized foci are surrounded by variably intense zones of macrophages and giant cells. Lymphocytes, neutrophils, and plasma cells may be observed in small numbers among foci. Fibrosis surrounds and separates lakes of mineral, and may predominate in late lesions. Osseous metaplasia may occur.

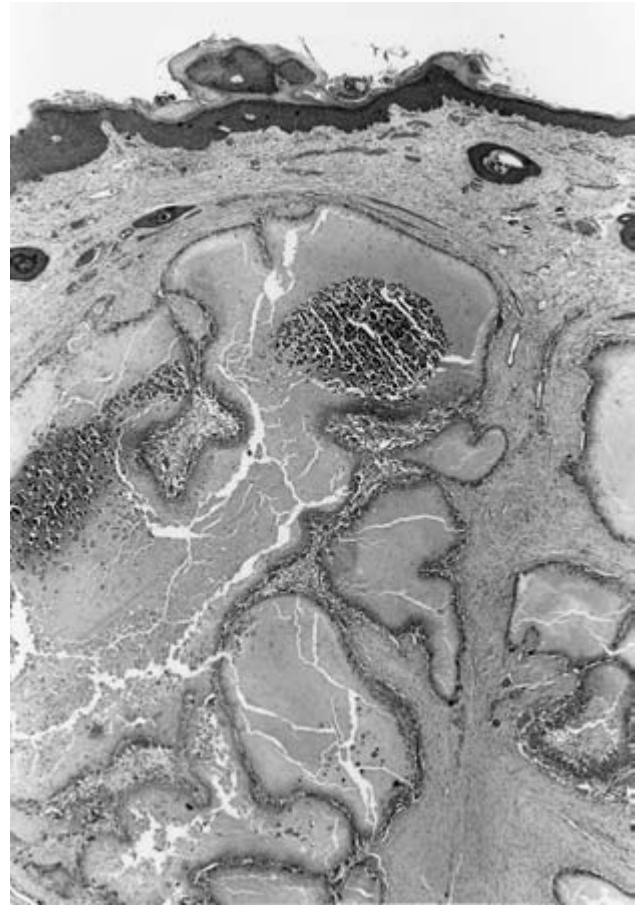


Fig. 15.10 Calcinosis circumscripta in a dog. Note irregular pale islands of mineral with darker foci intermingled.

In calcinosis circumscripta secondary to renal disease, mineralization extends to the superficial dermis of the pawpad and involves ulcer beds. The mineral deposition of calcinosis circumscripta due to renal disease may be more uniformly granular and looser in distribution than the classical form. Calcinosis circumscripta due to injections may be confined to the subcutis.

In apocrine cystic calcinosis, a very rare variant of calcinosis cutis, generation of the mineralized lesions from apocrine sweat glands is evident. Cystic but nonmineral-

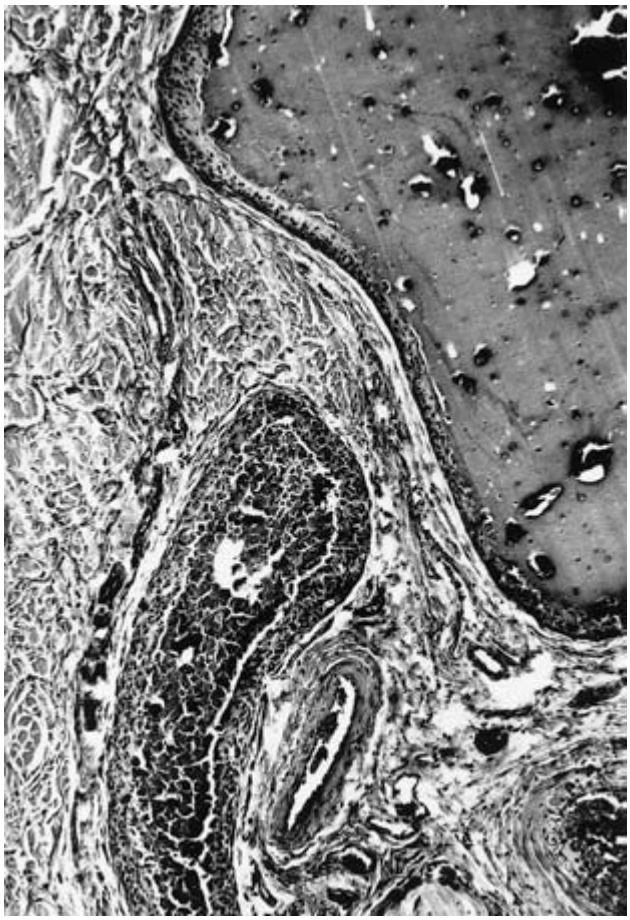


Fig. 15.11 Higher magnification of calcinosis circumscripta in a dog. Large lakes of darkly staining mineral are surrounded by a thin zone of granulomatous inflammation.

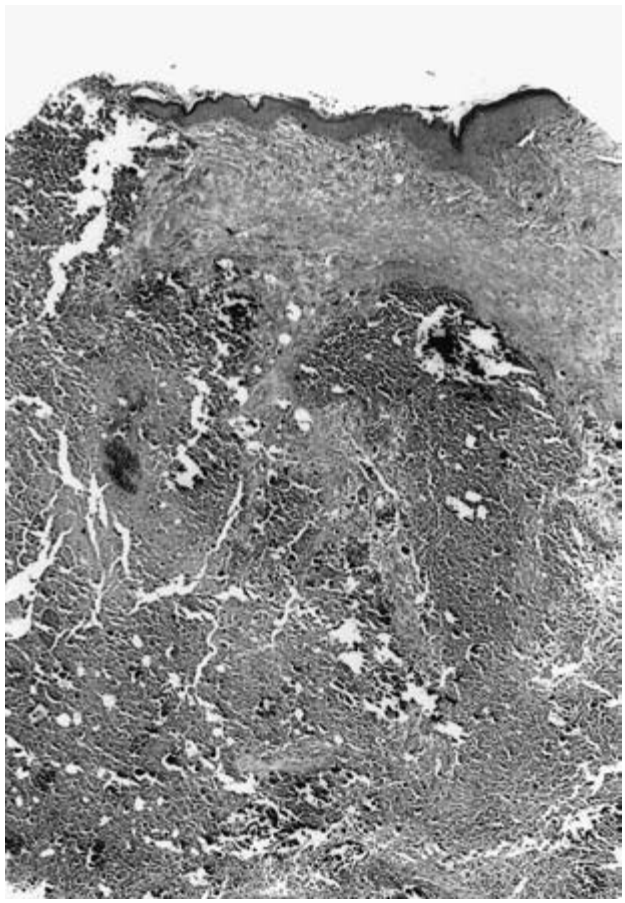


Fig. 15.12 Calcinosis circumscripta of the pawpads in a cat with renal failure. Mineralized foci are less discrete and more granular than in classical calcinosis circumscripta (see Figs 15.10 and 15.11).

ized apocrine glands are found at the edges of the lesions. Similar lesions have been encountered in conjunction with cystic eccrine glands in the scrotum of humans (Ito et al., 2001). Generation of calcinosis cutis from cystic apocrine sweat glands has been over-diagnosed in the past; disordered clusters of cells at the margins of mineralized foci believed to be epithelial in origin were more likely epithelioid macrophages. Although one author (T.L.G.) has seen lesions which appeared compatible with apocrine cystic calcinosis, confirmation of true apocrine origin would require CAM5.2 or CK13 expression in the marginal cells (see Chapter 25).

Typical calcinosis circumscripta is distinctive histopathologically. Milder and less organized dystrophic mineralization occasionally may accompany inflammatory lesions. Abundant mineralization may occur in pilomatricoma (see Chapter 23), but is found in the context of diagnostic features of that neoplasm (see Chapter 23).

CUTANEOUS MUCINOSIS

Clinical features (Figures 15.13 and 15.14)

Cutaneous mucinosis is a syndrome caused by the excessive accumulation or deposition of mucin in the dermis. Mucinosis is relatively common in the Chinese Shar Pei, rare in other breeds of dogs, and very rare in the cat (Dillberger & Altman, 1986; Rosenkrantz et al., 1987; Delverdier et al., 1995). Abnormal deposition of mucin may be focal, multifocal, or diffuse, and may vary from mild to severe. The clinical presentation of cutaneous mucinosis in dogs is highly variable, except in the Chinese Shar Pei. Mucinosis in humans also is a highly heterogenous disorder (Wilk & Schmoeckel, 1994).

Mucin, a jelly-like, clear, viscid glycosaminoglycan, is an acid mucopolysaccharide produced in the skin by dermal fibroblasts. The nonsulfated, carboxylated glycosaminoglycan, hyaluronic acid is the most common



Fig. 15.13 Cutaneous mucinosis in a Chinese Shar Pei. Multiloculated vesicles or bullae on the caudal thighs have the appearance of bubbles.



Fig. 15.14 Close-up of cutaneous mucinosis on the ventral chest of a Chinese Shar Pei. Turgid mucinous bullae span multiple hair follicles.

glycosaminoglycan noted to accumulate in diseases of both dogs and humans (Dillberger & Altman, 1986; Beale et al., 1991; Delverdier et al., 1995; Doliger et al., 1995; Fleischmajer, 2003). Sulfated and carboxylated glycosaminoglycans, such as chondroitin 4-sulfate and 6-sulfate and dermatan sulfate, also can contribute to mucinosis (Delverdier et al., 1995; Doliger et al., 1995).

Mucinosis may occur as a primary condition, presumably due to hereditary or acquired metabolic or endocrine defects, or may be seen as a clinically silent histopathologic abnormality in association with other diseases (secondary mucinosis). Although histologically prominent mucin contributes to the unusual 'normal' folding seen in the Chinese Shar Pei, this breed may also demonstrate clinically relevant mucinosis, presumed to be hereditary in origin. The profile of mast cell subtypes, as indicated by immunohistochemistry for specific enzyme products, is significantly different in Shar Peis with mucinosis, in contrast to normal dogs with no skin disease. This suggests a role for specific mast cell subtypes in the pathogenesis of mucinosis, at least in this breed (Welle et al., 1999).

Clinically, primary mucinosis can be divided into hereditary mucinosis, which may be generalized or multifocal (including tumor-like) in distribution, myxedema, papular mucinosis, and nodular mucinosis. The term 'myxedema' is used specifically to denote primary mucinosis observed with hypothyroidism; myxedema is very rare in the dog (Miller & Buerger, 1990). Papular and plaque-like primary mucinotic lesions have been reported in a puppy (Beale et al., 1991). Focal nodular mucinosis is reported in dogs (Dillberger & Altman, 1986). One dog reported by Delverdier et al. (1995) and one dog seen by one author (T.L.G.) had generalized papular mucinosis with abnormal serum gamma globulin profile (restricted polyclonal spike) similar to that noted in humans with papular mucinosis (Wu et al., 1997; Fleischmajer, 2003).

In secondary mucinosis, excessive dermal deposition of mucin occurs in a variety of different inflammatory skin diseases, including pyoderma, allergic skin disease, eosinophilic skin disease, and lupus erythematosus. Dermal mucin deposition also may occur in neoplastic diseases such as mast cell tumors (Delverdier et al., 1995). Mucinosis occurring in conjunction with these diseases usually is not clinically evident.

Generalized hereditary mucinosis, as seen predominantly in the Chinese Shar Pei, most often is manifested as thickened, nonpitting, puffy skin; vesicles and bullae may be seen. Subtle lesions may be noted in some dogs. Normal skin integrity is not compromised in generalized hereditary mucinosis. Severe multifocal mucinosis is associated with some degree of generalized mucinosis, and also occurs predominantly in the Chinese Shar Pei. Clinically, multifocal distinctive multiloculated vesicles or bullae have the appearance of bubbles or blisters, and may form plaques or ill-defined swellings. If multifocal mucinosis is severe, skin integrity is compromised and increased skin fragility results. Mucin may exude from abraded plaques, vesicles, or bullae to leave a sticky, viscid fluid on the skin surface. Primary hereditary mucinosis may be clinically asymptomatic unless secondary pyoderma or *Malassezia* dermatitis creates inflammation and pruritus. Mucinosis in the Chinese Shar Pei frequently coexists with allergic skin disease. In those circumstances, the clinical severity of visible mucinosis may increase.

Myxedema, a rare manifestation of canine hypothyroidism, presents as a symmetrical thickening of the facial skin resulting in folds, the so-called 'tragic facies'. Mucinous vesiculation without generalized myxedema has

been reported as an unusual manifestation of canine hypothyroidism (Miller & Buerger, 1990).

Rarely, focal or multifocal primary mucinosis, sometimes termed papular mucinosis, may be seen in any breed. In this form of mucinosis, solitary or occasionally multiple, white or yellow papules or clear 'blisters' are noted, and most frequently are localized to the head and neck as incidental findings. Solitary or, rarely, multifocal nodular mucinosis also can occur; lesions may be firm or rubbery (Dillberger & Altman, 1986). Generalized papular lesions may be associated with abnormal serum gamma globulin profiles (Delverdier et al., 1995).

Cutaneous mucinosis is rare in every breed except the Chinese Shar Pei. Age or sex predilections are not noted.

Clinical differential diagnoses for mucinosis may include vesicular and bullous skin diseases. Unlike other vesicular skin diseases, digital pressure is required to extract the fluid from intact mucinous vesicles and bullae. Mucinosis (especially of the Chinese Shar Pei) is clinically distinctive. Cytology of intact vesicles should be performed and will reveal an acellular, clear, viscid, sticky material. Histopathology is confirmatory.

Biopsy site selection

Biopsy specimens should be procured from areas of most obvious thickening or from vesicles or bullae, since mucinosis may be microscopically subtle in mild lesions. The use of larger biopsy punches (6 or 8 mm) or excisional wedge biopsy is recommended if mucinotic vesiculation is severe, since the lesions are exceedingly fragile. Excisional biopsy of severe focal lesions may be palliative in the Chinese Shar Pei and curative for other solitary lesions.

Histopathology (Figures 15.15 and 15.16)

The epidermis is variably acanthotic in nodular or papular mucinosis. Some lesions of papular mucinosis may have irregular epidermal hyperplasia, creating a polypoid surface contour. Epidermal changes also will vary based on the presence of any concurrent disease. For example, moderate acanthosis usually will be present in myxedema due to hypothyroidism. Inflammatory lesions, creating acanthosis, often accompany mucinosis of Chinese Shar Peis.

The dermis has widening of spaces between collagen fibers by a pale gray or gray-blue substance, as seen in hematoxylin and eosin (HE) stained sections. Mucin is blue or blue-green using Alcian blue stain (pH 2.5); concurrent periodic acid–Schiff (PAS) staining enhances interpretation as the background is colored pink (Doliger et al., 1995). Mucin separates collagen in the superficial to deep dermis, and may form lakes in severe lesions. Superficial dermal deposition may predominate. Deposition of mucin also may extend to the subcutis in generalized primary mucinosis of Chinese Shar Peis.

Variable fibrocytic proliferation may accompany mucin deposition, particularly in generalized papular mucinosis or focal nodular mucinosis of dogs (Dillberger & Altman, 1986; Delverdier et al., 1995). Cutaneous focal mucinosis in man is considered to be a fibroblastically-derived lesion (Wilk & Schmoeckel, 1994). Dilated lymphatic vessels, which may have incomplete endothelial linings, often

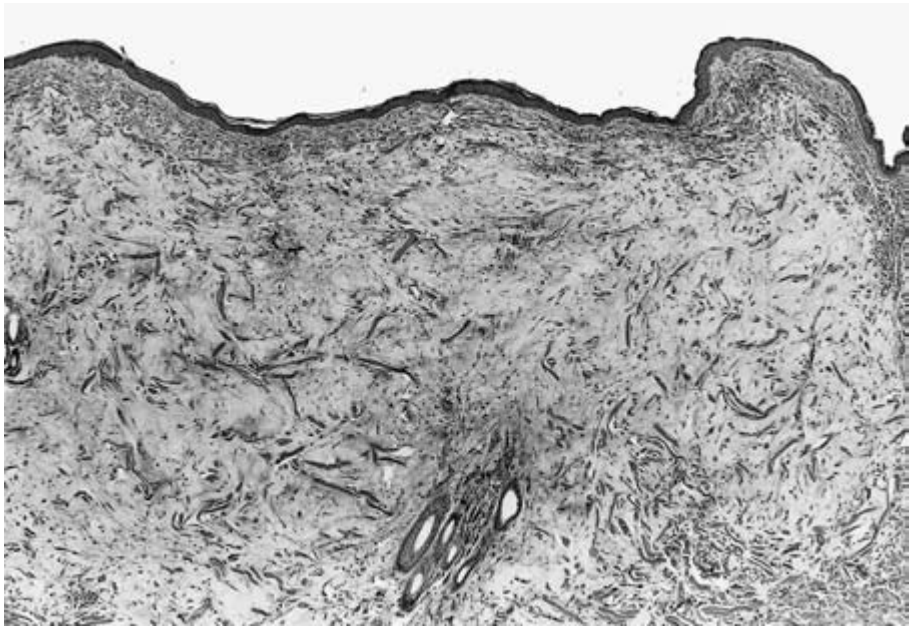


Fig. 15.15 Generalized papular mucinosis in a dog with a restricted polyclonal immunoglobulin spike. Collagen fibers are separated by lightly staining mucin; note mild diffuse fibrocytic proliferation.



Fig. 15.16 Focal cutaneous mucinosis in a dog. Note edema-like widening of spaces between collagen fibers by pale staining mucin.

are observed in Shar Peis with mucinosis, as reported (Mauldin et al., 1998), but are not invariably present. Moderately dilated blood vessels also may be present in papular mucinosis as well as in Shar Pei mucinoses.

Mucinosis may be accompanied by mild mixed dermal inflammation; however, inflammation usually is not a prominent feature of nodular or papular mucinosis or of myxedema. In contrast, specimens obtained from the Chinese Shar Pei often have concurrent inflammatory skin disease such as allergic dermatitis. Mucinosis is rarely the primary reason for skin biopsy in this breed, unless severe mucinosis creates a mass.

Clinically inapparent mucinosis has been reported as a histopathologic feature of discoid lupus erythematosus (Rosenkrantz et al., 1986). However, in the authors' and others' experience, microscopic evidence of mucin is an incidental feature of a variety of inflammatory conditions, including severe pyoderma (Delverdier et al., 1995), as well as eosinophilic diseases such as eosinophilic furunculosis of the face (see Chapter 17). Visualization of mucin in routine HE stained sections may depend on the staining technique used, and may vary from laboratory to laboratory.

Differentiation of mucinosis from urticaria may be necessary when the water content of the dermal mucin is high (resulting in pale staining with HE). Mucin stains are helpful; differentiating clinical features also may allow clear separation of these two entities. Correlation of histologic mucin deposition with clinical findings such as size and distribution of lesions, affected breed, or endocrine status may be required, as mucin deposition may be seen in many unrelated contexts, mostly inflammatory in origin.



Fig. 15.17 Cutaneous amyloidosis affecting a pawpad in a dog demonstrating multiple, pale, papular and plaque-like lesions. (Photograph courtesy Z. Alhaidari.)

CUTANEOUS AMYLOIDOSIS

Clinical features (Figures 15.17 and 15.18)

Cutaneous amyloidosis is characterized by the abnormal accumulation and deposition of pathologic fibrillar protein in the skin. It is very rare in the dog and cat. Amyloidosis refers to a wide variety of syndromes united by the extracellular deposition of any of a number of unrelated proteinaceous products in various organ systems (Touart & Sau, 1998; Breathnach, 1999). Regardless of the original nature of the protein, all forms of amyloid are united by a highly stable, insoluble,



Fig. 15.18 Amyloidosis affecting the tongue of the dog shown in Fig. 15.17. Multiple pale nodules, some of which are ulcerated, are present. (Photograph courtesy Z. Alhaidari.)

beta-pleated sheet configuration. Although amyloid appears hyaline or amorphous microscopically, it is composed of fibrils with distinctive ultrastructural characteristics. The deposition of amyloid in tissue leads to a wide variety of tissue dysfunction depending on the organ or organ system affected.

Much confusion abounds in the current literature with regard to the nomenclature of amyloidosis. Simplistically, amyloidosis may be categorized into systemic amyloidosis and localized (organ-limited) amyloidosis. Systemic amyloidosis (the most common form of amyloidosis seen in humans and domestic animals) is a visceral disease that most commonly affects the kidney, spleen, and liver (DiBartola & Benson, 1989; Touart & Sau, 1998; Breathnach, 1999). The two most common subgroups of systemic amyloidosis seen in humans are 'primary systemic amyloidosis' seen in conjunction with occult plasma cell dyscrasias and 'myeloma-associated systemic amyloidosis'. Although cutaneous involvement can be seen with systemic amyloidosis, involvement of visceral organs holds much greater import for the patient.

Localized, organ-limited amyloidosis can affect a wide variety of organs in humans, including the skin (Breathnach, 1999). Primary nodular cutaneous amyloidosis is the most common subgroup of localized, organ-limited amyloidosis, and also is the most common subgroup of cutaneous amyloidosis diagnosed in humans, dogs, and cats. Primary nodular cutaneous amyloidosis in dogs and cats occurs most often within cutaneous extramedullary plasmacytomas (see Chapter 37). The same is true in humans (Touart & Sau, 1998; Breathnach, 1999). Primary nodular amyloidosis probably results from an abnormal production of amyloidogenic immunoglobulin light chains by locally proliferating plasma cells. Most cutaneous amyloidosis observed to date in dogs and cats probably is derived from immunoglobulin light chains (AL).

Classification may not always be easy. A cat was reported with cutaneous nodular amyloidosis that developed within an extramedullary plasmacytoma; there were internal metastases with amyloid deposition and a monoclonal gammopathy (Carothers et al., 1989). Diffuse cutaneous immunoglobulin-derived amyloidosis has been diagnosed in a Cocker Spaniel (Schwartzman, 1984), a second Cocker Spaniel seen by one author (T.L.G.), and a Brittany (Alhaidari et al., 1991). Multiple myeloma was not found in any of the three dogs; the reported Cocker Spaniel had a monoclonal gammopathy (Schwartzman, 1984).

Clinically, primary nodular cutaneous amyloidosis presents most typically as solitary, or, rarely, grouped firm nodules of the dermis and/or subcutis. The nodules are asymptomatic, unless larger masses outgrow their blood supply resulting in necrosis and ulceration. Sites mirror those that favor plasmacytomas (see Chapter 37).

The Cocker Spaniel with diffuse cutaneous immunoglobulin-derived amyloidosis seen by one author (T.L.G.) had diffuse wrinkling and bullous lesions involving the ventrum and axillae. Mucocutaneous and cutaneous amyloidosis reported in a Brittany was characterized by multiple pale, papular and plaque-like lesions affecting the tongue, oral mucosa, pawpads, interdigital areas, and pressure points (Alhaidari et al., 1991). Some of the lesions ulcerated (Alhaidari et al., 1991).

The Cocker Spaniel reported with diffuse cutaneous immunoglobulin-derived amyloidosis and monoclonal gammopathy exhibited purpura upon flicking the skin (as in 'pinch purpura' in humans) and after traumatic hair epilation (Schwartzman, 1984). Purpura occurs through involvement of cutaneous blood vessels, which leads to vascular fragility. Although papules and plaques may be observed, amyloid often is not visible clinically, since deposits may be distributed diffusely in the dermis and dermal blood vessels. Unexplained purpura is the major cutaneous manifestation of primary systemic amyloidosis seen in humans (Breathnach, 1999). Systemic signs were not seen in any of the three dogs, although the Brittany was euthanized due to difficulties in managing the pedal ulcers (Alhaidari et al., 1991).

Age or sex predilections have not been reported for primary cutaneous amyloidosis. However, due to the association with multiple myeloma and extramedullary plasmacytoma, immunoglobulin-associated amyloidosis should be seen more frequently in older animals (see Chapter 37). Although most surveys do not report a breed predilection for cutaneous extramedullary plasmacytomas, the Cocker Spaniel may be more commonly affected based on some reports (see Chapter 37). Inter-

estingly, two of three dogs with diffuse cutaneous immunoglobulin-derived amyloidosis also were Cocker Spaniels.

Clinical differential diagnoses for primary nodular cutaneous amyloidosis should include solitary neoplasms, and infectious and noninfectious granulomas and pyogranulomas (see Chapters 12 and 13). Diffuse cutaneous amyloidosis should be considered in the differential diagnosis of unexplained cutaneous hemorrhage. Skin biopsy is confirmatory.

Biopsy site selection

If possible, solitary nodular lesions should be removed in their entirety by excisional biopsy, in order to provide a surgical cure. Partially removed masses do not heal well, due to the lack of integrity of amyloid-laden tissue which physically interferes with healing. Diffuse cutaneous amyloidosis may be confirmed by either punch or wedge skin biopsy. Site selection is not critical, but areas of intense hemorrhage probably should be avoided.

Histopathology (Figures 15.19 through 15.21)

Amyloid is amorphous and lightly eosinophilic to amphophilic on hematoxylin and eosin examination, and is birefringent and dichroic (changing from apple green to orange and back to apple green as the lens is rotated) using Congo red stain and a polarizing lens. Application of thioflavin T stain will result in fluorescence of amyloid using fluorescent microscopy. Ultrastructurally, amyloid has a highly organized fibrillar structure composed of proteinaceous deposits in cross-beta, antiparallel, beta-pleated sheets.

Primary nodular amyloidosis of dogs and cats occurs within amyloid-producing extramedullary plasmacytomas (see Chapter 37). Plasmacytomas of the skin of dogs are common, but amyloid is found only occasionally; thus, apparently, only a subset of plasma cell tumors possess the ability to elaborate immunoglobulin-associated amyloid (AL). Amyloid may overwhelm the lesion and an association with plasma cell proliferation or neoplasia may be impossible to prove in some cases.

Primary nodular amyloidosis is characterized by accumulations of amorphous-appearing eosinophilic deposits that may extend to the subcutis. Well-differentiated to occasionally atypical plasma cells accumulate in clusters or sheets amongst foci of amyloid, and are sometimes sparse. Fewer lymphocytes are intermingled. Macrophages and giant cells are seen in association with nodular amyloid, and frequently surround amyloid deposits. There may be cartilaginous metaplasia within amyloid deposits. Congo red staining is retained after oxidation with potassium permanganate (Rowland et al., 1991; Platz et al., 1997), which is indicative of AL. Immunohistochemistry demonstrated amyloid derived from the lambda light chain of immunoglobulin (A lambda) in extramedullary plasmacytomas containing amyloid in dogs and cats (Rowland & Linke, 1994; Platz et al., 1997). This dominant lambda light chain expression is likely due to the preponderance of lambda light chain immunoglobulin in plasma cells of these species (Platz et al., 1997).

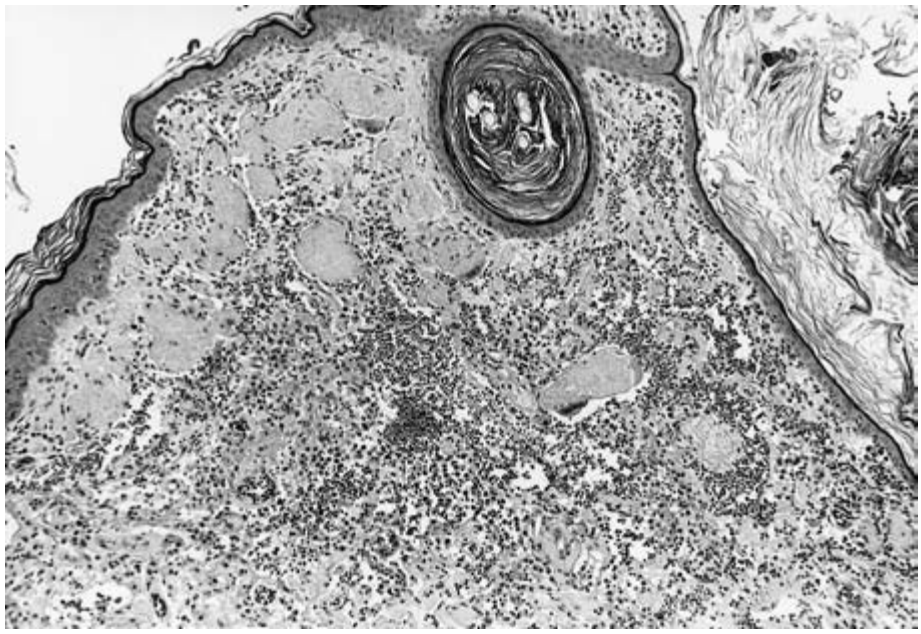


Fig. 15.19 Diffuse cutaneous amyloidosis in a dog. Pale irregular deposits of amyloid are distributed throughout the dermis; dark areas are hemorrhage.

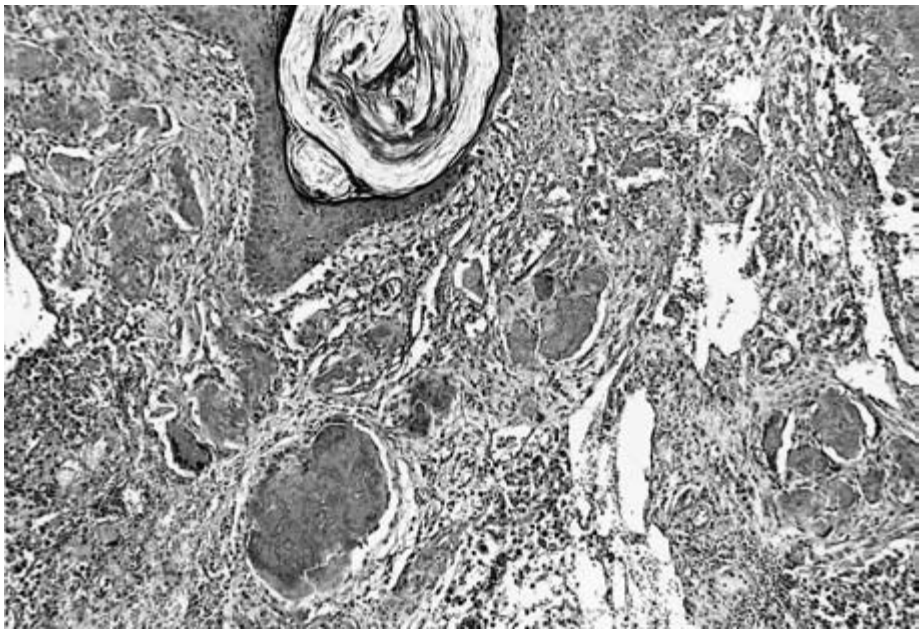


Fig. 15.20 Nodular cutaneous amyloidosis in a dog. Congo red-positive amyloid is homogenous and darkly staining. Most of the cellular infiltrate is composed of plasma cells.

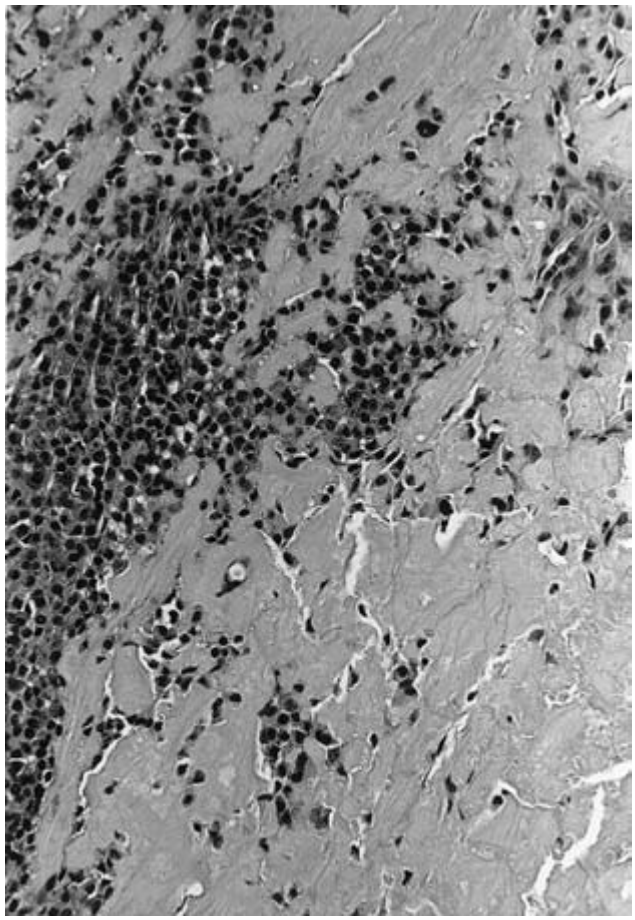


Fig. 15.21 Higher magnification of nodular cutaneous amyloidosis in a dog. Pale amorphous amyloid is accumulating amongst dark, monomorphous plasma cells.

In diffuse cutaneous immunoglobulin-derived amyloidosis, amyloid is deposited in a laminar fashion in the superficial dermis, as well as around blood vessels. Hemorrhage is observed. The reported Cocker Spaniel had no accompanying plasma cell infiltrates, the Brittany had a sprinkling of lymphocytes and plasma cells, and the observed Cocker Spaniel had focal accumulations of macrophages and plasma cells in extravascular foci of amyloid only. Multiple myeloma was not found in any of the three dogs. A monoclonal gammopathy in the reported Cocker Spaniel, and resistance of amyloid to potassium permanganate oxidation in the observed Cocker Spaniel and reported Brittany, confirmed AL in these three dogs (Schwartzman, 1984; Alhaidari et al., 1991).

Amyloid has a distinctive histopathologic appearance, but occasionally may be confused with serum or fibrin in inflammatory lesions. Appropriate staining and polarization will distinguish amyloid. Localized, nodular amyloidosis should be considered indicative of extramedullary plasmacytoma.

EHLERS–DANLOS SYNDROME

(Synonyms: cutaneous asthenia, dermatosparaxis)

Clinical features (Figures 15.22 through 15.24)

Ehlers–Danlos syndrome (EDS) is a genetically and biochemically diverse disorder that encompasses multiple heritable, congenital defects of dermal connective tissue. These congenital defects lead to variable degrees of skin



Fig. 15.22 Ehlers–Danlos syndrome in a Boxer. Marked hyperextensibility of the skin is demonstrated. (Photograph courtesy A.A. Stannard.)



Fig. 15.23 Ehlers–Danlos syndrome in a Dachshund showing severe hyperextensibility of the facial skin. (Photograph courtesy S.I. Reinke; case material University of California, Davis.)



Fig. 15.24 Ehlers–Danlos syndrome in a cat. The skin of the thorax is grossly hyperextensible. (Photograph courtesy G.A. Kunkle and J. Kunkle.)

hyperextensibility and fragility. Ehlers–Danlos syndrome is rare in both the dog and cat. In humans, at least eleven distinct subgroups of EDS have been documented (Wenstrup & Zhao, 2003).

The molecular basis of EDS in humans involves mutations that code either for fibrillar collagen genes or for the enzymes that catalyze intracellular or extracellular post-translational modifications (Wenstrup & Zhao, 2003). Defects include diminished collagen synthesis, intracellular collagen accumulation, improper collagen packing, procollagen structural mutations, and abnormal fibronectin formation. Molecular documentation is available for only some of the defects documented in the dog and cat (Scott et al., 2001). Considerable clinical variability in EDS of dogs and cats suggests that multiple defects exist in these species.

Autosomal dominant, autosomal recessive, and X-linked recessive modes of inheritance have been documented in humans (Wenstrup & Zhao, 2003). Most well-documented cases in the dog and cat exhibit autosomal dominance which probably is lethal for homozygous animals (Scott et al., 2001). Recessively inherited skin hyperextensibility and fragility have been best documented in cats in several reports, as compiled by Scott et al. (2001).

There is a continuum of clinical severity from mild to severe. Hyperextensibility and decreased tensile strength of the skin are the unifying clinical features, and may be present individually or in concert. Hyperextensibility is characterized clinically by the ability of the skin to stretch far beyond normal limits, and seemingly loose attachment of the skin to subjacent tissue. The skin is of normal thickness. Decreased tensile strength leads to lacerations resulting from minimal trauma. Large, gaping wounds have been likened visually to 'fish mouths'. Surprisingly little bleeding occurs from these clinically striking lesions. Rapid healing ensues, although the scars that form are thin, abnormally pigmented, and commonly lack the tensile strength normally associated with scar tissue; thus new lesions may form at the site of previous lesions. The term 'cigarette paper scars' has been used to describe these distinctive atrophic scars. Subcutaneous hematomas are a less common sequela to hyperextensibility. Lesions are most obvious on the trunk and head. Joint hyperextensibility, a common coexistent feature of some subgroups of EDS in humans, has been noted anecdotally rarely in the dog. Stannard observed a litter of Dachshunds with severe concomitant skin and joint hyperextensibility (Stannard, A.A., personal communication, 1990). Diaphragmatic and perineal hernias have been reported in the cat (Benitah et al., 2004).

Ehlers–Danlos syndrome has been seen in many breeds including the Boxer, Dachshund, English Springer Spaniel, English and Irish Setters, Keeshond, Greyhound, Beagle,

Saint Bernard, German Shepherd Dog, Manchester Terrier, Welsh Corgi, Red Kelpi, Soft-coated Wheaten Terrier, Toy Poodle, Garafiano Shepherd, Fila Brasiliero, and mixed-breed dogs, as compiled and reported by Scott et al. (2001). Affected cats reported include domestic shorthaired cats, unspecified longhaired cats, and Himalayans (Scott et al., 2001). As a congenital disease, signs of EDS should be noted shortly after birth. Sex predilections have not been noted in dogs or cats.

Clinical differential diagnoses for EDS are few; the disease is highly distinctive. Affected animals present with a lifelong history of skin hyperextensibility and fragility, gaping wounds resulting from minor trauma, and multiple scars. In contrast, feline skin fragility syndrome occurs as an adult onset disease and affected areas exhibit markedly thin skin. Topical corticosteroid reactions in the dog may feature skin fragility, but the lesions are localized and other differentiating clinical features are present (see p. 392). Skin biopsy may or may not be definitively diagnostic for EDS; ultrastructural and biochemical analysis may be required for definitive documentation.

Biopsy site selection

Skin specimens from markedly hyperextensible sites or adjacent to tears may be procured by either punch or wedge technique. Care should be taken in choosing sites such that self-trauma or normal activity does not extend the defect created by the biopsy. For this reason areas near pressure points should be avoided.

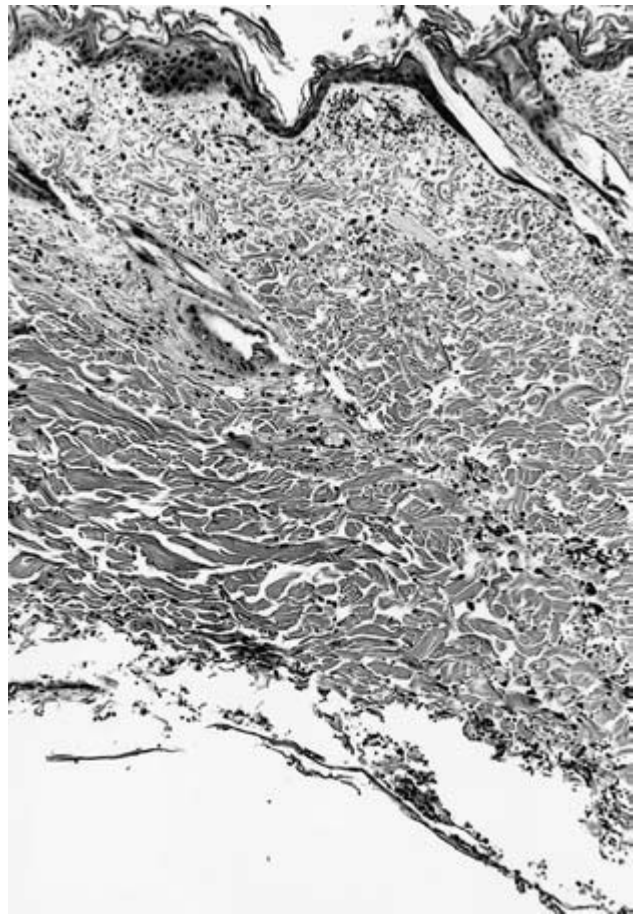


Fig. 15.25 Ehlers–Danlos syndrome in a cat. Note torn lower edge of dermis accompanied by mild hemorrhage.

Histopathology (Figures 15.25 and 15.26)

The epidermis is unremarkable. In the authors' experience, skin biopsies from young cats and dogs with clinical histories of fragile and hyperextensible skin usually demonstrate distinct histologic abnormalities of dermal collagen fibers. These alterations are also commonly reported in the literature. However, normal histology using hematoxylin and eosin (HE) staining has been described in affected cats (Fernandez et al., 1998) and dogs (Minor et al., 1983). In one reported cat, histologically obvious collagen fiber abnormalities were present in some sections, while collagen in other skin sites appeared normal (Sequeira et al., 1999). The variability of histopathologic lesions may be due to the existence of multiple syndromes, characterized by unique biochemical defects that have variable distribution and expression in the skin.

In some reports, the overall thickness of the dermis is reduced in comparison to control animals (Hegreberg et al., 1970; Holbrook et al., 1980; Minor et al., 1983); normal dermal thickness has also been reported (Sequeira et al., 1999). Abnormal collagen fibers are characterized by shortening, disarray, curling, uneven size and width, and widening of interfibrillar spaces. Interstitial mucin has been reported (Hegreberg et al., 1970). Increased eosinophilia of some fibers may be observed. In some cases, the abnormal fibers appear outlined by increased numbers of fibroblasts. Others may have diffuse thin and wispy fibers. Reported electron microscopic features are somewhat variable, but characteristically include collagen fibril disorganization (rather than the parallel arrangement of normal collagen fibrils), as well as abnormal fibril contour (Holbrook et al., 1980; Minor et al., 1983; Sequeira et al., 1999).

In dogs and cats with EDS, moderate numbers of putatively abnormal collagen fibers are demonstrated by staining with Masson's trichrome (Minor et al., 1983; Fernandez et al., 1998). This abnormality occurs even when there is a normal histologic appearance of collagen with HE staining. Affected fibers demonstrate red cores, in contrast to the diffuse blue staining of normal collagen (Fernandez et al., 1998; Sequeira et al., 1999). Ten control

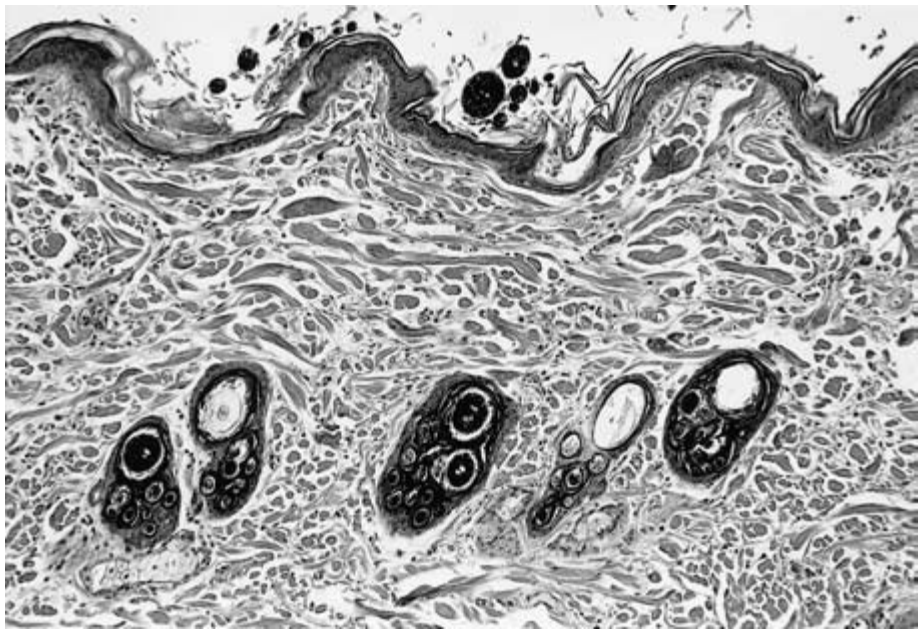


Fig. 15.26 Ehlers–Danlos syndrome in a dog. Dermal collagen fibers are markedly variable in size and shape. (Case material courtesy E.G. Clark.)

cats in one study did not display similar staining abnormalities of dermal collagen (Fernandez et al., 1998). This is not a qualitatively specific finding as similarly severe staining abnormalities have been reported in a cat with perforating dermatitis, and mild staining abnormalities were reported in feline skin fragility as well (see below). Scattered abnormally stained fibers also may be seen in other inflammatory conditions, including within eosinophilic granulomas and their adjacent normal dermis (see Chapter 14). Thus, results of Masson's staining in the diagnosis of EDS should be interpreted with caution.

Biopsy of tears or lacerations may reveal splitting within the dermis. In these lesions, the dermis ends abruptly and granulation tissue is evident at the deep margin, suggesting a recent separation in this location. Fibrosis may percolate up to surround collagen fibers above the tear. This finding may be used as a marker for skin fragility, and should prompt investigation for collagen fiber abnormalities.

Due to the occasional normal appearance of biopsy specimens, histopathologic diagnosis may be problematic in some cases. The striking fiber abnormalities usually observed will allow definitive diagnosis. Shearing trauma, such as that caused by degloving injury, may mimic the tears of EDS. Absence of collagen fiber abnormalities should suggest trauma over EDS, but correlation with clinical findings may be required. Feline skin fragility syndrome, also characterized by intradermal splitting, is distinct histopathologically in that severe dermal atrophy with marked thinning of collagen fibers is present.



Fig. 15.27 Feline acquired skin fragility syndrome. Skin friability has lead to irregular tears on the chest. (Photograph courtesy G.A. Kunkle.)

FELINE ACQUIRED SKIN FRAGILITY SYNDROME

Clinical features (Figures 15.27 and 15.28)

Feline acquired skin fragility syndrome is a very rare syndrome of multifactorial etiology. It is characterized by markedly fragile and thin skin, but without evidence of hyperextensibility. Minimal trauma leads to extensive tearing and shedding of the affected skin.

The pathogenesis is not known, but the syndrome most commonly is associated with iatrogenic and naturally-occurring hyperglucocorticoidism, diabetes mellitis, or



Fig. 15.28 Feline acquired skin fragility syndrome. Marked skin friability has lead to shedding of sheets of skin. (Photograph courtesy M.D. Song; case material University of California, Davis.)

the excessive usage of progestational compounds. Even less commonly, it has been seen in conjunction with severe liver disease (hepatic lipidosis, cholangiohepatitis, cholangiocarcinoma), phenytoin administration, feline dysautonomia, and nephrosis (Barthold et al., 1980; Regnier & Pieraggi, 1989; Diquelou et al., 1991; Canfield et al., 1992; Fernandez et al., 1998; Zur, 1998). Feline acquired skin fragility syndrome also has been idiopathic in a small number of cats seen by the authors and others. These cats have had normal hemograms, serum biochemical profiles, and adrenal function tests, and have not had a history of administration of corticosteroids, progestational compounds, or phenytoin. Iatrogenic and naturally-occurring hyperglucocorticoidism and diabetes mellitis should be ruled out before acquired skin fragility is considered to be idiopathic.

The skin of affected cats becomes markedly thin and is readily severely damaged by minor trauma. Skin friability leads to irregular tears and the shedding of large sheets of skin resembling wet tissue paper. The skin may be so attenuated that it acquires a translucent quality, allowing visualization of subjacent structures. Partial alopecia occurs in the most atrophic regions. For unknown reasons, lesions are seen most commonly on the dorsum of the trunk. Attempted repair often leads to more extensive damage, since the surrounding skin shares the same defect.

The majority of affected cats are middle-aged or older. Breed or sex predilections have not been noted.

Clinical differential diagnosis is not problematic due to the striking nature of the lesions. In comparison to Ehlers–Danlos syndrome, cats with acquired skin fragility syndrome have abnormally thin skin and develop the syndrome as older adults.

Biopsy site selection

If possible, intact skin rather than skin fragments from lacerations or tears should be selected. Due to the extreme thinness of the skin, skin biopsy generally is performed with great difficulty. The tissue often folds and twists similar to wet tissue paper, resulting in inferior specimens for histopathology. Care to include underlying adipose tissue and to maintain its attachment to the overlying dermis by gentle handling should be attempted. Placement of the specimen on a portion of a wooden applicator or tongue depressor should allow the shape to be retained for optimum tissue processing by the laboratory.

Histopathology (Figures 15.29 and 15.30)

The epidermis is thin and may consist of only a single layer of keratinocytes. The dermis also is severely atrophic. The biopsy specimen may be curled or irregular due to a lack of substantive dermis and twisting of the delicate specimen during fixation and processing. The subcutis usually is not represented in biopsy specimens, but when obtained, the comparative thickness of the adipose tissue layer above the panniculus muscle accentuates the remarkable dermal atrophy. Adipocytes of the deep dermis, if present, are also comparatively prominent in relation to the marked collagen fiber attenuation. This appearance may be accentuated by obesity (Canfield et al., 1992). The base of the specimen may have strands of collagen fibers which appear torn or stretched due to separation of the dermis from the underlying subcutis during procurement of the specimen.

Dermal collagen fibers are extremely attenuated and pale staining, often nearly to the point of extinction, and generally have a wispy appearance. Secondary inflammation and scarring may be present if older lesions have been selected. Elastin staining is normal (Canfield et al., 1992). Hair follicles may be uniformly small, short, and thin, as in feline hyperglucocorticoidism (see Chapter 19), but dermal atrophy usually is more striking than adnexal atrophy. In some cases, hair follicles are normal and contrast startlingly with dermal attenuation. Relatively enormous arrector pili muscles may be seen.

Mild numbers of putatively abnormal collagen fibers are demonstrated by staining with Masson's trichrome; three of four cats in one study showed this staining alteration (Fernandez et al., 1998). Affected fibers demonstrate red cores, in contrast to the diffuse blue staining of normal collagen (Fernandez et al., 1998). Ten control cats in one study did not display similar staining abnormalities (Fernandez et al., 1998). This is not a qualitatively specific finding, as similar but more severe staining abnormalities have been reported in cats with Ehlers–Danlos



Fig. 15.29 Feline acquired skin fragility syndrome. The epidermis and dermis are severely atrophic; residual arrector pili muscles are prominent.

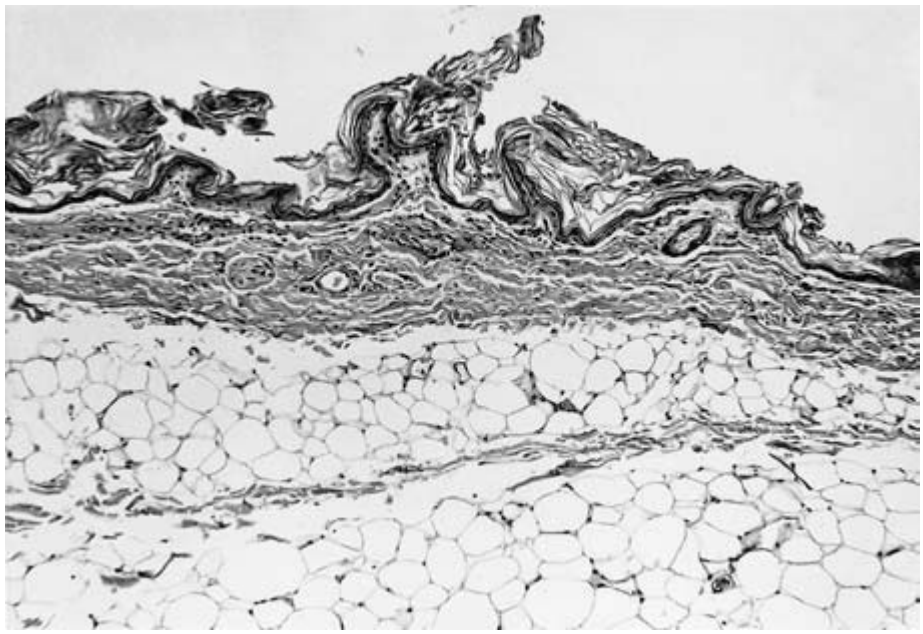


Fig. 15.30 Feline acquired skin fragility syndrome. The epidermis and dermis are severely atrophic. Note contrast of normal panniculus.

syndrome (see p. 386) and in one cat with perforating dermatitis (see p. 394). Scattered abnormally stained fibers also may be seen in other inflammatory conditions, including within eosinophilic granulomas and their adjacent normal dermis (see Chapter 14).

Electron microscopic studies showed collagen microfibrils of variable diameter and disorganized orientation in a cat with skin fragility and hepatic lipidosis (Diquelou et al., 1991), loosely packed and twisted fibrils forming spindly and haphazard fibers in a cat with cholangiocarcinoma (Regnier & Pieraggi, 1989), and sparse fibrils of normal appearance in a cat receiving phenytoin (Barthold et al., 1980). Electron microscopic studies have not been performed in affected cats with hyperglucocorticoidism. Some of these ultrastructural findings resemble those of cats with Ehlers–Danlos syndrome (see p. 386).

The histopathology of feline skin fragility syndrome is distinctive. Ehlers–Danlos syndrome, although manifested histopathologically by tears or splits in the dermis, generally has a dermis of normal thickness and lacks severe and diffuse attenuation of dermal collagen.



Fig. 15.31 Topical corticosteroid reaction on the umbilicus of a female Corgi-crossbreed. The skin is noticeably thinned and the linea alba is visible at the center. Striking comedones are present.

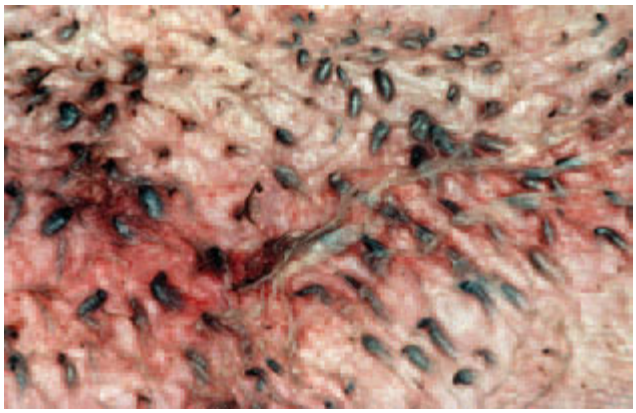


Fig. 15.32 Closer view of the dog in Fig. 15.31. Affected skin appears almost transparent between the comedones. Diminished elasticity is evidenced by prominent folds in the attenuated skin. Hemorrhage indicates fragility.

TOPICAL CORTICOSTEROID REACTION

Clinical features (Figures 15.31 through 15.33)

Topical corticosteroid reaction is a relatively common, but markedly under-diagnosed syndrome that is associated with the inappropriate, localized use of potent topical corticosteroid-containing creams, ointments, gels, and sprays. The syndrome is seen almost exclusively on the relatively sparsely haired ventral abdomen of dogs.

A wide variety of corticosteroid-containing products can induce these changes. However, certain corticosteroids such as triamcinolone and betamethasone may be more likely to produce this adverse reaction. The authors also speculate that there may be individual and breed-related variation in susceptibility for the development of this syndrome.

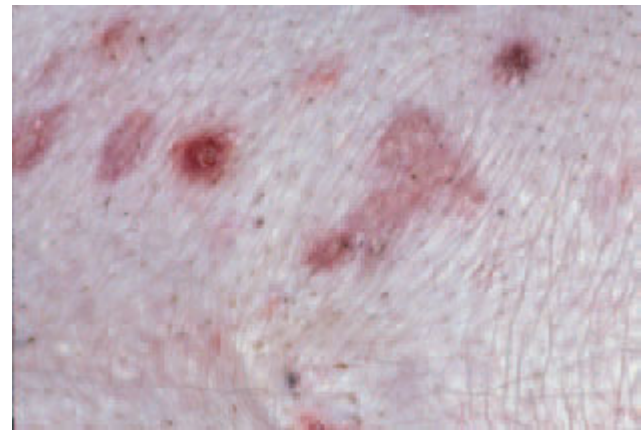


Fig. 15.33 Topical corticosteroid reaction on the groin of a female Golden Retriever with superficial folliculitis. The owner was treating the pyoderma with a potent topical corticosteroid-containing cream. Note thin, shiny, translucent quality of the skin and multiple comedones. Superficial folliculitis is still present.

Clinical features include mottled erythema, hyperpigmentation, and hypopigmentation overlying variable irregular atrophy and scarring. Focal areas may appear transparent, allowing enhanced viewing of subjacent structures. Striae (linear, depressed, atrophic, discolored, scar-like lesions due to weakened elastic tissues) and comedones may be present. In areas of marked cutaneous atrophy, comedones may appear as bluish-black, tiny, palpable, sausage-shaped nodules in the dermis. Mottled areas of hemorrhage and discrete hemorrhagic blisters are seen in more severe cases. Increased fragility may lead to erosions, focal ulceration, and scarring, prompting the vicious cycle of renewed, concerted topical overmedication (Gross et al., 1997).

The comparatively glabrous skin of the ventral abdomen is most commonly affected. This may be due to easy visualization of the lesions that initiate therapy, thinner epidermis in this body region perhaps leading to enhanced absorption, and the facile application of topical products to this area. Owners probably are less likely to apply topical corticosteroids repetitively to more well-haired areas. One author (P.J.I.) has noted that the most common initiators of the overuse of topical corticosteroid-containing products appear to be flea allergy dermatitis and superficial pyoderma.

Signalment predilections are not known. However, the German Shepherd Dog may be at increased risk. Affected dogs usually present with concomitant allergic or other inflammatory skin disease. Consequently, breed predilections may follow those predisposed to allergic and other inflammatory skin diseases that affect the ventrum.

Topical corticosteroid reactions are visually distinctive. However, since they occur in conjunction with underly-

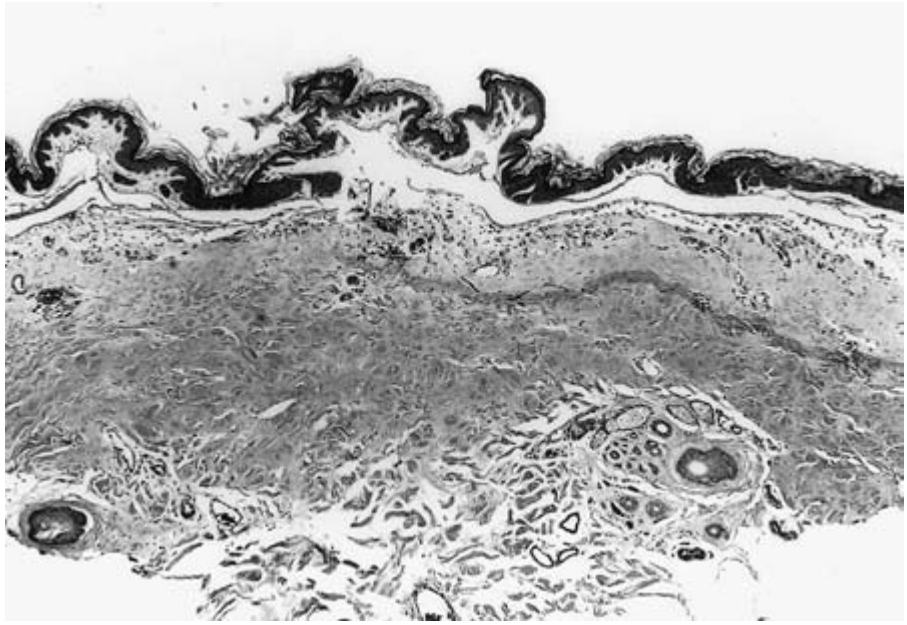


Fig. 15.34 Topical corticosteroid reaction in a dog with attenuation and homogenization of the dermis. Note intradermal cleft.

ing inflammatory skin disease, they may be confused with areas of exacerbating flea allergy dermatitis and superficial pyoderma. Comedones may resemble those of actinic origin or as seen in demodicosis. Clinicians should determine if prescribed or nonprescribed topical corticosteroid-containing products have been applied to the lesions. Skin biopsy may be needed for definitive differentiation.

Biopsy site selection

The clinician should harvest multiple specimens, attempting to sample comedones, erosions, and areas of atrophy. Atrophic regions must be sampled carefully as the lesions may be very fragile.

Histopathology (Figures 15.34 and 15.35)

The epidermis is mildly to moderately acanthotic and has a scalloped appearance to the lower border, in surprising contrast to the marked epidermal atrophy of classical canine hyperglucocorticoidism (see Chapter 19). Subepidermal dermal collagen is highly attenuated, resulting in a pale, often transparent or edema-like appearance. Beneath this superficial zone, the collagen is slightly pale, homogeneous, or 'smudged', often in a laminar pattern of distribution. Splitting through the attenuated superficial dermis is common and in some cases may be an artifact of handling and processing the extremely fragile tissue. Fibrin and/or hemorrhage may be present within the splits. There is proliferation of small superficial dermal blood vessels and phlebectasia (dilatation of venules);

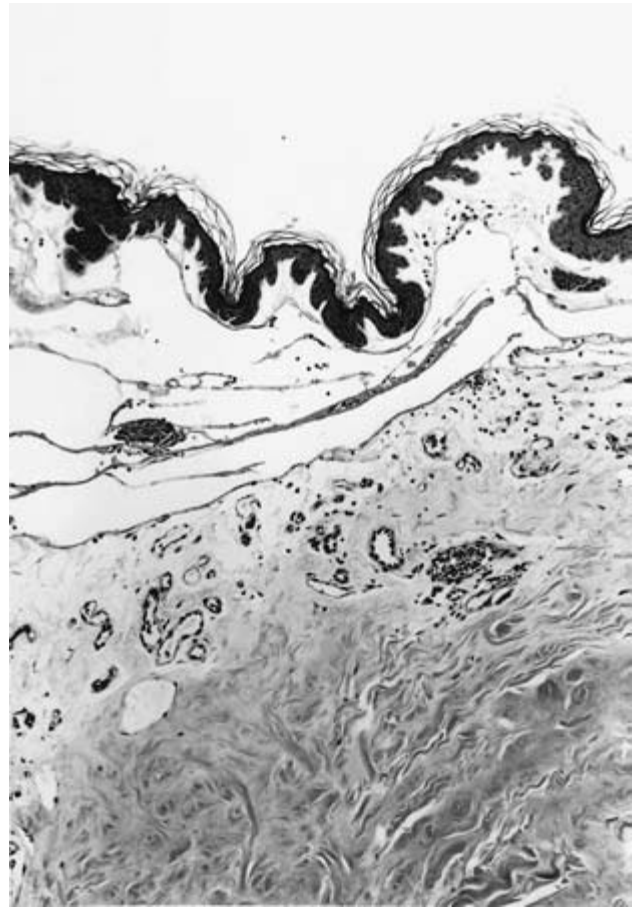


Fig. 15.35 Higher magnification of left edge of Fig. 15.34, featuring vascular proliferation and phlebectasia. Note delicate scalloping of epidermis, marked attenuation and homogenization of dermal collagen, and intradermal cleft.

neovascularization may be marked in areas of collagen depletion, and may be accompanied by fresh and resolving hemorrhage.

Ulcers with exudation and subjacent granulation tissue occur with more severe tissue disruption. Areas of previous splitting may be replaced by fibrosis. There is variable inflammation, including superficial pustules and pustular folliculitis (bacterial pyoderma). Chronic mixed inflammation may encircle blood vessels and adnexae, and is composed of neutrophils, histiocytes, lymphocytes, and plasma cells.

Hair follicles may have telogen type atrophy and variable comedones, as seen in hyperglucocorticoidism (see Chapter 19); this is not a consistent finding, however. Individual comedones may be larger than those occurring in hyperglucocorticoidism and may be grouped. Infundibular epithelium lining the comedones ranges from atrophic, as seen in hyperglucocorticoidism, to moderately hyperplastic. Follicular atrophy (with or without comedones) may occur in the absence of dermal attenuation and splitting in some lesions, thus resembling hyperglucocorticoidism but lacking the characteristic epidermal atrophy of that disease.

Histologic findings are distinctive, particularly the pronounced dermal collagen attenuation with splitting. In lesions lacking these features, the scalloped epidermal border in the setting of follicular atrophy and/or comedones is highly suggestive. The laminar homogenization of the dermis is similar to solar fibrosis (see p. 399); however, superficial collagen attenuation, splitting, and vascular proliferation are not features of solar disease. Because of the ventral abdominal location for both conditions, combined lesions may be observed. Topical corticosteroid-induced comedones resemble actinic comedones; the latter generally do not occur in the setting of epidermal scalloping and dermal attenuation. Actinic comedones may be surrounded by a pale zone of fibrosis (see Chapter 8), which is lacking in the comedones of topical corticosteroid reactions.

PERFORATING DERMATITIS

(Synonym: perforating collagenosis)

Clinical features (Figures 15.36 and 15.37)

Perforating dermatitis is a rare, distinctive reaction pattern reported to date only in two cats (Scott & Miller, 1991; Haugh & Swendrowski, 1995). The syndrome bears some clinical and histopathologic similarities to some of the perforating dermatoses in humans (Scott & Miller, 1991; Wolff-Schreiner, 2003). Firm, exophytic, horn-like lesions represent the extrusion of degenerated collagen fibers and accompanying intense inflammation.



Fig. 15.36 Perforating dermatitis in a cat. Parallel lesions are visible along the left caudal thigh. (Photograph courtesy J. Fontaine.)



Fig. 15.37 Closer view of the cat in Fig. 15.36. Two well-demarcated linear plaques exhibit multiple tenaciously adherent brownish horn-like crusts; note red erosions and ulcers where crusts have been pulled away. (Photograph courtesy J. Fontaine.)

The etiology of perforating dermatoses in humans and in cats is not understood (Scott et al., 2001; Wolff-Schreiner, 2003). Genetic susceptibility appears to be integral to some of the perforating dermatoses in humans (Wolff-Schreiner, 2003). It is tempting to speculate that feline perforating dermatitis is an unusual and severe tissue reaction occurring in genetically susceptible individuals. In the first reported case, no evidence of pruritus, pain, or chronic skin disease was noted (Scott & Miller, 1991). In the second reported case, the lesions seemed to be initiated and exacerbated by inflammation associated with self-trauma secondary to pruritic skin disease, and as a reaction to suture material (Haugh & Swendrowski, 1995). The majority of the cases of perforating dermatitis known to the authors seem to resemble the second

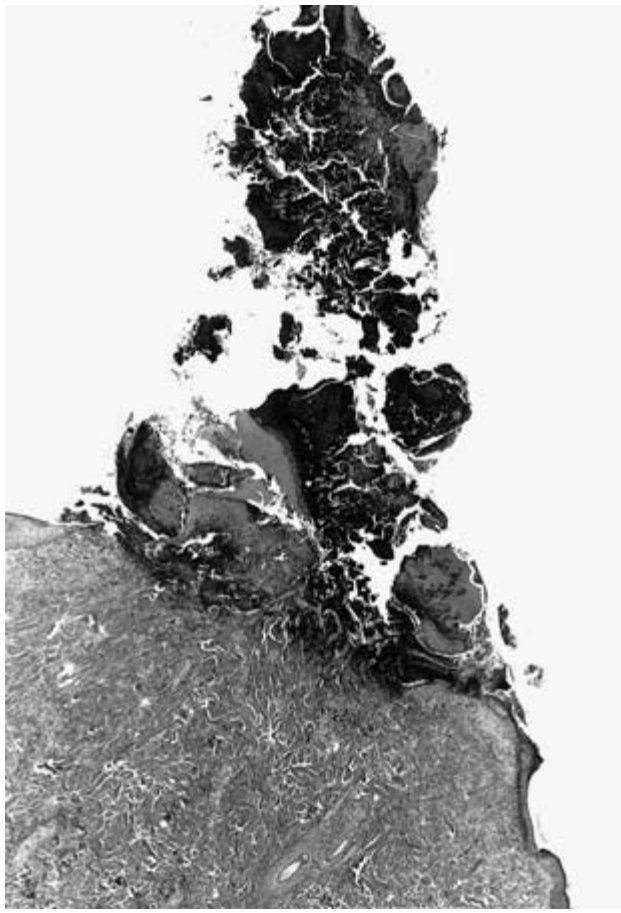


Fig. 15.38 Perforating dermatitis in a cat showing the characteristic vertical columnar crust of inflammatory debris and extruded collagen.



Fig. 15.39 Intermediate magnification of Fig. 15.38. Note vertical arrangement of collagen fibers as they enter the crust at its base.

reported case and occur in the context of self-trauma secondary to allergic skin disease.

Clinically, perforating dermatitis is characterized by multiple, visually distinctive, conical, brownish, horn-like projections arising from the skin. Multiple projections may be arranged in a striking linear configuration (Scott & Miller, 1991). The projections are tenaciously adhered to the underlying skin and cannot be readily pulled or scraped off (Scott & Miller, 1991). Visible inflammation is variable and is noted at the base of the lesions. Alopecia may be present. Affected sites have included the shoulder, neck axilla, flank, and hip (Scott & Miller, 1991; Haugh & Swendrowski, 1995). Laboratory abnormalities and systemic signs have not been noted. Signalment predilections have not been reported.

The lesions are visually striking. Few differential diagnoses are known, but may include cutaneous horns (see Chapter 22). Histopathology is required for definitive diagnosis.

Biopsy site selection

Care should be taken not to dislodge or damage the projecting material during skin biopsy. If possible sites should not include regions that can be easily self-traumatized.

Histopathology (Figures 15.38 through 15.40)

Massive columnar or conical crusts are confluent with the underlying dermis and contain cellular debris and numerous degenerate-appearing collagen fibers, largely oriented perpendicularly to the adjacent intact epidermal surface. Hyperplastic epidermis borders these foci and may be spongiotic or mucinotic. There may be single foci or several adjacent foci with intervening epidermis separating them. Early lesions may have a cap of necrotic overlying epidermis.

The underlying superficial to deep dermis contains moderate to severe inflammation that is often, but not invariably, eosinophilic. Neutrophils may predominate less commonly. Lymphocytes, macrophages, and

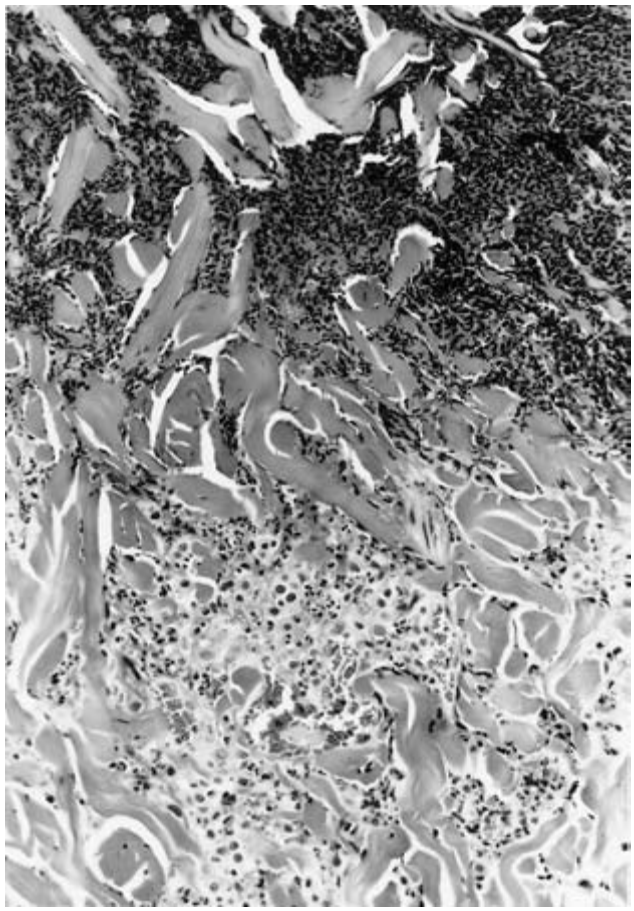


Fig. 15.40 High magnification of Fig. 15.39. Eosinophils and mast cells are clustered along the base of the crust.

plasma cells are present in varying proportions as well. Mast cells may be prominent in eosinophilic dermatitis. There may be subepidermal fibrosis in intact adjacent areas.

Masson's trichrome staining of affected collagen fibers demonstrates segmental red cores, in contrast to the diffuse blue staining of normal collagen fibers (Scott & Miller, 1991). This staining abnormality is not diagnostically specific and may be seen in Ehlers–Danlos syndrome and feline acquired skin fragility (see pp. 386 and 389); further, random abnormal staining of collagen fibers has been observed in inflamed and uninflamed areas of feline eosinophilic granuloma (see Chapter 14).

The appearance of perforating dermatitis is striking and unique histologically. Perforating dermatitis may be a severe tissue reaction, traumatic in origin, occurring in the context of allergic dermatitis or other pruritic conditions, at least in some cases. In these lesions, the massive focal crusting and unique collagen fiber alterations are superimposed upon otherwise typical allergic dermatitis.



Fig. 15.41 Morphea in a dog. A well-demarcated, depigmented, alopecic, smooth, sclerotic plaque is present. (Photograph courtesy D.-N. Carlotti.)

MORPHEA

(Synonym: localized scleroderma)

Clinical features (Figure 15.41)

Morphea is a rare, idiopathic, sclerosing skin disease reported in the dog and cat. It is characterized by a fibrosing dermatitis involving the dermis and/or subcutis (Scott, 1986; Scarampella & Noli, 1997; Bensignor et al., 1998). Reported cases bear resemblance to localized morphea, a subgroup of scleroderma seen in humans involving only the skin; either solitary or small numbers of lesions are seen (Yu & Eisen, 2003). The diagnosis of morphea is more controversial in domestic animals than it is in humans, since animals cannot communicate a history of antecedent trauma and resultant scarring. Since morphea and cicatricial alopecia have many histopathologic features in common, some reports in the veterinary literature may represent post-traumatic scarring and not morphea.

The etiology of morphea and scleroderma is not known. In humans, scleroderma and morphea are viewed as chronic obliterative, fibrosing diseases that affect the microvasculature and loose connective tissue (Yu & Eisen, 2003). Vascular abnormalities and damage, abnormal collagen metabolism, autoimmunity, adverse drug reactions, environmental toxins, and infection with the tick-borne spirochete *Borrelia burgdorferi* all have been implicated in humans; however, there is no identifiable trigger in most cases (Yu & Eisen, 2003).

Reported clinical features include well-demarcated, alopecic, smooth, sclerotic plaques. The surface may appear shiny, similar to cicatricial alopecia (see p. 397). Hypopigmentation may occur. Either solitary or small

numbers of lesions may be seen. Spontaneous resolution (similar to humans) in some cases supports a true equivalent of morphea, rather than scarring alopecia of unknown cause. One author (T.L.G.) has received anecdotal reports of slow expansion of lesions over time in carefully observed house cats. Signalment predilections have not been noted.

The prime clinical differential diagnosis for morphea is cicatricial alopecia secondary to previous trauma. A history of previous trauma or site-associated likelihood of trauma may aid in differentiation. Skin biopsy may reveal sequela of a traumatic cause, such as foreign material; otherwise, histopathology may not permit differentiation of these two lesions. Spontaneous resolution or slow expansion of a focal lesion supports a diagnosis of true morphea.

Biopsy site selection

An area with maximal alopecia should be chosen for biopsy. If surface irregularities suggest a focus of possible trauma, that site should be sampled as well.

Histopathology (Figure 15.42)

As reported in dogs (Scott, 1986; Scarampella & Noli, 1997), the dermis is replaced by collagenous connective tissue. The subcutis was affected in one reported canine case (Scott, 1986). The epidermis is normal. The fibrous tissue excludes essentially all normal architecture and may be moderately cellular, resembling scar tissue (Scott, 1986), or composed of dense cell-poor collagen bundles in fairly normal arrangement (Scarampella & Noli, 1997; Bensignor et al., 1998). Thin walled vessels arranged perpendicular to the epidermis were found in one putative case observed by the authors. Inflammation is very mild and consists of a superficial and deep perivascular infiltration of lymphocytes and macrophages. This inflammatory pattern has been seen in the superficial dermis at the margins of fibrotic lesions as well.

Morphea is characteristic histopathologically. However, this lesion should be differentiated from cicatricial alopecia, e.g. localized scarring that follows identifiable causes, including trauma and localized infection. Differentiation between these two entities may be impossible, particularly in cases of chronic cicatrices. If foreign material or traumatic residua cannot be identified, clinical differentiation may be required. However, morphea is more likely to feature a fairly normal arrangement of collagen fibers; in contrast, dense collagen of cicatricial alopecia is often laminar. Morphea reportedly is reversable (Scott, 1986; Bensignor et al., 1998), but other forms of traumatic scarring may not be; slow progression also may be supportive of morphea over a traumatic scar.

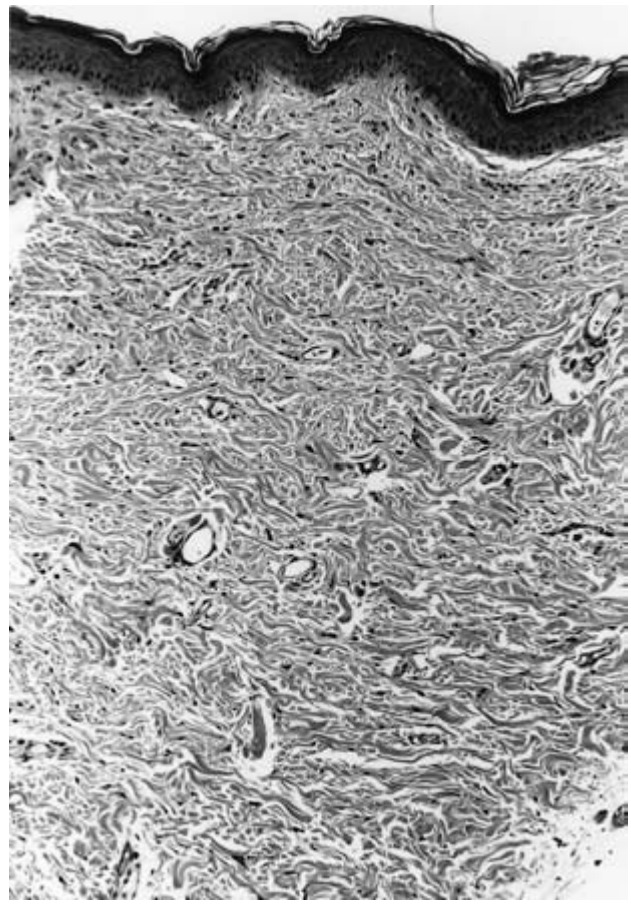


Fig. 15.42 Morphea in a cat. Note complete replacement of normal dermal structures by mature collagen in fairly normal arrangement.

CICATRICIAL ALOPECIA

(Synonyms: cicatrix, scarring alopecia)

Clinical features (Figure 15.43)

Cicatricial alopecia is a clinical syndrome characterized by permanent replacement of dermal structures, including hair follicles, such that hair regrowth does not occur. The causes of cicatricial alopecia are varied and include physical, chemical, or thermal injury, severe bacterial furunculosis (especially secondary to demodicosis and actinic disease), neoplasia, sterile nodular panniculitis, and rarely other diseases such as discoid lupus erythematosus and ischemic dermatopathy/canine dermatomyositis. Clinical absence of regrowth of hair may not necessarily correlate histologically with the classical obliterative fibrosis of a cicatrix. The authors prefer limiting the use of the term, 'cicatricial alopecia' to cases where a true fibrous scar is found microscopically.



Fig. 15.43 Cicatricial alopecia in an Old English Sheepdog due to a heating pad burn. Note the irregular margins, loss of pigment, and prominent linear markings associated with scarring.

Permanent alopecia results from irreversible injury to and ablation of adnexal units with replacement by scar tissue. The documentation of cicatricial alopecia is important clinically, since it proves conclusively that the hair loss is permanent, regardless of possible therapy. Although dermatologists and pathologists certainly are aware of 'cicatricial alopecia', to the authors' knowledge it is not directly reported in the literature.

Permanent hair loss is the unifying clinical feature. Loss of the normal surface cutaneous architecture including follicular ostial openings may be seen with physical, chemical, or thermal injury; visualization of these features is aided by the use of a hand lens. Lesions are shiny, variably firm, and often irregular in contour. Prominent crisscrossing linear markings may be visible in severe lesions. Mottled hyperpigmentation or hypopigmentation may occur and is partially breed dependent. The skin surface may be irregular, and nodular irregularities may be palpable in the dermis or subcutis. The distribution of traumatic cicatricial alopecia is asymmetric. The distribution of other cicatricial alopecias reflects the initiating disease.

Breed, age, or sex predilections are not seen with injury-related cicatricial alopecia. Signalment predilections for other causes of cicatricial alopecia follow those of the specific underlying disease.

Morphea, as reported, is a differential diagnosis for cicatricial alopecia. Morphea reportedly occurs without apparent antecedent trauma, but the absence of language in dogs and cats makes confirmation difficult. Cicatricial alopecia also can mimic any disease with visually non-inflammatory alopecia. Suspicion of cicatricial alopecia is aided by a history of physical, chemical, or thermal insult. Trauma-related cicatricial alopecia generally is focal and symmetry is lacking. Other alopecic diseases such as postrabies vaccination alopecia, ischemic dermatopathy/canine familial dermatomyositis, alopecia areata, and canine traction alopecia must be ruled out by history, clinical presentation, and histopathology. Both traction alopecia and ischemic dermatopathy may have components of cicatricial alopecia in severe or chronic cases. Histopathology is the single most valuable tool in differentiating cicatricial alopecia from nonscarring hair loss and in differentiating the multiple causes of cicatricial alopecia.

Biopsy site selection

Specimens from areas of most complete alopecia should be obtained in order to sample the most advanced changes present in the skin. Chronic lesions may be preferred to document fibrous tissue replacement of normal hair follicles. The skin biopsy is a prognostic tool in this regard as it can predict whether hair loss will be permanent.

Histopathology (Figures 15.44)

Scarring alopecia may be seen focally in many diseases, both inflammatory and traumatic. In general, the epidermis is acanthotic or ulcerated, depending on the stage and severity of the insult.

Hair follicles are absent due to replacement by fibrous connective tissue. Collagen may be laminar in distribution and will extend to a variable depth of the dermis or even the subcutis, depending on the severity of the previous tissue damage. Rudimentary persistent follicles may be entrapped by scar tissue, thus effectively preventing regrowth of hair. Scattered 'orphaned' sweat glands, i.e. lacking their associated folliculosebaceous units, may be seen. In very late stage lesions, a more normal meshwork pattern of dermal collagen may be present, accompanied by complete absence of adnexal tissue. Dermal inflammation is variable, based on the origin of the process that is inducing the dermal damage, and is dependent also upon the stage of the process at the time of biopsy.

Differential diagnoses for cicatricial alopecia without identifiable accompanying inflammatory diseases include severe and chronic lesions of traction alopecia, and morphea. Differentiation of traction alopecia from cicatricial alopecia may be moot, as severe forms of traction alopecia are essentially cicatricial. Complete absence of follicles and adnexal glands, and laminar deposition of collagen, are less common in traction alopecia than in cicatricial alopecia. Morphea may be impossible to distinguish from cicatricial alopecia, particularly chronic cicatrices; clinical differentiation may be helpful (see p. 396). However, morphea is more likely to feature a fairly normal arrangement of collagen fibers; in contrast, dense collagen of cicatricial alopecia is often laminar.

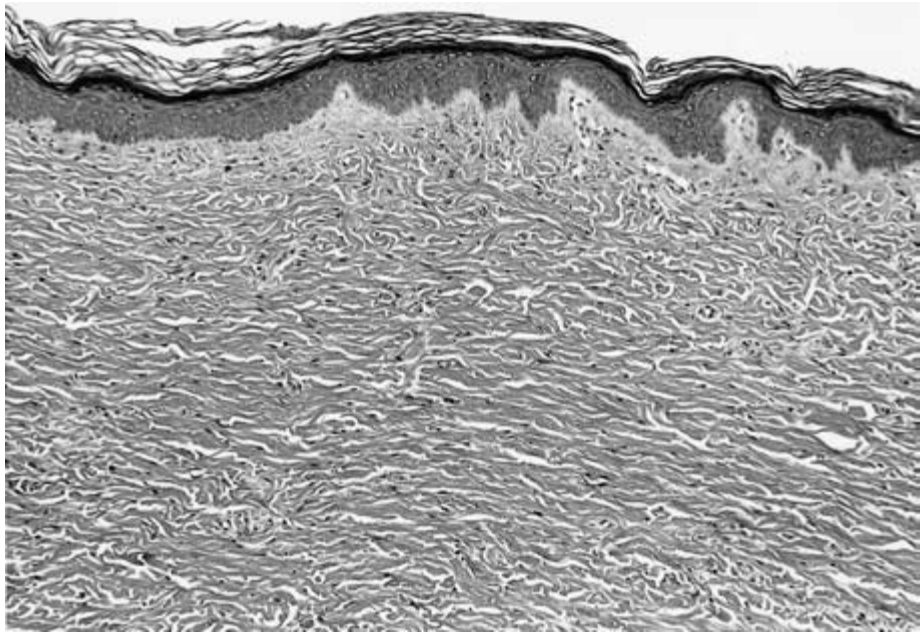


Fig. 15.44 Cicatricial alopecia featuring replacement of normal dermis by fibrosis. Note laminar arrangement of dense collagen.



Fig. 15.45 Solar elastosis and fibrosis in a Bull Terrier-crossbreed with a history of recumbent sunbathing. All biopsy specimens taken from affected glabrous skin showed solar elastosis and fibrosis. Fibrosis manifested clinically as a textural change on palpation. The large ulcerated plaque is a solar induced squamous cell carcinoma.

SOLAR ELASTOSIS AND FIBROSIS

(Synonym: solar dermatitis)

Clinical features (Figures 15.45)

Solar fibrosis and elastosis are associated microscopic features of multiple sun-associated clinical syndromes, including actinic keratosis (see Chapters 7 and 22), actinic comedones (see Chapter 8), and actinic furunculosis (see Chapter 17). A separate clinical diagnosis of solar elastosis and fibrosis is not made; fibrosis may produce firm texture of the affected skin.

Biopsy site selection

It is highly advantageous to delay skin biopsy of any suspected actinic lesions until the dog has received appropriate systemic antibiotics for at least 3 weeks in order to resolve secondary pyoderma. This may increase the likelihood of targeting solar-induced lesions for biopsy. Specimens for biopsy should be obtained from different types of lesions, or different stages of the disease, if known.

Histopathology (Figures 15.46 through 15.48)

Epidermal lesions of actinic origin (actinic keratosis) are described elsewhere, and principally include hyperplasia and dysplasia (see Chapters 7 and 22). Solar elastosis and fibrosis may also be seen in the setting of actinic comedones and actinic furunculosis (see Chapters 8 and 17) as well as solar-induced vascular neoplasia (see Chapter 28). Solar vasculopathy may be seen in some dogs (see Chapter 10).

In dogs, the dermis may contain perivascular to lichenoid inflammation. Plasma cells and lymphocytes predominate and are accompanied by variable numbers of neutrophils, macrophages, and occasional eosinophils. Pigmentary incontinence may be present. Lichenoid dermatitis generally is not observed in actinic lesions of cats; inflammation is mild and perivascular. However, some feline cases of actinic keratosis have more intense dermal

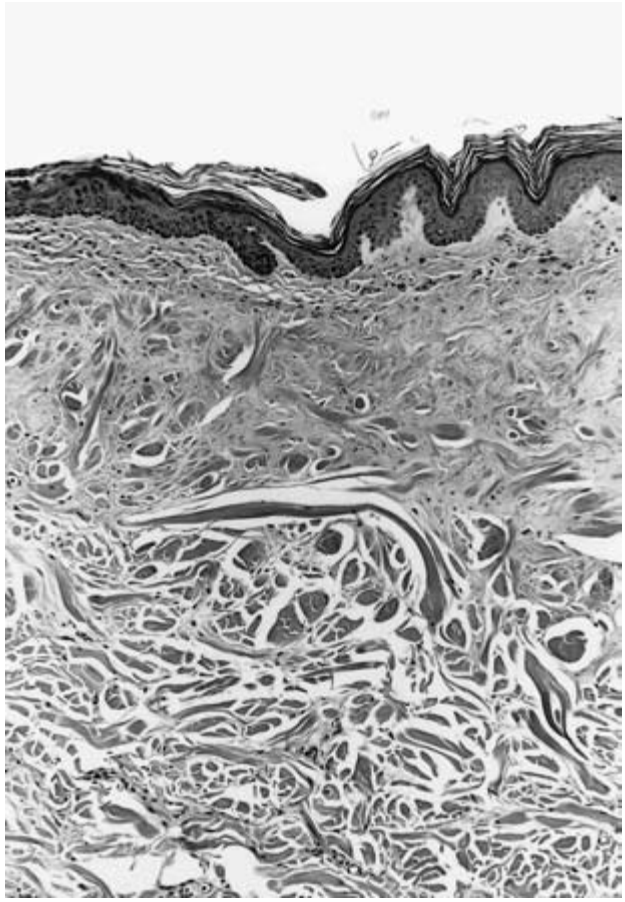


Fig. 15.46 Solar fibrosis in a dog. Note strikingly laminar zone of altered pale collagen.

inflammation. Superficial dermal vessels may be proliferative and ectatic.

In dogs, laminar alteration of collagen begins superficially and may extend deeply to replace hair follicles in rare cases. In general, the affected collagen is pale, hypocellular, and homogeneous in appearance, and is seen just beneath the epidermis. This altered layer of 'solar fibrosis' is not truly fibrotic. It consists of poorly staining collagen fibers separated by a pale ground substance, which is mucin-positive (blue-green) with Alcian blue periodic acid–Schiff (PAS) staining (pH 2.5). There also may be superficial true laminar fibrosis of varying depth, resembling traditional scar tissue, subtended by the pale hypocellular collagen layer. In other cases, true laminar fibrosis and inflammation predominate, and the layer of abnormal pale collagen is not seen. When scarring fibrosis of the dermis is intense, inflammation may lie immediately below the fibrotic layer. True laminar fibrosis sometimes is observed in cats. In cats, the pale, altered collagen of canine lesions is not common.

Solar elastosis may be seen in dogs or cats. Solar alteration of collagen without elastosis is common in dogs. Elastotic material is generally found in the pale collagen layer in dogs, and may be seen with or without fibrosis in cats. Degeneration of collagen and elastic fibers of the superficial dermis leads to replacement by distinctive thickened, wavy, basophilic fibers of elastotic material. Van Gieson's silver staining will accentuate subtle elastotic changes as foci of tangled, silver-dense elastotic fibers.

Solar elastosis and 'fibrosis' are histologically characteristic; other concurrent lesions of actinic origin (see

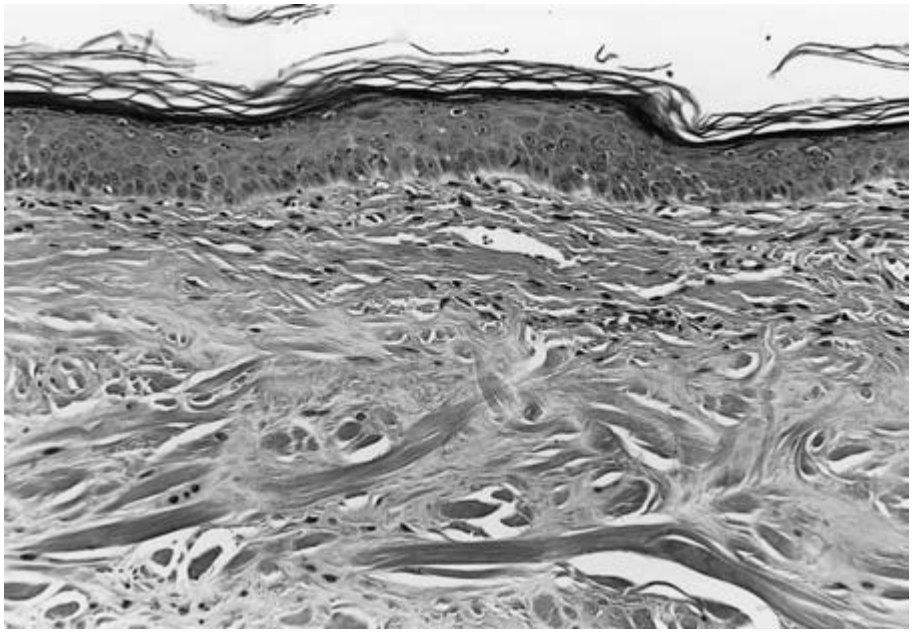


Fig. 15.47 Higher magnification of solar fibrosis in a dog. Note true laminar fibrosis above pale staining zone of altered collagen in the lower half of the photograph.

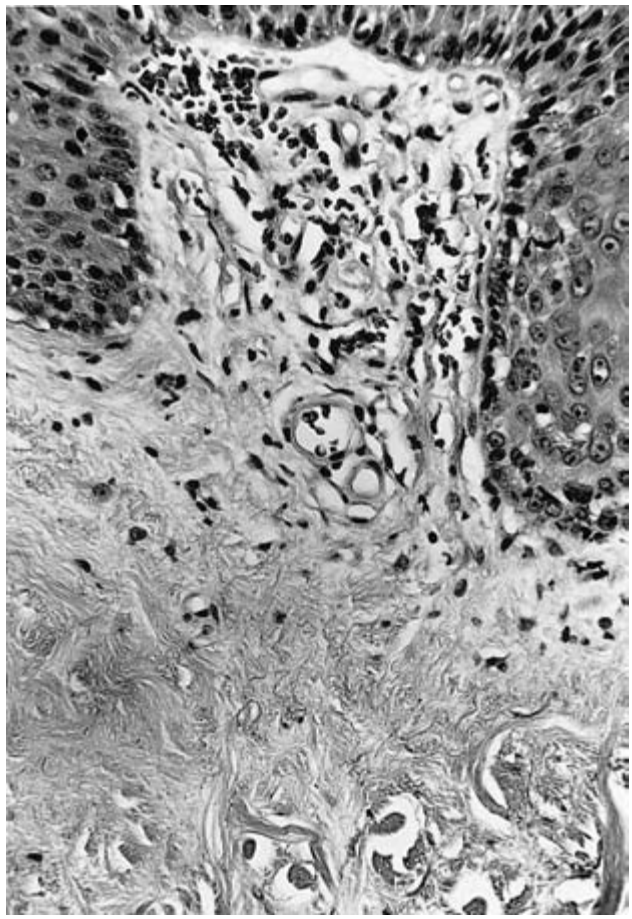


Fig. 15.48 Solar elastosis in a dog. Wavy, dark fibers of elastotic material are seen within altered, homogeneous collagen.

above) may aid in the diagnosis. The laminar homogenization of the dermis is somewhat similar to topical corticosteroid reaction (see p. 392); however, superficial collagen attenuation with splitting is not a feature of solar disease. Because of the ventral abdominal location for both conditions, combined lesions may be observed.

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Part III

Diseases of the Adnexa

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Chapter 16

Pustular and nodular diseases without adnexal destruction

The diseases of this chapter are characterized by pustular or nodular adnexal inflammation without prominent destruction and effacement of these structures. Clearcut delineation of this pattern from inflammation with structural damage to adnexa (see Chapter 17) is not always possible, as most adnexal inflammation may disrupt integrity to some degree. In general, the inflammation of the diseases of this chapter is less severe, less obliterating to normal tissue, and/or more superficial in location. Histopathologic differentiation among these diseases is generally accomplished by identification of an agent (dermatophytosis), recognition of an associated histopathologic feature such as acantholysis (pemphigus foliaceus), or by the predominance of eosinophils (sterile eosinophilic pustulosis).

SUPERFICIAL BACTERIAL FOLLICULITIS

(Synonym: superficial pyoderma)

Clinical features (Figures 16.1 and 16.2)

Superficial bacterial folliculitis is a bacterial skin infection affecting the hair follicle. It is seen commonly in the dog (Ihrke, 1996) and rarely in the cat (White, 1991). The only canine skin disease seen globally with greater frequency is flea allergy dermatitis. Both feline and canine bacterial folliculitis may be underdiagnosed, as superficial pustules rupture readily giving rise to less diagnostic crusted papules. However, the even more transient nature of feline pustules may foster a greater magnitude of underdiagnosis. *Staphylococcus intermedius* is the primary pathogen in most canine pyoderma and probably most feline pyoderma as well.

Most bacterial folliculitis is seen secondary to coexistent disease or other predisposing factors. Triggering diseases or syndromes in the dog include atopic dermatitis, flea allergy dermatitis, food allergy, primary seborrhea, hypothyroidism, demodicosis, naturally occurring and iatrogenic hyperglucocorticoidism, and genodermatoses such as color dilution alopecia (Ihrke, 1998). Other predisposing factors include pruritus of any origin, defects in the immune response, and poor grooming. Frequently, the specific initiating factors are not known. Canine superficial bacterial folliculitis may be seen in conjunction with superficial spreading pyoderma (see Chapter 1); deep folliculitis and furunculosis may evolve from more superficial lesions (see Chapter 17).

Cats that develop clinically obvious superficial bacterial folliculitis may be immunosuppressed, especially if pustules are clearly evident. The authors have seen superficial bacterial folliculitis in the cat secondary to feline immunodeficiency virus (FIV) infection. Mild feline superficial bacterial folliculitis may be seen secondary to allergic skin disease, ectoparasitic skin disease, and the overuse of glucocorticoids.

The clinical presentation of canine bacterial folliculitis is highly variable due to differences in breed response, individual host response, and possibly, intrinsic differences in bacterial virulence. The unifying clinical feature in bacterial folliculitis is the formation of follicular pustules. Pustules are transient due to their fragile nature and rupture easily, eventuating in crusted papules. Consequently, crusted papules are the most common lesion seen in superficial bacterial folliculitis. Pustules vary greatly in size and often may be difficult to identify with the naked eye. Less commonly, larger, firm papules, pustules, or nodules are seen; these lesions may represent superficial perforating folliculitis or may be indicative of accompanying furunculosis (see Chapter 17).

Intact pustules have an erythematous base and usually contain white or creamy yellow purulent material. A hand lens may be useful in determining if intact pustules are follicular rather than between follicles (as seen in pemphigus foliaceus, impetigo, and other superficial pustular diseases of the epidermis; see Chapter 1). Follicular pustules will have central protruding hairs unless the hair has been shed. Erythema and swelling are highly variable. After pustules rupture, collarettes may form peripherally as surrounding superficial keratin layers lift and peel. This phenomenon may actually represent superficial spreading pyoderma (see Chapter 1) coexisting with folliculitis.



Fig. 16.1 Superficial bacterial folliculitis on the abdomen of a Keeshond. Frank pustules, crusted papules, and mottled hyperpigmentation are present.



Fig. 16.2 Superficial bacterial folliculitis on the abdomen of a Bull Terrier. Brightly erythematous follicular pustules and crusted papules are seen in a partially intertriginous location. Inflammation is visually enhanced by the nonpigmented skin.

Rings of postinflammatory hyperpigmentation may form within the boundaries of the collarette, or small, hyperpigmented punctate foci may directly mark the sites of previously affected hair follicles and serve as additional diagnostic clues for superficial folliculitis.

Alopecia is variable, but is a common feature if substantial inflammation is present. Distinct circular patches of transient, nonscarring alopecia may form around previously affected hair follicles and are more obvious in short-coated breeds. These patches of alopecia may be due to focal postinflammatory telogen arrest.

Many cases of canine superficial bacterial folliculitis initially develop in the comparatively glabrous inguinal and axillary regions. The dorsal and ventral interdigital webs are additional predisposed sites. Superficial bacterial folliculitis can mirror the distribution pattern of any underlying skin disease. Lesions may generalize, especially in dogs with iatrogenic or naturally-occurring hyperglucocorticoidism. Pruritus may vary from nonexistent to severe, but some pruritus is common. Pruritus and attendant self-trauma may not correlate with the degree of erythema. Regional lymphadenopathy is a common finding.

The clinical features of feline superficial bacterial folliculitis are generally less obvious. This may be due the very transient nature of feline pustules. The most frequently identified lesion is a nondescript crusted papular eruption, commonly referred to as 'miliary dermatitis', a feline reaction pattern of multifactorial etiology. Similar to folliculitis in the dog, collarettes may be noted (White, 1991). The face and ventrum may be preferentially affected (White, 1991). Pruritus is variable but usually is present.

Breed predilections in dogs probably parallel those of any coexisting skin disease. Age or sex predilections have not been noted in the dog. Feline superficial folliculitis may be more common in older cats (White, 1991).

Differential diagnoses vary with clinical presentation. Superficial bacterial folliculitis may be mimicked by other causes of superficial folliculitis such as demodicosis and dermatophytosis. Superficial spreading pyoderma may coexist with superficial folliculitis, if pustules are accompanied by prominent collarette formation. Superficial spreading pyoderma may actually originate from superficial follicular pustules (see Chapter 1), but has more prominent collarette formation and less obvious pustulation than does superficial folliculitis. Clinically, other superficial pustular skin diseases such as bacterial impetigo, pemphigus foliaceus, subcorneal pustular dermatosis, and sterile eosinophilic pustulosis may resemble superficial bacterial folliculitis. Differentiation is accomplished by the microscopic examination of smears from pustules, skin scrapings, dermatophyte culture, bacterial culture, and histopathology. If only crusted papules are present, superficial bacterial folliculitis also must be differentiated from predominantly papular dermatoses such as flea allergy dermatitis.

Feline superficial bacterial folliculitis manifesting as miliary dermatitis must be differentiated from feline allergic miliary dermatitis. If intact pustules are present, bacterial folliculitis also must be differentiated from pemphigus foliaceus. Both types of lesions also may resemble dermatophytosis. Dermatophyte culture is advisable in all cases. Histopathology is required for the diagnosis of feline superficial bacterial folliculitis.

Biopsy site selection

Skin biopsy specimens should be obtained from intact pustules, if available. Crusted papules are not ideal as they represent pustules in advanced stages of degeneration. Lesions with excessive crusting should be avoided. Speci-

mens that have been punctured for smears or culture should not be used as specimens for skin biopsy. If intact pustules are not present, sampling a collarette may be helpful in determining probable bacterial etiology. In cats, regions of miliary dermatitis lacking self-trauma are more likely to lead to definitive diagnosis.

Histopathology (Figures 16.3 through 16.6)

The formation of pustules within the infundibulum or ostium of superficial follicles characterizes folliculitis. The alternative term 'luminal folliculitis' may be applied to this pattern of inflammation. Pustules are composed of neutrophils and variable eosinophils. Pustules may extend from openings of hair follicles into the infundibular wall, the adjacent superficial epidermis, or onto the epidermis beneath the stratum corneum. Intraepithelial pustules may have accompanying vesiculation (vesicopustulation). A subcorneal pustule that is perched within a follicular ostium is characteristic of superficial folliculitis. These pustules may extend beneath the stratum corneum nearly to the adjacent follicle. As pustules age, superficial follic-



Fig. 16.3 Superficial bacterial folliculitis in a dog. A pustule distends a follicular ostium.

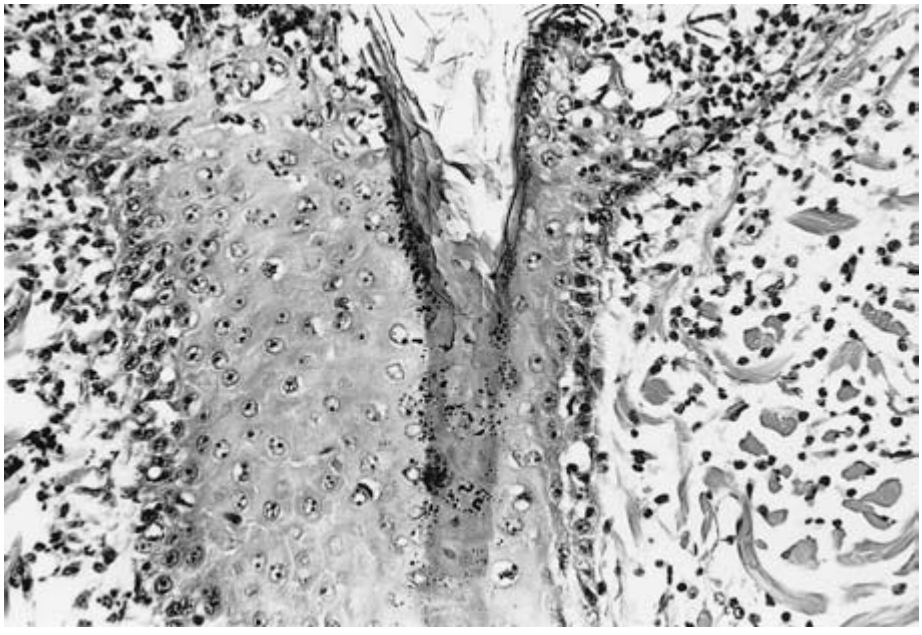


Fig. 16.4 Superficial folliculitis in a dog. Neutrophils are closely apposed to the outer wall of a superficial follicle and are infiltrating the epithelium of the ostium at top to form early vesicopustules.

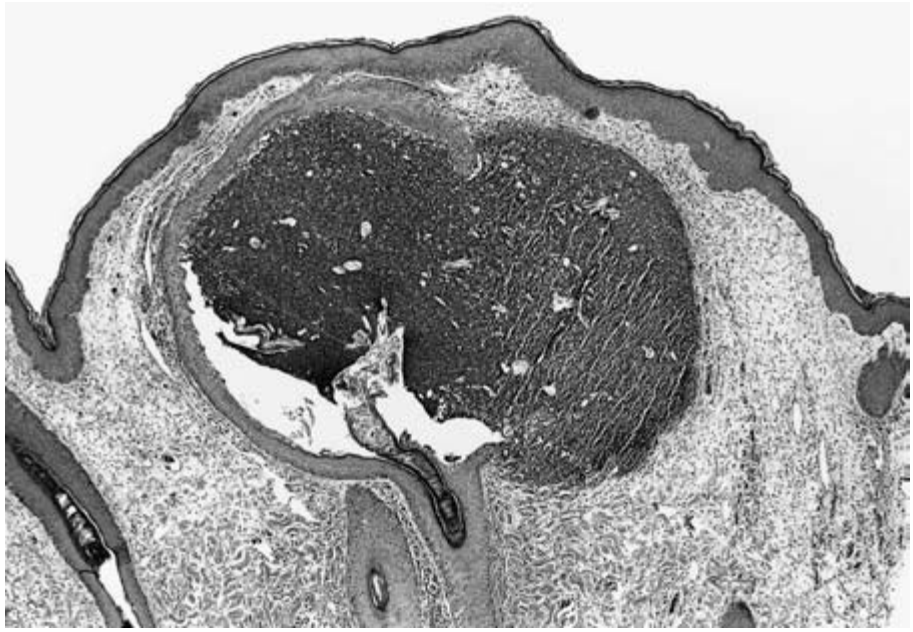


Fig. 16.5 Perforating superficial folliculitis in a dog. A superficial luminal pustule has just broken through the follicular infundibulum.

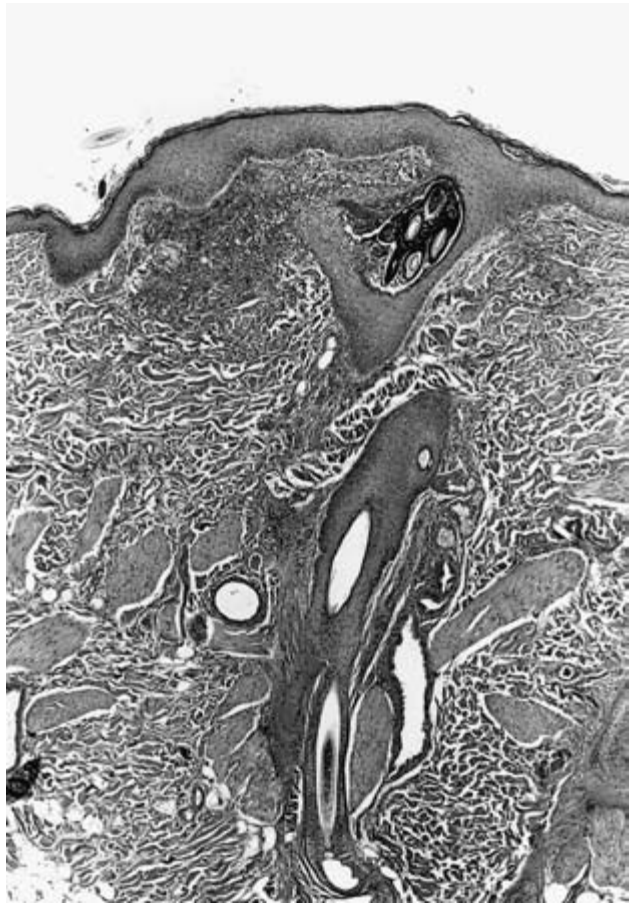


Fig. 16.6 Perforating superficial folliculitis in a dog. A superficial follicular pustule has extended to the adjacent superficial dermis.

ular and/or epidermal crusts occur. Bacteria (staphylococci) may be found in crusts or in superficial follicular keratin, but are less obvious within pustules.

In some cases, particularly in young dogs, eosinophils may be prominent. Purely eosinophilic folliculitis may be seen in allergic miliary dermatitis of cats, most notably in food allergy. Eosinophils may reflect hypersensitivity to bacterial superantigens or other products.

The epidermis is mildly to moderately acanthotic. The dermis is variably edematous and inflamed. Loosely organized accumulations of neutrophils, eosinophils, and fewer mixed mononuclear cells are perivascular to interstitial. Near foci of folliculitis, dermal inflammation closely surrounds follicles, and often trails to the isthmus where it encircles adnexal glands. Eosinophils may predominate in some cases. The superficial dermis in other areas of the specimen may have milder superficial accumulations of neutrophils, eosinophils, plasma cells, macrophages, and lymphocytes. In chronic lesions, perifollicular and perivascular infiltrations of plasma cells, macrophages, and a few neutrophils are present, rather than active pustular inflammation. Mild perifollicular fibrosis may be present.

'Superficial perforating folliculitis' is a common phenomenon characterized by focal rupture of a superficial pustule through the infundibulum of a follicle. This lesion is in contradistinction to furunculosis, since the process remains superficial and does not efface the entire follicle (see Chapter 17). Superficial dermal pustules containing keratin or hair may be present in one level of sectioning, while the disrupted follicle itself may not be apparent unless deeper sections are examined. Thus, superficial per-



Fig. 16.7 Feline dermatophytosis affecting multiple kittens in a litter. Patchy alopecia and scaling are present on the pinna, temporal region, and dorsal muzzle of the centrally located kitten.



Fig. 16.8 Generalized dermatophytosis in an adult Persian cat. Extensive alopecia, scaling, and hyperpigmentation are somewhat bilaterally symmetrical.

forating folliculitis can be inferred in specimens where no actual follicular inflammation is present, if pustules are found in the general vicinity of the hair follicle and if they contain follicular debris.

Differential diagnoses are few if follicular pustules or superficial dermal pustules with follicular debris are found. Dermatophytosis should always be ruled out by culture in cats with folliculitis, even if organisms are not seen in tissue, since this is the more common cause of follicular pustulation in this species. Sterile eosinophilic pustulosis of dogs is characterized in part by follicular pustules, and thus eosinophil-predominant folliculitis may appear similar. Care should be taken not to rely exclusively on the type of inflammatory cell present, since antibiotic-responsive eosinophilic folliculitis may be encountered, particularly in the young dog. Clinical differentiation is required. Superficial spreading pyoderma of dogs may generate from superficial follicular pustules of the infundibulum or ostium, but folliculitis is difficult to observe in random biopsy specimens of that condition (see Chapter 1). In contrast, superficial follicular or dermal pustulation (secondary to follicular perforation) is obvious in most biopsy specimens of superficial folliculitis.

FELINE DERMATOPHYTOSIS

(Synonym: feline ringworm)

Clinical features (Figure 16.7 through 16.9)

Feline dermatophytosis is a common skin disease caused by infection of the hair follicle and hair with keratinophilic fungi. Wide variation in incidence exists globally; warm temperatures and high humidity encourage dermatophyte infection. The great majority of cases of feline dermatophytosis worldwide probably are caused by



Fig. 16.9 Severe dermatophytosis affecting three Persian kittens. Note the extensive crusting and facial alopecia.

Microsporum canis. The species designation '*canis*' actually is a misnomer, since the cat is the natural host for this organism. Since this well-adapted dermatophyte induces minimal host response in the cat, inapparent carriers are common, especially in the Persian cat and other long-haired breeds. *Trichophyton mentagrophytes*, *Microsporum gypseum*, and various other keratinophilic fungi may, on occasion, cause feline dermatophytosis.

Keratinophilic fungi invade actively growing hair, follicular keratin, and less frequently, the stratum corneum of the epidermis. Transmission is achieved via direct contact with infected hair and scale or fomites. Cats with compromised immune function, as seen with naturally occurring or iatrogenic hyperglucocorticoidism, feline leukemia virus (FeLV) infection, or feline immunodeficiency virus (FIV) infection, are at greater risk for acquiring dermatophytosis, as well as for developing more

serious, prolonged, or generalized disease (Foil, 1998). Feline dermatophytosis is the most common zoonotic skin disease.

Clinical features of feline dermatophytosis vary considerably. Classically, ring lesions characterized by expanding circular patches of alopecia with central healing and peripheral small papules may be seen. Follicular pustules, when present, are very transient in the cat. Follicular papules are much more frequent. However, irregular, patchy alopecia is more frequently the only obvious clinical abnormality. Affected hairs are irregularly broken, leading to shorter, disheveled haircoats. Hair stubble may appear thickened. Subtle alopecia with minimal other signs is seen more frequently in long-haired cats. Scaling and crusting can vary from absent to severe. The face, ears, and forelegs are the most common initial sites, but infection may generalize.

Crusted papules with minimal alopecia also can be a feature of feline dermatophytosis. This rather generic feline reaction pattern is termed 'miliary dermatitis', and is of multifactorial etiology.

Inapparent carriage of *Microsporum canis* is noted, particularly in cats from large catteries and in long-haired breeds (Scott et al., 2001). Feline dermatophytic pseudomycetoma (see Chapter 12) and claw infection (onychomycosis) are rare clinical variants. Pruritus is variable but not common with feline dermatophytosis.

Long-haired cats such as Persians may be at increased risk for both asymptomatic and symptomatic dermatophytosis (Scott et al., 2001). Overt dermatophytosis is seen most commonly in kittens and in adult cats in association with stresses such as queening. Sex predilections are not noted.

Clinical differential diagnoses are contingent upon clinical presentation. Dermatophyte-associated alopecia without other obvious skin changes must be differentiated from pruritic self-traumatic alopecia, psychogenic alopecia, and demodicosis. A history of self-grooming (a manifestation of any of these diseases) may not be forthcoming, as excessive grooming may be clandestine in the cat. Feline dermatophytosis presenting as miliary dermatitis must be differentiated from feline allergic miliary dermatitis (see Chapter 6), and the rare other nonallergic causes of miliary lesions such as bacterial impetigo or folliculitis. Rarely, cases of severely exfoliative, crusting, or pustular dermatophytosis may resemble pemphigus foliaceus. However, bilateral symmetry usually is a feature of pemphigus foliaceus (see Chapter 1), in contrast to feline dermatophytosis. Skin scrapings, dermatophyte cultures, and skin biopsy should be performed to differentiate among these diseases.

Biopsy site selection

Biopsy specimens should be obtained from areas exhibiting broken hairs or exfoliation. Sites just within the outer boundaries of expanding foci of alopecia are most beneficial. Centers of alopecic foci may not be as helpful in establishing a diagnosis since dermatophytes may no longer be present in these healing lesions.

Histopathology (Figures 16.10 through 16.12)

The epidermis may be mildly to moderately acanthotic and hyperkeratotic. In some cases, superficial epidermal pustules predominate (superficial pustular dermatophyto-

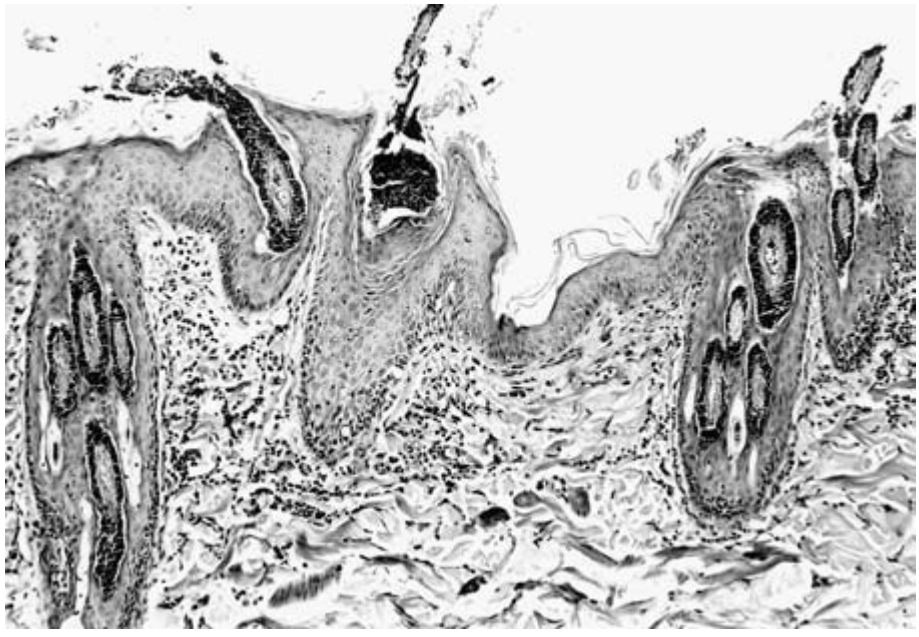


Fig. 16.10 Feline dermatophytosis. Darkly-staining spores surround hair shafts, many of which protrude from follicular ostia. Note scant inflammation around hair follicles and in the superficial dermis (periodic acid–Schiff).

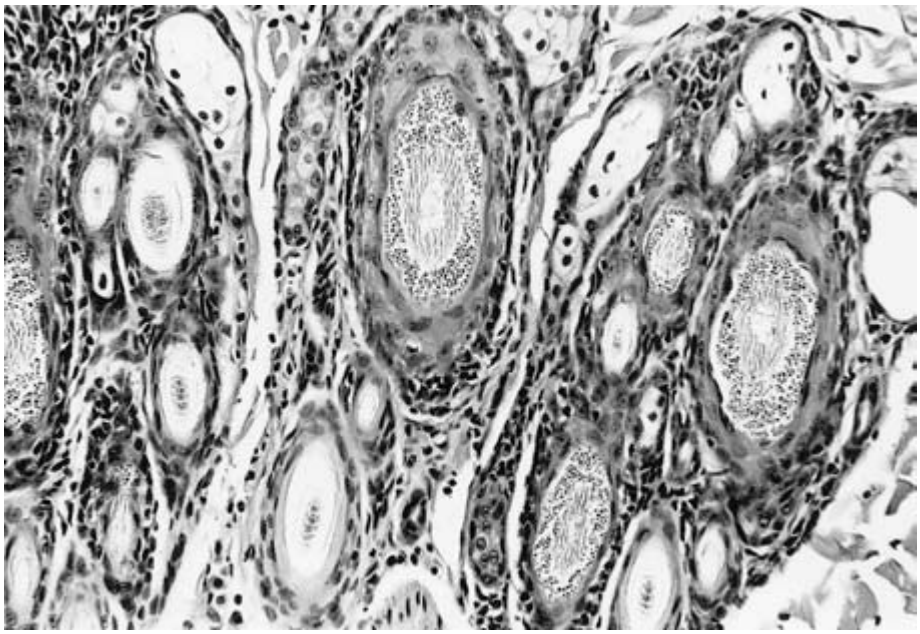


Fig. 16.11 Higher magnification of feline dermatophytosis. Spores and hyphae heavily colonize hairs. Note scant inflammation.

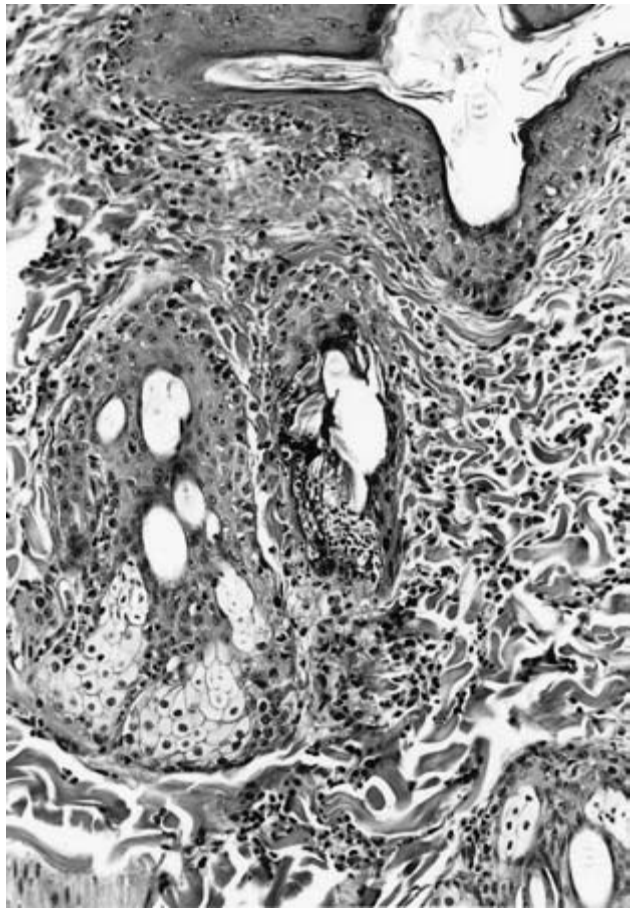


Fig. 16.12 Luminal folliculitis in feline dermatophytosis. Organisms are not present in this field.

sis; see Chapter 1). Crusts composed of degenerating neutrophils may be present around protruding hairs or free in superficial keratin. Hair follicles as well as superficial vessels are surrounded by lymphocytes, macrophages, and neutrophils. Neutrophils are variable in number and distribution, and may be accompanied by fewer eosinophils.

Neutrophils may closely surround and abut hair follicles in tight clusters, but true luminal neutrophilic folliculitis often is not evident. When found, folliculitis in cats is highly suspicious for dermatophytosis. Neutrophils and fewer eosinophils are present within follicular pustules. Follicular pustules may rupture, giving way to furuncles in which macrophages intermingled with neutrophils and eosinophils surround free hair shafts.

Surface as well as intrafollicular hairs usually are colonized by large numbers of refractile or slightly basophilic dermatophytic spores and hyphae. These are colored bright magenta with periodic acid–Schiff (PAS) stain or black with Gomori's methenamine silver (GMS) stain. Colonized hairs may be scant; it is not uncommon for only a single hair to be affected in a given biopsy specimen. Deeper sectioning may be required to locate the organisms and provide an etiologic diagnosis.

In some cases of feline dermatophytosis, epidermal hyperkeratosis is the only histopathologic feature other than the presence of dermatophytes. Dermatophytes may be sparse in these cases; careful search using a PAS stain, if necessary, should always be made in any uninflamed specimen of skin obtained from a cat, particularly if scaling or alopecia is reported. Infiltration of the wall of the middle follicle, generally by lymphocytes (mural fol-



Fig. 16.13 Dermatophytosis in a Dalmatian. Erythema and crusting are within well-demarcated alopecic plaques. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)



Fig. 16.14 Dermatophytosis of the head and neck of a blue Toy Manchester Terrier with color dilution alopecia. Note crusting and erythema. Some hair regrew on the head following therapy for dermatophytosis.

liculitis) may also be a feature of feline dermatophytosis (see Chapter 18).

Differential diagnoses of feline dermatophytosis with folliculitis principally include demodicosis and superficial bacterial folliculitis, both of which are rare in the cat. Identification of dermatophytes is diagnostic in these cases, but even in the absence of histopathologically identifiable organisms, pustular folliculitis is a strong indication for dermatophytosis and should be pursued via dermatophyte culture. Tightly arranged, perifollicular neutrophilic inflammation is also suspicious for dermatophytosis in this species.

CANINE DERMATOPHYTOSIS

(Synonym: canine ringworm)

Clinical features (Figures 16.13 and 16.14)

Canine dermatophytosis is a relatively common skin disease caused by infection with keratinophilic fungi. Wide variation exists globally for the incidence of dermatophytosis in general and for the prevalence of causative species. Warm temperatures and high humidity encourage dermatophyte infection. Canine dermatophytosis is caused most frequently by *Microsporum canis*, *Trichophyton mentagrophytes*, and *Microsporum gypseum* (Foil, 1998; Carlotti & Bensignor, 1999). *Microsporum canis* is the most commonly isolated organism in most parts of the world (Scott et al., 2001). Less commonly, *Microsporum persicolor* and other species may be seen (Carlotti & Bensignor, 1999). *Trichophyton mentagrophytes* var. *erinacei* has been reported in conjunction with exposure to hedgehogs (Fairley, 2001). This organism may more commonly cause superficial pustular dermatophytosis (see Chapter 1).

Transmission occurs via direct contact or by fomites contaminated with hair or scale from affected cats or other dogs. Dermatophytes invade actively growing hair, follicular keratin, and less frequently, the stratum corneum of the epidermis (see superficial pustular dermatophytosis, Chapter 1). Well-adapted dermatophytes (usually *Microsporum canis*) induce minimal host response, and affected dogs may become inapparent carriers. Infection with *Trichophyton mentagrophytes*, *Microsporum gypseum*, or other dermatophytes which are poorly adapted to the dog elicits a greater inflammatory reaction. Dermatophytosis usually is self-limiting in healthy dogs because the normal host inflammatory response eliminates infection. Dogs with compromised immune systems are at greater risk for chronic and generalized disease. Canine dermatophytosis is a zoonotic disease.

Dermatophytosis is one of the most pleomorphic canine skin diseases. Classically, canine dermatophytosis presents as an expanding circular patch of alopecia with an erythematous active crusted border and an area of central clearing and healing. Lesions may be well circumscribed with a slowly expanding border. Affected hairs at the margin or remaining within the alopecic patch are thickened and broken creating short stubble. Follicular papules or frank pustules may be seen. Scaling and crusting vary from minimal to severe, and may be generalized. Hyperpigmentation occurs with chronicity in dog breeds predisposed to inflammatory pigmentation.

The face and forelegs are common sites for initial infection, since these sites on dogs interface most prominently with the environment. The planum nasale is involved

rarely, despite active infection in adjacent haired skin. Onychomycosis usually is manifested by chronic infection of the ungual fold (Foil, 1998). Somewhat bilaterally symmetric facial involvement (especially involving the muzzle) with marked exfoliation and crusting may be seen with *Trichophyton mentagrophytes*, and *Microsporum gypseum*; many of these cases may correspond microscopically to superficial pustular dermatophytosis (see Chapter 1). Pruritus or pain may be seen with more florid inflammation. An uncommon and distinctive subgroup termed 'kerion' is characterized by intense focal inflammation and follicular destruction (see Chapter 17).

Breed or sex predilections have not been determined statistically. However, one author (P.J.I.) suspects that the Dalmatian, Poodle, Jack Russell Terrier, Manchester Terrier, and Yorkshire Terrier may be at increased risk for generalized disease. Dogs less than 1 year of age are at greater risk for dermatophytosis (Scott et al., 2001). Older dogs with decreased immune function also may be at increased risk for generalized dermatophytosis.

Clinical differential diagnoses are legion for this protean disease. Canine dermatophytosis is greatly overdiagnosed; conversely, bona fide cases often are misdiagnosed. Superficial bacterial folliculitis and superficial spreading pyoderma are the major differential diagnoses, since they may present with rings of alopecia and crusting. Frank pustules and peripheral collarettes are substantially less common with dermatophytosis than with bacterial folliculitis. Seborrheic dermatitis in dogs with primary seborrhea may mimic dermatophytosis, especially in the Cocker Spaniel. Severe exfoliative and crusting dermatophytosis (especially bilaterally symmetric lesions involving the muzzle) may be visually similar to facially-oriented autoimmune skin disease such as pemphigus foliaceus or pemphigus erythematosus. Unlike facially-oriented autoimmune skin disease, the planum nasale is rarely violated in facial dermatophytosis. Dermatophyte culture is critical in the differential diagnosis; histopathology also will allow differentiation.

Biopsy site selection

Biopsy specimens should be obtained from areas of broken hairs or exfoliation. Areas just inside the margins of expanding foci of inflammation and alopecia are most beneficial. Centers of alopecic foci may not be as helpful in establishing a diagnosis, since fungal organisms may no longer be present in these healing lesions.

Histopathology (Figures 16.15 and 16.16)

The epidermis and follicular infundibula are variably acanthotic and may be hyperkeratotic. In some cases, surface serocellular crusting is evident. Protruding hair shafts may be entrapped by keratin and crusts. Dermatophytes may be seen in or around protruding hairs, or occasionally free within epidermal keratin. Canine dermatophytosis involving keratin-colonizing organisms, such as *Trichophyton* spp. (superficial pustular dermatophytosis or keratin-colonizing dermatophytosis) may be manifested predominantly as superficial epidermal pustular inflammation, sometimes with acantholysis (see Chapter 1). However, mixed patterns are common, and may include mural folliculitis (see Chapter 18).

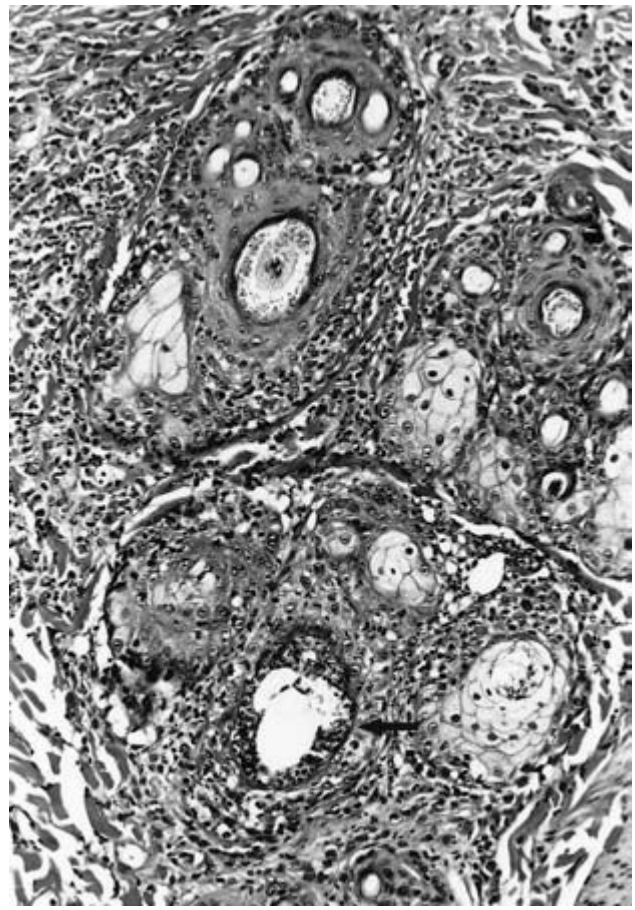


Fig. 16.15 Canine dermatophytosis. Dark spores surround hair shafts at top; luminal folliculitis is at bottom (arrow).

Mild or moderate neutrophilic folliculitis is sometimes accompanied by follicular rupture. Discrete granulomas surrounding central free hair may be seen. A nodular lesion of focally extensive furunculosis due to dermatophytes is referred to as a kerion (see Chapter 17). There may be follicular acantholysis in some cases, resembling pemphigus foliaceus (see p. 415). Neutrophils, lymphocytes, and macrophages mildly to moderately infiltrate the superficial to middle dermis and surround hair follicles. In other cases, inflammation is minimal and predominantly perifollicular. Hair shafts are variably infiltrated

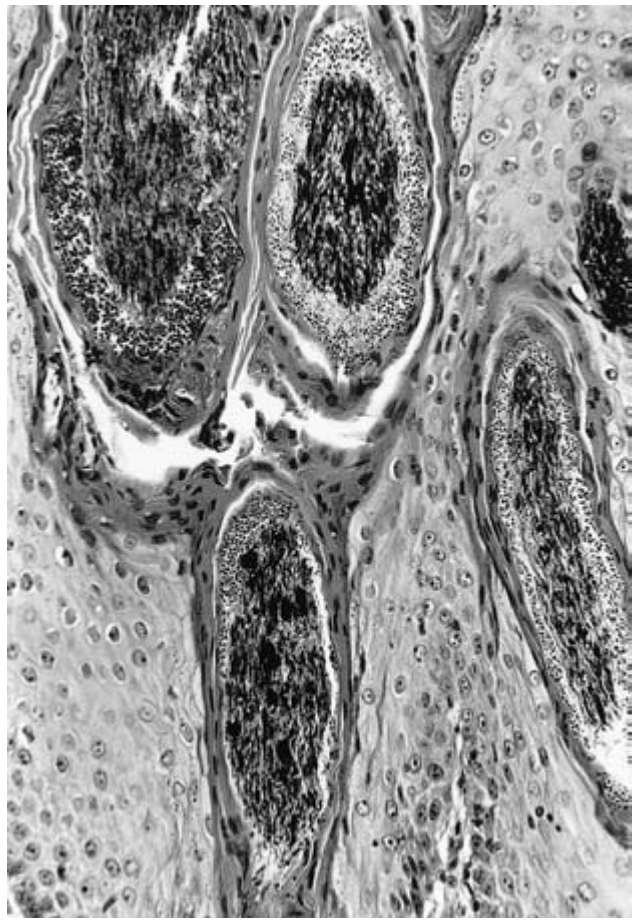


Fig. 16.16 Canine dermatophytosis demonstrating heavy colonization of hairs by numerous dermatophytic spores and wavy, poorly stained hyphae.

and surrounded by dermatophytic spores and hyphae, the latter of which are orange-pink and refractile with hematoxylin and eosin. A periodic acid–Schiff (PAS) stain will accentuate dermatophytes as bright magenta; Gomori's methenamine silver (GMS) colors them black.

The folliculocentric inflammation of dermatophytosis may be similar to bacterial folliculitis and furunculosis and to demodicosis. Differential diagnosis is facilitated by identification of the offending agent.

PEMPHIGUS FOLIACEUS

Clinical features (Figures 16.17 through 16.19)

See Chapter 1.

Biopsy site selection

See Chapter 1.

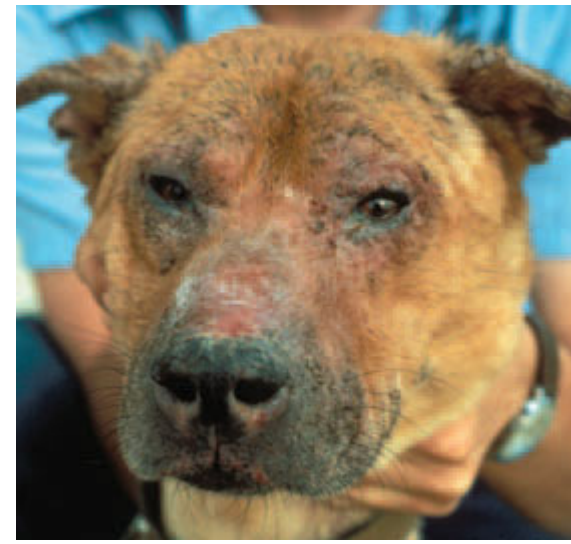


Fig. 16.17 Canine pemphigus foliaceus in a Labrador Retriever-crossbreed. Bilaterally symmetric alopecia and adherent crusting are present on the dorsal and lateral muzzle, periorbitally, on the pinnae, and on the temporal region. The planum nasale also is affected.



Fig. 16.18 Side view of the same dog as in Fig. 16.17. Diffuse erythema is present in the affected areas.

Histopathology (Figures 16.20 and 16.21)

Epidermal features of this disease have been previously described (see Chapter 1), and principally include subcorneal pustules with acantholysis. In some cases of canine pemphigus foliaceus, particularly those that are localized to the face, pustules with acantholysis also form within follicular infundibula, or less commonly as deeply as the isthmus of the hair follicle. These follicular pustules often form in 'subcorneal' location, i.e. beneath the keratin lining the outer root sheath, and may extend through the entire wall of the follicle ('panfollicular pemphigus'). Small, early pustules may form within the center



Fig. 16.19 Canine pemphigus foliaceus in an aged Spitz-crossbreed. Bilateral symmetry is striking in the lesions of the face and distal extremities.



Fig. 16.20 Follicular pemphigus foliaceus in a dog. The follicular pustule at top contains acantholytic cells.

of the follicular wall. In some cases, larger pustules may rupture into the follicular lumen. Pustules contain neutrophils, variable eosinophils, and acantholytic and/or apoptotic keratinocytes.

Variable admixtures of lymphocytes, macrophages, plasma cells, neutrophils, and eosinophils surround follicles. Follicular rupture with release of clusters or 'rafts' of acantholytic cells into the surrounding dermis may be associated with severe suppurative and pyogranulomatous dermal inflammation, as seen in deep folliculitis and furunculosis (see Chapter 17). Folliculitis and furunculosis without evidence of acantholysis has been documented in biopsy specimens from cases of otherwise histopathologically typical pemphigus foliaceus; presumably these cases had concurrent deep pyoderma. Immunofluorescence or immunohistochemistry may reveal deposition of IgG in intercellular spaces of the superficial portions of hair follicles in addition to the epidermis.

Deep follicular pustulation in hair follicles, as seen in 'panfollicular' pemphigus foliaceus, may be comparable to pemphigus vegetans because the pustules may lie in suprabasilar location, thus mimicking suprabasilar clefting of pemphigus vegetans (a variant of pemphigus vulgaris in humans). The case in the first edition of this textbook was most likely panfollicular pemphigus foliaceus and not pemphigus vegetans. The authors have not seen a convincing case of pemphigus vegetans in the dog or cat.

Differential diagnoses principally include deep bacterial folliculitis and furunculosis, and dermatophytosis. Active acantholysis is a differential feature of follicular pemphigus foliaceus, but may be absent from foci of severe follicular inflammation observed in isolated lesions. Conversely, secondary acantholysis due to the proteolytic action of neutrophils may be a feature of bacterial folliculitis and dermatophytosis. This difficulty may be accentuated by the coexistence of pemphigus foliaceus and bacterial folliculitis and furunculosis in some dogs. Clinical data may be critical in these cases. Examination of multiple specimens will increase the chances of locating diagnostic histopathologic features of pemphigus foliaceus. A positive result from immunofluorescence or immunohistochemistry is supportive, but is not always forthcoming in random specimens obtained for biopsy.

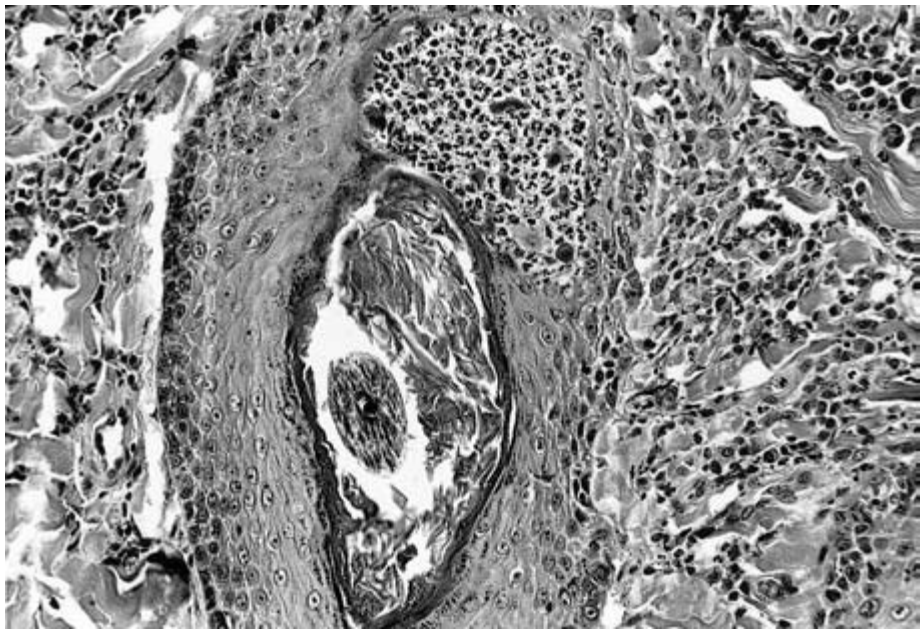


Fig. 16.21 Higher magnification of follicular pemphigus foliaceus. Note large 'subcorneal' follicular pustule containing acantholytic cells.

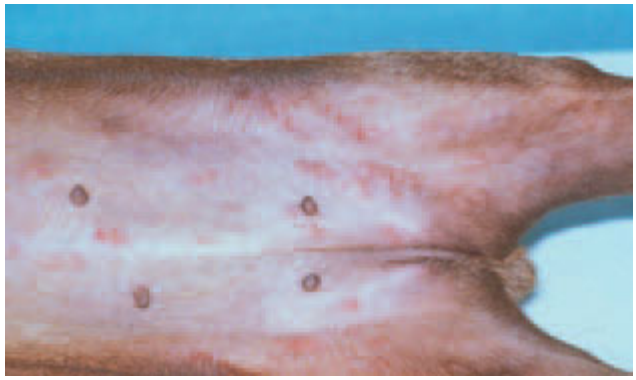


Fig. 16.22 Sterile eosinophilic pustulosis on the abdomen of a dog. Multiple intact pustules are seen. (Photograph courtesy D.-N. Carlotti.)

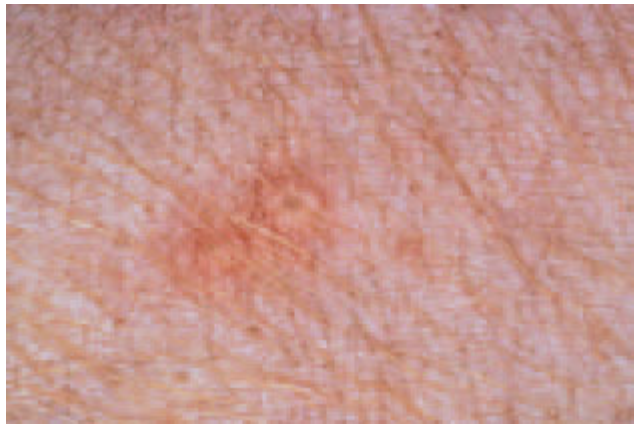


Fig. 16.23 Closer view of the dog in Fig. 16.22. A hair protruding from the central intact pustule indicates follicular orientation. (Photograph courtesy D.-N. Carlotti.)

STERILE EOSINOPHILIC PUSTULOSIS

Clinical features (Figures 16.22 and 16.23)

Sterile eosinophilic pustulosis is a very rare, idiopathic canine skin disease characterized by sterile eosinophilic pustules and peripheral eosinophilia (Scott, 1984, 1987; Carlotti et al., 1989). Marked tissue and peripheral eosinophilia coupled with response to immunosuppressive dosages of glucocorticoids suggest immune dysfunction as the pathogenesis of this disease (Scott, 1987).

Erythematous follicular and nonfollicular pustules and papules develop rapidly. Pustules may be circular or irregular in outline. Central healing with hyperpigmentation and the formation of peripheral epidermal collarettes lead to distinctive target lesions. Annular erosions may form within the confines of the collarettes. Reported cases have primarily involved the ventral abdomen or have been more generalized. The head is affected uncommonly. Pruritus is marked and self-trauma may lead to excoriation. Fever, anorexia, depression, and regional lymphadenopathy have been reported as inconsistent findings (Scott, 1984, 1987; Carlotti et al., 1989).

Breed, age, or sex predilections have not been noted. Clinical differential diagnoses should include superficial spreading pyoderma, superficial bacterial folliculitis, and pustular drug reactions. Dermatophytosis, demodicosis,



Fig. 16.24 Sterile eosinophilic pustulosis in a dog. A large eosinophilic pustule has ruptured the affected hair follicle.

pemphigus foliaceus, and subcorneal pustular dermatosis also may resemble sterile eosinophilic pustulosis. Smears of pustular contents, bacterial culture from intact pustules, skin scrapings, and dermatophyte cultures should be performed to differentiate among these diseases. Sterile eosinophilic pustulosis must be diagnosed by ruling out the above-mentioned diseases and by supportive histopathology.

Biopsy site selection

Skin biopsy specimens should include multiple intact pustules. Care must be taken in sampling not to disrupt fragile pustules.

Histopathology (Figure 16.24)

Acanthosis is mild to moderate. The epidermis has delicate, superficial and often subcorneal pustules that contain predominantly eosinophils and fewer neutrophils. There may be accompanying mild to moderate spongiosis. Frank vesiculation was reported (Carlotti et al., 1989). Occasional acantholytic keratinocytes were described (Scott, 1987).

Pustules may be confined to the subcorneal epidermis (Craig, 1993); in other cases eosinophilic folliculitis may affect superficial and sometimes deep hair follicles. There may be rupture to form eosinophilic furuncles. Eosinophils also may surround affected follicles in a nodular configuration and may be distributed diffusely throughout the superficial and middle dermis. Mixed infiltrations of neutrophils, lymphocytes, and macrophages also are present. In some cases seen by Scott, eosinophilic degranulation to form flame figures was observed (Scott, D.W., personal communication, 1990).

Differential diagnoses include eosinophilic furunculosis of the face, or superficial bacterial folliculitis in which eosinophils are predominant. Pemphigus foliaceus may need to be considered for lesions that are confined to the subcorneal epidermis and which feature acantholytic keratinocytes. Eosinophilic pustulosis tends to be a more superficial process than eosinophilic furunculosis of the face; although eosinophilic furuncles occur in both, the furuncles of the latter are often much more explosively destructive to hair follicles. Pemphigus foliaceus should feature more acantholysis and fewer eosinophils than sterile eosinophilic pustulosis. Clinical differentiation may be required. Response to appropriate antibiotic therapy usually is required to differentiate sterile eosinophilic pustulosis from pyoderma with prominent eosinophils.

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See Chapter 1.

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Chapter 17

Pustular and nodular diseases with adnexal destruction

The diseases of this chapter mostly are characterized by prominent pustular inflammation of the adnexa, leading to rupture and destruction of these structures. Subsequent inflammation at the site of a destroyed adnexal appendage is often nodular in distribution; a granulomatous infiltrate is common as a 'foreign body' response to released hair and keratin, as well as glandular secretion. Most of the diseases have an infectious or parasitic cause that is often apparent in tissue (demodicosis, kerion, and rhabditic dermatitis); arthropod insult is implicated in eosinophilic furunculosis. Furunculosis may also be secondary to trauma (postgrooming furunculosis and furunculosis occurring in acral lick dermatitis). In several diseases, characteristics of the follicle or hair shafts, including primary accumulation of keratin in the infundibulum, lead to secondary rupture and pyoderma; some of these are also aggravated by trauma (canine callus, feline acne, actinic comedones, and interdigital furunculosis). Sebaceous adenitis is included here due to its basic pattern of inflammatory-mediated effacement of sebaceous glands

DEEP BACTERIAL FOLLICULITIS AND FURUNCULOSIS

(Synonym: deep pyoderma)

Clinical features (Figures 17.1 through 17.3)

Deep bacterial folliculitis and furunculosis is a relatively common, somewhat heterogeneous group of canine bacterial skin diseases united by similar histopathologic features (Ihrke, 1996, 1998). It is convenient to separate some forms of deep bacterial folliculitis and furunculosis where either clinical or histopathologic features are distinctive. German Shepherd Dog pyoderma, for example, is a unique clinical entity and is discussed separately (see p. 424).

Deep bacterial folliculitis and furunculosis may be manifested in skin diseases with a traumatic component, and may be termed 'traumatic furunculosis' in that context. Diseases featuring traumatic furunculosis include acral lick dermatitis, interdigital furunculosis, callus pyoderma, postgrooming furunculosis, and canine acne; these entities also are discussed separately in this chapter. Briefly, traumatic furunculosis in acral lick dermatitis probably is precipitated by self-inflicted follicular trauma resulting from persistent licking. Interdigital furunculosis probably is initiated by short, bristly hairs rubbing against the skin of apposing digits, creating trauma in the dorsal interdigital webs, leading to follicular rupture and secondary infection. Callus pyoderma develops as a sequela to repeated trauma to the callus; the comedones of callus likely are predisposed to trauma-induced rupture. Another distinctive subgroup, termed 'postgrooming furunculosis', probably is partially precipitated in some cases by back-combing, back-clipping, or overly aggressive bathing against the direction of hair growth.

Deep pyoderma may be seen without evidence of prior superficial pyoderma or as a sequela to superficial bacterial folliculitis (see Chapter 16). Deep bacterial folliculitis and furunculosis commonly coexist, as deep follicular inflammation leads to follicular rupture creating furuncles. In furunculosis, traumatically released hair fragments and remnants of follicular keratin accentuate inflammation via a foreign body response, which may lead to scarring.

As in other canine pyoderma, *Staphylococcus intermedius* is the primary pathogen. However, secondary invaders such as *Proteus* sp., *Pseudomonas* sp., and *Escherichia coli* are seen more frequently in deeper infections. *Pseudomonas* sp. also has been isolated from dorsal furunculosis following shampooing (postgrooming furunculosis; see p. 427).

Underlying triggers commonly initiate deep pyoderma. Generalized demodicosis is one of the most common triggers and must be ruled out in any case of deep pyoderma. Other predisposing causes include hyperadrenocorticism, the injudicious use of glucocorticoids (iatrogenic hyperglucocorticoidism), widespread actinic disease (see actinic furunculosis, p. 429), and immunologic defects. Comedonal diseases such as calluses, actinic comedones, and Schnauzer comedo syndrome (see Chapter 8) also predis-

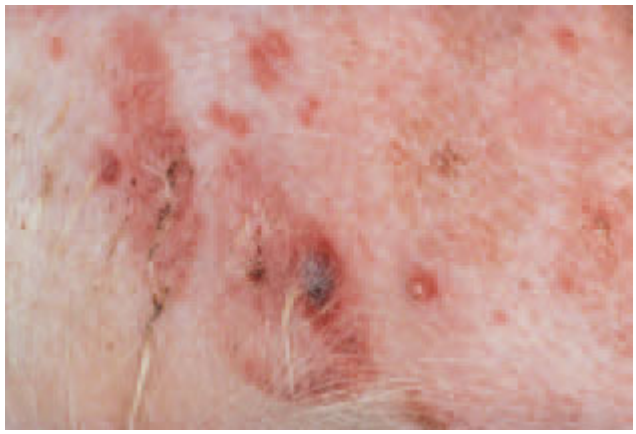


Fig. 17.1 Deep bacterial folliculitis and furunculosis on the abdomen of a dog. An intact hemorrhagic bullae is surrounded by intact and ulcerated pustules.



Fig. 17.2 Deep bacterial folliculitis and furunculosis with attendant self-trauma ('pyotraumatic furunculosis') in a Golden Retriever. A well-demarcated eroded plaque is present ventral to the ear.



Fig. 17.3 Deep pyoderma affecting the pressure points of the stifle in a Boxer. Multiple fistulous tracts with hemorrhage are present.

pose to deep pyoderma via rupture of the abnormal follicle. Triggers are not always identified in deep pyoderma.

Since deep pyoderma may develop from superficial pyoderma, the lesions of superficial pyoderma may precede and coexist with deeper infection. The pustules of deep bacterial folliculitis and furunculosis tend to be larger and vary in color from white to yellow-gray; additionally, firm nodules usually are present. Pustules and nodules rupture, forming fistulas and hemorrhagic crusts. Erosions and ulcers develop secondary to inflammation, necrosis, and self-trauma initiated by pain or pruritus. Alopecia is a sequel to follicular inflammation and destruction. Hyperpigmentation and lichenification also are common. Scarring may be present.

Hemorrhagic bullae are a distinctive clinical feature in some cases of canine deep pyoderma. Hemorrhagic bullae are seen most often in the German Shepherd Dog (see p. 424), but may be present occasionally in many breeds including Bull Terriers and Dalmatians. Hemorrhagic bullae may be seen with deep pyoderma secondary to demodicosis and in actinic furunculosis. Well-circumscribed, firm nodules exhibit a deep red to dark blue hue. Newer lesions are brightly red, signifying fresh hemorrhage. Hemorrhagic rings sometimes are present surrounding the bullae.

Regularly affected sites include the comparatively glabrous intertriginous zones of the groin, axillae, and interdigital webs, plus pressure points. Lesions may be generalized in some dogs, particularly the German Shepherd Dog (see p. 424). Severity of infection and magnitude of spread commonly relate to the severity of underlying disease. As an example, dogs with more severe immunosuppressive disease tend to develop deeper and more widespread infection. Regional and generalized lymphadenopathy is common. Pain and pruritus are frequent features. Constitutional signs such as fever, lethargy, and inappetence may be seen contingent on the severity and extent of infection.

An additional subgroup of deep pyoderma clinically mimics pyotraumatic dermatitis (see Chapter 6). Deep pyoderma is not secondary to classical pyotraumatic dermatitis in this syndrome, but instead deep pyoderma initiates a similar clinical appearance through relentless self trauma superimposed over subjacent deep infection (Ihrke, 1996). This syndrome, termed 'pyotraumatic furunculosis', begins with painful, focal erythema and swelling overlying areas of developing deep pyoderma. Presumably, pain induces self-trauma, leading to severe ulceration, exudation, and the lesions of pyotraumatic dermatitis. The lesions occur predominantly on the head and neck regions. Pyotraumatic furunculosis is seen primarily in the Golden Retriever, but also in other large breeds including the Saint Bernard and Bernese Mountain Dog.

Breed predilections have been observed for deep bacterial folliculitis and furunculosis. Predisposed long-coated dogs include the German Shepherd Dog, Golden Retriever, and Irish Setter. The German Shepherd Dog is predisposed to develop deep rather that superficial pyoderma (Denerolle et al., 1998). Among the short-coated breeds, the Bull Terrier, Dalmatian, Doberman Pinscher, and Great Dane are at apparently increased risk. Deep pyoderma secondary to demodicosis or other diseases follows the predilections of the underlying disease. Age or sex predilections have not been noted.

Clinical differential diagnoses for deep bacterial folliculitis and furunculosis should include cutaneous infections of systemic fungi, opportunistic fungi or algae, and opportunistic mycobacterial infection. Differentiation is accomplished by the microscopic examination of smears of exudate, bacterial and fungal cultures, and histopathology. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see Chapter 12). Once deep pyoderma is diagnosed, the clinician must assess for underlying triggers.

Biopsy site selection

Early intact pustules, nodules, or bullae are recommended lesions for biopsy. Ulcerated or scarred lesions may be less likely to yield diagnostic follicular inflammation due to loss of normal tissue architecture. If most of the available affected tissue is friable due to severe inflammation or hemorrhage, larger punch biopsy or wedge resection is preferable, since smaller punch biopsy creates traumatic artifact in fragile tissue.

Histopathology (Figures 17.4 through 17.7)

The epidermis usually is acanthotic and may be ulcerated. Superficial serocellular or sanguinocellular crusting is common. Features of pyotraumatic dermatitis (see Chapter 6) may be present in breeds such as the Golden Retriever and Saint Bernard that are prone to pyotraumatic furunculosis.

Deep folliculitis is characterized principally by neutrophilic inflammation that accumulates within the confines of the follicular wall, generally at and below the level of the isthmus. Deep folliculitis invariably leads to follicular rupture and the formation of a furuncle as the integrity of the follicular wall breaks down due to inflammatory mediators, proteolytic enzymes, and the physical disruption of expanding inflammation. Follicles may be completely effaced and replaced by severe nodular accumulations of neutrophils, variable eosinophils, macrophages, and plasma cells. Free hair shafts may remain within large furuncles. Neutrophils, eosinophils, and macrophages tend to localize at the center of these inflammatory foci, whereas plasma cells are found at the periphery. Granulomas with giant cells may organize around displaced hair fragments to form trichogranulomas or around free keratin to form keratogranulomas (foreign body reactions). Mixed and variably intense inflammatory infiltrates of neutrophils, lymphocytes, macrophages, eosinophils, and plasma cells extend to surround adjacent intact hair follicles and adnexal glands. There is variable edema and usually mild to occasionally moderate hemorrhage. Bacteria (staphylococci) may be present in the keratin of superficial follicles, but are rarely obvious in severely inflamed foci.

Inflammation may become diffuse in the deep dermis as adjacent furuncles coalesce. Extension of inflammation to the subcutis is not uncommon; frank cellulitis (diffuse inflammation of the subcutis) occasionally may be



Fig. 17.4 Furunculosis in a Golden Retriever with pyotraumatic dermatitis. Severe pustular inflammation is replacing most of a deep follicle.

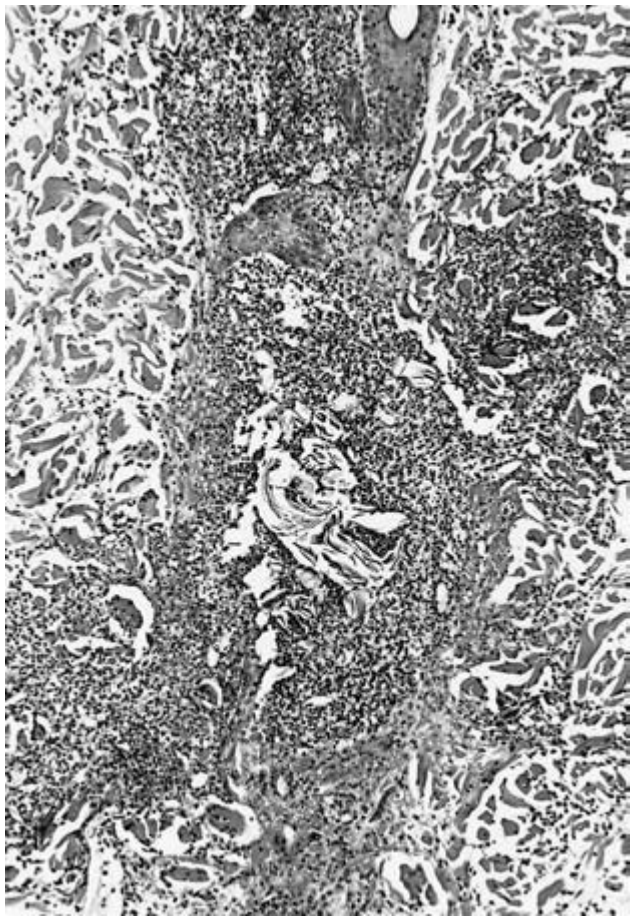


Fig. 17.5 Furunculosis in a dog. A severely inflamed follicle has ruptured; free follicular keratin is surrounded by extensive pustulation.



Fig. 17.6 Follicular bridging in a Pitt Bull Terrier-crossbreed with chronic deep pyoderma. A deep partially inflamed cyst is formed by interconnecting follicles.

observed, but is more commonly secondary to demodicosis (see p. 442). Cavitation of the severely inflamed tissue may occur, and hemorrhage may be severe in these lesions. Granulation tissue and fibrosis arise deep and peripheral to lesions in the later stages. In some cases laminar, full- or partial-thickness mature fibrous scars (cicatrices) replace previously inflamed tissue.

In some cases of deep follicular pyoderma there is 'bridging' of follicular infundibula such that adjacent follicles connect by a common, large flattened or irregular cyst formed by the lower infundibulum. These may be distended with keratin and/or large pustules. Rupture of these lesions leads to formation of large, sometimes flattened, horizontally-oriented cavities filled with neutrophils and hemorrhage. Most lesions of this type occur in a chronic clinical setting and in breeds predisposed to deep folliculitis and furunculosis, such as Bull Terriers. However, it is unknown whether defective follicles result from or contribute to severe pyoderma in these dogs.

Suppurative hidradenitis in dogs is characterized by dilatation and intraluminal neutrophilic inflammation of sweat glands. Neutrophils and variable eosinophils distend the walls of sweat glands and may extend beyond the wall to surround the glands as large pustules. Often, there is concurrent evidence of folliculitis or furunculosis; furunculosis is more common in the authors' experience. Concurrent follicular inflammation may be lacking in random biopsies from dogs with clinical pyoderma that demonstrate suppurative hidradenitis. However, as suppurative sweat gland inflammation has necessarily extended directly from the hair follicle, hidradenitis supports the presence of follicular pyoderma in these cases (Scott, 1995).

Deep bacterial folliculitis and furunculosis are complications of skin diseases with a traumatic component (traumatic furunculosis) such as acral lick dermatitis, interdigital furunculosis, canine callus pyoderma, post-grooming furunculosis, and canine acne. Specific features

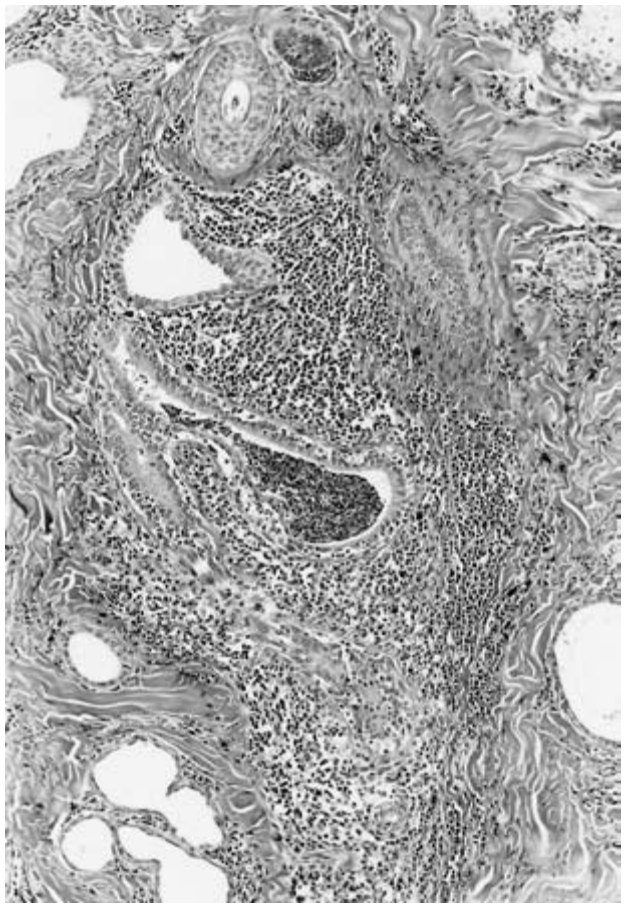


Fig. 17.7 Suppurative hidradenitis in a dog with chronic deep pyoderma. The lumen of a gland at center is filled with neutrophils.



Fig. 17.8 German Shepherd Dog pyoderma. Affected areas have been clipped to show the extent of the disease. (Photograph courtesy B.A. Atlee; case material University of California, Davis.)

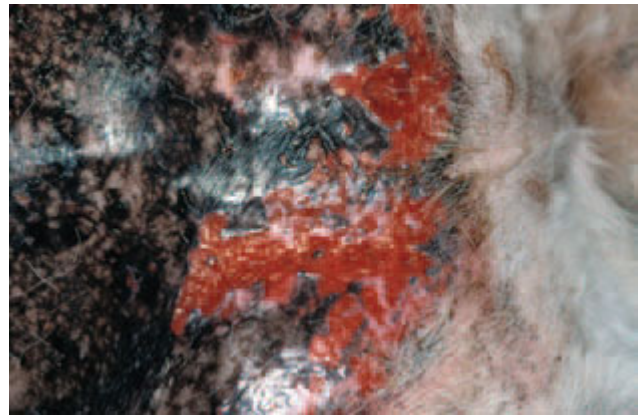


Fig. 17.9 Closer view of German Shepherd Dog pyoderma. Coalescing plaques of ulcerated, friable, devitalized tissue are present on the ventral abdomen. (Photograph courtesy T. DeManuelle; case material University of California, Davis.)

of those conditions, including anatomic site, should allow diagnosis in most cases (see elsewhere in chapter).

Other differential diagnoses include folliculitis or furunculosis resulting from dermatophytosis or demodicosis, juvenile sterile granulomatous dermatitis and lymphadenitis, and eosinophilic furunculosis of the face. Identification of organisms is required for differentiation of dermatophytosis and demodicosis. Chronic furunculosis due to dermatophytosis (kerion) may not have apparent organisms, which may make differentiation difficult on histopathologic grounds alone. In some lesions of juvenile sterile granulomatous dermatitis and lymphadenitis, inflammation is predominantly pustular and suppurative. However, luminal pustular follicular inflammation is not a typical feature of juvenile sterile granulomatous dermatitis and lymphadenitis, which features perifollicular pyogranulomas instead. Eosinophilic furunculosis of the face is superficially similar, but has a predominance of eosinophils, as well as more striking dermal edema, hemorrhage, and mucin.

GERMAN SHEPHERD DOG PYODERMA

Clinical features (Figures 17.8 through 17.10)

German Shepherd Dog pyoderma (GSDP) is a clinically distinctive, chronic, aggressive, and severe deep bacterial infection of the skin. It occurs predominantly in the German Shepherd Dog and related crossbreeds (Wisselink et al., 1985; Krick & Scott, 1989; Denerolle et al., 1998; Rosser, 1998; Ihrke & DeManuelle, 1999). The syndrome typically begins over the lateral surface of the hindlegs and the lumbosacral region, and then progresses to more generalized distribution (Krick & Scott, 1989). A familial predisposition has been documented, and an autosomal recessive mode of inheritance has been

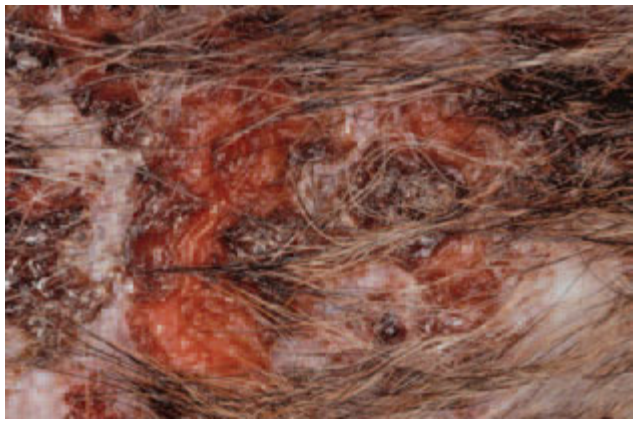


Fig. 17.10 Closer view of German Shepherd Dog pyoderma. Acute infection is superimposed on chronic lesions. (Photograph courtesy C.B. Vitale; case material University of California, Davis.)

hypothesized (Wisselink et al., 1989). It should be emphasized that German Shepherd Dogs can develop other forms of bacterial pyoderma, both superficial and deep (see p. 420 and Chapter 16), that do not meet the criteria for GSDP.

The etiology of GSDP remains unclear. Defects in cell-mediated immunity, aberrations in serum immunoglobulins, and lymphocyte subset abnormalities have been reported (Wisselink, 1988; Miller, 1991; Chabanne et al., 1995; Rosser, 1997). It is not known if these defects lead to pyoderma or occur as sequelae to persistent, severe bacterial infection. The striking and inappropriate magnitude of inflammation suggests that an exaggerated tissue response to staphylococci in these dogs might initiate an inappropriate release of cytokines and other mediators of inflammation (Ihrke & DeManuelle, 1999). Some cases of GSDP are linked to underlying flea allergy dermatitis, hypothyroidism, atopic dermatitis, and food allergy (Wisselink et al., 1985, Krick & Scott, 1989; Chabanne et al., 1995; Rosser, 1997). Chronic ehrlichiosis triggered GSDP in a small study from southern Italy (Cerundolo et al., 1998). A larger study of GSDP also performed in an endemic area for ehrlichiosis (southern France) did not identify any dogs with coexistent ehrlichiosis (Denerolle et al., 1998). Rather than viewing GSDP as a disease of multifactorial etiology, it may be more useful to view it as a characteristic clinical syndrome that can be triggered by a variety of other diseases in susceptible individuals (Ihrke & DeManuelle, 1999).

Clinical features of GSDP include erythematous papules, pustules, furuncles, hemorrhagic bullae, and fistulous tracts. Early lesions may be surrounded by strikingly circular erythematous halos. Lesions may develop rapidly, forming confluent plaques of ulcerated and eroded, friable and devitalized skin. The skin lesions of GSDP may be disproportionately severe in comparison to most other forms of pyoderma with the exception of deep pyoderma secondary to generalized demodicosis. Tenaciously adherent crusting occurs in heavily haired regions, and may shield the extent and severity of the lesions. Hyperpigmentation occurs with chronicity.

The distribution pattern is distinctive; the lateral thighs, rump, back, ventral abdomen, elbows, and distal extremities are most frequently affected. The syndrome may generalize. The chest wall and neck are additional severely affected sites, and the perioral region also may be affected. Partial bilateral symmetry is common. Pruritus and pain usually are present and may be severe. Severely affected dogs may be anorectic, cachectic, and lethargic. Regional lymphadenopathy is common. Occasionally, GSDP is seen in conjunction with perianal fistulas or metatarsal fistulation of the German Shepherd Dog (see Chapter 21).

German Shepherd Dog pyoderma is seen predominantly in the German Shepherd Dog and related crossbreeds; however, it has been observed in similar breeds such as the Belgian Malinois, Belgian Sheepdog, and the Belgian Tervuren (Rosser, 1998). One of the authors (P.J.I.) also has seen this syndrome in Belgian herding breeds. Rarely, similar lesions are seen in the Dalmatian and Bull Terrier. A marked predilection for males has been noted in two studies (Koch & Peters, 1996; Denerolle et al., 1998). German Shepherd Dog pyoderma occurs predominantly in middle aged dogs.

German Shepherd Dog pyoderma is clinically distinctive, and clinical diagnosis is generally not problematic. Clinical differential diagnoses may include deep pyoderma secondary to demodicosis, and cutaneous infections of systemic fungi and opportunistic fungi or algae, including pythiosis and entomophthoromycosis. Physical examination, cytology from fistulous tracts, and negative skin scrapings should confirm deep pyoderma without underlying demodicosis. Skin biopsy may be indicated to rule out other diseases. Culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see Chapter 12).

Biopsy site selection

Multiple specimens should be taken from intact early lesions and areas of more advanced inflammation to provide prognostic as well as diagnostic information. If most of the available affected tissue is friable due to severe inflammation or hemorrhage, larger punch biopsy or wedge resection is preferable, since smaller punch biopsy creates traumatic artifact in fragile tissue.



Fig. 17.11 German Shepherd Dog pyoderma featuring extensive dermal pustulation with disruption of a hair follicle at center.

Histopathology (Figures 17.11 and 17.12)

There is variable acanthosis with ulceration and exudation. Hemorrhagic bullae, the hallmark feature of GSDP, consist of large pustules in the superficial to middle dermis, accompanied by severe hemorrhage. Early hemorrhagic bullae may exclude follicular involvement and are often localized strikingly in interfollicular spaces. However, flakes of keratin have been observed by one author (E.J.W.) within pustules, suggesting superficial follicular perforation may occur. Larger pustules may severely disrupt and replace dermal architecture, often creating 'lakes' of neutrophils in the skin. Neutrophils predominate, but small numbers of eosinophils and macrophages may be present within pustules; keratin and hair shaft fragments may be intermingled if there is follicular destruction. Frank folliculitis and furunculosis are less commonly observed. Granulation tissue and fibrosis occur deep and peripheral to lesions in the later stages. In some cases, laminar, full- or partial-thickness mature fibrous scars (cicatrices) replace previously inflamed tissue.

Differential diagnosis is not problematic if typical hemorrhagic bullae are present. Interfollicular location of lesions tends to separate this syndrome from classical deep bacterial folliculitis and furunculosis (see p. 420); late fibrosing lesions or lesions with furuncles may be difficult to distinguish, however. Clinical differentiation may be required.



Fig. 17.12 Higher magnification of Fig. 17.11. Neutrophils, erythrocytes, keratin, and hair shafts are intermingled.

POSTGROOMING FURUNCULOSIS

Clinical features (Figures 17.13 and 17.14)

Postgrooming furunculosis is an uncommon, distinctive subgroup of deep pyoderma believed to be precipitated by bathing or grooming. The syndrome is dramatically acute, fulminant, and markedly painful.

Grooming activities such as back-combing, back-clipping, or overly aggressive bathing 'against the haircoat' may traumatically displace hairs through the walls of hair follicles, creating follicular perforation. Postgrooming furunculosis of this type may be more likely to occur in dog breeds with short, stiff haircoats. The dorsal midline of the trunk often is most severely affected, supporting back-grooming as a trigger, as larger dorsal hairs may perforate hair follicles more readily.



Fig. 17.13 Postgrooming furunculosis in a Dogo. The dog had been bathed at a self-service dog washing facility. Alopecia and inflammation are noted predominantly along the dorsum.



Fig. 17.14 Closer view of the dorsal midline region of the dog in Fig. 17.13. Patchy partial alopecia with scattered erythematous papules is present. Nodular inflammation was palpable.

Bacterial contamination of shampoo or bathing equipment may be pivotal in the development of many cases of postgrooming furunculosis. Shampoo is frequently applied to the dorsal trunk before bathing begins, reflecting the dorsal midline distribution of subsequent lesions. Self-serve dog washing facilities and grooming parlors using large communal containers of shampoo, made by adding tap water to a concentrate, have been implicated historically by the authors as a source of postgrooming furunculosis. Communal grooming instruments may also play a role. Typically, lesions occur acutely and fulminantly within 24 to 48 hours after attending these facilities, suggesting cause and effect.

Various bacteria, including *Staphylococcus intermedius*, *Pseudomonas aeruginosa*, *Proteus* sp., and *Escherichia coli*, have been grown in pure or mixed culture from pustules. Some of the recently reported cases of acute, dorsal truncal deep pyoderma due to *Pseudomonas aeruginosa* infection (Hillier et al., 2003) may, in fact, be examples of postgrooming furunculosis. Recently, various bacteria including *Pseudomonas* spp. were cultured from shampoo implicated in a case of postgrooming furunculosis.

Localized foci of intense erythema and swelling rapidly eventuate in the formation of erythematous pustules and hemorrhagic bullae. Punctate foci of erosion or ulceration lead to fistulation and drainage. Early in the clinical course, edema may cause the hairs in affected areas to stand straight up. As severity of infection increases, hairs are shed from affected hair follicles. Lesions begin as well-demarcated foci, but may generalize if not treated. The dorsal trunk is most commonly affected, and lesions may be in a dorsal stripe down the neck and back, particularly in cases due to putative contaminated shampoo. Lesions are markedly painful. Severely affected dogs may be febrile.

Postgrooming furunculosis can occur in any breed. Dog breeds with short, stiff, bristly hairs probably may be at increased risk for postgrooming furunculosis, primarily due to ease of traumatic follicular rupture. The authors have seen this syndrome in Boxer Dogs, Doberman Pinschers, Rottweilers, and Great Danes. Long-coated breeds such as Cocker Spaniels, English Setters, Siberian Huskies and Chesapeake Bay Retrievers have been seen with postgrooming furunculosis linked to dog washing facilities or shampooing.

Postgrooming furunculosis is visually distinctive. Clinical differential diagnoses include deep bacterial follicul-

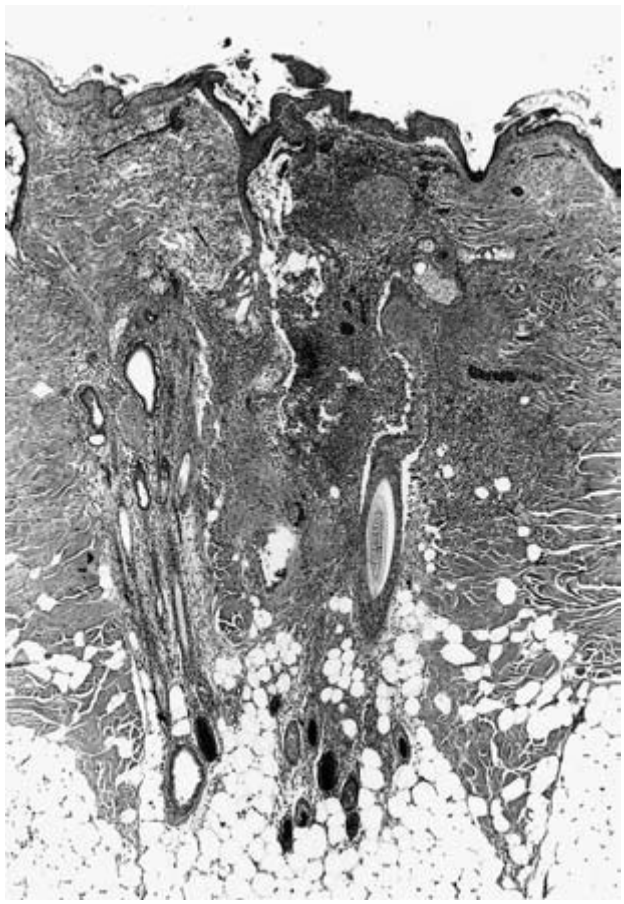


Fig. 17.15 Postgrooming furunculosis. A large pustule has broken through the follicular wall; note the relatively superficial location of the furuncle.

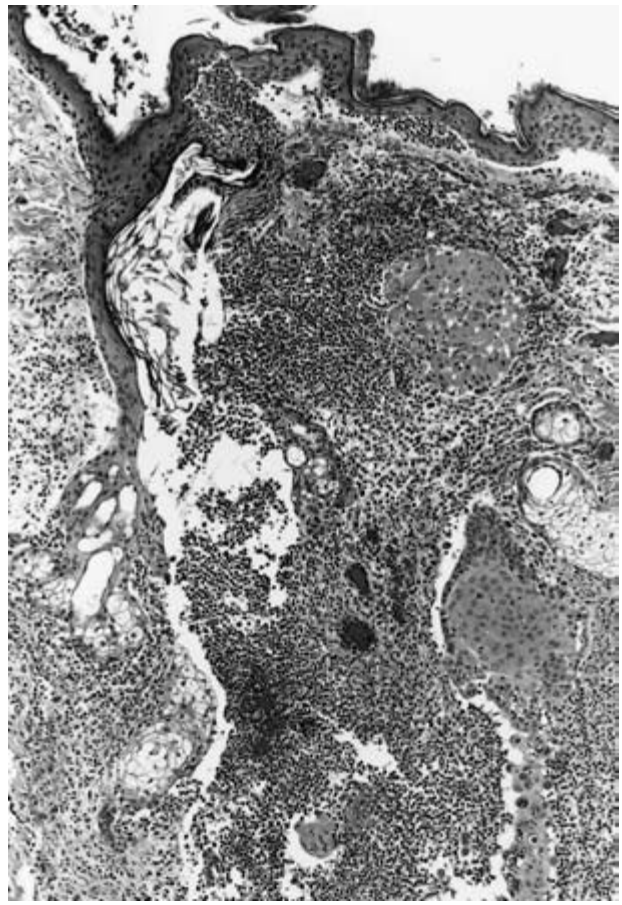


Fig. 17.16 Higher magnification of Fig. 17.15. Note abundant, darkly staining, congested blood vessels as well as free hemorrhage (near bottom).

itis and furunculosis due to other triggers (see p. 420). A correlative history of recent grooming or the use of a self-service dog washing facility increases the likelihood of the diagnosis. In that historical setting, typical physical and histopathologic findings confirm the diagnosis.

Biopsy site selection

Biopsy specimens should be procured from pustules and hemorrhagic bullae. Larger punch biopsy is preferable, since smaller biopsy may create artifact in friable tissue.

Histopathology (Figures 17.15 and 17.16)

The epidermis is generally acanthotic. There may be attenuation or ulceration over areas of pustule formation. There is generally massive neutrophilic pustulation in and around destroyed hair follicles. Hemorrhage is often abundant, but nonhemorrhagic furuncles are also evident. Pustular inflammation, mingled with hemorrhage and edema, extends to the surrounding dermis and in some cases to the panniculus as well. Often furuncles are surprisingly superficial in location, given their severity, and may project slightly above the epidermis. Free hair shafts lie at the centers of large pustules. Fewer eosinophils and macrophages are intermingled. Edema, congestion, and mild inflammation extend to the regional nonpustular dermis. Chronic lesions of furunculosis, including granuloma formation and scarring, are rarely presented, perhaps due to the acute and severe nature of this entity, which results in early biopsy.

Differential diagnoses principally include nongrooming-associated bacterial furunculosis and eosinophilic furunculosis of the face. The former tends not to feature severe hemorrhage unless lesions are deep and severe; the latter is prominently eosinophilic. The pustules of postgrooming furunculosis are often more superficial. Deep bacterial folliculitis and furunculosis are complications of other skin diseases with a traumatic component such as acral lick dermatitis, interdigital furunculosis, canine



Fig. 17.17 Acral lick dermatitis on the medial aspect of a foreleg. The lesion is raised and well-demarcated, and has several fistulas associated with deep secondary bacterial infection. (Photograph courtesy A. Werner; case material University of California, Davis.)

callus pyoderma, and canine acne. Specific features, including anatomic location, should allow definitive diagnosis in most cases.

ACRAL LICK DERMATITIS

Clinical features (Figure 17.17)

See Chapter 7.

Biopsy site selection

See Chapter 7.

Histopathology (Figures 17.18 and 17.19)

Acral lick lesions demonstrate severe acanthosis, ulceration, vertical streaking fibrosis, and perihidradenitis (see Chapter 7). In addition there may be traumatic furunculosis. Free keratin and hair shafts are often displaced well beneath the level of the hair follicles. Hair may be found in the superficial subcutis. Inflammation is generally deep as well, and may progress to cellulitis (diffuse inflammation of the subcutis) in severe cases. Foreign body granulomas or pyogranulomas with giant cells may form around fragments of hairs (trichogranulomas), or around keratin (keratogranulomas). There is often fibrosis deep and peripheral to inflammatory foci. Fibrous connective tissue may surround displaced hair shafts.

Displaced hairs imply pressure or frictional trauma, but are not necessarily specific to a traumatic etiology. Severe follicular inflammation alone may be sufficient to 'explode' hair follicles and result in displaced hair shafts. However, very deep embedment of hair shafts is highly suggestive of trauma. Traumatic furunculosis sometimes is inferred from the clinical setting in cases where furunculosis is not accompanied by displaced hairs.



Fig. 17.18 Furunculosis in acral lick dermatitis. A large pustule has exploded through the wall of the central hair follicle.

Differential diagnosis includes traumatic furunculosis in other settings, such as canine callus pyoderma, interdigital furunculosis, canine acne, and postgrooming furunculosis. The anatomic location of the lesions and concurrent histologic features of acral lick dermatitis usually allow differentiation.

ACTINIC FURUNCULOSIS

Clinical features (Figure 17.20)

Actinic furunculosis is a relatively uncommon, solar-induced, deep bacterial pyoderma that is seen most frequently in environments with enhanced solar exposure. Actinic furunculosis usually occurs in conjunction with a spectrum of other solar-induced preneoplastic and neoplastic changes, including actinic keratosis (see Chapters 7 and 22), actinic comedones (see Chapter 8), solar elastosis and fibrosis (see Chapter 15), and squamous cell carcinoma (see Chapter 22). Actinic furunculosis can develop

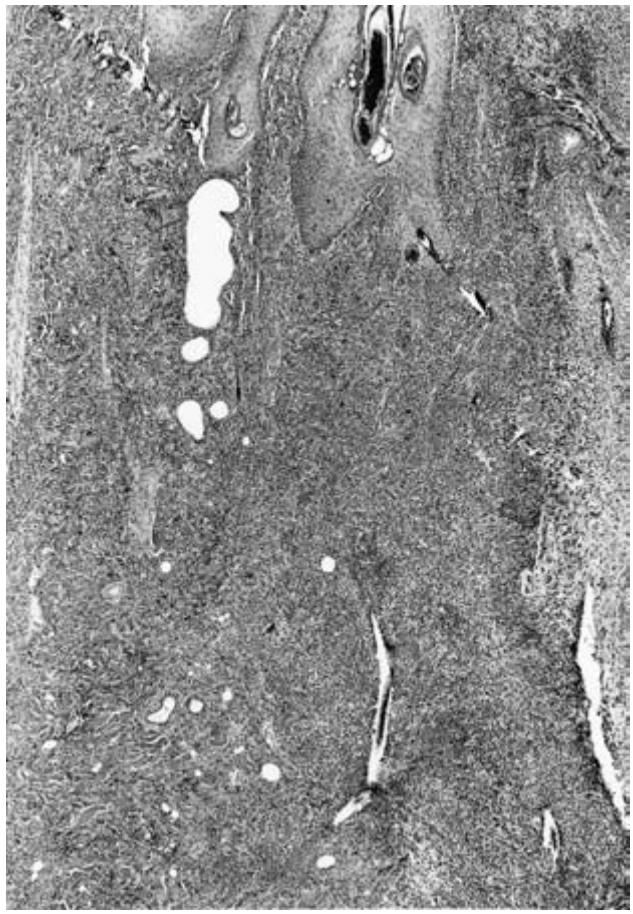


Fig. 17.19 Traumatic furunculosis in acral lick dermatitis. A deeply displaced hair shaft (near bottom) lies in a sea of suppurative inflammation. A broken hair shaft is extruding from a hair follicle near the top right.

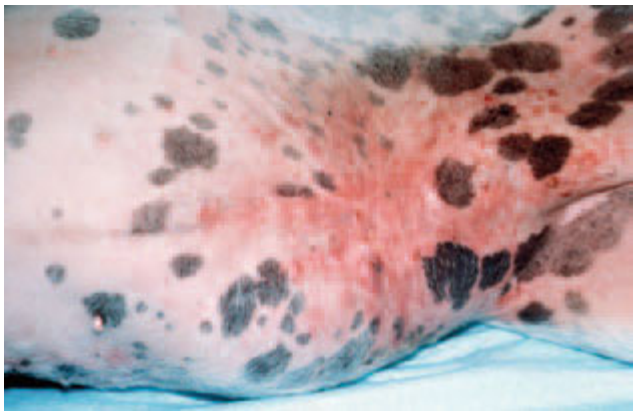


Fig. 17.20 Actinic furunculosis amid widespread actinic damage on the ventrum of a Dalmatian prone to sunbathing. Erythematous nodules and papules have developed in the setting of actinic damage.

in any hair follicle located in regions of solar damage, or can arise directly from actinic comedones.

Crusted, erythematous nodules and hemorrhagic bullae are the most common lesions seen with actinic furunculosis. Nodules may be intact or fistulated. Adherent crusts usually are hemorrhagic. The clinical features of actinic furunculosis occur in the context of other solar-induced lesions; for example, actinic furuncles may develop in conjunction with the roughened, exfoliating, indurated erythematous plaques of actinic keratosis. Affected regions exhibit varying degrees of irregular firmness and thickening, suggesting more widespread solar-induced change. The glabrous skin of the ventral and lateral abdomen, inner thighs, and dorsal muzzle is most frequently affected. Lesions may be painful or pruritic, eliciting self-grooming of exudate and crusts.

As for other actinic lesions, lightly pigmented, sparsely haired animals are more likely to develop actinic furunculosis. Dalmatians, Whippets, Italian Greyhounds, Greyhounds, American Staffordshire Terriers, Bull Terriers, Beagles, and Basset Hounds are at increased risk for all actinic lesions. Actinic furunculosis occurs most commonly in older animals, but has been seen in dogs as young as 2 years of age. Animals spending substantial time outdoors in areas of the world with increased solar exposure are at greater risk. Many affected dogs are reported to be sunbathers and spend long periods of time in dorsal or lateral recumbency in direct sunlight.

Clinical differential diagnoses for actinic furunculosis include other causes of deep bacterial folliculitis and furunculosis, demodicosis with secondary deep pyoderma, and infections of systemic fungi or opportunistic fungi or algae (see Chapter 12). Diagnosis is aided by a correlative history of breed, coat color and length, long-term solar exposure, and lesion localization to body sites commonly affected by solar damage. The presence of other lesions (especially comedones) suspicious for solar damage also is useful. Skin biopsy is necessary to confirm actinic furunculosis.

Biopsy site selection

Multiple nodules or hemorrhagic bullae should be surgically excised. Intact as well as fistulated nodules should be sampled. If present, erythematous macules, crusted plaques, areas of induration, and margins of ulcers also should be obtained in order to reveal the spectrum of disease present and to uncover possible coexistent solar-induced neoplasia.

Histopathology (Figure 17.21)

Rupture of affected follicles leads to severe inflammation as seen in bacterial furunculosis (see p. 420). Actinic

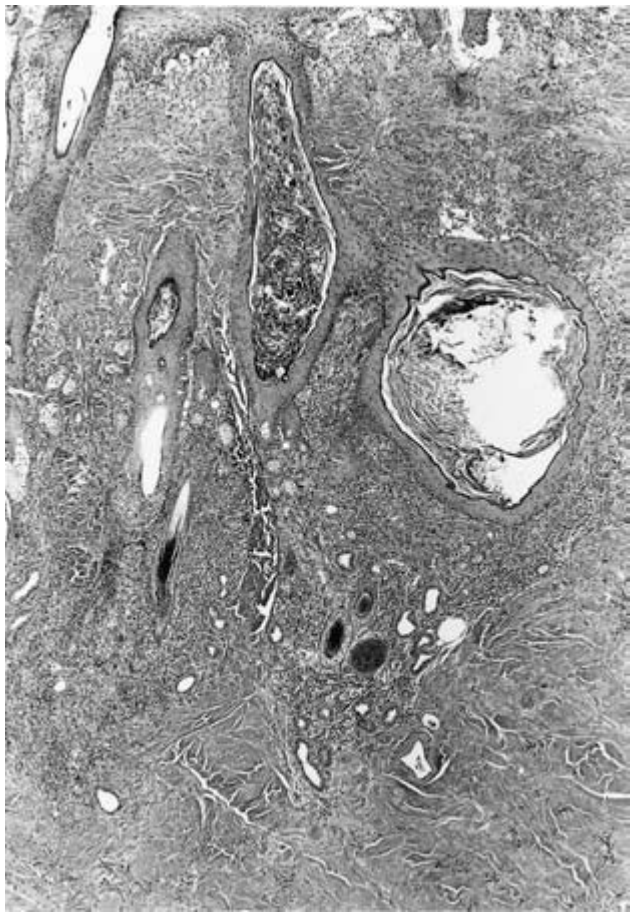


Fig. 17.21 Actinic furunculosis. A furuncle at left is occurring in a noncomedonal follicle. An actinic comedone is at right.

furunculosis often occurs in the context of actinic comedones (see Chapter 8). Affected follicles are distended with keratin and are surrounded by pale, slightly basophilic layers of collagen. The inflammation may be more consistently deep dermal and diffuse than in classical deep bacterial folliculitis and furunculosis (see p. 420), as if the bottom had 'dropped out' of the comedones. Severe folliculitis and furunculosis also may be found in specimens obtained from sun-exposed skin of white dogs without histopathologic evidence of comedo formation. Actinic comedones may have been destroyed by inflammation in these specimens; alternatively, there may be another solar-related mechanism, other than formation of comedones with rupture, which induces severe pyoderma in these animals. Concurrent features of other solar lesions such as actinic keratosis, solar fibrosis, or solar elastosis may be present (see Chapters 7, 15, and 22).

Differential diagnoses for actinic furunculosis occurring with actinic comedones include other comedonal diseases in which secondary furuncles occur. These include callus pyoderma, some lesions of interdigital furunculosis, and



Fig. 17.22 Interdigital furunculosis in a dog. Severe palpably nodular inflammation is present both interdigitally and on the margins of the pawpads, accompanied by alopecia, exudative crusting, and erosion.

Schnauzer comedo syndrome. The presence of solar changes in the superficial dermis (see Chapter 15) supports an actinic cause for the comedones observed. The concentric accumulation of pale staining collagen around the distended follicle is suggestive for actinic comedones, but is not always present. Also, this pattern of fibrosis is occasionally seen in the comedones of callus (see Chapter 8). Correlation with clinical features such as site or breed affected may be required; actinic furunculosis in the absence of actinic comedones or other solar changes always requires clinical differentiation.

INTERDIGITAL FURUNCULOSIS

(Synonym: pedal folliculitis and furunculosis, interdigital pyoderma)

Clinical features (Figure 17.22)

Interdigital furunculosis is a common subgroup of canine deep pyoderma. Lesions occur predominantly in the interdigital webs, but may affect the digits as well. Although interdigital furunculosis is multifactorial, trauma to hair follicles probably is a common precipitating cause. Interdigital furunculosis that occurs without initiating inflammatory skin disease may be induced by short, bristly hairs rubbing against the skin of apposing digits. This directly promotes follicular trauma and rupture leading to secondary pyoderma in the dorsal interdigital webs. Interdigital pyoderma also may be promoted by rupture of obstructed, keratin-filled follicles that are produced from chronic friction or other trauma, as seen in callus pyoderma (see p. 433). Dogs with abnormal foot conformation ('fat feet') may have increased friction of this type and therefore may be predisposed.

Trauma or self-trauma enhances susceptibility to interdigital furunculosis. Various foreign bodies such as foxtails, other grass awns, slivers, and thorns may initiate inflammation and licking. Damage also may be initiated by running on irregular or sharp terrain, bruising contact with nonpenetrating foreign bodies (vegetation stubble, gravel), and contact with irritant substances. Repetitive, interdigital self-trauma caused by pruritus probably is an additional trigger; thus, allergic skin disease such as canine atopic dermatitis and food allergy may initiate this syndrome. Congenital or acquired immunodeficiency can promote interdigital as well as generalized pyoderma.

The clinical features seen with interdigital furunculosis are varied, but nodular inflammation is the unifying element. Erythema, edema, and pustules are common features. Hemorrhagic bullae may be present. Erosions and ulceration with fistulation and alopecia occur with advancing disease. Constant licking leads to maceration, chronic moistness, and surface bacterial and *Malassezia* overgrowth. Self-grooming usually removes purulent or serosanguinous crusts. Secondary paronychia is common. Scarring may be severe in chronic cases. Chronicity fosters increased pruritus and pain, and commonly leads to lameness.

The dorsal interdigital webs most commonly are affected first in cases not initiated by ventral foreign bodies or trauma associated with running on irregular or rough surfaces. Involvement of the ventral interdigital webs usually occurs after dorsal disease is present. Penetrating foreign bodies lead to nonsymmetric disease; one foot may initially be affected or may be more severely affected. Isolated lesions due to follicular keratin accumulation and rupture (interdigital 'cysts') are also observed. The front feet are most commonly and usually most severely affected, particularly with underlying allergic disease, due to increased ease of self-trauma at these sites; however, frequently all four feet are affected. Regional lymphadenopathy is common.

Marked breed predilections offer clues to pathogenesis. Brachycephalic breeds such as Boxers, English Bulldogs, Mastiffs, and Bull Mastiffs may be predisposed in conjunction with having short, bristly interdigital hairs and poor foot conformation. Other affected dogs with similar hair coat characteristics include Bull Terriers, Dachshunds, Great Danes, Dalmatians, Weimaraners, and German Shorthaired Pointers. Predisposed breeds with different hair coat characteristics include the Pekingese, Golden Retriever, Labrador Retriever, German Shepherd Dog, and Irish Setter (Scott et al., 2001). Hunting breeds may be predisposed due to lifestyles that encourage pedal trauma (Scott et al., 2001). Age or sex predilections have not been reported.

Clinical differential diagnoses include interdigital furunculosis secondary to demodicosis (pododemodicosis), deep fungal infections, and hookworm dermatitis. Many cases of interdigital furunculosis involve all four feet to varying degrees. If lesions occur elsewhere in addition to the interdigital webs, than all other causes of deep bacterial folliculitis and furunculosis must be investigated (see p. 420). Multiple, deep skin scrapings should always be performed to rule out underlying demodicosis. If scarring is severe, skin biopsy may be required to rule out demodicosis; skin biopsy commonly is required to rule out other causes of interdigital skin disease.

Biopsy site selection

Early intact pustules, nodules, or bullae are recommended lesions for biopsy. Ulcerated or scarred lesions may be less desirable as they are less likely to yield diagnostic follicular lesions due to loss of normal tissue architecture. If isolated lesions are present, complete excision may offer the best method of clinical management.

Histopathology (Figure 17.23 and 17.24)

The epidermis is severely acanthotic and may demonstrate erosion or ulceration. There is variable suppurative to

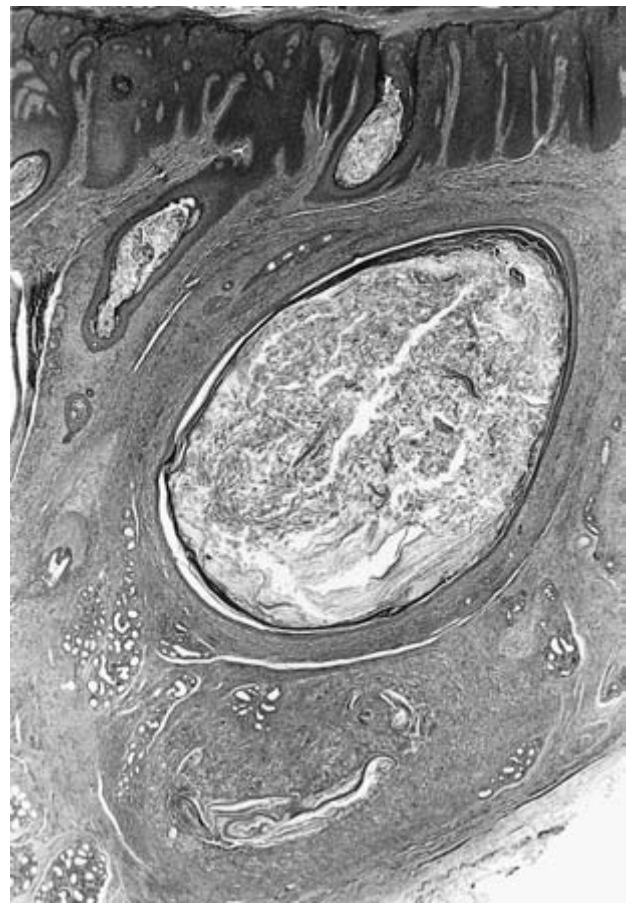


Fig. 17.23 Interdigital follicular cyst with furunculosis. Note inflammation and free keratin beneath the dilated follicle.

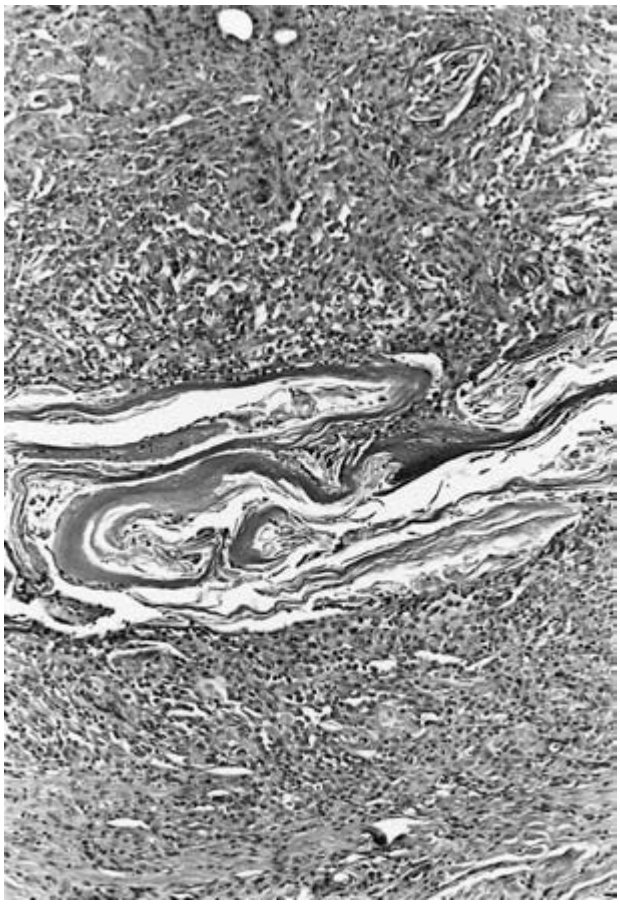


Fig. 17.24 Higher magnification of Fig. 17.23. Free keratin is surrounded by neutrophils and larger macrophages.

pyogranulomatous inflammation with follicular rupture, as described for furunculosis (see p. 420). Fibrosis is severe in chronic lesions. A consistent feature of interdigital furunculosis is the presence of keratin-plugged follicles; however, this is not present in all cases (or in all lesions selected for biopsy). Extreme follicular keratosis with comedo or cyst formation may occur. There may be features of traumatic furunculosis, including deep displacement of hair shafts well below the level of hair follicles. Foreign body granulomas or pyogranulomas with giant cells may form around fragments of hairs (trichogranulomas), or around keratin (keratogranulomas).

Differential diagnoses include other syndromes of furunculosis with follicular keratosis, specifically actinic furunculosis with actinic comedones, Schnauzer comedo syndrome, and canine callus pyoderma. Deep bacterial folliculitis and furunculosis are complications of other skin diseases with a traumatic component (traumatic furunculosis) such as acral lick dermatitis, and canine acne; these differential diagnoses may be considered for lesions in which follicular plugging is not found. Knowledge of the site and breed affected is the key to differentiation.



Fig. 17.25 Severe callus pyoderma affecting the lateral stifle region of a Beagle-crossbreed. Draining tracts are present within the lobular callus.



Fig. 17.26 Chronic callus pyoderma on the dorsal muzzle of a Bull Terrier that habitually slept in a dorsiflexed position.

CALLUS PYODERMA

(Synonym: pressure-point pyoderma)

Clinical features (Figure 17.25 through 17.27)

Callus pyoderma is a subset of traumatic furunculosis that occurs from repeated trauma to calluses over bony prominences and other pressure points. Callus pyoderma is common in dogs and rare in cats. Uninflamed calluses act as a protective response to ongoing environmental trauma, especially from habitual contact with hard and rough surfaces (see Chapter 8). Rupture of the follicular cysts that are a frequent component of 'calluses' in dogs and cats leads to release of hair and keratin, which provokes secondary bacterial furunculosis and a foreign body response to the displaced hairs and keratinous debris, creating callus pyoderma.

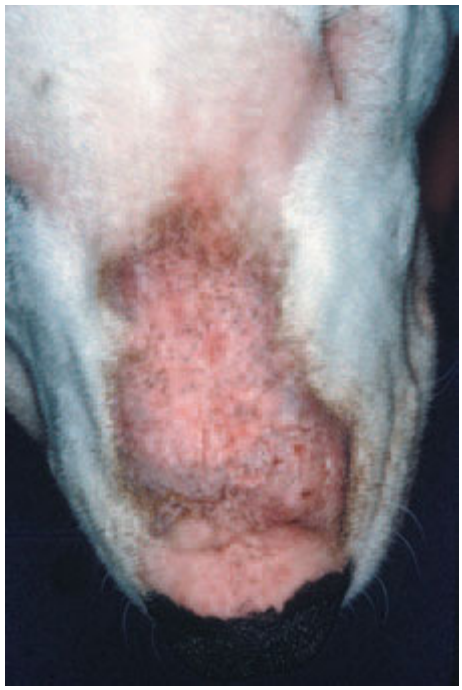


Fig. 17.27 Closer view of the dog in Fig. 17.26. Note dramatic thickening, erythema, and comedones. However, grossly visual confirmation of active secondary pyoderma is lacking. Severe scarring associated with previous infection has deformed the normal contour of the muzzle.

Visible inflammation occurring in a callus is the clinical hallmark of callus pyoderma. Inflammation may affect the entire callus, or be localized. Frank pustules and nodules with or without obvious fistulation confirm callus pyoderma. Erosion or ulceration may be present. It is generally assumed that visually noninflamed gray or white calluses do not exhibit callus pyoderma. However, since these calluses rarely are biopsied, subtle or mild callus pyoderma may be more common than assumed currently. Multiple hairs emanating from abnormally enlarged hair follicles may indicate previous episodes of callus pyoderma with recanalization after severe furunculosis. Lesional distribution and breed predilections are as for callus (see Chapter 8).

Canine and feline callus pyoderma is visually distinctive. Canine acral lick dermatitis may superficially resemble callus pyoderma, but has different site predilections. Plaques of coalescing actinic comedones may resemble calluses with pyoderma, but usually are not associated with pressure points. Specifically, sternal callus pyoderma may resemble actinic comedones with actinic furunculosis.

Biopsy site selection

See Callus, Chapter 8.

Histopathology (Figures 17.28 and 17.29)

The epidermis is severely acanthotic, and hyperplasia usually extends to follicular infundibula, creating an undulating or papillated surface to the lesion. In most

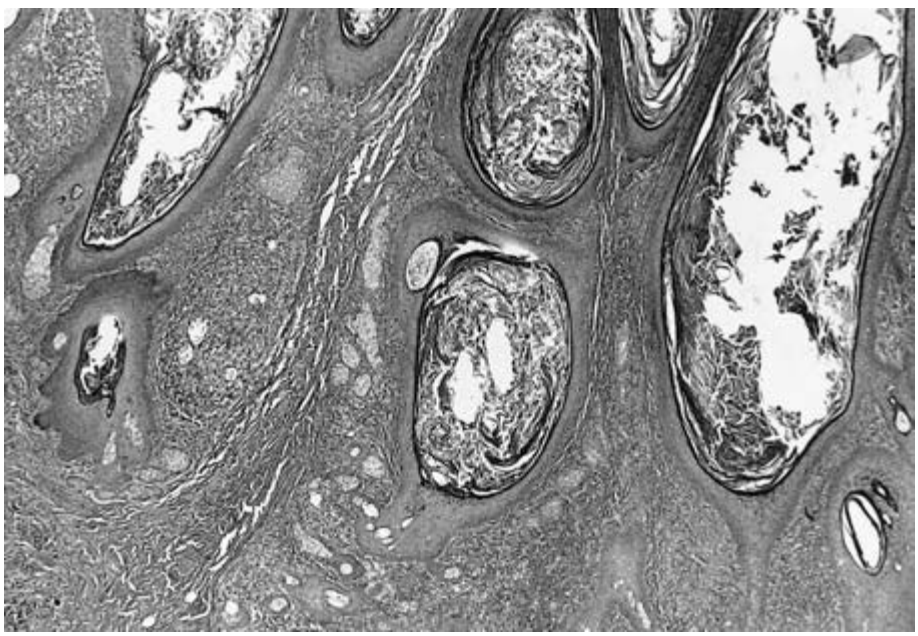


Fig. 17.28 Canine callus pyoderma. Thickened and keratin-distended hair follicles are surrounded by severe inflammation.

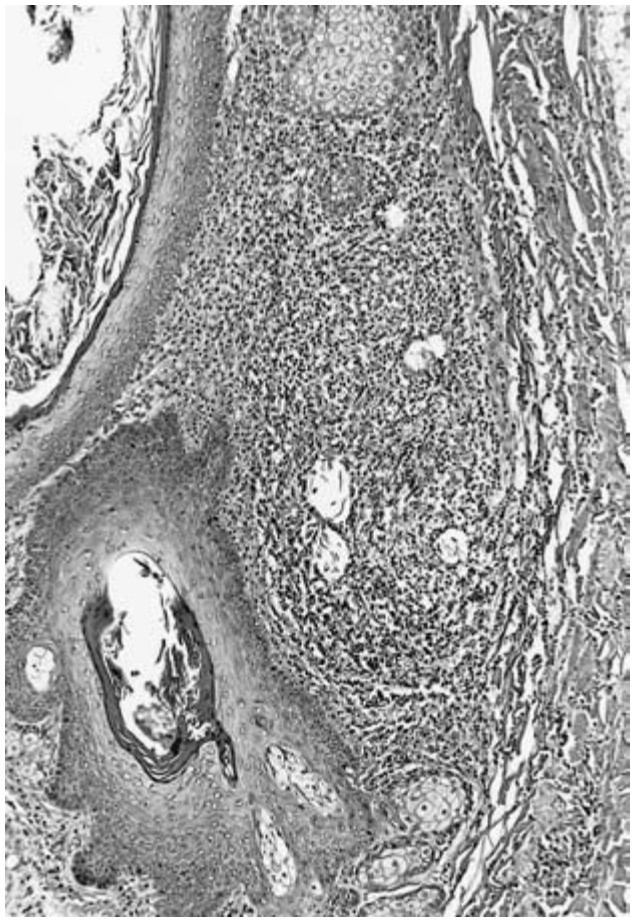


Fig. 17.29 Higher magnification of Fig. 17.28. Pustular inflammation surrounds free keratin from a ruptured hair follicle.

cases, follicular infundibula are severely acanthotic, but may be only mildly to moderately affected in some lesions. There is variable superficial hyperkeratosis and parakeratosis, and crusting or ulceration may be a feature of inflamed lesions.

Superficial hair follicles are greatly distended with keratin to form cysts as in uninflamed callus (see Chapter 8). Rupture of these cysts leads to release of hair and keratin which provokes severe suppurative and pyogranulomatous inflammation in the dermis and the subcutis (callus pyoderma). There may be cavitation of severely inflamed tissue. Trichogranulomas, or the accumulation of macrophages, giant cells, and neutrophils around free hair, may form around deeply imbedded hair shafts (traumatic furunculosis). Foreign body granulomas may also form around free keratin (keratogranulomas). Granulation tissue and mature fibrosis may be prominent in severe and chronic lesions.

Differential diagnoses for callus pyoderma include diseases with comedones in which secondary furunculosis occurs, such as actinic comedones, Schnauzer comedo syndrome, or in interdigital furunculosis in which follicular plugging is featured. These other syndromes usually do not have the severe epidermal and follicular infundibular hyperplasia that is seen in most cases of canine callus. The concentric accumulation of pale staining collagen around the distended follicle is suggestive of actinic comedones; however, this pattern of fibrosis occasionally is seen in callus (see Chapter 8). Knowledge of the site and breed affected may be required for differentiation. Feline acne may resemble feline callus pyoderma; however, the large sebaceous glands of the chin allow differentiation in most cases.



Fig. 17.30 Canine acne affecting the ventral muzzle of a Doberman Pinscher. Active, erythematous furuncles are present amid alopecia and scarring from previous inflammation.

CANINE ACNE

(Synonym: muzzle folliculitis and furunculosis)

Clinical features (Figures 17.30 and 17.31)

Canine acne is a common inflammatory skin disease of young dogs characterized by deep folliculitis and furunculosis affecting the chin and haired skin adjacent to the lips. The cause of canine acne is not known. However, it is seen almost exclusively in young dogs of short haircoated breeds. Similarities to 'acne' in humans are minimal. Bacterial involvement, when present, probably is secondary.



Fig. 17.31 Severe canine acne affecting the ventral muzzle of a blue Doberman Pinscher. Coalescing nodules and severe scarring are accompanied by ulceration and occasional small fistulae.

It is speculated that genetic predilection coupled with localized trauma initiate the lesions of canine acne (Scott et al., 2001). The short, bristly haircoats of affected breeds afford little protection for the underlying skin during aggressive play (Scott et al., 2001). Hair follicle trauma may initiate follicular keratin accumulation, inflammation, and traumatic furunculosis; the histopathology of canine acne supports this hypothesis.

Prominent papules centered on hair follicles are the initial lesion of canine acne. Papules enlarge, form pustules, rupture, shed the central hair, and evolve to firm nodules. Nodules may fistulate and drain. Variable degrees of erythema and alopecia accompany the primary lesions. Fistulous tracts may occur as sequelae to follicular rupture, leading to scarring. Erosion or ulceration may be seen in unusually severe cases. Much less commonly, comedones containing dark, inspissated material may develop from affected hair follicles and, when present, are most prominent centrally on the rostral portion of the chin.

Canine acne is seen on the chin and less commonly in the skin surrounding the lower lip. The haired skin adjacent to the upper lip and lateral muzzle may be affected in more severe cases. Partial bilateral symmetry is common. Pruritus, if present, usually is mild. Pain may occur with severe secondary deep bacterial folliculitis and furunculosis. Affected dogs are otherwise normal.

Canine acne is seen most frequently in large short-coated breeds with short, bristly haircoats such as the Doberman Pinscher, Great Dane, English Bulldog, German Shorthaired Pointer, Boxer, Weimaraner, and Mastiff (Scott et al., 2001). However, many members of these breeds do not develop canine acne, leading to speculation of variable genetic susceptibility (Scott et al., 2001). The onset of disease generally occurs at less than 6 months of age and persists through the first year of life. Sex predilections have not been noted.

Canine acne usually is visually distinctive; clinical differential diagnoses are few. Occasionally, localized demodicosis, dermatophytosis, and early, mild juvenile sterile granulomatous dermatitis and lymphadenitis may mimic canine acne. Negative skin scrapings for demodicosis, dermatophyte culture, and the lack of more generalized or systemic signs should aid in ruling out these diseases. Early stages of canine acne rarely are biopsied as they are clinically pathognomonic. Consequently, most cases that are biopsied are more severe and characterized by more obvious furunculosis.

Biopsy site selection

Punch biopsy specimens should be obtained from characteristic lesions. Cosmetic results are best achieved by sampling the ventral chin. Sampling of larger comedones or furuncles using a 4 mm punch may be curative for individual lesions.

Histopathology (Figures 17.32 and 17.33)

The epidermis is generally moderately acanthotic and may be crusted. Ulceration is rare and limited to very severely inflamed lesions that have been aggravated by self-trauma.

Early lesions occasionally may show intact comedones surrounded by mixed inflammatory cells, including neutrophils, macrophages, and plasma cells. However, lesions of canine acne submitted for histopathology most often are those of folliculitis and furunculosis only, without evidence of follicular comedones. There may be traumatic furunculosis, characterized by hair shafts that are displaced below the level of inflamed hair follicles. These extruded hairs are surrounded by suppurative to pyogranulomatous inflammation (trichogranulomas); keratogranulomas around keratin fragments may also be present. Bacteria (staphylococci) may be present in superficial follicles. A single case of bacterial pseudomycetoma (see Chapter 12) occurring in the setting of canine acne was observed by the authors. Sebaceous glands are large, as is expected for the chin; sebaceous ducts may be dilated.

Canine acne usually is indistinguishable from classical deep bacterial folliculitis and furunculosis. Deep bacterial folliculitis and furunculosis are complications of other skin diseases with a traumatic component (traumatic furunculosis) such as acral lick dermatitis and interdigital furunculosis. If comedones are present, differential diag-

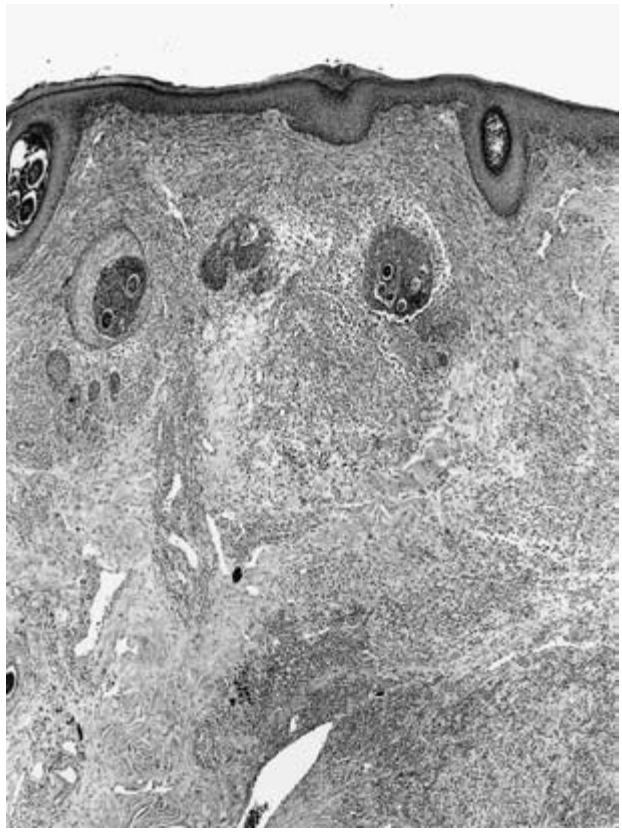


Fig. 17.32 Canine acne. Severe diffuse inflammation includes folliculitis and furunculosis.

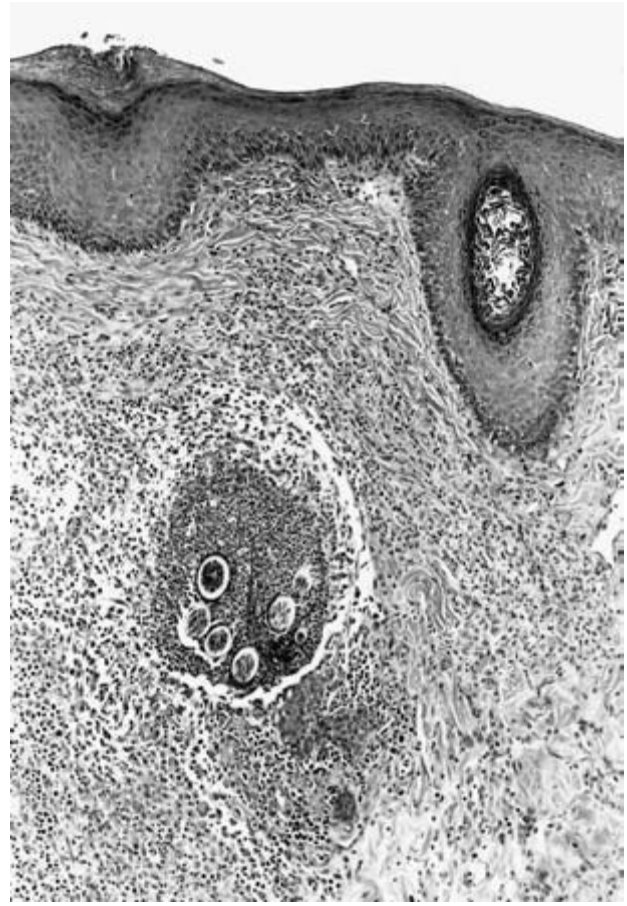


Fig. 17.33 Higher magnification of Fig. 17.32. A furuncle contains central hair shafts.

noses include those diseases characterized by comedones and complicated by furunculosis, such as Schnauzer comedo syndrome, interdigital furunculosis with follicular plugging, canine callus pyoderma, and actinic furunculosis with comedones. The presence of typical large sebaceous glands of the chin will allow differentiation of canine acne from these other diseases.

FELINE ACNE

Clinical features (Figures 17.34 and 17.35)

Feline acne is a relatively common feline skin disease characterized by comedo formation and secondary inflammation on the chin and skin adjacent to the lips. The etiopathogenesis of feline acne is not understood. Unlike acne in humans and dogs, feline acne is not associated with young age.

Poor grooming habits and defects in follicular keratinization have been suggested as causes (Scott et al., 2001). The cyclical or periodic nature of the disease may relate to the inability of the new anagen hairs to extrude the developing keratosebaceous plugs. A localized corni-

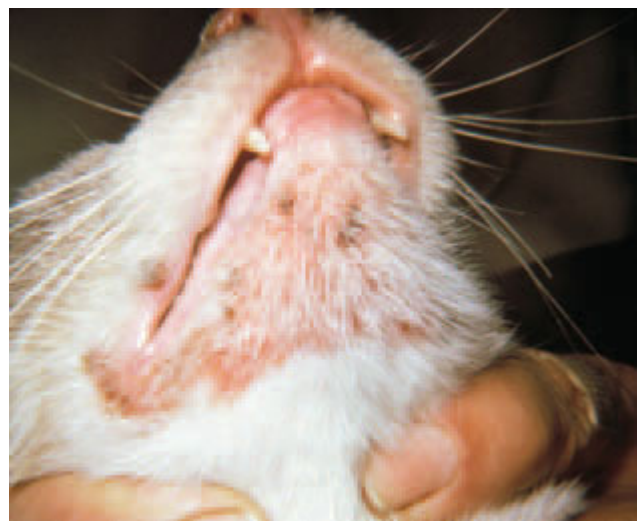


Fig. 17.34 Severe feline acne. Extensive crusting with alopecia is present on the ventral muzzle. (Photograph courtesy E.M. Sleeper.)



Fig. 17.35 Severe feline acne with chronic and deep inflammation. Note swelling and fistulous tracts.

fication defect might be exacerbated by altered sebum composition or production from the large sebaceous glands in the chin. Bacterial involvement, when present, probably is secondary and associated with follicular rupture. A variety of bacteria including *Staphylococcus* spp., *Streptococcus* spp., and *Pasteurella multocida* have been isolated (White et al., 1997). *Malassezia* spp. may be revealed by cytology. Unexplained, seemingly contagious feline acne may occur within multicat households on rare occasion. Occasionally, there may be severe and diffuse inflammation, histologically reminiscent of sterile granuloma and pyogranuloma syndrome (see Chapter 13). The relationship of this presentation to classical feline acne is not known; the authors suspect an exaggerated immunologic reaction.

Early and mild feline acne is characterized by comedones, mildly erythematous crusted papules, and pustules that develop on the chin, and less commonly on the skin adjacent to both the upper and lower lips. Swelling of the chin is variable and may be diffuse. Solitary comedones containing dark, inspissated material are most prominent around the lateral commissures of the mouth and the margins of the lower lip. Multiple small flakes of discolored keratinous debris may be distributed through the haircoat of the chin, creating the appearance of sprinkled black pepper. Firm nodules and less distinct diffuse firm swelling indicate progression to furunculosis. Diffuse firm swelling, severe crusting, variable erythema, and alopecia characterize severe and chronic cases. Individual lesions may fistulate, leading to focal abscessation and scarring. Partial bilateral symmetry is common. Feline acne usually is asymptomatic; pruritus or pain is uncommon unless severe deep pyoderma is present.

Breed or sex predilections have not been noted. Feline acne often commences at less than 1 year of age and remains a lifelong disease, cyclically varying in severity.



Fig. 17.36 Feline acne. Pustular inflammation surrounding a ruptured follicle lies adjacent to a dilated follicle; note prominent sebaceous glands of the chin.

Paradoxically and infrequently, clinical disease may be limited to a single episode or small numbers of episodes.

The clinical features of feline acne are visually distinctive such that clinical differential diagnosis rarely is a problem. Occasionally, dermatophytosis, feline demodicosis, *Malassezia* dermatitis, or canine tooth root abscesses leading to regional cellulitis may mimic feline acne. Bilateral symmetry and frank comedone formation are helpful differentiating features of feline acne. Skin scrapings, dermatophyte culture, cytology, and histopathology will also allow differentiation. Histopathology generally is performed in severe refractory cases only.

Biopsy site selection

Punch biopsy specimens should be obtained from discrete comedones. Cosmetic results are best achieved by sampling the ventral chin. Sampling of larger comedones using a 4 mm punch may be curative for individual lesions.



Fig. 17.37 Higher magnification of feline acne. A keratin filled follicle has ruptured creating a furuncle.

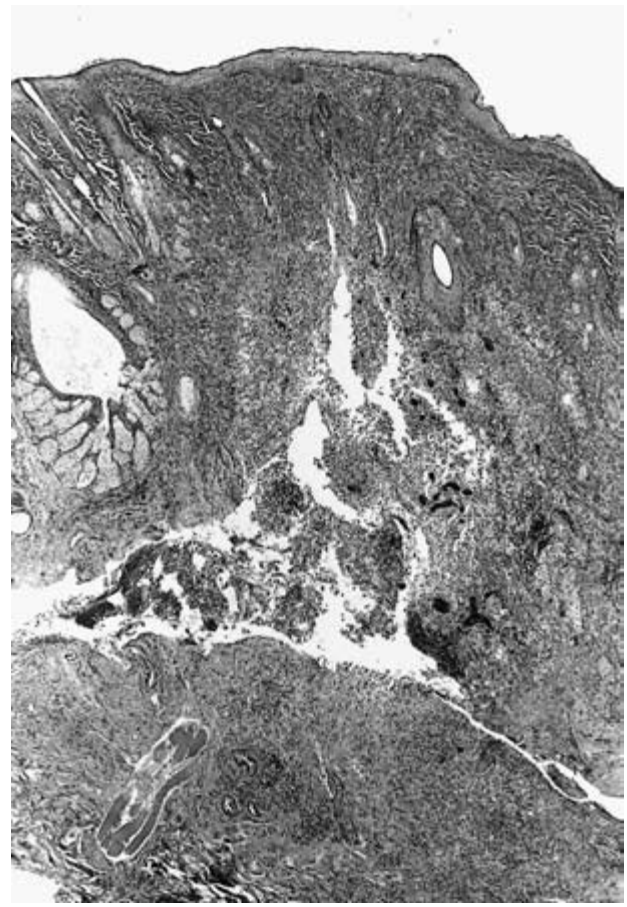


Fig. 17.38 Apical abscess of lower canine tooth mimicking feline acne. The inflammation is extensive and cavitating; however, note that an adjacent folliculosebaceous unit demonstrates only mild dilatation.

Histopathology (Figures 17.36 through 17.38)

The epidermis is acanthotic and occasionally eroded and crusted. Typically, superficial hair follicles are distended with keratin (comedones), occasionally to the point of frank cyst formation. Portions of this follicular keratin, as well as overlying epidermal keratin, may exhibit light brown to dark brown, agranular discoloration, the nature of which is not known. It resembles ceroid or lipofuscin pigment (but is acid-fast negative) and may possibly represent oxidized lipid or other products of sebaceous gland origin. Bacterial degradation of sebum and/or keratin may also be a factor. Occasionally, *Malassezia* are seen within comedones, and staphylococci are not uncommon. Affected follicles may be uninflamed and are surrounded by large sebaceous glands that identify the skin of the chin. Sebaceous ducts are commonly distended with sebum. There may be mild encircling inflammation of lymphocytes, plasma cells, and neutrophils. Rupture of keratin-filled follicles is common, leading to furunculosis and its attendant inflammatory changes (see p. 420).

Some clinically refractory lesions feature diffuse pyogranulomatous inflammation. In these cases, the inflammation is severe throughout the dermis and is often obliterative; it is not folliculocentric as in classical feline acne. The mechanism of generation of these lesions is not known. Pyogranulomatous inflammation resembles that of sterile granuloma and pyogranuloma syndrome or opportunistic fungal or mycobacterial diseases (see Chapters 12 and 13) and diffusely surrounds dilated sebaceous ducts or hair follicles, without evidence of rupture or furunculosis. Special stains for fungi and mycobacteria are negative. Diffuse pyogranulomatous dermatitis of the chin may be a separate syndrome in cats.

Early lesions are diagnostic for feline acne, particularly when the typically prominent sebaceous glands of this area of skin are identified. Diffuse pyogranulomatous lesions may mimic those of sterile granuloma and pyo-



Fig. 17.39 Kerion due to *Microsporum canis* on the ventral muzzle of a Keeshond. Characteristic minute oozing fistulas are visible within the alopecic nodule.

granuloma syndrome, or fungal or mycobacterial infections. Special stains will not reveal agents in feline acne, other than staphylococcal bacteria or occasional intrafollicular yeasts. Focal fistulating, pustular lesions of the chin (without evidence of follicular keratosis) occasionally have been seen in cats with confirmed apical root abscesses of the lower canine teeth. Clinical differentiation via dental radiography is critical in these cases.

KERION

Clinical features (Figures 17.39 and 17.40)

Kerion is an uncommon florid variant of canine dermatophytosis characterized by intense focal inflammation with swelling. The cause of kerion formation is not known. However, since kerion dermatophytosis is associated with marked inflammation and commonly leads to spontaneous resolution, one may speculate that an enhanced host immune response may be responsible. Kerion is reportedly seen most frequently in conjunction with *Microsporum gypseum* infection (Foil, 1998). However, kerion may be seen with a variety of dermatophytes, including *Trichophyton mentagrophytes* and *Microsporum canis*. In humans, kerion dermatophytosis is seen most often with organisms that are maladapted to human skin and thus cause more florid inflammation (Martin & Kobayashi, 1999). The zoonotic potential of kerion seems to be less than for other varieties of canine dermatophytosis; this may be due to the depth of infection and the paucity of viable organisms present on the surface of these highly inflamed lesions.

Kerion develop acutely as erythematous, exudative, alopecic, domed nodules. Kerion vary in diameter from 1 to 5 cm. A hand lens may reveal broken hairs studding the boggy nodule, as well as minute fistulous tracts on the surface of the nodules; gentle pressure expresses beads of serous fluid from the tracts. Erosion or ulceration may occur. Peripheral scale is common, and crusting may be evident if the lesion is located where the dog cannot groom away the exudate.



Fig. 17.40 Kerion on the dorsal muzzle of a Golden Retriever. Note foci of hemorrhagic fistulation. The adjacent (nonhaired) planum nasale is not affected.

Most kerion are solitary, but occasionally multifocal lesions may be seen. Most kerion develop on the face or forelegs, but lesions may occur at any site. Regional lymphadenopathy is a common feature. Pruritus or pain is minimal, but may occur with larger lesions. Spontaneous regression occurs in the majority of cases followed by the authors.

Breed, age, or sex predilections have not been established. However, the Boxer may be at increased risk for solitary lesions and the Golden Retriever may be at increased risk for widespread, multifocal lesions.

Clinical differential diagnoses include neoplasms that may be nodular, erythematous, and alopecic (such as mast cell tumors or histiocytomas), foreign body reactions, and infectious nodules such as canine leproid granulomas (see Chapter 12). Dermatophyte culture may not be helpful as kerion may yield negative results. Early skin biopsy is recommended for differentiation, since neoplasia is a differential diagnosis.

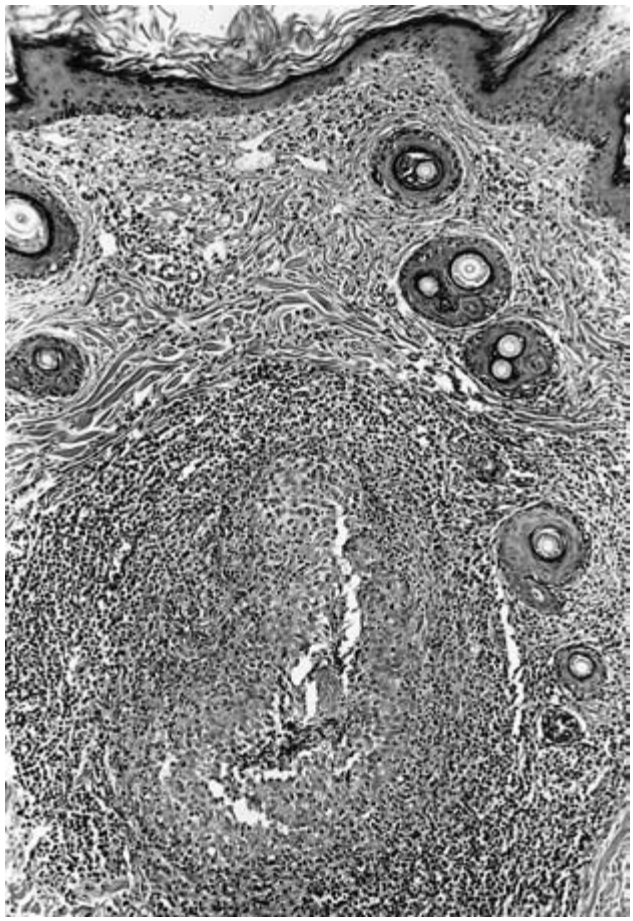


Fig. 17.41 Kerion in a dog. A large pyogranuloma surrounds a free dermatophyte-colonized hair fragment.

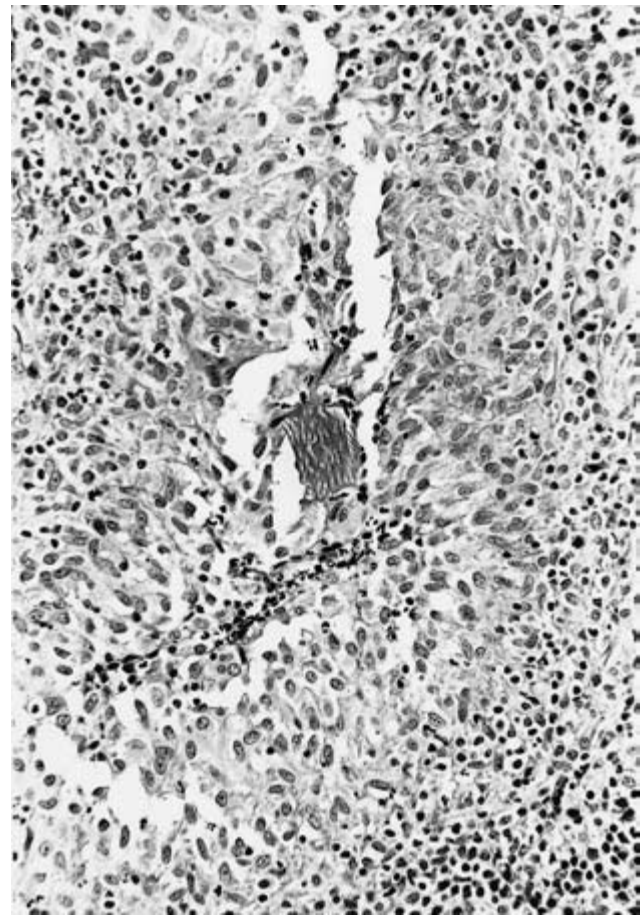


Fig. 17.42 Higher magnification of Fig. 17.41. Note wavy, pale, somewhat refractile dermatophytic hyphae within hair shaft.

Biopsy site selection

Since kerion are usually solitary lesions, complete resection is indicated, as the added benefit of a surgical cure will be obtained. In addition, wedge resection is advisable diagnostically, as kerion can mimic cutaneous neoplasia clinically.

Histopathology (Figures 17.41 and 17.42)

The epidermis is acanthotic and may be ulcerated or crusted. Severe furunculosis is present throughout. Hair follicles are ruptured and replaced by tightly oriented, nodular pyogranulomas, or less often, granulomas. Pyogranulomas are large, often very discrete, and contain central neutrophils surrounded by macrophages, and sometimes giant cells. Moderate to large numbers of eosinophils are often present, but can be sparse or absent. These lesions may surround hair fragments. Inflammation may become confluent, resulting in a diffuse distribution in the dermis.

Remnants of hair shafts at the centers of inflammatory foci may contain dermatophytic spores and hyphae; occasional colonization of surface hairs is seen. Heavy colonization results in a pink-peach, slightly refractile appearance of hairs upon low power examination; this pigmentary alteration is most obvious in colonized hairs within pyogranulomas. Sparse colonization may appear as scattered, almost clear, linear, or wavy hyphae within the hair fragments. Dermatophytes may not be evident in severely inflamed lesions, since organisms cannot persist in these conditions. A periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) stain will color dermatophytes magenta or black, respectively.

Differential diagnosis, if organisms are not located, principally includes deep bacterial folliculitis and furunculosis. However, the often strikingly discrete pyogranulomatous inflammation around free hairs in kerion is different from most cases of bacterial furunculosis, in which inflammation tends to be more pustular and loosely organized. If eosinophils are abundant, eosinophilic furunculosis of the face may be considered. Eosinophilic



Fig. 17.43 Juvenile-onset generalized demodicosis in a blue merle Shetland Sheepdog. Note the partial, patchy alopecia. Crusting is present on the exposed, erythematous skin.

furunculosis generally features more explosive furunculosis with extensive hemorrhage and mucin.

CANINE DEMODICOSIS

(Synonym: demodectic mange, demodectic acariasis)

Clinical features (Figures 17.43 through 17.45)

Canine demodicosis is a noncontagious parasitic skin disease caused by an overpopulation of the host-specific follicular mite of various *Demodex* species. The great majority of cases of canine demodicosis are caused by *Demodex canis*, although two other species of demodicid mites are seen. Canine demodicosis may be divided into juvenile-onset and the less common, adult-onset forms; both forms may be localized or generalized. Localized demodicosis, a mild and benign self-limiting disease, is very common in dogs. Generalized demodicosis, a serious and potentially life-threatening disease, is seen less frequently, but is relatively common. Since demodectic mites are part of the normal canine fauna, very small numbers of mites may be present in the hair follicles of most healthy dogs, particularly on the face and muzzle. Transmission to the newborn puppy is achieved by direct contact with the bitch during the first few days after birth (Scott et al., 2001).

Demodex canis is the species identified in most cases of canine demodicosis and as a commensal in normal canine skin. Much less commonly, a short-bodied demodicid mite is identified in conjunction with canine skin disease (Chen, 1995; Chesney, 1999; Saridomichelakis et al., 1999). A third longer-bodied demodicid mite, residing in either hair follicles or sebaceous glands, was recently



Fig. 17.44 Juvenile-onset generalized demodicosis in a Shih Tzu characterized by scarred erythematous plaques. Note that widespread alopecia is not a feature of demodicosis in this breed; the dog has been clipped to enhance visualization of the lesions.



Fig. 17.45 Generalized demodicosis affecting the ventral abdomen of a German Shepherd Dog. Erythematous nodules and plaques are indicative of secondary bacterial furunculosis.

named *Demodex injai* (Hillier & Desch, 2002; Desch & Hillier, 2003).

Although all species of demodectic mites are categorized as hair follicle mites (Order: Acari; Genus: *Demodex*) (Desch & Hillier, 2003), the only canine species that are true follicular mites are *Demodex canis* and *Demodex injai*. Current data suggest that the as yet unnamed short-bodied species of canine demodicid mite is predominantly a surface dweller in the stratum corneum (Chen, 1995; Chesney, 1999; Saridomichelakis et al., 1999). However, caution should be exercised in drawing definitive conclusions regarding the ecologic niche of various canine demodicid mites: there may be variation in the size and location of mite life stages.

Localized demodicosis is a benign, predominantly cosmetic skin disease characterized by intense focal colonization by demodicid mites. It is usually juvenile in onset and is seen in puppies less than 6 months of age. Immunologic abnormalities have not been noted in dogs with localized demodicosis (Scott et al., 2001). The great majority of dogs self-cure by 12 to 18 months of age. Rarely, localized demodicosis may be a transient phenomenon in adult dogs.

In contrast, generalized demodicosis is a severe and potentially life-threatening skin disease. Most cases are juvenile in onset and develop in dogs less than 1 year of age. Generalized demodicosis requires a cutaneous environment that is ecologically or immunologically favorable for extreme colonization by demodectic mites. A genetically preprogrammed immunologic defect probably is responsible for the unchecked replication of demodectic mites in dogs with juvenile-onset, generalized demodicosis; however, to date, immunologic studies have not documented clear-cut evidence of a specific defect. Suppressed T cell function, specifically cytotoxic T cells activated by alterations in T helper cell function, is implicated (Scott et al., 2001). The immunologic origin of generalized demodicosis is further supported by the induction of adult-onset demodicosis by immunosuppressive therapy, such as antilymphocyte serum, glucocorticoids, or cytotoxic drugs. Immunosuppressive diseases such as canine hyperglucocorticoidism, iatrogenic hyperglucocorticoidism, neoplasia (especially lymphoma), leishmaniasis, and hypothyroidism also can induce adult-onset demodicosis (Scott et al., 2001). However, immunosuppression is not always documented in adult-onset demodicosis.

Marked breed predilections and familial involvement support a hereditary basis for juvenile-onset generalized demodicosis. A similar, although focally expressed defect may be present in localized, juvenile-onset canine demodicosis, based on identical breed predilections and the progression from localized to generalized disease in a small number (less than 5%) of dogs (Scott et al., 2001). Incidence data suggests an autosomal recessive mode of inheritance in dogs with generalized demodicosis (Scott et al., 2001). Based on the heritability of this disease, the American Academy of Veterinary Dermatology (AAVD) adopted a resolution in 1981 sponsored by Robert Kirk recommending 'neutering all dogs who have had generalized demodicosis so that the incidence of the disease is decreased and not perpetuated'.

Localized demodicosis is characterized by the development of one to six patchy, moderately well-demarcated, partially alopecic macules or subtle plaques in one body area. Lesions are occasionally nodular. Erythema and mild micaceous scaling are common features. Follicular plugging and comedo formation may be present, particularly in the German Shepherd Dog and related crossbreeds. Mild pruritus may be observed, but is not a consistent feature. The periorbital region, lateral commissures of the mouth, other areas of the face, and the forelegs are the most common sites. Rarely, localized demodicosis may present as a bilateral ceruminous otitis externa (Scott et al., 2001). Regional lymphadenopathy is common.

Generalized demodicosis usually begins with multifocal, erythematous, partially alopecic, crusted macules that eventuate in plaques. As these original lesions enlarge, coalesce, and thicken, multiple new lesions develop. As inflammation becomes more severe, lesions evolve into boggy, crusted plaques, and hair loss is more extensive. Exfoliation may be severe. Follicular openings may be markedly dilated and visually accentuated in the formation of comedones. Conical plugs of keratinous debris may fill hair follicles, and follicular casting may be present (Scott et al., 2001). Similar to localized demodicosis, occasionally generalized demodicosis may be nodular. Hyperpigmentation, lichenification, and scarring occur with chronicity. Secondary pyoderma is common and may be characterized by generalized deep folliculitis and furunculosis, and in some cases cellulitis. Hemorrhagic bullae may be present. Tissue devitalization may be marked in regions of boggy inflammation, and affected sites may be friable.

The head, trunk, and legs usually are affected in the early stages of generalized demodicosis. Less commonly, lesions begin diffusely, affecting most body regions. Ear canal and medial pinnal involvement may occur in conjunction with facial disease. The paws often are severely affected. Severe involvement of the feet (pododemodicosis) may occur alone, in conjunction with generalized demodicosis, or as a sequel to generalized demodicosis after other body sites have responded to miticidal therapy. Erythema, swelling, and secondary deep pyoderma with marked scarring are noted on the digits, in the interdigital webs, between the pawpads ventrally, and surrounding the clawbeds. Breed based variability in clinical features may be prominent. Pruritus, pain, and

generalized lymphadenopathy are frequent features of generalized demodicosis. In severe cases of generalized demodicosis, septicemia may occur.

Rarely, localized or generalized 'occult demodicosis' may present as very small nodules (2 to 3 mm in diameter), or as patchy alopecia with variable scale. Occult demodicosis is usually correlated microscopically with parafollicular granulomas and mural folliculitis, or both (see below and Chapter 18). Mites are difficult to demonstrate by skin scraping in this presentation. Occult demodicosis is seen most frequently in the Chinese Shar Pei. Skin biopsy is required to rule out demodicosis in this breed.

In contrast to short-coated breeds, alopecia may be surprisingly minimal in long-coated breeds with long anagen hair cycles such as the Maltese, Shih Tzu, Lhasa Apso, and Miniature Poodle. This may lead to a decreased index of suspicion for demodicosis in those breeds. Severe exfoliation may be the paramount sign of generalized demodicosis in breeds such as the West Highland White Terrier, Scottish Terrier, and Cairn Terrier.

Purebred dogs are at greater risk for developing juvenile-onset localized and generalized demodicosis. Shorthaired breeds at increased risk include the Doberman Pinscher, Pit Bull Terrier, Chinese Shar Pei, American Staffordshire Terrier, Dalmatian, English Bulldog, Great Dane, Boston Terrier, Chihuahua, Boxer, and Pug (Scott et al., 2001). Commonly affected medium-haired breeds include the West Highland White Terrier, Scottish Terrier, and Airedale. Long-haired breeds at increased risk include the Old English Sheepdog, German Shepherd Dog, Collie, and Afghan Hound. Acquired adult-onset generalized demodicosis without demonstrable underlying immunosuppressive disease may be seen more frequently in the Cocker Spaniel. The subgroup of 'occult demodicosis' characterized by multiple, well-demarcated nodules or alopecia with scale is seen most frequently in brachycephalic breeds such as the English Bulldog, Boxer, and Pit Bull Terriers, as well as Chinese Shar Peis. Juvenile-onset demodicosis is seen most commonly in dogs between 3 and 12 months of age, before sexual maturity has been reached. Sex predilections are not noted with canine demodicosis.

Diagnosis is not difficult in the vast majority of dogs with either localized or generalized demodicosis, as skin scrapings readily demonstrate mites. However, skin scrapings are not performed in many cases of demodicosis as the index of suspicion is low. Clinical differential diagnoses for juvenile-onset localized canine demodicosis include dermatophytosis, focal trauma, and less commonly, canine familial dermatomyositis in Collies and Shetland Sheepdogs. Skin scrapings should be performed in all cases if focal alopecia is a salient feature. The finding of demodectic mites in a Shetland Sheepdog or Collie with facial and pedal alopecia should not preclude skin biopsy, as localized demodicosis and canine familial dermatomyositis may coexist (see Chapter 3). Negative skin scrapings do not preclude a diagnosis of demodicosis; skin biopsies may be required to rule out demodicosis in at-risk breeds.

The prime clinical differential diagnosis for generalized demodicosis is deep folliculitis and furunculosis due to other causes. Unexplained pyoderma should always initiate deep skin scraping. Demodicosis presenting as generalized exfoliation (especially in terriers) must be differentiated from primary seborrhea. Demodicosis may be especially difficult to diagnose by skin scrapings in the Chinese Shar Pei and in other breeds with 'occult demodicosis'. Mites also may be especially difficult to demonstrate in dogs with severe pododemodicosis with extensive scarring, since mites may be more deeply located and thus less available for diagnosis by skin scraping. Demodicosis can never be ruled out entirely without skin biopsy.

Biopsy site selection

Generally, clinicians do not submit skin biopsy specimens to a pathologist expecting a diagnosis of demodicosis, since skin scraping is the most efficient diagnostic method. Despite negative skin scrapings, skin biopsy specimens should be taken from unexplained foci of alopecia, and plaques and nodules of unknown origin. If pododemodicosis is suspected but cannot be confirmed by skin scrapings, multiple specimens should be obtained from maximally affected sites that are normally well-haired, such as the dorsum of the digits.

Histopathology (Figures 17.46 through 17.50)

The epidermis is acanthotic, crusted, or ulcerated. Hyperkeratosis may be severe and affects follicular infundibula. Single or small numbers of mites without associated inflammation may be seen in skin biopsies from the face and are of no significance.

Three principal patterns of inflammation exist in canine demodicosis due to *Demodex canis*: folliculitis and furunculosis, parafollicular granulomas, and mural folliculitis (see Chapter 18). All three patterns may coexist, or individual patterns may predominate. Although some degree of mural folliculitis is present in all cases (Caswell et al., 1995), in most cases the predominant histologic lesions are as seen with deep bacterial folliculitis and furunculosis (see p. 420). Eosinophils are variable. Large numbers of plasma cells and lymphocytes surround follicles and apocrine sweat glands in chronic cases, and there may be perifollicular pigmentary incontinence. Hair follicles usually are colonized by moderate to large numbers of elongated *Demodex canis* mites (150 to 300 μm in length)

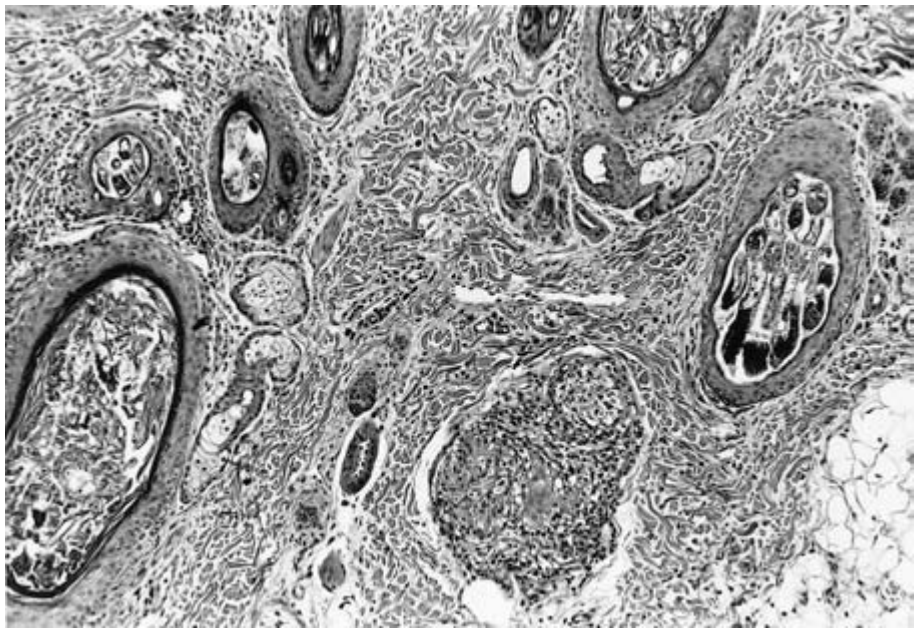


Fig. 17.46 Demodicosis in a dog. Dilated follicles contain elongated *Demodex* mites; there is scant perifollicular inflammation. Note adjacent large pyogranuloma.

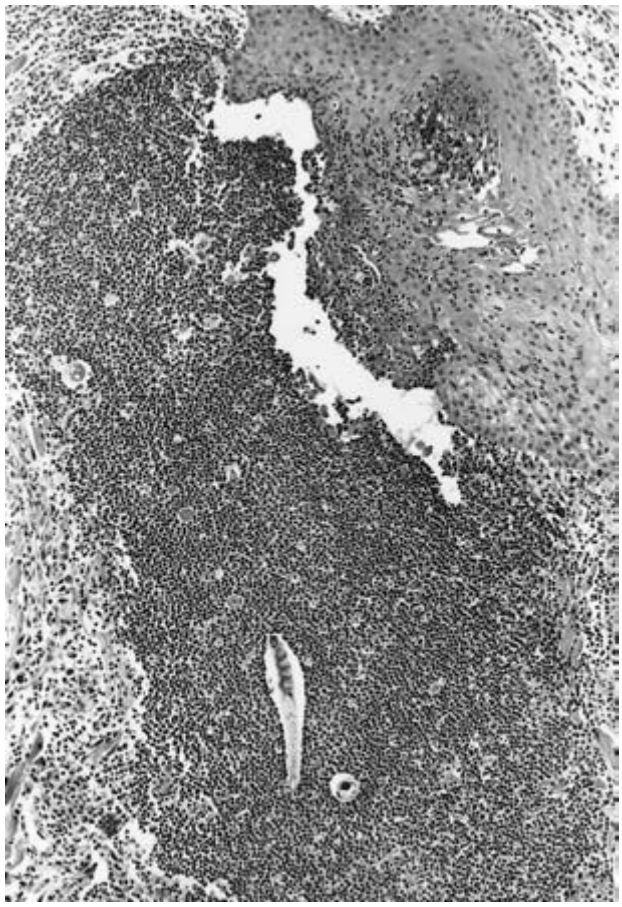


Fig. 17.47 Furunculosis in canine demodicosis. A furuncle contains an escaped mite and mite fragments.



Fig. 17.48 Higher magnification of canine demodicosis demonstrating an extrafollicular mite within a large pyogranuloma.

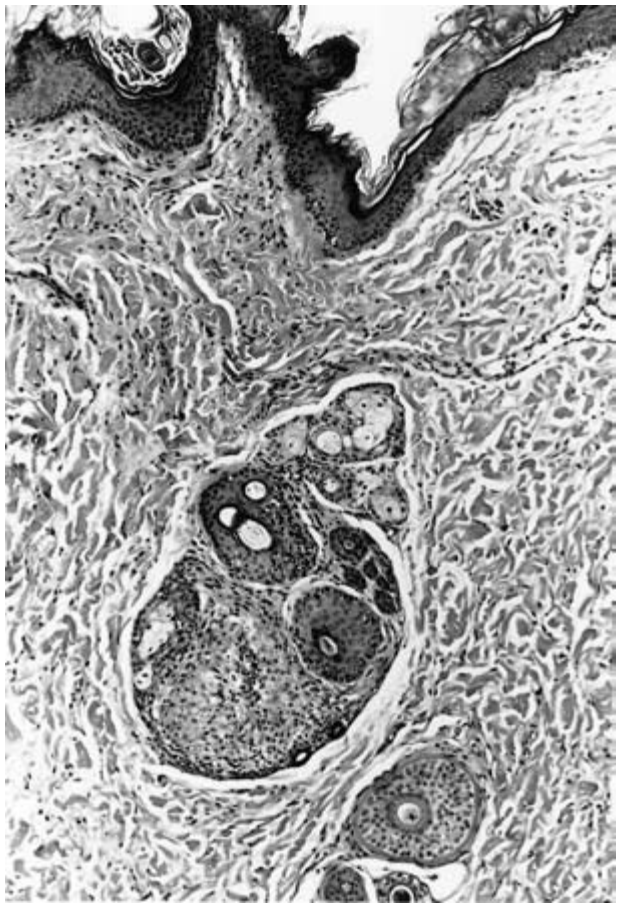


Fig. 17.49 Parafollicular pyogranuloma in canine demodicosis. Mites are not observed in this view.

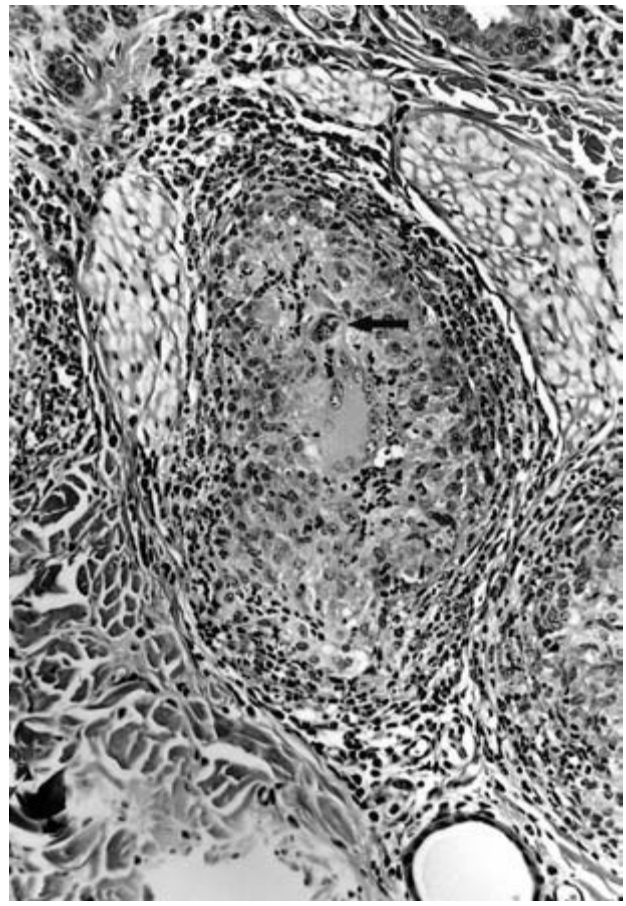


Fig. 17.50 Higher magnification of parafollicular granuloma in canine demodicosis. Note mite fragment (arrow) and large multinucleated giant cell.

with six or eight legs in two rows (larvae versus nymphs and adults). *Demodex injai*, measuring 334 to 368 µm, may be identified in some cases (Hillier & Desch, 2002). In cases of heavy infestation, mites may protrude from the follicular ostia or be extruded onto the surface of the specimen. Ruptured hair follicles (furuncles) result in release of free mites into the dermis, which are surrounded by extensive pustular or pyogranulomatous inflammation. In rare cases, mites may greatly distend superficial hair follicles to form comedone-like lesions.

A short form of *Demodex* sp., as yet unnamed, may cohabitate with *Demodex canis* in some cases (Chen, 1995; Chesney, 1999; Saridomichelakis et al., 1999). These mites, which range from 90 to 148 µm in length (Chesney, 1999), apparently inhabit the surface keratin layer of the follicular ostium or epidermis (Saridomichelakis et al., 1999).

Discrete parafollicular granulomas or pyogranulomas, often containing giant cells, may organize adjacent to or beneath hair follicles, or within sebaceous glands or ducts. In some cases this pattern is dominant, notably in those cases that are negative for mites on skin scrapings ('occult demodicosis'). Early lesions are characterized by degeneration of the wall of the isthmus, often near sebaceous glands, accompanied by histiocytes and giant cells. These foci evolve to sharply demarcated nodules that lie adjacent to hair follicles (thus, 'parafollicular'). Mites are frequently difficult to locate in these lesions; occasional scattered fragments may be seen within sebaceous gland ducts or associated hair follicles, as well as in the centers of the granulomas. When inflammatory lesions of this type are found in the skin biopsy, demodicosis should be suspected until proven otherwise, and step-sectioning of the specimen should be performed to search for the mites.

Differential diagnoses for demodicosis in dogs include other causes of folliculitis and furunculosis. In most cases, the relative ease of identification of the offending mites allows easy diagnosis. Clinically occult demodicosis with parafollicular granulomas is the notable exception; however, this pattern is distinctive and highly suggestive for demodicosis. Dermatophytosis may rarely feature similar parafollicular granulomas (as well as mural folli-

culitis; see Chapter 18); step-sectioning and appropriate special staining may be required for differentiation.

FELINE FOLLICULAR DEMODICOSIS

(Synonym: demodectic mange, demodectic acariasis)

Clinical features (Figures 17.51 and 17.52)

Feline demodicosis is a rare or regional parasitic skin disease caused by an overpopulation of one of at least three different species of host-specific mites, *Demodex* spp. *Demodex cati* is a feline follicular mite with morphologic features resembling *Demodex canis* in dogs (Scott et al., 2001). *Demodex gatoi* is a considerably shorter, nonfollicular species of demodicid mite that predominantly inhabits the stratum corneum (Desch & Stewart, 1999). A third, as yet unnamed, species of mite that resembles *Demodex gatoi*, but is larger, also has been identified (Chesney, 1988; Desch & Stewart, 1999).



Fig. 17.51 Feline demodicosis localized to the muzzle in a white Persian cat. (Photograph courtesy I. Feleccia.)

Wide clinical variability is noted; feline demodicosis may be localized and follicular, or generalized and follicular with features resembling canine generalized demodicosis. Feline follicular demodicosis seems to be caused predominantly by *Demodex cati*. However, difficulties may arise in the delineation and differentiation of skin diseases due to these three species of demodicid mites, as reports may not all accurately reflect appropriate morphologic differentiation of species and life stages of the mites. Feline superficial demodicosis, which is generalized and contagious, involves mites (*Demodex gatoi*) that inhabit the surface stratum corneum only; that disease is discussed separately (see Chapter 9) (Morris & Beale, 1997; Beale, 1998; Guaguère, 2000; Scott et al., 2001).

Feline demodicosis due to *Demodex cati* is a rare disease. The pathogenesis, transmission, and immunology of localized and generalized demodicosis caused by *Demodex cati* resemble those seen with *Demodex canis* in dogs (see p. 442).

Demodex cati is responsible for both localized and generalized demodicosis in cats. Feline localized demodicosis is a mild and self-limiting disease. Similar to canine generalized demodicosis, feline generalized demodicosis due to *Demodex cati* infection seems to require a cutaneous environment that is ecologically or immunologically favorable for intense colonization by demodectic mites. Alteration in the host immune system is likely responsible. The immunologic origin of feline generalized demodicosis due to *Demodex cati* is supported by the association of acquired adult-onset demodicosis with immunosuppressive diseases such as feline immunodeficiency virus infection (FIV), feline leukemia virus (FeLV), diabetes mellitus, hyperglucocorticoidism, and neoplasia (Guaguère, 2000; Scott et al., 2001). As in adult-onset



Fig. 17.52 Generalized feline demodicosis. Alopecia, crusting, and hyperpigmentation are subtly present on the legs, shoulder, neck, and face. Note the linear lesion of the foreleg. (Photograph courtesy C. Collinot.)

canine generalized demodicosis, immunosuppression or underlying disease is not always documented in adult-onset feline generalized demodicosis.

The clinical features of localized demodicosis due to *Demodex cati* include patchy alopecia with variable erythema, scaling, and crusting. The disease most frequently affects the eyelids, periorbital region, and perioral regions, and usually is limited to the head and neck. Mild ceruminous otitis may be the only clinical sign or may be present in conjunction with other facial lesions. Clinical features resemble those seen with mild, localized canine demodicosis.

Feline generalized follicular demodicosis caused by *Demodex cati* is a less severe disease than its canine counterpart. In most affected cats, the skin disease is relatively asymptomatic. Subtle erythema, variable alopecia, scaling, and crusting are the predominant features. Lesions may be surprisingly linear. Hyperpigmentation may be seen with chronicity. Coat coloration changes may occur. The hair in lesional skin may become darker in breeds in which haircoat pigmentation may be temperature dependent, such as Siamese cats. Secondary pyoderma is rare. Lesions are noted most commonly on the face, neck, trunk, or extremities. Pruritus is variable, but rarely prominent. Clinical signs referable to underlying immunosuppressive systemic diseases such as FIV or FeLV infection, diabetes mellitis, hyperglucocorticoidism, and neoplasia may be noted. Signalment predilection data for feline follicular demodicosis are not available.

Dermatophytosis is the prime clinical differential diagnoses for feline localized demodicosis caused by *Demodex cati*. Clinical differential diagnoses for feline generalized demodicosis caused by *Demodex cati* are legion, since the clinical features are pleomorphic and variable. Dermatophytosis, superficial pyoderma, and cutaneous epitheliotropic lymphoma are possible differential diagnoses in nonpruritic cats. In pruritic cats, the above-mentioned diseases, plus diseases associated with excessive grooming such as allergic dermatitis and psychogenic alopecia should be considered. Skin scrapings should be performed to find the mites. All cats with unidentified skin disease exhibiting subtle skin or haircoat changes should be scraped for demodicosis. If scrapings do not afford a definitive diagnosis, then skin biopsy should be performed. Since generalized demodicosis due to *Demodex cati* is seen most frequently in conjunction with underlying immunosuppressive systemic diseases, affected cats should be assessed for FIV or FeLV infection, diabetes mellitus, hyperglucocorticoidism, and neoplasia.

Biopsy site selection

Since skin scraping is the most efficient diagnostic method, clinicians usually do not submit skin biopsy specimens to a pathologist expecting a diagnosis of follicular demodicosis. The exception is pruritic feline superficial demodicosis in which mites may be absent in scrapings due to excessive grooming (see Chapter 9).

Histopathology (Figures 17.53 and 17.54)

The epidermis is mildly to moderately acanthotic. There may be follicular keratosis and mild crusting. Feline demodicosis due to *Demodex cati* is manifested as mild perifollicular inflammation generally composed of lymphocytes, macrophages, and neutrophils. Mural inflammation of variable degree accompanies the perifollicular inflammation (see Chapter 18). Follicular mural spongiosis or mucinosis may be present. There may be occasional luminal pustular folliculitis or granulomatous degeneration of follicles or sebaceous glands. The mites are of similar length but are slimmer than *Demodex canis* (see p. 442). Demodicosis may be found in association with bowenoid *in situ* carcinoma (see Chapter 22). Often, only



Fig. 17.53 Feline follicular demodicosis. Perifollicular inflammation extends slightly to the outer follicular wall (mural folliculitis); note moderate numbers of mites within follicles.

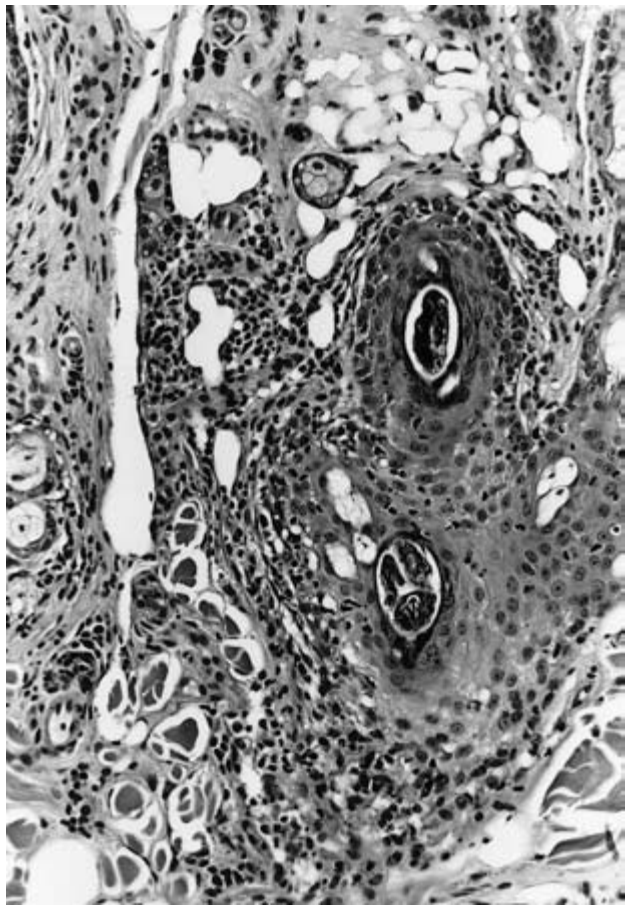


Fig. 17.54 Higher magnification of feline follicular demodicosis.

hair follicles within the lesion are colonized; adjacent skin is normal.

Definitive diagnosis is easy to accomplish as mites are identifiable in tissue. In cats, luminal pustular folliculitis is most often due to dermatophytosis rather than demodicosis. As concurrent demodicosis and dermatophytosis may occur in this species, dermatophytosis should be ruled out by appropriate staining (periodic acid–Schiff [PAS] or Gomori's methenamine silver [GMS]) if folliculitis is observed.

PELODERA DERMATITIS

(Synonyms: rhabditic dermatitis)

Clinical features (Figures 17.55 and 17.56)

Pelodera dermatitis is a rare canine skin disease caused by invasion of the skin by larvae from the free-living nematode, *Pelodera strongyloides*. The disease has been reported rarely, predominantly from the midwestern United States (Schwartzman, 1964; Willers, 1970; Horton, 1980). Sporadic individual cases also have been reported in France and Germany (Bourdeau, 1984; Morisse et al., 1994). Cattle, horses, and sheep also may be affected. Three cases of the disease are reported in the human literature (Jones et al., 1991). The actual frequency of occurrence of *Pelodera* dermatitis is unknown. Rhabditic dermatitis is seen in conjunction with filthy, contaminated environmental conditions.



Fig. 17.55 *Pelodera* dermatitis in an English Pointer. Note the ventral contact distribution pattern affecting the extremities and ventral trunk. (Photograph courtesy D.W. Angarano, C.E. Griffin, and J.M. MacDonald.)

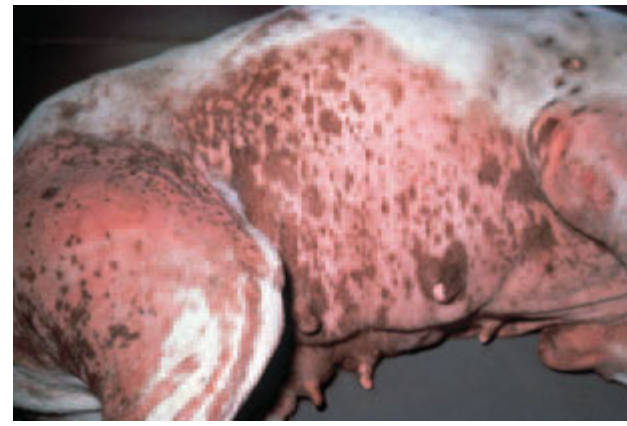


Fig. 17.56 Closer view of the dog in Fig. 16.55. Extensive alopecia and a fine papular rash are present. (Photograph courtesy D.W. Angarano, C.E. Griffin, and J.M. MacDonald.)

As in most parasitic dermatoses, hypersensitivity to the invading parasite is the presumed mechanism of disease production. The free-living adult nematode is thought to have a direct life cycle, and is found most frequently in longstanding, decaying organic debris, especially straw, rice hulls, or hay stored in long-term contact with the

ground in damp conditions. Dogs and other mammals presumably become infected by contact with contaminated organic debris that is used as bedding (Scott et al., 2001).

Clinical features include an erythematous, maculopapular rash with crusting. Alopecia is variable, but often profound. The magnitude of self-trauma is dependent upon the degree of pruritus, which frequently is severe. Extreme pruritus usually is reported, but classical lesions in the absence of pruritus have also been described (Bourdeau, 1984). Intact and ruptured pustules indicate secondary pyoderma. Affected body sites correlate with sites of contact with contaminated bedding. The ventral paws, distal legs, perineum, tail, and comparatively glabrous skin of the ventral abdomen and thorax are most commonly affected.

Most reported canine cases have been in short-coated dogs (Schwartzman, 1964; Willers, 1970; Horton, 1980; Bourdeau, 1984; Morisse et al., 1994), perhaps indicating greater ease of parasitic exposure. Signalment predilections have not been reported.

Clinical differential diagnoses should include canine sarcoptic acariasis, demodicosis, canine dirofilariasis, hookworm dermatitis, contact dermatitis, and superficial bacterial folliculitis. Skin scrapings should readily reveal motile nematode larvae measuring approximately 600 µm in length. Histopathology also is diagnostic.

Biopsy site selection

Multiple biopsy specimens should be submitted from new papular lesions. Excoriated skin should be avoided.

Histopathology (Figures 17.57 through 17.59)

The epidermis is severely and irregularly acanthotic. Hyperkeratosis is accompanied by keratin accumulation in follicular infundibula.

Large numbers of elongated nematode larvae up to 600 µm in length are seen free within superficial keratin as well as within superficial to middle hair follicles. Smaller numbers of organisms are found deeper within follicles. Large and often discrete pyogranulomas replace deep follicles or are subjacent to ruptured follicles. Pyogranulomas frequently contain fragments of nematodes. Folliculitis and furunculosis with hemorrhage may be evident. Moderate to large numbers of eosinophils, lymphocytes, macrophages, and mast cells are accumulated around follicles, sometimes in a nodular pattern, and are present loosely throughout the superficial and middle dermis. Mural folliculitis, characterized by migration of lymphocytes into the isthmus of hair follicles, is observed in some lesions.

Because of the presence of characteristic nematodes, the histopathologic appearance of rhabditic dermatitis is diagnostic. The patterns of inflammation seen (folliculitis and furunculosis, pyogranulomas, and mural folliculitis) are, interestingly, essentially those of canine demodicosis.

EOSINOPHILIC FURUNCULOSIS OF THE FACE

Clinical features (Figures 17.60 and 17.61)

Eosinophilic furunculosis of the face is an uncommon canine skin disease of peracute onset and a rapidly ful-

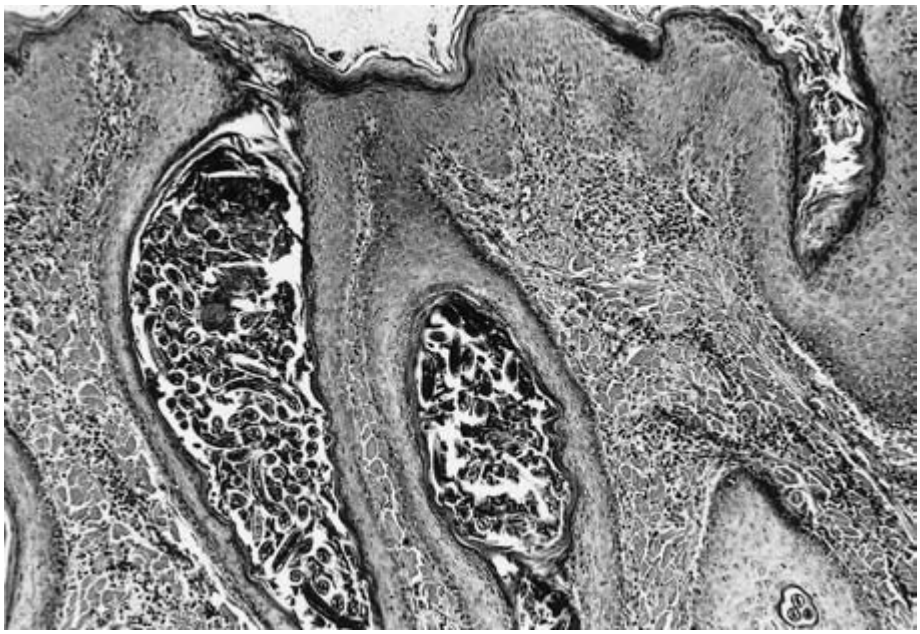


Fig. 17.57 *Pelodera* dermatitis in a dog. Superficial hair follicles are distended with elongated larvae of *Pelodera strongyloides*. (Case material courtesy D.W. Scott.)

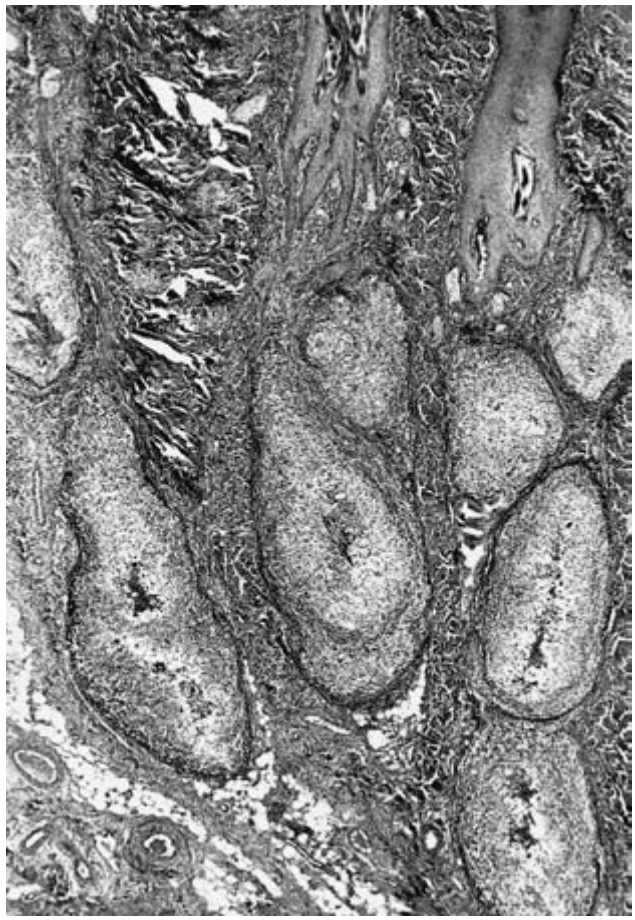


Fig. 17.58 *Pelodera* dermatitis in the dog of Fig. 17.57, demonstrating numerous deep follicular pyogranulomas. Note larvae within superficial follicles.



Fig. 17.59 Higher magnification of Fig. 17.58. A deep follicular pyogranuloma surrounds a fragment of a nematode larva.

minating course. It is characterized by predominantly facial hemorrhagic ulcers with edema (Gross, 1993). The syndrome may be underdiagnosed; some dogs diagnosed in the past with 'nasal pyoderma' probably had eosinophilic furunculosis of the face.

A hypersensitivity response to arthropod venom is proposed based on history, site, clinical course, and histopathologic features (Gross, 1993). Definitive documentation of arthropod insult is difficult to obtain (Gross, 1993; Curtis et al., 1995; Guaguère et al., 1996; Fondati & Mechelli, 1998). In the initial case series, the common inciting feature was a history of exposure to stinging insects, including wasps, hornets, and bees (Gross, 1993). Recent exposure to outdoor, relatively undeveloped environments where arthropod stings were possible was noted in 11 of 12 additional cases (Guaguère et al., 1996), and has been consistently noted by the authors. A recent history of exposure to ants (digging in ant hills) and spiders was present in several cases seen by one author (P.J.I.). Although the majority of reported cases have



Fig. 17.60 Eosinophilic furunculosis of the face in a mixed-breed dog. Multiple hemorrhagic nodules have coalesced on the dorsal muzzle.



Fig. 17.61 Eosinophilic furunculosis of the face in a white German Shepherd Dog. Ulcerated, coalesced nodules are present on the dorsal muzzle. Lesions are more chronic than those in Fig. 17.60.

occurred in warmer months, some cases have been noted in indoor dogs in the winter (Scott et al., 2001). In one notable case, an indoor dog, affected in winter in the midwestern United States, was observed playing with bees that had escaped from a hive in the wall of the home (Hargis, A., personal communication, 1999). The syndrome bears marked clinical and histopathologic similarities to feline mosquito bite hypersensitivity (see Chapter 14).

Severely erythematous or hemorrhagic papules and pustules, as well as edematous nodules and plaques develop acutely and ulcerate to form a hemorrhagic crust. Pustules, nodules, and plaques rapidly fistulate and drain serosanguinous exudate. Lesions commonly are localized in a somewhat bilaterally symmetric pattern on the dorsal and lateral muzzle and periorbitally. However, similar lesions may be seen on the comparatively glabrous skin of the axillae and ventral abdomen, thoracic wall, distal legs, lips, and pinnae. Severe, acute lesions commonly are exquisitely painful and affected dogs resist examination. Pruritus is variable, but may be severe. Severely affected dogs may be febrile, lethargic, and anorectic (Curtis et al., 1995; Guaguère et al., 1996). Peripheral blood eosinophilia is seen in the majority of cases (Guaguère et al., 1996).

The age of onset is less than 2 years in approximately 50% of affected dogs (Gross, 1993; Scott et al., 2001). It is tempting to speculate that young, inquisitive dogs are more likely to provoke arthropod assault. Most reported cases have been in large or moderately large breeds with abundant access to the outdoors, also adding credence to an environmental arthropod attack. German Shepherd Dogs and Rottweilers may be at increased risk. Toy and miniature breeds have not been reported (Scott et al., 2001). Sex predilections are not noted.

Clinical differential diagnoses include nasal deep bacterial folliculitis and furunculosis, tick bite hypersensitivity, and severe dermatophytosis. None of these diseases share the fulminant rapid onset of eosinophilic furunculosis of the face. Surface cytology from draining fistulous tracts reveals numerous eosinophils. History, likelihood of exposure to arthropods, cytology, a complete blood count (CBC) to detect eosinophilia, dermatophyte culture, and histopathology will aid in differentiation. Clinicians commonly mistake eosinophilic furunculosis of the face for facially-oriented autoimmune skin diseases such as pemphigus foliaceus. Eosinophilic furunculosis is a fulminant, peracute dermatosis, whereas autoimmune skin diseases commonly develop gradually from subtle beginnings.

Biopsy site selection

Biopsy specimens should be taken from intact papules, pustules, or nodules; areas of frank ulceration should be avoided. If newer primary lesions are not evident, areas of maximal erythema and swelling should be sampled. General anesthesia is recommended for skin biopsy, since dogs commonly are in pain and resist manipulation.

Histopathology (Figures 17.62 and 17.63)

The epidermis is moderately to severely acanthotic and may be covered with a serocellular crust. Spongiosis is often present and varies from mild to moderately severe. Erosion or ulceration may be severe.

The dermis is characterized by intense, predominantly eosinophilic and destructive folliculocentric inflammation. In some cases, neutrophils are prominent. Typically, there is accompanying severe dermal edema and/or mucin deposition. Hemorrhage is variable but sometimes severe. Explosive follicular rupture is characteristic, although not universal. Large numbers of eosinophils and variable neutrophils fill intact hair follicles, and surround free hair shafts from ruptured hair follicles. Eosinophils often degranulate within follicular walls (eosinophilic mural folliculitis) or around free hairs, which may be displaced below the level of the damaged follicle. Hair follicle walls may be replaced entirely by degenerated eosinophils to form follicular 'casts' or 'molds' which may surround

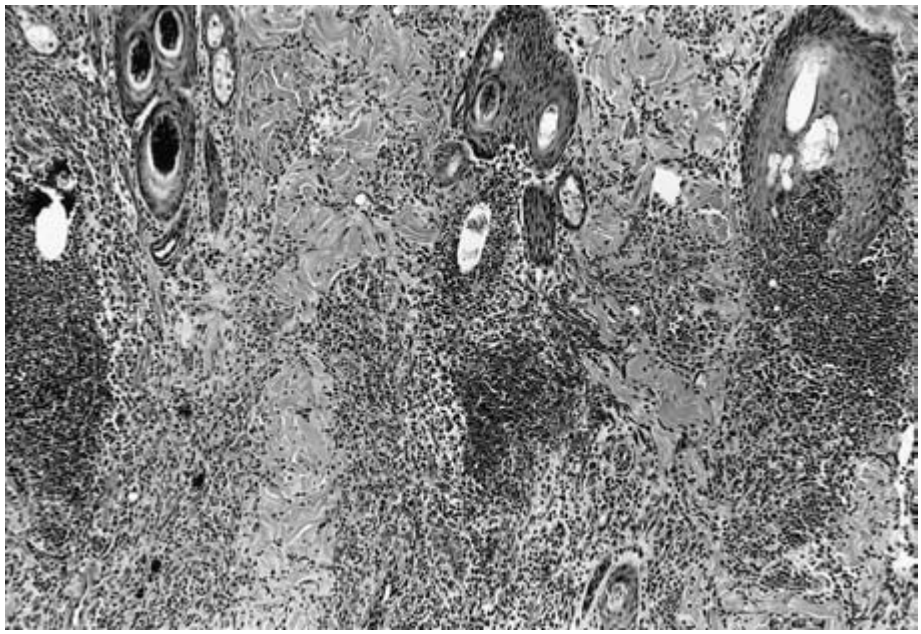


Fig. 17.62 Eosinophilic furunculosis in a dog. Follicles are ruptured by darkly staining eosinophilic pustules.

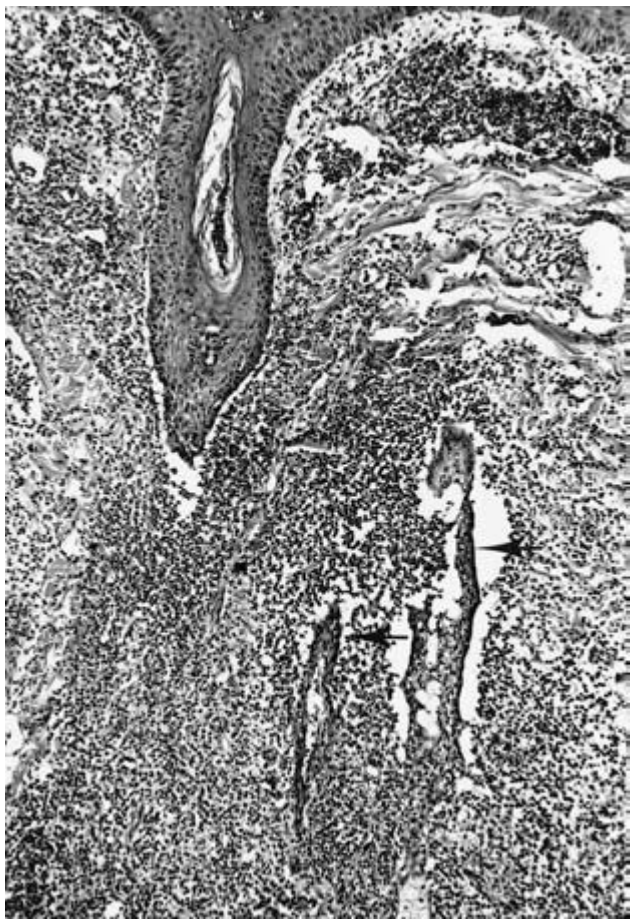


Fig. 17.63 Higher magnification of eosinophilic furunculosis demonstrating follicular 'explosion' by severe inflammation. Note residual follicular fragments (arrows).

residual hairs or hair-shaped spaces left by drop out of these fragments. Smaller foci of eosinophil degranulation are seen around collagen fibers (flame figures). Mixed infiltrations of mononuclear cells, eosinophils and fewer neutrophils often fill the dermis in later lesions. Inflammation and edema may extend to the panniculus.

Differential diagnoses principally include deep bacterial folliculitis and furunculosis, and sterile eosinophilic pustulosis. Although furunculosis with a predominance of eosinophils can be seen with bacterial infections, neutrophils usually are a more significant component. Flame figures and eosinophilic mural folliculitis are much more characteristic of eosinophilic furunculosis than of bacterial infections. Sterile eosinophilic pustulosis is similar to eosinophilic furunculosis in that eosinophils predominate in both diseases and flame figures may be seen. Overall, eosinophilic pustulosis tends to be a more superficial and milder process than eosinophilic furunculosis of the face. Although eosinophilic furuncles occur in both, the furuncles of the latter are often much more explosively destructive to hair follicles. Clinical differentiation may be required.

SEBACEOUS ADENITIS

Clinical features (Figures 17.64 and 17.65)

See Chapter 8.

Biopsy site selection

See Chapter 8.



Fig. 17.64 Sebaceous adenitis in a black Standard Poodle. Matted keratinaceous debris is present diffusely in a dry, poor quality haircoat. (Photograph courtesy H.T. Power; case material University of California, Davis.)

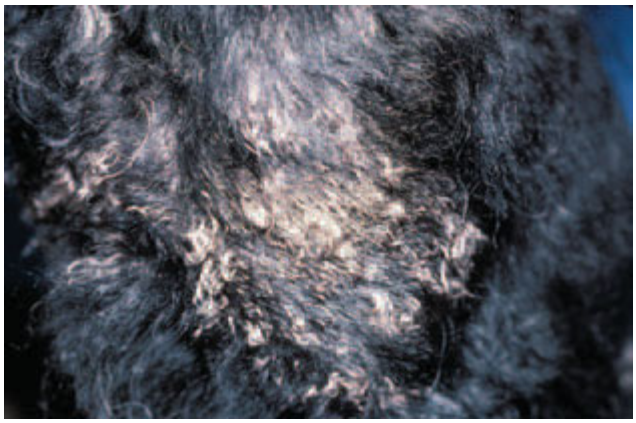


Fig. 17.65 Closer view of the dog in Fig. 17.64. Keratin debris ensheathes hairs. (Photograph courtesy H.T. Power; case material University of California, Davis).

Histopathology (Figures 17.66 through 17.71)

Lesions of the epidermis have been discussed and consist principally of severe hyperkeratosis that also fills superficial hair follicles to form follicular fronds (see Chapter 8). In sebaceous adenitis of dogs, sebaceous glands usually are diffusely absent from all specimens, particularly in late, relatively uninflamed lesions. Identification of hyperkeratosis, particularly in a breed known to be commonly affected, warrants careful search for sebaceous glands; absence of these structures can be overlooked easily. One author (T.L.G.) has seen specimens from typical canine breeds with typical clinical lesions, and correlative histopathologic changes, in which a few sebaceous glands were present. It is unknown whether these lesions are very early, or whether sebaceous gland regeneration has occurred.



Fig. 17.66 Sebaceous adenitis in a Standard Poodle. This early lesion demonstrates prominent periadnexal inflammation at the site of previous sebaceous glands.

Random biopsy specimens from affected dogs, notably but not exclusively Standard Poodles, often have scant inflammation at the follicular isthmus in the vicinity of previous sebaceous glands. Inflammation consists of minimal to mild, loosely organized accumulations of lymphocytes, macrophages, plasma cells, and variable neutrophils. Eosinophils are rare. Lymphocytes and macrophages may infiltrate the wall of the follicular isthmus (mural folliculitis). Inflammation may not be present at every follicle.

In some putative early lesions, inflammation may be moderate and more nodular. Dermal inflammation often is lopsided, since it parallels the unilateral location of sebaceous glands in the pilosebaceous unit. Macrophages are prominent in these lesions, and are intermingled with neutrophils and lymphocytes with fewer plasma cells. Some lesions are distinctly pyogranulomatous. In the rare severely inflamed lesions, the lopsided distribution may not be obvious, and the inflammation may surround hair follicles at the isthmus.

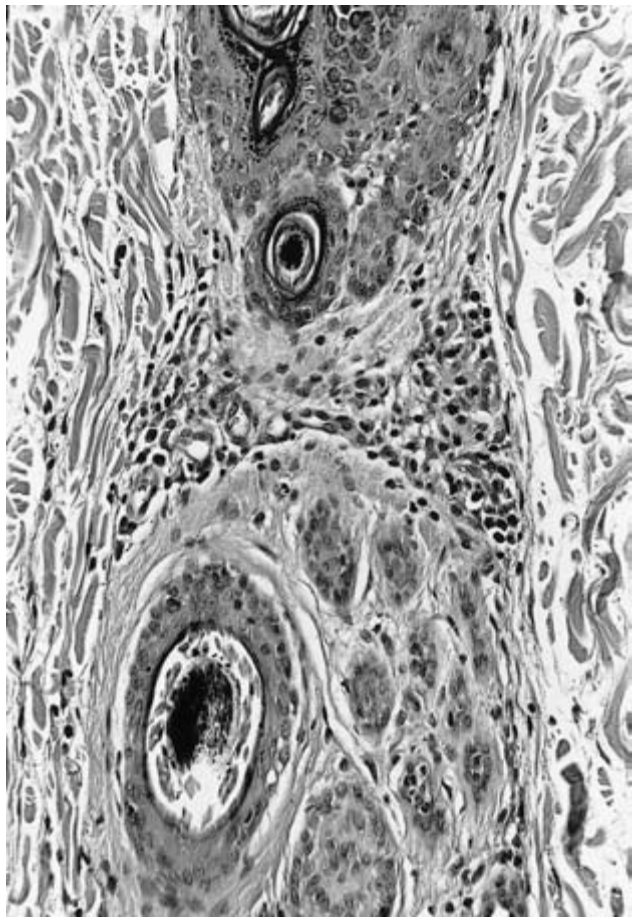


Fig. 17.67 Sebaceous adenitis in a dog demonstrating scant periadnexal, mixed mononuclear inflammation typical of chronic lesions.

Immunohistologic examination of dogs with sebaceous adenitis revealed a preponderance of antigen-presenting dendritic cells and T lymphocytes in inflamed lesions. These findings in the face of negative circulating autoantibodies, as studied by indirect immunoperoxidase testing on normal skin, suggested a cell-mediated immunopathogenesis for sebaceous gland destruction (Rybnicek et al., 1998).

Late stages of the disease in Standard Poodles or other breeds may be characterized by follicular atrophy or dysplasia, or normal follicular growth activity. Secondary folliculitis or furunculosis is common in affected Akitas, and has been described in Belgian Sheepdogs (Guaguère et al., 1997).

Vizslas and other short-coated breeds may have sebaceous adenitis that is characterized by more discrete, usually large foci of nodular, lopsided granulomatous or pyogranulomatous periadnexal inflammation that is centered at the site of previous sebaceous glands. Extension to deeper tissue has been described (Scott, et al., 2001). Inflammation is more consistently prominent in this subgroup of sebaceous adenitis, and is present at all stages of the disease. There may be perifollicular fibrosis occasionally.

In cats with sebaceous adenitis, hyperkeratosis and crusting are present (see Chapter 8). The inflammatory lesions may be less lopsided in distribution, and include a major component of mural folliculitis (see Chapter 18). Inflammation generally is mild overall. Lymphocytes migrate into the follicular wall from the lower infundibula through the isthmus, and in some lesions are centered at the site of previous sebaceous glands as small nodular

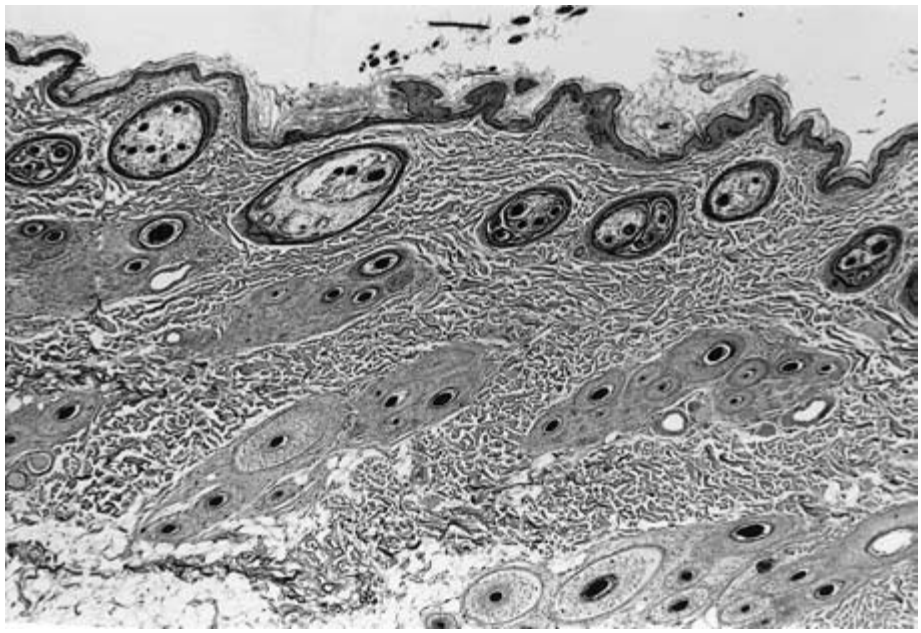


Fig. 17.68 Late stage sebaceous adenitis in a dog. Note complete absence of sebaceous glands.

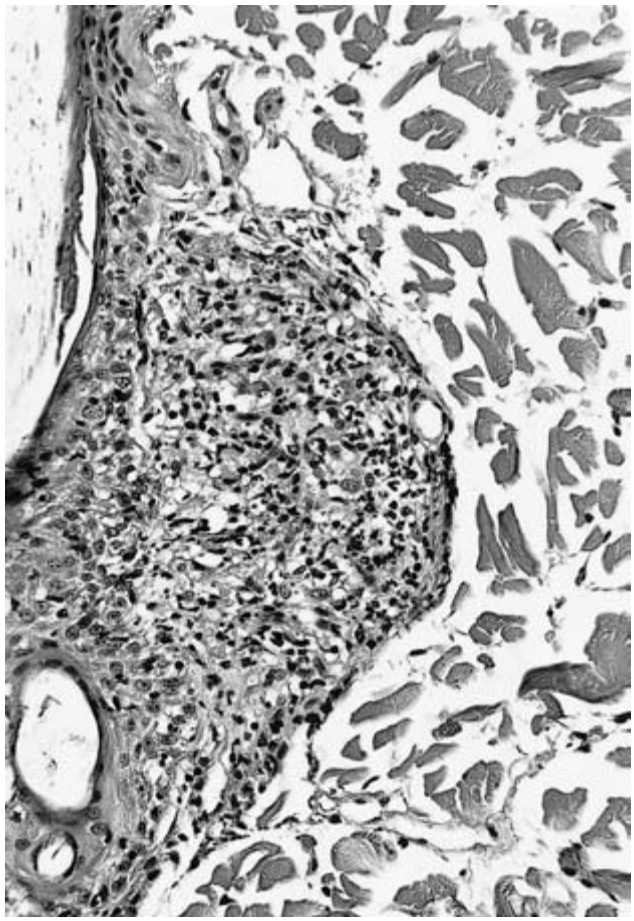


Fig. 17.69 High magnification of granulomatous sebaceous adenitis in a Vizsla. A discrete nodule of histiocytes, neutrophils, and lymphocytes is seen at the site of a previous sebaceous gland.

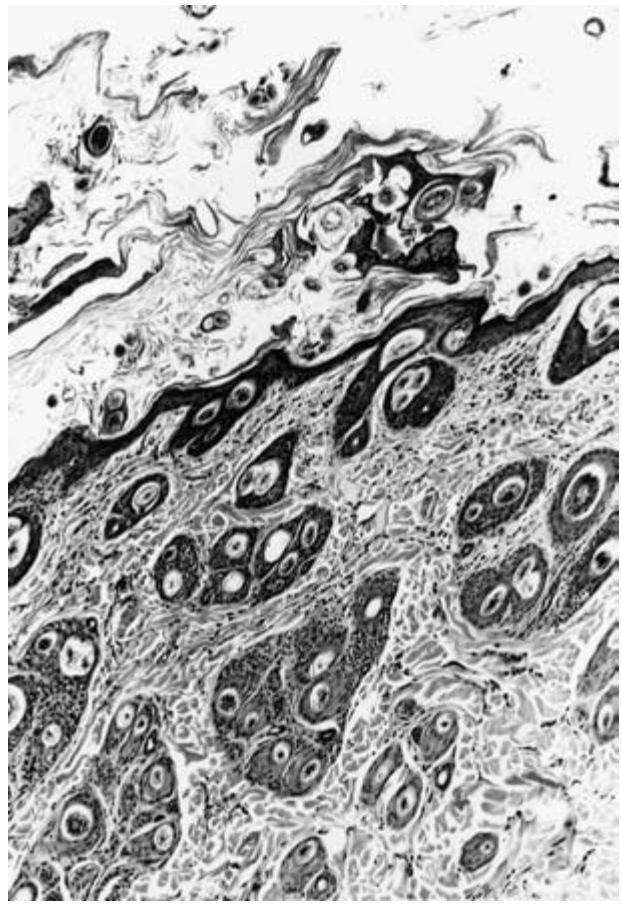


Fig. 17.70 Sebaceous adenitis in a cat. Sebaceous glands are diffusely absent; note perifollicular and mural inflammation.

foci. Putative early lesions are more inflamed and have lymphocytes, macrophages, and fewer neutrophils adjacent to follicles at the isthmus. Perifollicular pyogranulomas have been reported (Scott, 1989). Sebaceous glands are uniformly absent in most specimens. Follicular atrophy may be present in late lesions. Lymphocytes, plasma cells, macrophages, and neutrophils mildly infiltrate the superficial and perifollicular dermis.

For dogs, the diagnosis for the sparsely inflamed late lesions of sebaceous adenitis is straightforward. The absence of sebaceous glands in at least two 6 or 8 mm punch biopsy specimens, accompanied by minimal periadnexal inflammation, is confirmatory. Differential diagnosis for the severely inflamed forms of sebaceous adenitis principally includes sterile granuloma and pyogranuloma syndrome or reactive histiocytosis (see Chapter 13). Inflamed lesions of sebaceous adenitis may be easily confused with these inflammatory disorders, in which sebaceous glands are nonspecifically destroyed as they are swept up by periadnexal infiltrates. Inflammation in granulomatous sebaceous adenitis localizes particularly to the isthmus, even when severe. Sterile granuloma and pyogranuloma syndrome and reactive histiocytosis tend to surround entire adnexal units, including hair follicles and apocrine sweat glands, and often track along the complete length of the follicle in a sausage-shaped pattern. Clinical differentiation may be required.

Less often in dogs, demodicosis, Vogt–Koyanagi–Harada-like syndrome, or leishmaniasis also may be considered. In some lesions of demodicosis parafollicular granulomas (or pyogranulomas) occur in and around sebaceous glands and hair follicles (see p. 442). Identification of mites (which may be scarce in this form of demodicosis) may be difficult, and step sectioning may be required. Absence of sebaceous glands throughout the specimen supports sebaceous adenitis; this is not a feature of parafollicular granulomas in canine demodicosis.

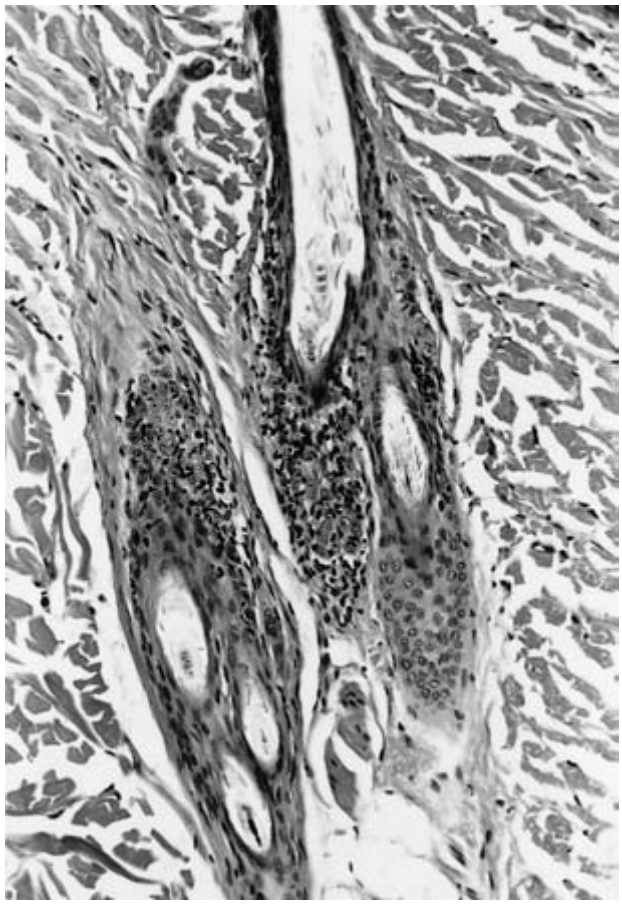


Fig. 17.71 Higher magnification of sebaceous adenitis in a cat. Note lopsided inflammation at putative sites of sebaceous glands (glands are absent).

Nodular periadnexal histiocytic inflammation may be prominent in some cases of Vogt–Koyanagi–Harada like syndrome and may obscure sebaceous glands; however, the more typical lichenoid band of inflammation usually is also present to allow differentiation from sebaceous adenitis. Sebaceous gland inflammation in cutaneous leishmaniasis might be confused with more severely inflamed forms of sebaceous adenitis; identification of organisms in tissue allows differentiation of this disease.

In cats, sebaceous adenitis is similar to mural folliculitis secondary to dermatophytosis, drug reaction, or food allergy, or may resemble pseudopelade (see Chapter 18). Critical diagnostic features of sebaceous adenitis include complete absence of sebaceous glands and hyperkeratosis. Inflammation that is lopsided or directed to the site of previous glands is also diagnostic, but less consistently present. Some syndromes of feline mural folliculitis will result in haphazard sebaceous atrophy secondary to isthmus-directed inflammation; clinical differentiation may be required in these cases.

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Chapter 18

Mural diseases of the hair follicle

Mural diseases of the hair follicle are characterized by inflammation that is directed to the follicular wall. Inflammation involving only the infundibular portion of the follicle generally is associated with adjacent epidermal inflammation. Although also technically 'mural', diseases with only infundibular inflammation are covered in Part I, Diseases of the Epidermis. The diseases here primarily target the follicular isthmus (the middle portion of the follicle) or the follicular bulb (the deepest portion of the follicle) (see Chapter 23 for more detailed follicular microanatomy). Many of these diseases are putatively allergic or immunoreactive in origin, and may involve follicular presentation of foreign antigen or immunologic targeting of follicular host antigens.

Mural folliculitis may be seen in the context of other inflammatory reaction patterns, including spongiotic and perivascular allergic dermatitis (see Chapters 5 and 9). Clinically confirmed food allergy in cats may have lymphocytic mural folliculitis, but this is seen in concert with perivascular and spongiotic dermatitis; concomitant epidermal inflammation and apoptosis also have been reported (DeClercq, 2000). Seasonal lymphocytic mural folliculitis with spontaneous resolution was reported in a cat, suggesting seasonal triggering by allergens (Marignac et al., 2002). Some drug reactions may have a profound lymphocytic mural component. Experimental allergic contact dermatitis may include lymphocytic mural folliculitis at patch test sites (Krawiec & Gaafar, 1975) (see Chapter 5). Although this may be due to induction techniques that reach deeper epithelium, the presence of mural folliculitis in this context reflects the role of the hair follicle as an allergic target.

The diseases of this chapter are largely those in which mural inflammation is the central feature histopathologically, i.e. 'primary' mural folliculitis. Some may have concurrent dermatitis, but mural folliculitis is the striking pathologic change. Due to incomplete clinical categorization of some of these morphological entities, multiple etiopathogeneses may exist for individual diseases that are described. There are many individual cases in which microscopic delineation of primary mural folliculitis is difficult. Until the clinical divisions of mural folliculitis are better understood, this difficulty will remain.

ALOPECIA AREATA

Clinical features (Figures 18.1 and 18.2)

Alopecia areata (AA) is an uncommon, or perhaps underrecognized, putative autoimmune skin disease seen in the dog characterized by nonscarring alopecia. As in humans (Olsen, 2003), canine AA is a benign cosmetic disease. Alopecia areata is common in humans (Madani & Shapiro, 2000; Tobin et al., 2003), and most commonly affects the scalp and face, causing patients rapidly to seek diagnosis and treatment. Some dogs with AA may not have skin biopsies performed since the prime clinical feature of canine AA commonly is mild, subtle, and visually innocuous noninflammatory hair loss.

Clinical, histopathologic, and immunopathologic similarities between AA in dogs and humans are well documented (Olivry et al., 1996; Tobin et al., 1998; Tobin et al., 2003). As in humans (Olsen, 2003) dogs with AA may self-cure, respond to immunosuppressive therapy, or seemingly be resistant to therapy. This may indicate subsets of AA, perhaps reflecting variations in antigen targeting or severity and extent of inflammation (see below). In humans, a high frequency of occurrence within families sharing certain human leukocyte antigens (HLA) indicates genetic predilection (Madani & Shapiro, 2000). Too few dogs with AA have been reported from institutions where comparisons can be made with hospital populations to determine if statistically significant breed predilections and thus genetic predispositions exist.

Alopecia areata in dogs results from selective and reversible damage to anagen hair follicles (Tobin & Olivry, 2004). Although AA is a mild disease, the syndrome exhibits many features highly suggestive of an autoimmune etiology. Inflammatory cells consist principally of cytotoxic T lymphocytes, helper T cells, and dendritic antigen-presenting cells (Olivry et al., 1996). Direct



Fig. 18.1 Alopecia areata in a German Shepherd Dog-crossbreed dog. Hair loss is confined to one coat color and is strikingly bilaterally symmetric.



Fig. 18.2 Closer view of the dog in Fig 18.1. The affected area is almost totally alopecic.

immunofluorescence detects hair follicle-specific IgG, indirect immunofluorescence reveals circulating antihair follicle IgG autoantibodies to various follicular proteins, and immunoblotting reveals IgG reactivity to multiple hair follicle proteins including trichohyalin and other inner root sheath proteins (Tobin et al., 1998, 2003). This documentation of antibodies directed towards hair follicle-specific target proteins is shared with AA in humans (Tobin et al., 2003). Trichohyalin is necessary for inner root sheath differentiation, and defects or damage may result in defective hair follicle formation (Tobin et al., 2003).

Morphologic changes in follicular melanocytes, indicating that melanocytes may be one of the targets of immunoreactivity, have been reported in acute AA in humans (Tobin et al., 1990). A similar phenomenon in dogs could explain the occasionally striking restriction of the disease to hair of one coat color, as well as the occasional concomitant leukotrichia. The melanocytic targeting in dogs may be more severe than that seen in humans, since the hair regrowth that occurs as the result of either spontaneous remission or immunosuppressive therapy may remain nonpigmented for multiple hair cycles (Tobin & Olivry, 2004).

Presenting initial lesions include alopecia (92%) and leukotrichia (8%) (Tobin et al., 2003). Focal or multifocal areas of well-circumscribed alopecia develop. The alopecic skin has minimal or no visible inflammation. Areas of alopecia may expand gradually as waves of follicular damage move centrifugally. Hyperpigmentation of exposed skin may occur in chronic cases in breeds likely to hyperpigment. Short, stubby 'exclamation-mark hairs' with dystrophic tapered proximal portions and frayed damaged distal portions have been described in humans with AA. One author (P.J.I.) has seen hairs consistent with this description in a dog. Trachyonychia, or nail dysplasia, may be seen concomitantly with AA in humans; trachyonychia affecting all of the claws, characterized by ridging, striations, and an irregular surface, has been reported in dogs with AA (Jonghe et al., 1999; Madani & Shapiro, 2000). Prognosis varies with canine AA; some cases self-cure, others seemingly respond to mildly immunosuppressive dosages of corticosteroids, while others do not regrow hair.

Alopecia occurred initially on the face in 92% of dogs in one large study (Tobin et al., 2003). The dorsal and lateral muzzle, temporal region, chin, periorbital region, and ears may be affected. Less commonly, lesions also may involve the legs and trunk. In multicolored breeds, AA may be restricted to hair of one color. In 24% of dogs with multiple hair colors, dark brown or black hairs were affected preferentially (Tobin et al., 2003). Facial bilateral symmetry was noted in 80% of affected dogs (Tobin et al., 2003). In breeds with symmetric bicolor facial patterns such as the German Shepherd Dog or Dachshund, restriction of the disease to facial hair of one color may create dramatic mask-like patterns of hair loss.

Breed predilections are not statistically proven, as reference populations are lacking in studies pooled from multiple sources. In the largest study of canine AA to date, which gathered data from many sources, 19 of 25 dogs were purebreds, with German Shepherd Dogs, Dachshunds, Beagles, Labrador Retrievers, and 'setters' all having more than one dog affected (Tobin et al., 2003). However, owners of purebred dogs may be more willing to pursue a cosmetic disease through referral to a spe-

cialist. Based on additional cases seen by the authors, German Shepherd Dogs and Dachshunds may be at increased risk. The age of onset varies greatly, ranging from 1 to 11 years of age (median of 5 years) (Tobin et al., 2003). Sex predilection is not apparent (Tobin et al., 2003).

Clinical differential diagnoses of AA include virtually any skin disease characterized by relatively noninflammatory, asymptomatic alopecia, especially affecting the face. Possible differential diagnoses include acquired pattern alopecia, follicular dysplasia, traction alopecia, pseudopelade, endocrinopathies, demodicosis, and dermatophytosis. Skin scrapings and dermatophyte culture should be performed to rule out demodicosis and dermatophytosis which occasionally may not exhibit clinically visible inflammation. If darker haired regions are affected preferentially and symmetrically, the index of suspicion for AA increases. Skin biopsy is required for diagnosis.

Biopsy site selection

Multiple specimens should be obtained from sites located sequentially along the radius from the center towards the advancing margin of alopecia. In human dermatology, a biopsy specimen from the outer margin of alopecia is less useful than a specimen obtained slightly more centrally. The outer, or advancing margin may demonstrate abnormal anagen hairs, but with only minimally evident follicular inflammatory insult. Specimens should include only abnormal tissue, particularly if a biopsy punch is used.



Fig. 18.3 Alopecia areata in a dog demonstrating inflammation of small bulbs at the base of a hair follicle (arrow). Note dystrophic hair shafts (double arrows).

Histopathology (Figures 18.3 through 18.5)

The epidermis is normal to mildly acanthotic in lesions of AA. In early lesions, lymphocytes and variable neutrophils invade the anagen hair bulb ('bulbitis'). Inflammation may be mild to severe. Keratinocytes of the bulb often appear swollen and there may be nuclear pyknosis or karyorrhexis. Neutrophils may migrate preferentially into foci of marked swelling and degeneration. Similar mild to moderate inflammation, accompanied by histiocytic cells and plasma cells, encircles the affected bulb, often in a tight nodular pattern. Eosinophils may be present around follicles and can be numerous. Perifollicular mucin may be observed, and there may be perifollicular pigmentary incontinence characterized by accumulations of melanin-laden macrophages around the hair bulb.

Inflammation may progress superficially to include the isthmus, but generally does not prominently affect that level of the follicle. Sebaceous glands are normal. In a recent study, T cell lymphocytic inflammation affected the isthmus in 54% (7/13), the inferior segment in 85% (11/13), and the bulb in 100% of dogs studied; the infundibulum was not affected (Tobin et al., 2003). In some cases, inflammation of the bulb and the wall to the level of the isthmus are both severe. It is unknown if these cases represent a distinct clinical subtype of AA. Correlation with clinical outcome may be useful. It is of interest that some dogs with AA recover hair growth, while others do not; however, the relationship of these outcomes to histopathologic features has not been studied to date.

In some, probably late-stage lesions, hair follicles are small, sometimes distorted in contour (dysplastic), and have a telogen configuration. Hair shafts may be dysplastic as well ('trichodysplasia'), characterized by diffuse eosinophilic staining, lack of internal detail, and variable fragmentation. Mild and predominantly lymphocytic inflammation persists within some bulbs and around the deep hair follicles. There may be follicular keratin plugging. Mild, concentrically-layered perifollicular fibrosis may be observed.

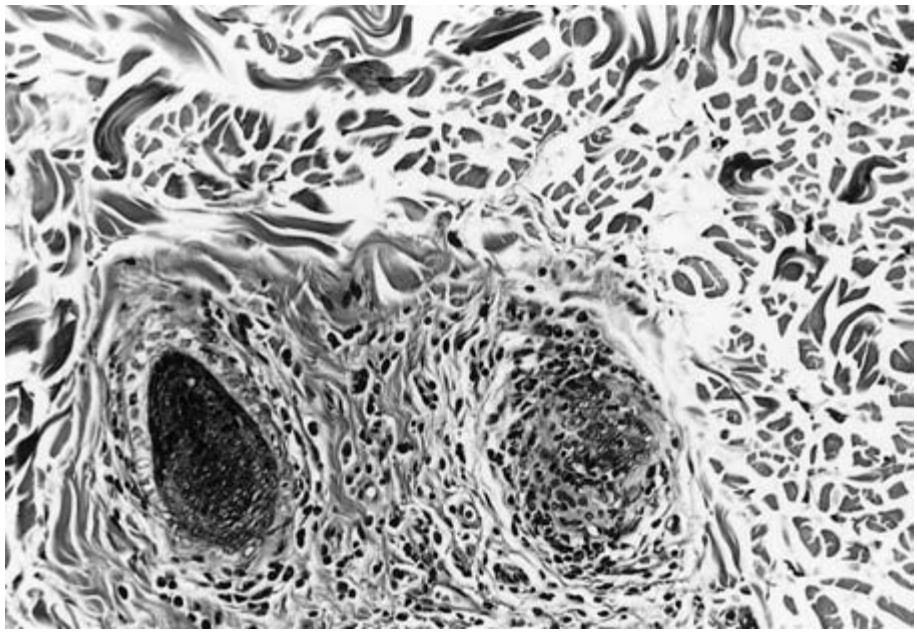


Fig. 18.4 Higher magnification of alopecia areata in a dog. A heavily inflamed anagen follicular bulb at right (bulbitis) is adjacent to an uninflamed bulb at left.

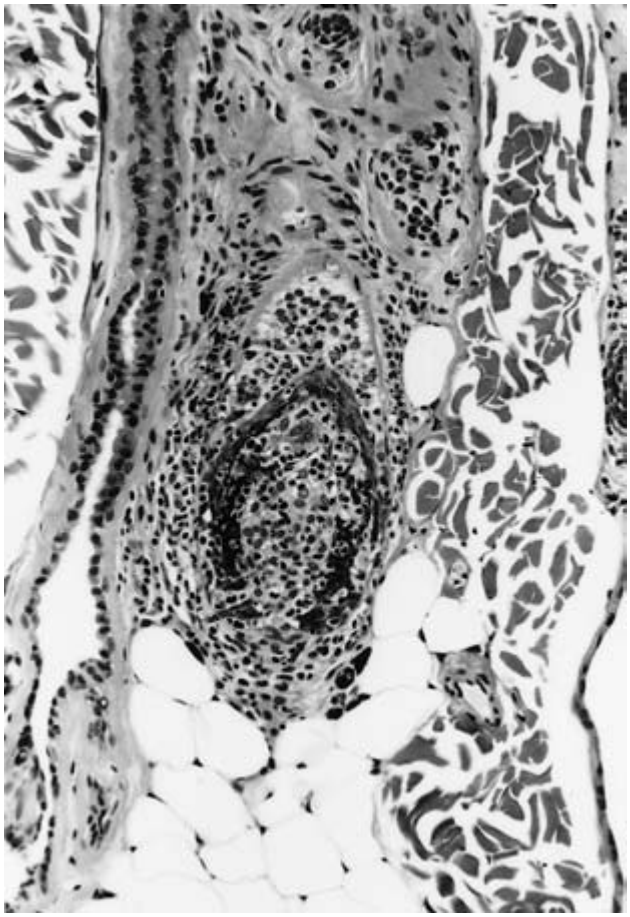


Fig. 18.5 Higher magnification of alopecia areata. An anagen bulb is infiltrated with lymphocytes which also closely surround it. At the left is an elongated apocrine sweat gland.

Immunohistochemistry identifies intrafollicular lymphocytes as predominantly CD3+, CD8+ cytotoxic T cells (Olivry et al., 1996). Dendritic cells are increased in number surrounding affected hair follicles (Olivry et al., 1996). There is prominent apoptosis of bulbar keratinocytes, as demonstrated by *in situ* labeling of nicked DNA (Olivry et al., 1996). Direct immunofluorescence for IgG showed deposition within lower hair follicle structures in 11 of 15 dogs tested (Tobin et al., 2003). Indirect immunofluorescence reveals autoantibodies reactive to multiple hair follicle structures (Tobin et al., 2003). Multiple follicular antigens of 40–60 kDa, and a 200–220 kDa doublet (a double band) are targeted, as demonstrated by immunoblotting; immunoprecipitation shows that this targeting included an intense, specific reactivity to trichohyalin (Tobin et al., 2003).

Differential diagnosis for AA is uncomplicated if bulbitis is found. Although inflammation of AA may progress superficially toward the isthmus, and isthmus mural folliculitis of many syndromes may progress deeply towards the bulb, the bulb itself is not affected in these latter syndromes. Late lesions of AA that demonstrate predominantly follicular atrophy and residual mild inflammation may be confused with late stage pseudopelade, or other forms of isthmus mural folliculitis. This diagnostic difficulty is due to the relatively inapparent hair bulbs in the atrophic follicles of late stage AA, and may be aggravated by lack of proper linear orientation of the follicle in processing. Differential diagnosis is prognostically important, specifically from pseudopelade, as hair loss in AA often is transient, while the alopecia of pseudopelade is usually permanent (see p. 466). Step-sectioning or reorientation

of the specimen may be required to detect subtle bulbitis in suspected cases.

MURAL FOLLICULITIS DUE TO DEMODICOSIS AND DERMATOPHYTOSIS

Clinical features

Mural folliculitis may be a histopathologic feature of either demodicosis or dermatophytosis in the dog and the cat. Presumably, this reaction pattern occurs as an immunologic response to follicular infection with either demodicid mites or surface or follicular dwelling dermatophytes. Mural folliculitis due to demodicosis or dermatophytosis is a histopathologic and not a clinical entity. Thus, the clinical diagnosis of demodicosis and dermatophytosis exhibiting a mural pattern of inflammation usually is difficult, as there are no specific clinical features that are seen in concert with mural folliculitis that are not also seen with other inflammatory forms of demodicosis and dermatophytosis. The reader is referred to sections describing the general clinical features of superficial pustular dermatophytosis (Chapter 1), canine and feline dermatophytosis (Chapter 16), and canine and feline demodicosis (Chapter 17).

Mural folliculitis is a common feature of canine demodicosis; 100% of dogs with clinical demodicosis exhibited this histopathologic reaction pattern in one study (Caswell et al., 1995). In a small percentage of cases of demodicosis, mural folliculitis may be the prime histopathologic pattern. Clinically, these cases of mural folliculitis due to demodicosis are characterized by mild to moderate, predominantly asymptomatic patchy alopecia, without secondary bacterial infection. Skin scraping may not be effective as a diagnostic procedure, as mites either may be present in small numbers or may be absent. This form of 'occult demodicosis' with mural folliculitis may be more common in young dogs. There may be a history of treatment for demodicosis but with persistent alopecia despite negative skin scrapings. One author (T.L.G.) has observed a single case of mural folliculitis due to localized demodicosis in a cat. Demodectic mites were few to moderate. Clinically, a linear lesion was present on the ventral neck.

Mural folliculitis in canine dermatophytosis is seen most often in conjunction with superficial pustular dermatophytosis due to keratin-colonizing dermatophytes (see Chapter 1). Crusted papules and pustules are located predominantly on the face, and especially involve the muzzle and periorbital region. Mural folliculitis also may be a feature of follicular canine dermatophytosis (see Chapter 16), but does not correlate with any unique or specific clinical features.

Mural folliculitis may be the predominant feature of some cases of feline dermatophytosis. These cases are characterized by patchy, partial alopecia. Trichograms may be ineffective as a diagnostic procedure, as only very small numbers of organisms may be present. Dermatophyte culture is most likely to confirm dermatophytosis. The relative lack of organisms occurring in the context of mural folliculitis suggests that the few organisms present may be provoking an inappropriate immunologic reaction which is targeting antigens of the hair follicles as well as the organisms themselves.

For diseases in which mural folliculitis is one component of a mixed inflammatory pattern, such as superficial pustular dermatophytosis, pustular follicular dermatophytosis, and classical demodicosis, the reader is referred to the appropriate sections for differential diagnoses (see Chapters 1, 16, and 17). Clinical differential diagnoses for feline dermatophytosis with predominant mural folliculitis include pruritic self-traumatic alopecia, psychogenic alopecia, demodicosis, and cutaneous epitheliotropic lymphoma. Clinical differential diagnoses for canine demodicosis with predominant mural folliculitis include dermatophytosis, canine familial dermatomyositis/ischemic dermatopathy, alopecia areata, and pseudopelade.

Biopsy site selection

Multiple skin biopsies from areas of maximum alopecia should be sampled. Sectioning of multiple specimens may be crucial as organisms may be sparse. It should be emphasized that demodectic or dermatophytic mural folliculitis rarely is an expected diagnosis because organisms are difficult to demonstrate clinically.

Histopathology (Figures 18.6 through 18.8)

Lesions of folliculitis, furunculosis, and parafollicular granulomas have been described for canine demodicosis (see Chapter 17). In demodicosis of dogs, mural folliculitis is common. One hundred percent of dogs with clinical demodicosis demonstrated this pattern in one large study (Caswell et al., 1995). In some lesions of canine demodicosis, often clinically occult, mural folliculitis is the only pattern observed; in most cases it accompanies other patterns (see Chapter 17).

Typically in canine demodectic mural folliculitis, lymphocytes and fewer histiocytes infiltrate the isthmus portion of the hair follicle. Infiltrating lymphocytes were reported to be primarily CD3+, CD8+ cytotoxic T cells (Caswell et al., 1997). Lymphocytes, histiocytes, plasma cells, and usually eosinophils tightly encircle the follicles. Inflammation often obscures the follicular–dermal interface, and thus can be more specifically characterized as

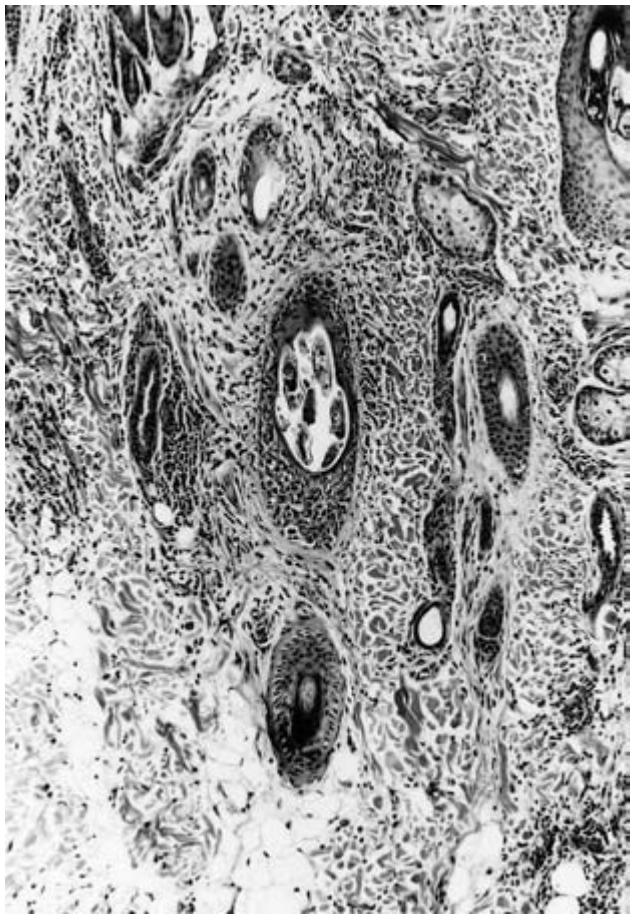


Fig. 18.6 Mural folliculitis in canine demodicosis. Mononuclear inflammatory cells infiltrate the wall of a mite-infested hair follicle.

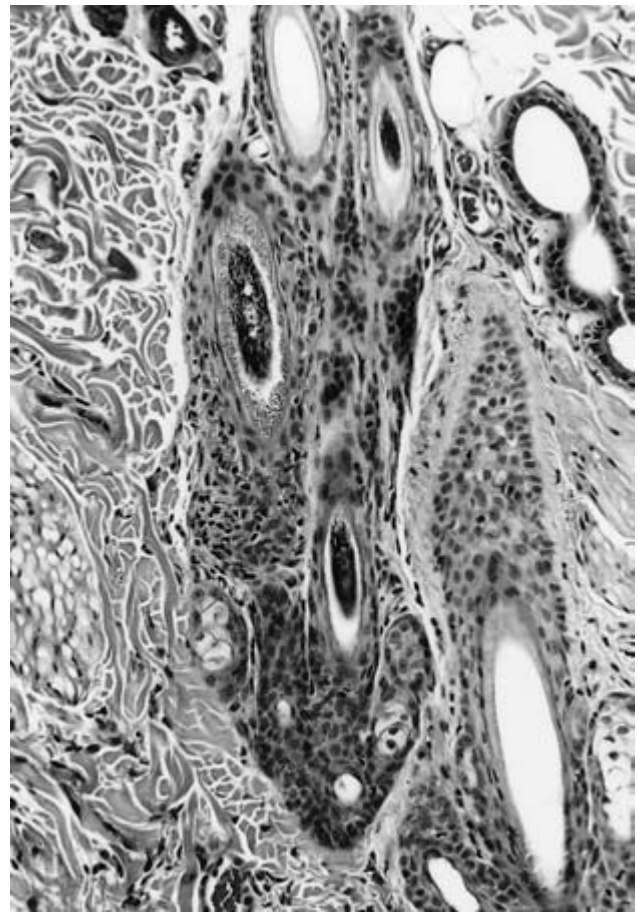


Fig. 18.7 Mural folliculitis in feline dermatophytosis. Small numbers of lymphocytes infiltrate the wall of a hair follicle; note dermatophytic spores surrounding the hair shaft.

interface mural folliculitis (interface folliculitis). As observed in interface dermatitis (see Chapter 3) there is vacuolation and variable apoptosis of keratinocytes of the outer layer of the external root sheath with occasional apoptosis of suprabasilar keratinocytes as well. T cells may lie adjacent to apoptotic cells (lymphocyte satellitosis) (Caswell et al., 1995). Perifollicular pigmentary incontinence is common and reflects damage to the follicular wall. There may be mild to occasionally moderate mucin accumulation around follicles with occasional mild extension to the follicular wall. Mild perifollicular fibrosis is seen occasionally. Sebaceous glands are normal. The follicular infundibula are plugged with keratin. Inflammation extends to the superficial and middle dermis in a perivascular to interstitial pattern, even in cases in which mural folliculitis is the only pattern observed.

Mural folliculitis may be the sole pattern in chronic cases which persist with alopecia despite negative skin scrapings ('occult demodicosis'). Mural inflammation in these cases may be mild overall. Mite numbers may be very low and careful searching of step sections may be required. Eosinophilic mucinotic mural folliculitis, a distinctive reaction follicular pattern in dogs with some similar features (see p. 469), also may be associated with persistent demodicosis in which mites are nearly absent.

One author (T.L.G.) has observed mural folliculitis due to localized demodicosis in a cat. Moderate acanthosis extended to the follicular isthmus. Inflammation surrounded the superficial and middle portion of hair follicles and adnexal glands, and included lymphocytes, histiocytes, plasma cells, and occasional neutrophils and eosinophils. Lymphocytes and fewer histiocytes infiltrated the follicular isthmus. Mild spongiosis accompanied the mural inflammation. Occasionally there was pyogranulomatous degeneration of the follicular wall with giant cells. Follicular mites were present in few to moderate numbers.

Like demodicosis, canine mural folliculitis due to dermatophytosis may be accompanied by other patterns of inflammation including luminal folliculitis (see Chapter 16) and superficial pustular dermatitis (see Chapter 1). Mural folliculitis is associated more often

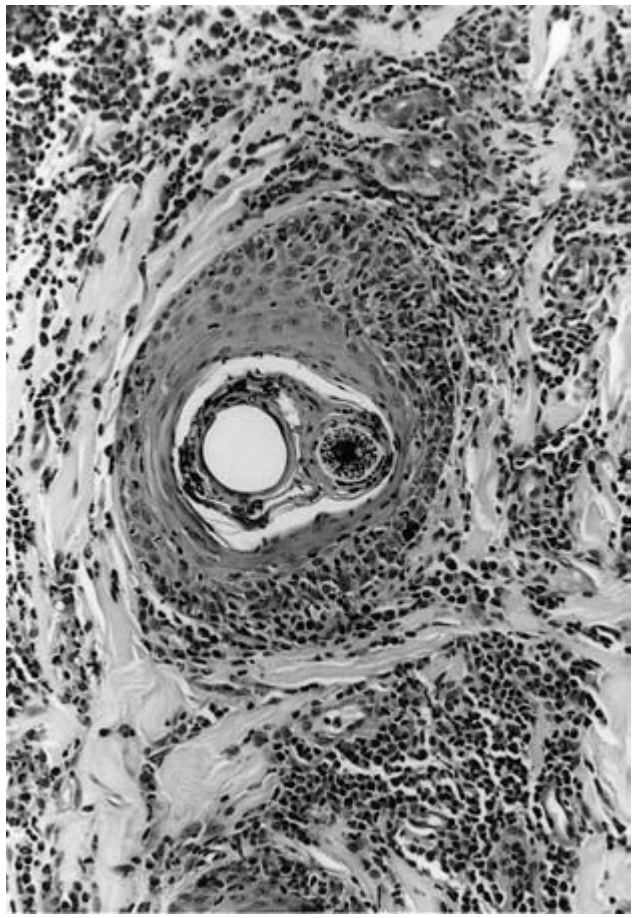


Fig. 18.8 Mural folliculitis in canine dermatophytosis. Lymphocytes are migrating into the follicular wall; darkly staining dermatophytic spores and hyphae are within the keratin surrounding the hair shaft (keratin-colonizing dermatophytes) (periodic acid–Schiff).

with keratin-colonizing *Trichophyton* spp. infection that features superficial pustulation (see Chapter 1) (Parker & Yager, 1997). There are isthmus mural infiltrations of lymphocytes accompanied by mild spongiosis. Inflammation may obscure the follicular–dermal interface, and often is accompanied by vacuolation of outer follicular keratinocytes or apoptosis (interface folliculitis). Lymphocytic spongiotic or interface inflammation may extend to the epidermis. Lymphocytes, plasma cells, and fewer neutrophils surround follicles, often densely, and extend to the surrounding dermis and around adnexal glands. Organisms are scant to numerous.

Mural folliculitis in cats with dermatophytosis is similar, but less severely inflamed. Mural folliculitis may be the sole or predominant pattern in some cases of feline dermatophytosis, particularly when organisms are rare. Lymphocytes migrate into the follicular isthmus. Lymphocytes, histiocytes, and sometimes neutrophils and plasma cells surround the follicles. Inflammation may extend to the superficial dermis. Less often, there is mild interface folliculitis characterized by inflammation concentrated to the follicular–dermal interface, with vacuolation and rare shrinking and increased eosinophilia (apoptosis) of outer follicular cells. Lymphocytic interface or spongiotic dermatitis affecting the epidermis accompanies this pattern, the latter suggesting an allergic reaction to dermatophytes that is targeting the epidermis and hair follicles alike. There may be concurrent superficial crusting or sparse luminal folliculitis (see Chapter 16). Neutrophils may tightly surround hair follicles in some lesions. Organisms are usually scant to absent; discovery of dermatophytosis only via culture is not uncommon.

Differential diagnosis of mural folliculitis in dogs due to demodicosis is not relevant if mites are present. In cases of mural folliculitis of unexplained cause, particularly in young dogs, step sectioning to search for mites is most prudent. Eosinophilic mucinotic mural folliculitis is similar, and in fact, may be due to clinically occult demodicosis in some cases. Idiopathic eosinophilic mucinotic mural folliculitis generally features more prominent intrafollicular mucin than mural folliculitis due to demodicosis.

Differential diagnosis of mural folliculitis in dogs due to dermatophytes is not difficult as organisms are usually demonstrable. However, keratin-colonizing *Trichophyton* spp. are difficult to detect on hematoxylin and eosin evaluation; special staining is required, as has also been reported (Poisson et al., 1998). Periodic acid–Schiff (PAS) and Gomori's methenamine silver (GMS) will color organisms magenta and black, respectively. The concurrence of superficial pustules and/or pustular folliculitis with mural and interface folliculitis is highly suspicious for dermatophytosis and warrants special staining if organisms are not obvious.

Differential diagnosis of mural folliculitis in cats with dermatophytosis often is problematic. Organisms may be scant or absent; subsequent culture may provide the definitive diagnosis. Concurrent pustular folliculitis or perifollicular neutrophilic inflammation is highly suspicious for dermatophytosis in this species. Lymphocytic mural folliculitis may occur in other contexts in the cat, including drug eruption, food allergy, or idiopathic cases, some of which are transient and self-limiting. Ultimately, clinical differentiation may be required.

PSEUDOPELADE

Clinical features (Figures 18.9 through 18.12)

Pseudopelade is a rare immune-mediated skin disease reported in the dog and cat. It is characterized by a novel lymphocytic isthmus mural folliculitis which manifests



Fig. 18.9 Pseudopelade in a Maltese. Generalized truncal, visually noninflammatory alopecia is present. (From Gross, T.L., Olivry, T. & Tobin, D.J. (2000) Morphologic and immunologic characterization of a canine isthmus mural folliculitis resembling pseudopelade of humans. *Vet Dermatol* **11**, 17–24. Reprinted with permission.)



Fig. 18.10 Pseudopelade in a Border Collie. Note focal alopecia on the right shoulder. (From Gross, T.L., Olivry, T. & Tobin, D.J. (2000) Morphologic and immunologic characterization of a canine isthmus mural folliculitis resembling pseudopelade of humans. *Vet Dermatol* **11**, 17–24. Reprinted with permission.)



Fig. 18.11 Closer view of the dog in Fig. 18.10. Alopecia, macular hyperpigmentation, and mild scaling are present. (Photograph courtesy H.T. Power.)



Fig. 18.12 Pseudopelade in a cat. Extensive alopecia is present on the legs, flanks, and abdomen. (Photograph courtesy H.T. Power.)

clinically as a visually noninflammatory alopecia (Gross et al., 2000; Olivry et al., 2000). Hair loss usually is permanent. Immunologic studies performed in dogs and one cat revealed predominantly CD3+, CD8+ cytotoxic T lymphocytes in the follicular wall; indirect immunofluorescence and immunoblotting studies identified circulating IgG autoantibodies that targeted lower hair follicle proteins including keratins and trichohyalin (Gross et al., 2000; Olivry et al., 2000).

Marked similarities are shared between canine and feline pseudopelade, and with pseudopelade in humans, including similarly targeted proteins. However, pseudo-

pelade in humans always is permanent (Sahl, 1996). One author (T.L.G.) is aware of dogs with alopecic skin disease histopathologically compatible with pseudopelade where some hair regrowth occurred. Similarly, hair of diminished quality has regrown partially in two affected cats that were treated with cyclosporine (Power, H.T., personal communication, 2001); one was the case previously reported by Olivry et al. (2000). Cotsarelis and coworkers showed in their seminal papers that the source of hair follicle regeneration resided not in the matrix region but in the 'bulge region', an outer root sheath protrusion at the level of the attachment of the arrector pili muscle (Cotsarelis et al., 1990; Paus & Cotsarelis, 1999). Cell-labeling studies in the dog did not reveal the presence of a localized anatomic region analogous to the 'bulge' documented in mice and humans (Credille et al., 1999). If the source of follicular regeneration is more dispersed in the canine and feline hair follicle, this could explain occasional hair regrowth seen with an isthmus-destructive disease such as pseudopelade.

Clinically, canine pseudopelade is characterized by well-demarcated, generally visually noninflammatory, usually patchy alopecia. Scaling and hyperpigmentation are present in some dogs. Affected areas vary from focal or multifocal lesions that are 2 to 8 cm in diameter, to more diffuse alopecia affecting the trunk and legs (Gross et al., 2000). Pruritus or systemic signs have not been reported (Gross et al., 2000).

Feline pseudopelade, as observed in one cat, presented similarly as patchy, visually noninflammatory alopecia (Olivry et al., 2000). Hair loss was gradually progressive. Hyperpigmentation was present. Onychorrhexis and onychomadesis were noted. Partial bilateral symmetry was also reported. The muzzle, ventrolateral trunk, legs, and paws were affected. To date, signalment predilections have not been noted in either dogs or cats.

Clinical differential diagnoses include virtually any skin disease characterized by relatively noninflammatory, asymptomatic alopecia. Possible differential diagnoses include alopecia areata, acquired pattern alopecia, follicular dysplasia, traction alopecia, psychogenic alopecia, endocrinopathies, demodicosis, and dermatophytosis. Absence of hair regrowth or poor hair regrowth suggests, but does not confirm, pseudopelade over alopecia areata (see p. 460); alopecia areata also is more likely to be facially predominant. Skin scrapings and dermatophyte culture should be performed to rule out demodicosis and dermatophytosis. Skin biopsy is required for diagnosis.

Biopsy site selection

Multiple specimens should be obtained from regions of maximal alopecia. Specimens should include only abnormal tissue, particularly if punch biopsy technique is used.

Histopathology (Figures 18.13 and 18.14)

The epidermis is normal to mildly acanthotic. In dogs, lymphocytes migrate into the wall of the hair follicle at the level of the isthmus. Mural inflammation may be mild to severe. Inflammation may extend to the infundibular wall and slightly below the isthmus; inflammation of the hair bulb is not observed. Follicular keratinocytes may appear degenerated or swollen. Lymphocytes, histiocytes, and plasma cells compactly surround the follicle at the isthmus. There may be perifollicular pigmentary incontinence. Milder inflammation may extend to the superficial dermis. In putative late lesions, follicular atrophy predominates and inflammation is relatively sparse. Sebaceous glands are retained in some adnexal units and absent from others.

Hair follicles are shrunken and telogenized in late lesions of pseudopelade, sometimes remarkably so, and mild to moderate distortion may also be present. The connective tissue of the external root sheath is prominent,

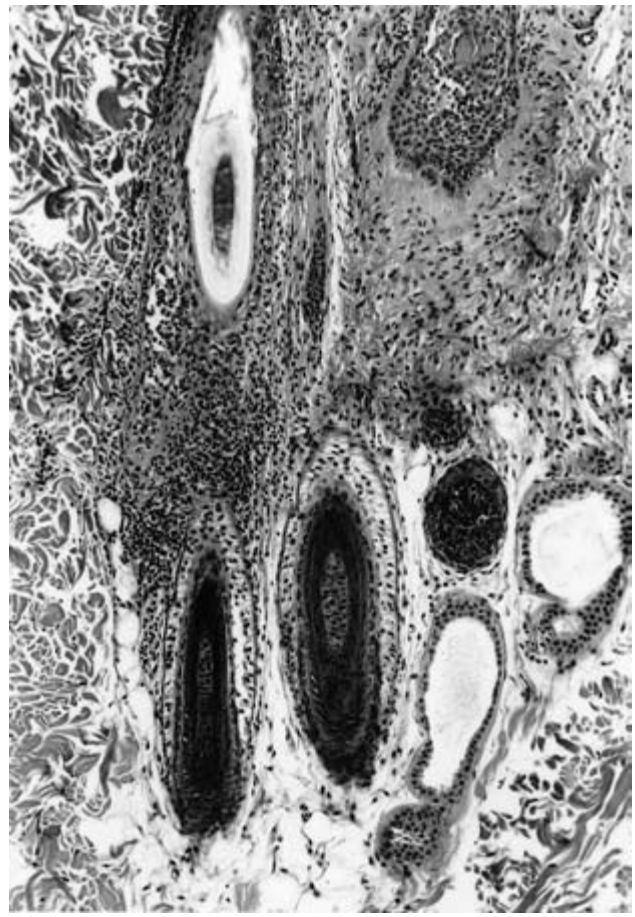


Fig. 18.13 Canine pseudopelade demonstrating severe inflammation of the mid portion of the follicular wall. Note that the deeper follicle is unaffected.

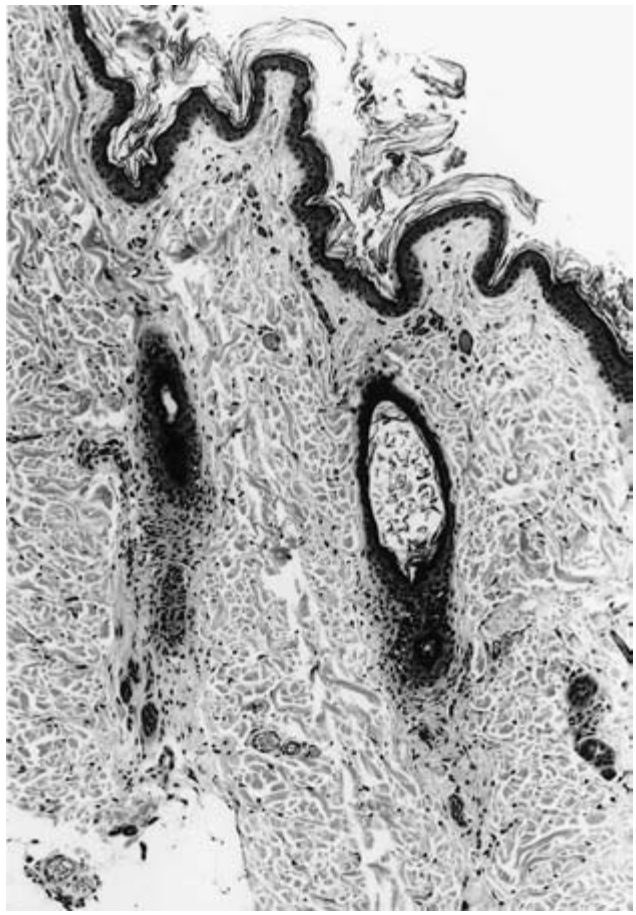


Fig. 18.14 Late lesion of canine pseudopelade. Note severe follicular atrophy and mild residual inflammation of the middle follicle.

and there may be a fibrous root sheath tract or 'stele' (after Headington) at the site of previous hair follicles if atrophy is severe. In the authors' opinion, this does not constitute true scarring; increased prominence of connective tissue is a necessary end result of severe atrophy in this context. A similar case for the nonscarring nature of pseudopelade in humans has recently been made (Sahl, 1996).

In the single cat reported (Olivry et al., 2000), lesions were similar. Lymphocytes infiltrate the wall of the isthmus and are accompanied by variable neutrophils. There may be frank degeneration of the follicular wall. Free hair shafts ejected from degenerate follicles are within small granulomas. Lymphocytes, histiocytes, and neutrophils encircle the follicle at the isthmus. Hair follicles become markedly atrophic, and follicular connective tissue is prominent. Sebaceous glands are retained.

In the authors' opinion, pseudopelade is difficult to differentiate histologically from other lymphocytic isthmus mural folliculitides, such as those due to drugs or allergens (see introduction, p. 460). Inflammation that closely

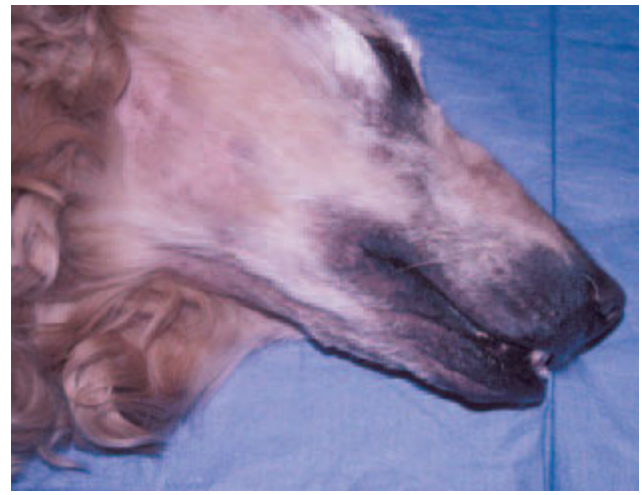


Fig. 18.15 Eosinophilic mucinotic mural folliculitis in a Labrador Retriever-crossbreed. Patchy, visually noninflammatory alopecia is present on the head and neck. (Photograph courtesy K.J. Boyanowski.)

targets the follicle only is suggestive for pseudopelade, as drug and other immunologic reactions often include prominent dermatitis and/or other features such as spongiosis and apoptosis. Perhaps the division is artificial in some cases, as the underlying trigger of pseudopelade generally is unknown. For example, some lesions histopathologically typical of pseudopelade may be focal over the neck and shoulders, suggesting a reaction to local antigens such as vaccines or other injected substances.

Late lesions of pseudopelade in dogs that demonstrate predominantly follicular atrophy may be confused with lesions of late stage alopecia areata and granulomatous mural folliculitis. If inflamed hair bulbs of alopecia areata are not apparent, clinical differentiation may be required (see above). The degree of atrophy in granulomatous mural folliculitis is generally more diffuse and severe than in pseudopelade; residual granulomatous versus predominantly lymphocytic inflammation may allow differentiation. Feline sebaceous adenitis may appear similar to pseudopelade, but in contrast, inflammation usually targets the sebaceous gland, and glands are uniformly absent (see Chapter 17).

EOSINOPHILIC MUCINOTIC MURAL FOLLICULITIS IN DOGS

Clinical features (Figures 18.15 and 18.16)

Eosinophilic mucinotic mural folliculitis of dogs is a rare, presumed immunologic skin disease characterized clinically by alopecia. The highly variable clinical presentation may indicate that multiple antigenic triggers may initiate



Fig. 18.16 Closer view of the legs of the dog in Fig. 18.15. Patchy alopecia and mottled hyperpigmentation are present on the legs. (Photograph courtesy K.J. Boyanowski.)

a similar follicular reaction pattern. Persistent antigenic drive associated with occult demodicosis may be one possible etiology, as small numbers of mites or mite fragments are found histologically in some cases. Eosinophilic mucinotic mural folliculitis has been observed in conjunction with T cell lymphoma of the lymph node in a dog (case material courtesy M.B.C. Mays, 1999). Follicular mucinosis is not a specific finding, and may be the effect of certain T cell milieus, as described in humans (Fanti et al., 1992). Eosinophilic inflammation with follicular mucinosis has been reported in humans with either cutaneous epitheliotropic T cell lymphoma ('mycosis fungoides') or in conjunction with several inflammatory diseases (Wood, 2003). Eosinophilic mucinotic mural folliculitis resembles follicular mucinosis in dogs and cats; eosinophils are not featured in the latter (see p. 477).

Clinically, as in most other syndromes characterized by mural folliculitis, alopecia is the predominant clinical presentation. The alopecia usually is patchy, often roughly circular, and moderately well-demarcated. Erythema, crusting, hyperpigmentation and 'greasiness' of the haircoat have been noted. Distribution patterns of alopecia also are highly variable; lesions affect the face, periorbital region, pinnae, neck, trunk, or legs. Generalized, partial, patchy alopecia may be seen. Marked facial bilateral symmetry similar to alopecia areata also has been noted. In severe cases, focal ulceration may be present within alopecic areas. Pruritus and attendant self-trauma are inconsistent features.

Retrievers and their crossbreeds appear to be overrepresented in cases seen to date by the authors and others; however, breed predilections have not been shown. Sex and age predilections have not been noted. Older dogs may be predisposed to idiopathic eosinophilic mucinotic mural folliculitis, while younger dogs may be more likely to develop the form associated with occult demodicosis.

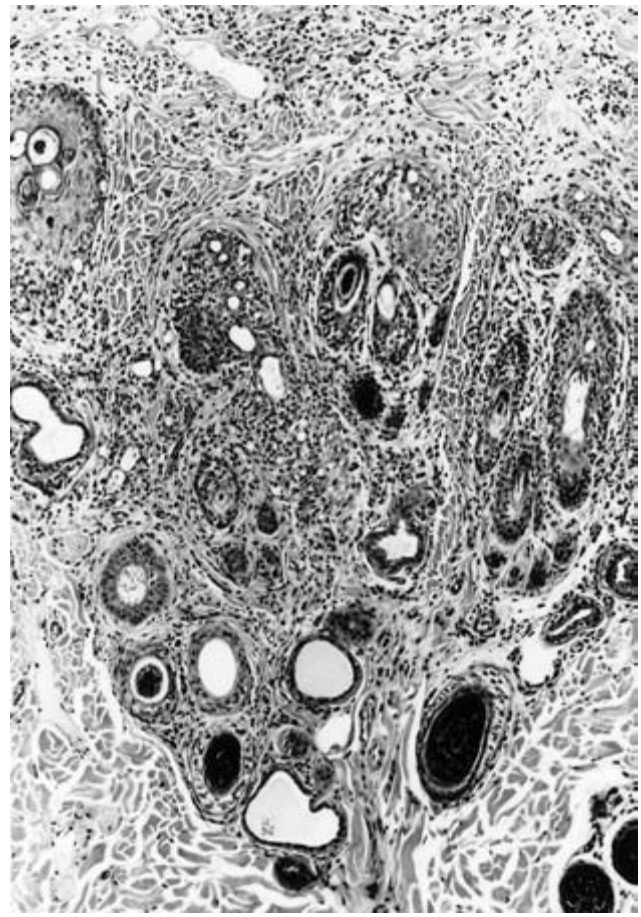


Fig. 18.17 Eosinophilic mucinotic mural folliculitis. Severe inflammation of the middle follicular walls spares the deep follicles at bottom.

Clinical differential diagnoses include other skin diseases characterized by variable patterns of alopecia. Possible differential diagnoses include alopecia areata, pseudopelade, acquired pattern alopecia, follicular dysplasia, traction alopecia, demodicosis, and dermatophytosis. Frank demodicosis is an important differential diagnosis, especially in younger dogs. Skin scrapings and dermatophyte culture should be performed to rule out frank demodicosis and dermatophytosis. Skin biopsy is required for diagnosis.

Biopsy site selection

Multiple specimens should be obtained from regions of maximal alopecia. Specimens should include only abnormal tissue, particularly if punch biopsy technique is used.

Histopathology (Figures 18.17 through 18.19)

There is mild to moderate acanthosis, sometimes with parakeratotic scaling and/or serocellular crusting. Hair follicles may be superficially plugged with keratin. There

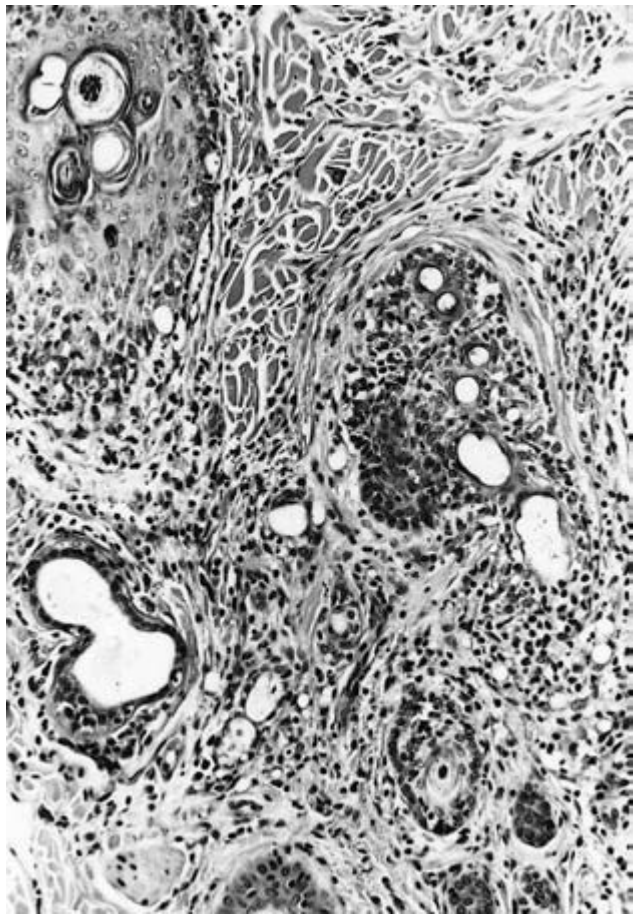


Fig. 18.18 Higher magnification of Fig. 18.17. Lymphocytes infiltrate the follicular walls; pale intercellular spaces in the follicles contain mucin.

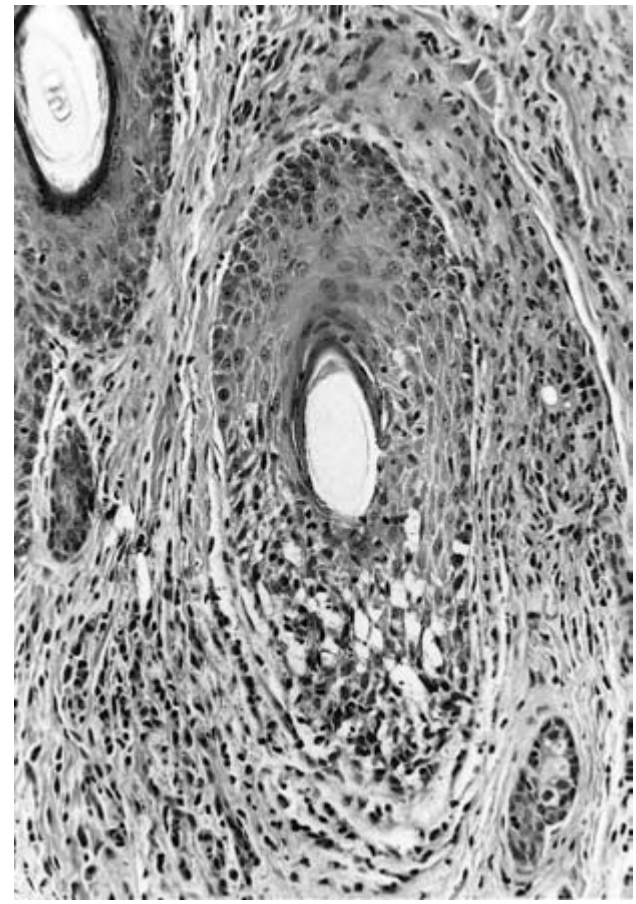


Fig. 18.19 High magnification of eosinophilic mucinotic mural folliculitis demonstrating marked intercellular accumulation of mucin (clear spaces).

is tightly encircling, mild to moderate inflammation at the level of the isthmus. Perifollicular inflammation includes lymphocytes, histiocytes, plasma cells, and eosinophils. In more highly inflamed lesions, similar inflammation extends to the perifollicular and superficial dermis. Mural inflammation is predominantly lymphocytic and usually mild. There may be associated mural spongiosis.

Mucin deposition is both perifollicular and mural; the former is generally more prominent than the latter. Mucin deposition may be mild and patchy in distribution, but often is focally striking and severe. In some lesions the follicular wall is greatly distended with mucin, and may appear degenerate. In those follicles, keratinocytes are dissociated and may appear necrotic. Rarely, granulomas, including giant cells, are seen in the degenerated follicular wall.

Lesions of eosinophilic mucinotic mural folliculitis may occasionally be seen in the setting of occult demodicosis; parasites are difficult to find and often stepsectioning is required. In some cases, only mineralized fragments of putative organisms are identified. Because the lesions are similar to the mural folliculitis of demodicosis, which also includes eosinophils and variable mucin, it is probable that this subtype of eosinophilic mucinotic mural folliculitis represents a continuum or variation upon the theme of mural immunoreactivity secondary to persistent mites. In general, mites are easier to find histologically in typical mural folliculitis due to demodicosis.

The lesions of follicular mucinosis in dogs are histologically similar to those of eosinophilic mucinotic mural folliculitis in dogs, except for the presence of eosinophils in the latter. Many cases of canine eosinophilic mucinotic mural folliculitis feature more prominent perifollicular (rather than intrafollicular) mucin than hitherto observed or reported in canine follicular mucinosis (see p. 477). Mucin accumulation may be subtle in some cases of eosinophilic mucinotic mural folliculitis, but is a central feature of follicular mucinosis. However, the possibility



Fig. 18.20 Degenerative mucinotic mural folliculitis in a cat. Severe generalized alopecia is present. (From Gross, T.L., Olivry, T., Vitale, C.B. et al. (2001) Degenerative mucinotic mural folliculitis in cats. *Vet Dermatol* **12**, 279–83. Reprinted with permission.)



Fig. 18.21 Closer view of the head of the cat in Fig. 18.20 showing the highly characteristic bilaterally symmetric thickening and swelling with alopecia. Note narrowing of the eye openings (Photograph courtesy H.T. Power.)

that these two entities actually represent one disease process cannot be ruled out. In humans, follicular mucinosis, which often features eosinophils, is a reaction pattern with several clinical settings or outcomes, including epitheliotropic T cell lymphoma (Wood, 2003). It has been reported that eosinophil-predominant forms are more likely to have a benign outcome (Mehregan et al., 1991).

DEGENERATIVE MUCINOTIC MURAL FOLLICULITIS IN CATS

Clinical features (Figures 18.20 through 18.22)

Degenerative mucinotic mural folliculitis is a rare, unique, presumptively immunological skin disease of cats. It is characterized clinically by generalized alopecia, striking thickening of the facial skin, and varying degrees of lethargy (Gross et al., 2001). Despite suspicion of an immunoreactive pathogenesis, affected cats do not respond to vigorous immunomodulatory therapy. Lethargy and lack of response to immunosuppression may suggest underlying visceral disease, but necropsy was not permitted in six of seven cats (Gross et al., 2001). Three of seven reported cats were positive for feline immunodeficiency virus (FIV), and all cats were negative for feline leukemia virus (FeLV) (Gross et al., 2001).

Clinical features include diffuse, generalized alopecia of variable severity. Facial skin, and especially the muzzle, becomes alopecic, thickened, and swollen in a bilaterally symmetric manner. This leads to highly characteristic thickening of the lid margins and narrowing of the space between the eyelids. The affected skin of the muzzle becomes shiny and waxy, and has a rubbery feel. Scaling and crusting may be present. Alopecia commonly begins on the muzzle and neck, and after generalization, becomes most pronounced on the head, neck, and shoulders. Pruritus was observed in four of seven cats and was severe in one cat (Gross et al., 2001). Lethargy is a common feature and some cats experience weight loss.

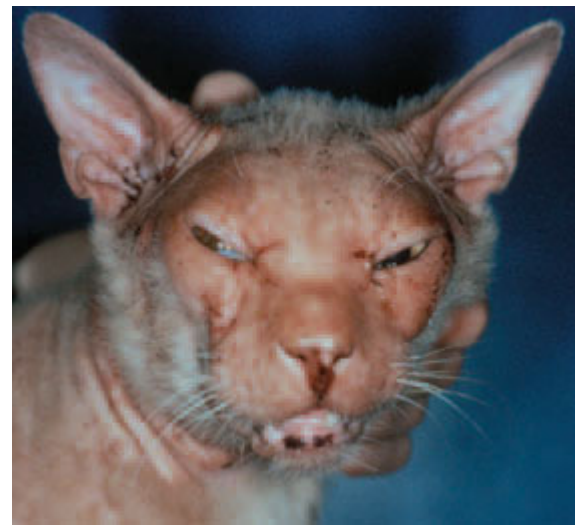


Fig. 18.22 Degenerative mucinotic mural folliculitis in a cat. Note the striking resemblance to the cat in Fig. 18.21. (From Gross, T.L., Olivry, T., Vitale, C.B. et al. (2001) Degenerative mucinotic mural folliculitis in cats. *Vet Dermatol* **12**, 279–83. Reprinted with permission.)



Fig. 18.23 Degenerative mucinotic mural folliculitis demonstrating intense intramural and perifollicular inflammation in the isthmus region of the hair follicles.

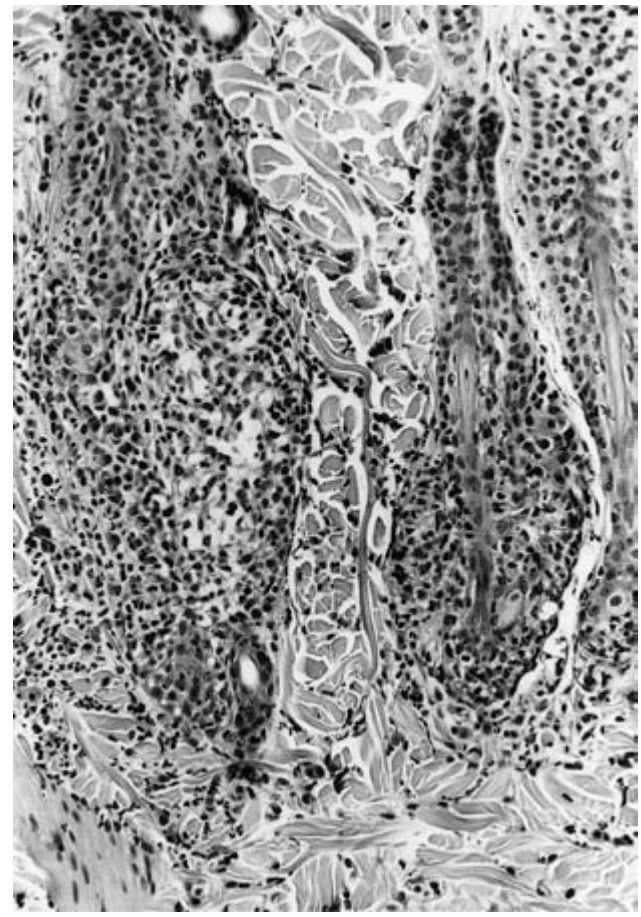


Fig. 18.24 Higher magnification of degenerative mucinotic mural folliculitis. The walls of two adjacent follicles are expanded and partially destroyed by pale mucin and mixed inflammation featuring many lymphocytes and histiocytes.

General health screening tests do not show consistent abnormalities.

All affected animals to date have been domestic shorthaired or domestic longhaired cats. Cats have been middle aged or older. Six of seven cats reported were males (Gross et al., 2001).

Clinical differential diagnoses for early cases of degenerative mucinotic mural folliculitis in cats may include demodicosis, dermatophytosis, sebaceous adenitis, pseudopelade, and cutaneous epitheliotropic lymphoma. Clinical diagnosis is not problematic if the highly characteristic symmetric facial thickening with alopecia and narrowing of the eyelid openings is present. Testing for FIV should be performed. Skin biopsy is confirmatory.

Biopsy site selection

Multiple specimens should be obtained from regions of maximal alopecia and skin thickening. Specimens should include only abnormal tissue, particularly if punch biopsy technique is used.

Histopathology (Figures 18.23 through 18.25)

Moderate irregular acanthosis extends to follicular infundibula and is often accompanied by mild spongiosis. There may be parakeratotic scale/crusts that are sometimes extensive. Moderate to severe inflammation is centered upon the follicular isthmus, but extends to the infundibulum. Lymphocytes, histiocytes, and neutrophils are present in variable numbers and proportions with the wall. Mucin widens the follicular epithelial intercellular spaces; it is light gray or gray-blue with hematoxylin and eosin staining, and turquoise blue with Alcian blue–periodic acid–Schiff (PAS) staining at pH 2.5. Rarely, individual follicles appear 'blown apart' by mucin. Mucin may also surround hair follicles.

In severely inflamed follicles there may be neutro-

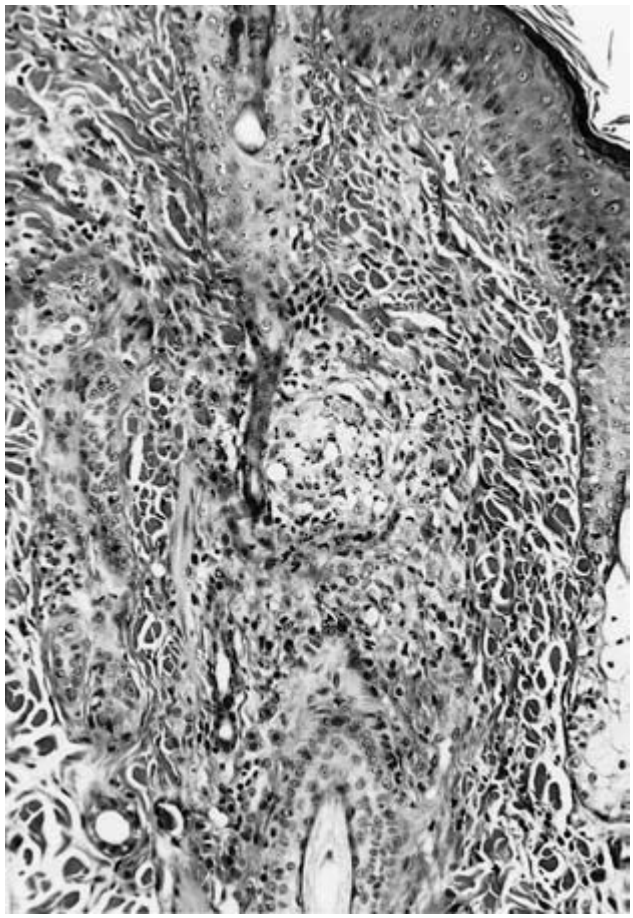


Fig. 18.25 Higher magnification of degenerative mucinotic mural folliculitis. Note pale pyogranuloma at site of follicular inflammation and degeneration.

philic luminal folliculitis. Degeneration of the severely inflamed follicular wall occurs, and may eventuate in complete effacement by large pyogranulomas, which may include giant cells. Hair shafts may remain in these degenerate, inflamed foci. Follicular atrophy is moderate to severe and multifocal; normal anagen hair follicles may be interspersed, particularly in less inflamed or putatively early lesions. Sebaceous glands are conserved in general, but may be small or absent in some regions.

Lymphocytes, histiocytes, neutrophils, and plasma cells surround hair follicles and infiltrate the superficial dermis in moderate numbers. Eosinophils are rare. There may be mild to moderate edema.

Degenerative mucinotic mural folliculitis is striking histologically. However, occasionally, similar folliculitis with mucinosis is seen in cats that lack correlative clinical features (particularly complete alopecia of the head and narrowing of eye openings). The significance of these clinically different cases is not yet known; they may represent a variation of the same condition. Follicular mucinosis is not a specific finding, and may be the effect of certain T cell milieus, as described in humans (Fanti et al., 1992).



Fig. 18.26 Granulomatous mural folliculitis in a dog. Striking patchy alopecia, as observed on the head and neck in this view, affects the entire dog. (Photograph courtesy C.A. Sousa.)

Follicular mucinosis in cats (see p. 477) may be similar to degenerative mucinotic mural folliculitis. A clinical photograph of one of two reported cats with follicular mucinosis showed clinical features indistinguishable from degenerative mucinotic mural folliculitis, including narrowed eye openings (Scott, 1987). However, both reported cases of follicular mucinosis developed cutaneous lymphoma (Scott, 1987), which has not been observed in cases of degenerative mucinotic mural folliculitis seen by the authors. Further, a feline case of follicular mucinosis observed by one author (T.L.G.) had clinical and histological features that were distinct from degenerative mucinotic mural folliculitis.

GRANULOMATOUS MURAL FOLLICULITIS IN DOGS

Clinical features (Figures 18.26 through 18.28)

Granulomatous mural folliculitis is a rare, presumed immunological syndrome of dogs that is characterized clinically by highly variable alopecia. The wide range in severity of lesions noted both clinically and histopathologically suggests a possible multifactorial etiology. Most cases described in the literature to date have been seemingly associated with adverse drug reactions (Scott, 1999; Scott et al., 2001). Drugs reported to induce granulomatous mural folliculitis in dogs include amitraz, cefadroxil, L-thyroxin, and various topical agents (Scott, 1999; Scott et al., 2001). Some dogs have regrown hair after the offending drug is terminated, while others have not. Some



Fig. 18.27 Granulomatous mural folliculitis in a dog. Nearly total alopecia is present; note mottled leukoderma.



Fig. 18.28 Closer view of the head of the dog in Fig. 18.27. Follicular plugging with whitish inspissated keratinous debris gives a stippled appearance, and accompanies almost complete alopecia and strikingly patterned leukoderma.

cases observed by the authors had received various medications, including antibiotics, prior to the onset of skin lesions.

Clinical features include variable alopecia that may be patchy and multifocal, or coalescing and generalized. Erythema, scaling and crusting may be present. Erosion or ulceration with exudation may occur in regions of alopecia in more severe cases. Consistent patterns of hair loss have not been noted; patchy lesions may involve the trunk, head, and extremities. One dog seen by one author (P.J.I.) lost over 90% of truncal hair over a period of 6 months. Follicular plugging may be noted with chronicity. In long-standing cases, irregular mottled leukoderma and leukotrichia can be visually striking. Although true scarring is not a feature, the alopecic skin of advanced cases feels very smooth, as virtually no hair remains in affected areas. Pruritus usually is not present. Secondary bacterial folliculitis may occur. Signalment predilections have not been noted.

Clinical differential diagnoses for granulomatous mural folliculitis in dogs include other skin diseases characterized by multifocal to generalized alopecia. Possible differential diagnoses include alopecia areata, pseudopelade, follicular dysplasia, endocrinopathies, demodicosis, and dermatophytosis. Skin scrapings and dermatophyte culture should be performed to rule out demodicosis and dermatophytosis. Skin biopsy is required for diagnosis.

Biopsy site selection

Multiple biopsy specimens should be obtained from regions of maximal alopecia. Specimens should include only abnormal areas, particularly if punch biopsy technique is used.

Histopathology (Figures 18.29 and 18.30)

There is mild to severe acanthosis. In some cases, erosion to ulceration, and marked exudation and crusting are seen. Occasionally, hair follicles may be plugged with parakeratotic and inflammatory debris; parakeratosis was prominent in a reported case (Scott, 1999).

In mature lesions, many hair follicles are completely effaced by granulomatous to pyogranulomatous inflammation that also extends along follicles to form large linear, or less often, nodular foci. Hair shafts may remain centrally, but are often obliterated. Inflammation includes histiocytes, lymphocytes, and neutrophils. Multinucleated giant cells may be present and can be numerous. Follicular inflammation centers on the isthmus, but may extend from the ostium to the bulb. There may be pale linear or nodular centers due to degeneration of follicular epithelium and a predominance of large histiocytes in that location. Sebaceous glands often are obliterated, but apocrine sweat glands usually remain. Secondary pustular folliculitis and dermatitis have been observed. In some locations, inflammation tightly surrounds the follicular wall but effaces only the follicular–dermal interface. Perifollicular nodular inflammation may be prominent in some locations. Scattered individual shrinkage and increased eosinophilia (apoptosis) of follicular keratinocytes may be seen.

Associated dermal inflammation is variable and may be absent or minimal. In some cases, there may be superficial perivascular to diffuse inflammation, sometimes forming a loose lichenoid band. Intense lichenoid and

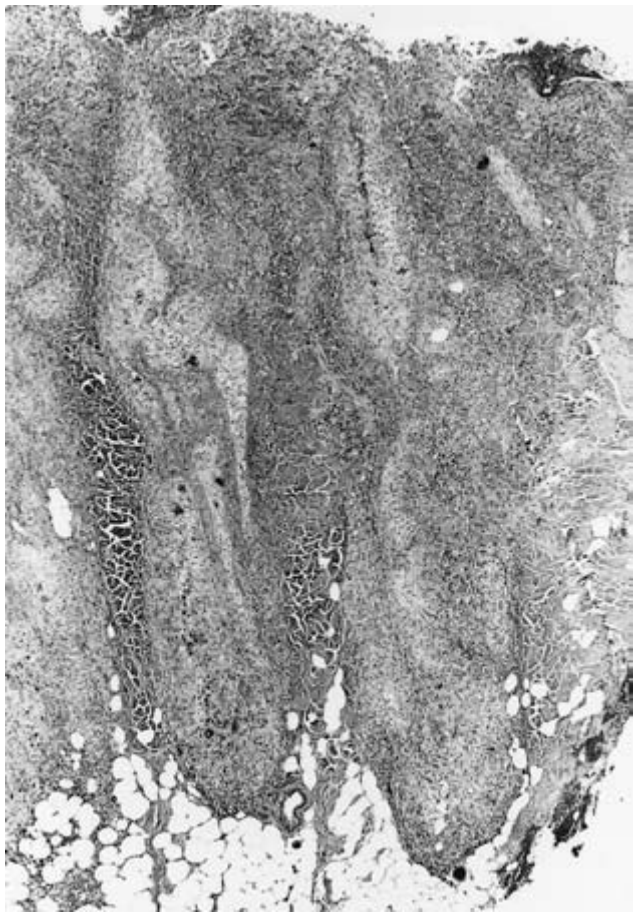


Fig. 18.29 Granulomatous mural folliculitis in a dog. Hair follicles are effaced by linear granulomas. Note ulceration.

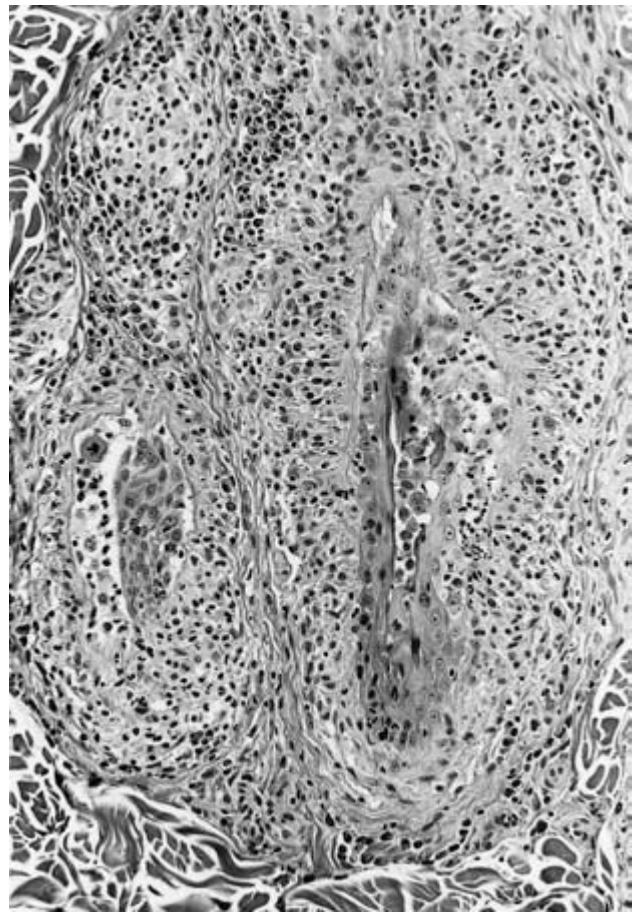


Fig. 18.30 Higher magnification of granulomatous mural folliculitis. Central residual follicular epithelium is surrounded by expansive granulomatous inflammation.

interface inflammation may be associated with epidermal degeneration and ulceration. Milder interface inflammation with rare basal cell apoptosis may be present. In other cases, superficial lymphocytic dermatitis is accompanied by exocytosis and mild spongiosis.

Chronic lesions are characterized by striking and often diffuse atrophy of hair follicles. This sometimes is manifested by complete drop-out of follicles and often sebaceous glands, leaving only arrector pili muscles and apocrine sweat glands. There may a few clusters or cords of follicular epithelial cells intermingled with melanophages and a few lymphocytes and histiocytes. Follicular infundibula sometimes remain and are dilated with keratin. Obliterative scarring is not found; external root sheath connective tissue may form a fibrous tract that remains as a place-holder or 'stele' (after Headington) for the previous follicle.

Like other forms of mural folliculitis, granulomatous mural folliculitis may be a reaction pattern with variable causation. This is suggested by the range in severity of lesions, the variable pattern and intensity of associated dermatitis, and the occurrence of apoptosis in some cases. Some lesions of granulomatous mural folliculitis, particularly those in which nodular perifollicular inflammation predominates, may be easily confused with sterile granuloma and pyogranuloma syndrome (see Chapter 13) or severely inflamed sebaceous adenitis (see Chapter 17). In cases with lichenoid dermatitis, Vogt–Koyanagi–Harada-like syndrome may be considered. The differentiating feature of granulomatous mural folliculitis is severe panfollicular mural inflammation.

Granulomatous mural folliculitis also may resemble severe follicular erythema multiforme (see Chapter 4). In the latter, pustular to pyogranulomatous inflammation follows confluent follicular apoptosis, and results in ultimate destruction of the hair follicle. Apoptosis is uncommon and generally mild in granulomatous mural folliculitis. Differentiation from follicular erythema multiforme may be unimportant in some cases, as both conditions may be drug-induced. It is also possible that both reaction patterns may coexist in some cases.

End-stage lesions of granulomatous mural folliculitis, in which severe follicular atrophy and drop-out predominate, may need to be distinguished from chronic pseudopelade. The degree of atrophy in granulomatous mural folliculitis is generally more diffuse and severe than in pseudopelade; residual granulomatous versus predominantly lymphocytic inflammation may allow differentiation.

FOLLICULAR MUCINOSIS

(Synonym: alopecia mucinosa)

Clinical features

Follicular mucinosis is a very rare, presumed immunologically-mediated, alopecic skin disease of the dog and cat. It has been reported in one dog (Bell & Oliver, 1995) and two cats (Scott, 1987). It has also been observed in an additional dog and cat by one author (T.L.G.). Multiple triggers may initiate lymphocytic immunologic attack on hair follicles. In the single canine case seen by one author (T.L.G.), immunohistochemistry revealed CD3+ T lymphocytes prominently within and surrounding hair follicles. Histopathologic and clinical similarities exist between this disease and eosinophilic mucinotic mural folliculitis in dogs (see p. 469); the lack of eosinophils in follicular mucinosis is the prime distinguishing feature. Mural inflammation and follicular mucinosis (with or without eosinophils) has been reported in humans with either cutaneous epitheliotropic lymphoma ('mycosis fungoides') or in conjunction with several inflammatory diseases (Wood, 2003). Follicular mucinosis has been reported in conjunction with epitheliotropic lymphoma in two cats (Scott et al., 1987).

Clinical features of follicular mucinosis in dogs include alopecia and scaling. Lesions vary from patchy to diffuse and are widespread, affecting the head, trunk, and legs (Bell & Oliver, 1995). Hyperpigmentation may be noted. Pruritus has not been reported or observed. Affected dogs are otherwise normal. Both dogs were older retrievers; the observed dog was a Labrador Retriever and the reported dog a Golden Retriever (Bell & Oliver, 1995).

Clinical features of follicular mucinosis in cats, as described, include well-demarcated alopecia with fine scaling involving the head, ears and neck (Scott, 1987). The two affected adult cats were otherwise healthy at presentation, but developed epitheliotropic lymphoma and were subsequently lost to follow-up (Scott, 1987).

Clinical differential diagnoses include other causes of relatively noninflammatory alopecia. Differential diagnoses include alopecia areata, pseudopelade, follicular dysplasias, endocrinopathies, demodicosis, and dermatophytosis. Skin scrapings and dermatophyte culture should be performed to rule out demodicosis and dermatophytosis. Skin biopsy is required for diagnosis.

Biopsy site selection

Multiple biopsy specimens should be obtained from regions of maximal alopecia. If punch biopsy technique is used, specimens should include only abnormal tissue.

Histopathology (Figure 18.31)

A single canine case has been observed by one author (T.L.G.) and is similar to the case reported by Bell & Oliver (1995). Acanthosis is mild, and may be associated with focal spongiosis (Bell & Oliver, 1995). Mixed inflammation surrounds and variably infiltrates the isthmus portion of the hair follicle. This includes lymphocytes, histiocytes, plasma cells, and neutrophils. Similar inflammation extends to the surrounding and superficial dermis. Mild interface dermatitis with apoptosis

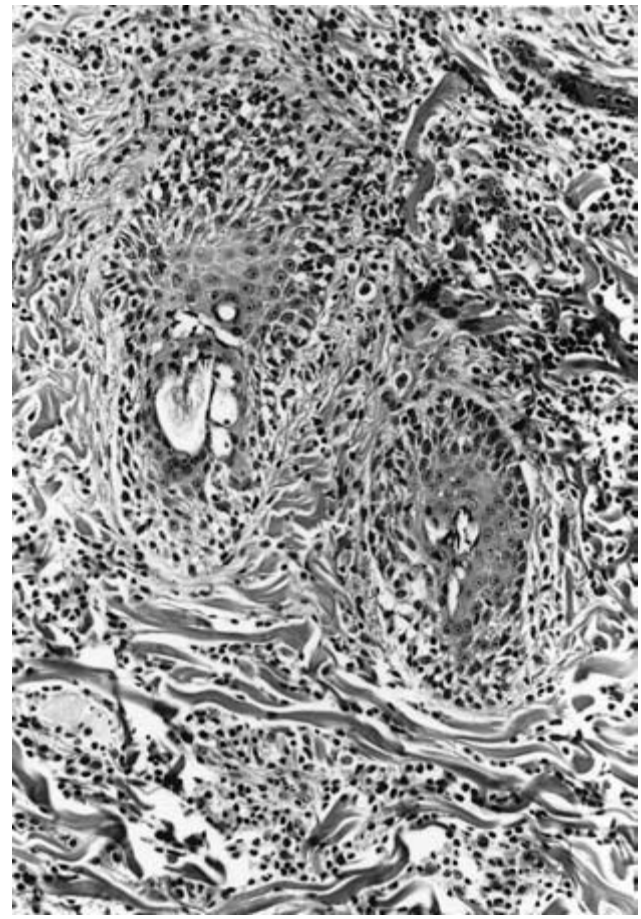


Fig. 18.31 Follicular mucinosis. The follicular walls are expanded by pale intercellular mucin. Note intramural and perifollicular lymphocyte-rich inflammation.

and pigmentary incontinence was reported by Bell & Oliver (1995).

Mucin accumulation is variable but often striking. Follicles are not equally affected and many are spared. Pools of mucin may contain free follicular keratinocytes and lymphocytes. Central cystic degeneration due to mucinosis was reported by Bell & Oliver (1995). Immunohistochemistry showed CD3+ T lymphocytes prominently within and surrounding follicles in the author's case.

As reported in cats (Scott, 1987), acanthosis was moderate to severe and was accompanied by mild lymphocytic exocytosis. There was perivascular mixed mononuclear dermatitis. Mucin accumulation in hair follicles was accompanied by reticular degeneration and spongiosis of the follicular wall with lymphocytic infiltration. A similar case has been observed by one author (T.L.G.).

The lesions of follicular mucinosis in dogs are histologically similar to those of eosinophilic mucinotic mural folliculitis in dogs (see p. 469), except for the presence of eosinophils in the latter. Many cases of eosinophilic mucinotic mural folliculitis feature more prominent perifollicular (rather than intrafollicular) mucin accumulation than hitherto observed or reported in follicular mucinosis. Mural mucin accumulation may be subtle in eosinophilic mucinotic mural folliculitis, but is a central feature of follicular mucinosis. Still, the possibility that these two entities actually represent one disease process cannot be ruled out at this time. In humans, follicular mucinosis, which often features eosinophils, is a reaction pattern with several clinical settings or outcomes, including epitheliotropic T-cell lymphoma (Wood, 2003). It has been reported that eosinophil-predominant forms are more likely to be benign (Mehregan, 1991).

Follicular mucinosis in cats may be similar to degenerative mucinotic mural folliculitis in cats. A clinical photograph of one of two reported cases showed clinical features indistinguishable from degenerative mucinotic mural folliculitis, including narrowed eye openings (Scott, 1987). However, both reported cases of feline follicular mucinosis developed cutaneous lymphoma, which has not been observed in cases of degenerative mucinotic mural folliculitis seen by the authors. Further, the feline case of follicular mucinosis observed by one author (T.L.G.) had clinical and histological features that were distinct from degenerative mucinotic mural folliculitis; follow-up clinical information was not available.

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Chapter 19

Atrophic diseases of the adnexa

Atrophic diseases of the adnexa include those in which the follicle has undergone hair cycle arrest. True follicular atrophy (reduction in follicular size over what would be expected for the given stage of the follicular growth cycle), may exist alone, or occur in conjunction with cycle arrest. These diseases may have an endocrine or other metabolic stimulus, or an inflammatory cause. Dysplasia, or malformation of the follicular unit, is not a uniform feature of diseases of this chapter; however, a recent study has shown that occasional follicular dysplasia is observed in the setting of endocrine follicular disorders (Rothstein et al., 1998).

In the hair cycle, the catagen or regression phase is characterized by involution of the hair bulb and dermal follicular papilla, upward migration of the follicle and papilla, and disintegration of the inner root sheath. The outer root sheath continues to keratinize as it regresses; the outer root sheath keratin may merge with the keratin of the hair cortex, resulting in a brush-like mass of brightly eosinophilic tricholemmal keratin. This prominent cornified layer may help to anneal the hair shaft to the outer root sheath during the prolonged telogen phase that follows (Dunstan, R.W., personal communication, 2004). The telogen or resting phase of the hair follicle is characterized by a widened infundibulum and narrow base of outer root sheath that terminates at the level of the sebaceous glands. Hair shafts usually are retained. There is some breed variation in the appearance of the telogen phase, which is partly due to variation in the amount of annealing keratins deposited during the catagen phase around the hair shaft. A thin cord or cluster of hair germ cells lies beneath the outer root sheath above the quiescent dermal follicular papilla. The telogen hair shaft is extruded (shed) when the new emerging anagen hair pushes it out. Evaluation and designation of stages of the hair cycle are currently based on morphologic parameters originally adapted from mice and humans. Definite identification of hair follicle stages in dogs and cats will involve further studies, for example, TUNEL staining for the presence of apoptosis that is central to the catagen regression phase.

The difficulty in evaluating hair cycle arrest in dogs arises from the marked breed variation in hair cycles and follicular morphology (Credille et al., 2001). That study suggests that determining the presence or absence of hairs within telogen follicles (haired or hairless telogen, respectively) may be of greater value in the assessment of alopecia, as haired telogen predominance may occur normally in many dog breeds (Credille et al., 2001). Haired telogen phase may be prolonged in many breeds of dogs as an energy saving feature to retain the insulating coat without frequent shedding. Hairless telogen follicles form a small percentage of total follicles observed in normal dogs; these may function as follicles in reserve, perhaps as a method of increasing coat density during periods of cold (Dunstan, R.W., personal communication, 2004). In contrast, a predominance of hairless telogen follicles characterizes many of the diseases of this chapter.

Exaggerated forms of regressing hair follicles, in which large spikes of fused keratin appear to protrude through the outer root sheath to the vitreous layer, occur in the setting of some atrophic adnexal diseases. These have been dubbed 'flame follicles' by Dunstan. The flame follicle may result from an abnormal or accentuated catagen phase in which there has been over-abundant deposition of tricholemmal keratin, with subsequent passage into telogen, or the resting phase. Thus some argument may be made for consideration of the flame follicle as an abnormal or exaggerated telogen follicle. However, it is also reasonable to consider the flame follicle as an 'arrested' catagen follicle, since the 'flames' morphologically reflect an exaggeration of the keratin pattern which emerges in the catagen phase (see above). In addition there is retention of the pale pink outer root sheath keratinocytes from the isthmus region that gives normal catagen follicles their predominant tinctorial properties. Further studies to determine the true nature of the flame follicle are needed. True flame follicles may be most prominent in plush-coated breeds, and may be a manifestation of hair growth cycle arrest, regardless of type of endocrine stimulus.



Fig. 19.1 Canine hypothyroidism in a German Shepherd Dog-crossbreed, demonstrating somewhat symmetric alopecia, hyperpigmentation, and lichenification.



Fig. 19.2 Closer view of the dog in Fig. 19.1. Alopecia, lichenification, and hyperpigmentation are present on the ventral neck and chest.

Difficulty in the definitive diagnosis of many of the atrophic adnexal diseases arises from a variation in clinical presentation. Biopsy of cases with poor hair coat quality and an absence of complete alopecia may not yield diagnostic results. Areas of advanced or long-standing hair loss should provide the optimal lesions. Further, differentiation among the uninflamed atrophic adnexal diseases on histopathologic grounds alone may be very difficult because adnexal atrophy has limited morphologic variation. Other adjunctive features such as epidermal or sebaceous gland atrophy or proportion of flame follicles, for example, may be helpful. However, clinical data, such as sexual status, endocrine assays, etc., usually are required for definitive diagnosis.

HYPOTHYROIDISM

Clinical features (Figures 19.1 and 19.2)

Hypothyroidism is the most common endocrinologic skin disease of the dog. In comparison, naturally occurring, spontaneous hypothyroidism has been reported convincingly in only one cat (Rand et al., 1993). Naturally occurring deficiency of thyroid hormones initiates a wide variety of noncutaneous and cutaneous signs. Thyroid hormone physiology and the noncutaneous signs of hypothyroidism are beyond the scope of this book; the reader is referred to standard textbooks (Scott-Moncrieff & Guptill-Yoran, 2000; Scott et al., 2001; Feldman & Nelson, 2004).

The frequency of occurrence of cutaneous signs in hypothyroidism is controversial. The most common cutaneous signs, when present, include alopecia and poor haircoat quality. Paradoxically, although acquired canine hypothyroidism is common, it also is one of the most overdiagnosed canine diseases. Since thyroid hormone promotes cycling into the active anagen phase of hair growth (Credille et al., 2001), other skin diseases characterized by alopecia may be partially thyroid-hormone-responsive. This encourages overdiagnosis.

Most documented cases of canine hypothyroidism are caused by either lymphocytic thyroiditis or idiopathic thyroid necrosis and atrophy (Feldman & Nelson, 2004). Lymphocytic thyroiditis is thought to be due to a complex autoimmune process involving derangements in both cellular and humoral immunity (Feldman & Nelson, 2004). Idiopathic thyroid necrosis and atrophy may be an end-stage result of lymphocytic thyroiditis. Thyroid hormone is necessary for normal cellular metabolic functions in all organ systems. Major mechanisms of action include stimulation of amino acid transport, mitochondrial oxygen consumption, and protein synthesis (Feldman & Nelson, 2004). Deficiency of thyroid hormone affects metabolic processes throughout the body.

The most common cutaneous clinical features of canine hypothyroidism include bilaterally symmetric truncal alopecia, poor coat quality, coat color change, hyperpigmentation, and lichenification. Retarded regrowth of hair after clipping may be noted. These signs may be present in any combination and may be subtle. Enhanced

susceptibility to solar and other environmental damage to hair, giving rise to lightening of the haircoat and diminished hair coat quality, may be due to abnormally prolonged retention of telogen hairs in hypothyroidism. Alopecia and broken hairs leading to stubble occur first in frictional regions such as the neck (under a collar), the tail, and pressure points such as the elbows, lateral thighs, and lateral hocks. In general, truncal alopecia is much more common than hair loss of the distal extremities or head. As an exception, pinnal alopecia and scaling presenting as ear margin seborrhea (see Chapter 8) is relatively common. Rarely, large or giant breed dogs may exhibit a reversed pattern of alopecia affecting the distal extremities and head.

Skin thickening due to cutaneous mucinosis and myxedema can be a feature of hypothyroidism (see Chapter 15). Secondary pyoderma or bacterial overgrowth is common, and secondary *Malassezia* dermatitis also may be present. Secondary seborrhea, characterized by scaling and crusting, may occur. Otitis externa may be present with or without associated seborrheic changes or secondary pyoderma. Pruritus is uncommon, unless secondary infection is present.

In addition to the classical cutaneous signs of hypothyroidism, common breed-based characteristics such as hypertrichosis and haircoat lightening in Irish Setters may be noted. A striking 'zebra-striped' pattern of alopecia in multiple Rhodesian Ridgebacks with hypothyroidism has been observed (White, S.D., personal communication, 2003). Classical noncutaneous signs of hypothyroidism, including lethargy, obesity, mental dullness, and heat-seeking, may not be present in dogs with skin disease.

As reported in one cat, spontaneously occurring adult-onset acquired feline hypothyroidism led to a dull, dry, seborrheic haircoat, lightening of the haircoat, and poor hair regrowth after clipping (Rand et al., 1993). Hair loss was predominantly truncal. Systemic clinical signs included lethargy, heat-seeking, obesity, and loss of appetite (Rand et al., 1993).

Breeds at probable increased risk include the Chinese Shar Pei, Chow Chow, Great Dane, Irish Wolfhound, Boxer, English Bulldog, Dachshund, Afghan Hound, Newfoundland, Alaskan Malamute, Doberman Pinscher, Brittany Spaniel, Standard Poodle, Golden Retriever, Miniature Schnauzer, Airedale Terrier, and Irish Setter. However, hypothyroidism may affect any breed. Most dogs are between 6 and 10 years of age, but dogs of any age may be affected (Scott et al., 2001). Sex predilections are not noted, although neutered dogs may be at increased risk (Scott et al., 2001). Signalment data are not available for cats.

Clinical differential diagnoses of canine hypothyroidism with alopecia and poor haircoat as the prime clinical features include other endocrinopathies, follicular dysplasia, postclipping alopecia, acquired pattern alopecia, telogen effluvium, and excessive physiological shedding. Differentiation is based on ruling out these diseases and laboratory evaluation of the thyroid gland; histopathology may not be supportive in all cases. Thyroid testing can include resting thyroid hormone levels, thyroid function testing, and assays for thyroid stimulating hormone (TSH) (Scott-Moncrieff & Guptill-Yoran, 2000; Scott et al., 2001; Feldman & Nelson, 2004). Clinical differential diagnoses for feline hypothyroidism include diseases characterized by alopecia, such as feline psychogenic alopecia and hyperglucocorticoidism.

Biopsy site selection

It is important in all cases of suspected endocrine disease to obtain skin from areas of most advanced hair loss for optimal identification of atrophic follicular changes. Skin from the junctional zone between normal and alopecic skin should be avoided, as should lesions with obvious secondary pyoderma.

Histopathology (Figures 19.3 and 19.4)

In dogs, epidermal and follicular infundibular hyperplasia usually is present, and variable hyperpigmentation may be observed. In some cases, the epidermis and follicular infundibula thickness may be normal. There is often mild to occasionally severe follicular infundibular orthokeratotic hyperkeratosis.

Skin biopsy often is not diagnostic in cases of hypothyroidism. However, if specimens are obtained from areas of advanced alopecia, hair follicles may be in growth cycle arrest (physiologic atrophy) and are predominantly in telogen phase, generally without hair shafts (hairless telogen). Secondary follicles may be preferentially affected in some specimens. The thickened follicular infundibulum often tapers to the cord-like deep follicle, creating a 'v'-shaped ('toe-dancing hippo') configuration. Sebaceous glands are normal or slightly hyperplastic if there is secondary inflammation.

In Beagles with experimentally induced hypothyroidism, telogen follicles predominated in both normal and affected dogs; however, hairless telogen follicles were more numerous in hypothyroid dogs (Credille et al., 2001). The difficulty in evaluating telogen arrest in dogs arises from the marked breed variation in hair cycles and follicular morphology (Credille et al., 2001). The study suggests that determining the presence or absence of hairs within telogen follicles may be of greater value in the assessment of alopecia, as haired telogen predominance may occur normally in many breeds (Credille et al., 2001).

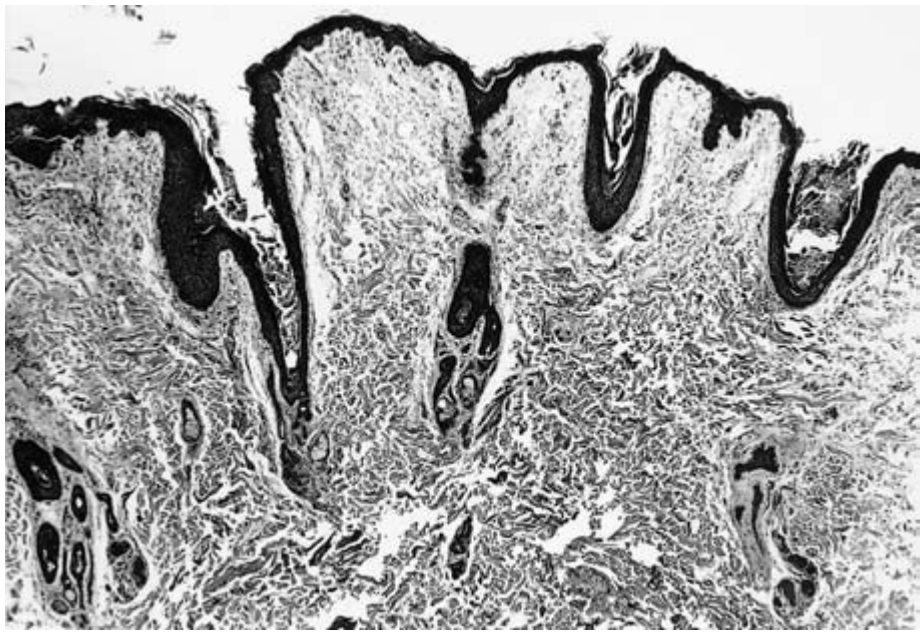


Fig. 19.3 Canine hypothyroidism. Hair follicles are in hairless telogen; note hyperplasia of the epidermis and follicular infundibula.

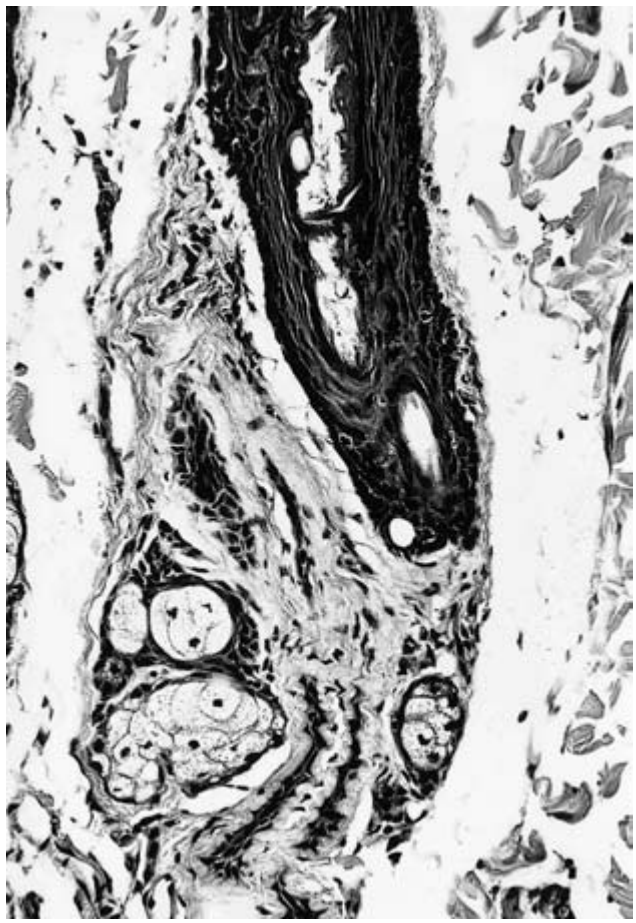


Fig. 19.4 Higher magnification of canine hypothyroidism, demonstrating thin cord-like remnants of the hairless telogen follicle beneath hyperplastic superficial follicular epithelium.

Flame follicles (see introduction, p. 480) have been reported to occur in some cases of canine hypothyroidism, particularly in the plush-coated breeds (Scott, 1989; Credille et al., 2001). Flame follicles are likely a manifestation of an abnormal growth cycle in these dogs regardless of type of endocrine stimulus. In some cases there are occasional 'dysplastic' follicles characterized by irregular or wavy outer contours. A recent study has shown that occasional follicular dysplasia is observed in the setting of endocrine follicular disorders (Rothstein et al., 1998).

Affected dogs frequently have secondary pyoderma, and variable numbers of lymphocytes, macrophages, plasma cells, and neutrophils may be present in the superficial dermis or around hair follicles. Frank folliculitis or superficial epidermal pustulation may be seen. Myxedema (cutaneous mucinosis) uncommonly is present (see Chapter 15), but may be striking in rare cases. Ear margin seborrhea (orthokeratotic hyperkeratosis) (see Chapter 8) may be a manifestation of hypothyroidism in some dogs. Pyoderma, mucinosis, and hyperkeratosis may occur in the absence of follicular atrophy.

In the single reported case of adult-onset hypothyroidism in a cat, histologic findings were as observed in dogs. There was moderate acanthosis of the epidermis and follicular infundibula, as well as diffuse telogenization of hair follicles. Inflammation was not observed. Dermal mucinosis (myxedema) was reported (Rand et al., 1993).

Differential diagnoses for the follicular lesions of hypothyroidism principally include other endocrine alopecias and telogen effluvium. When hair growth cycle arrest is observed, all other endocrine-related alopecias



Fig. 19.5 Naturally occurring hyperglucocorticoidism in a Labrador Retriever-crossbreed. Extensive bilaterally symmetric alopecia is present. A markedly pendulous abdomen and muscle wasting are obvious nondermatologic clinical signs.

must be considered, including Sertoli cell tumor-associated skin disease, alopecia X, female hyperestrogenism, and hyperadrenocorticism. Acanthosis and hyperplasia of the follicular infundibulum in the face of follicular growth cycle arrest are suggestive for hypothyroidism, but Sertoli cell tumor-associated skin disease or, occasionally, canine female hyperestrogenism may present with similar changes. Clinical differentiation is required. Hyperglucocorticoidism features epidermal and sebaceous atrophy, in contrast to hypothyroidism. Telogen effluvium is uncommon, and hair follicles are often returning to anagen phase by the time of biopsy, in contrast to endocrine alopecia.

CANINE HYPERGLUCOCORTICOIDISM

(Synonyms: canine hyperadrenocorticism, canine Cushing's disease, canine Cushing's syndrome)

Clinical features (Figures 19.5 and 19.6)

Canine hyperglucocorticoidism encompasses both naturally occurring, endogenous canine hyperadrenocorticism and iatrogenic hyperglucocorticoidism resulting from excessive administration. Both syndromes are common. The frequency of occurrence and the severity of iatrogenic hyperglucocorticoidism vary with the quality of veterinary care; the number of dogs seen with severe iatrogenic hyperglucocorticoidism may have diminished over the past decade. The term 'iatrogenic hyperglucocorticoidism' is preferred to 'iatrogenic hyperadrenocorticism', since this nomenclature does not imply overproduction of glucocorticoids by the adrenal gland.



Fig. 19.6 Naturally occurring hyperglucocorticoidism in an aged Dachshund. Increased prominence of subcutaneous blood vessels indicates thinning of the skin. Focal erythematous areas on the groin and legs represent secondary pyoderma.

Endogenous canine hyperadrenocorticism is associated with aberrations in the adrenal–pituitary–hypothalamic axis. Overproduction of glucocorticoids is due to either bilateral adrenocortical hyperplasia as a result of pituitary stimulation (functional tumors of the pituitary gland are not always recognized) or a functional tumor of the adrenal cortex which induces contralateral adrenocortical atrophy. Corticosteroid hormone physiology and the etiopathogenesis of Cushing's disease are beyond the scope of this book. The reader is referred to standard textbooks (Feldman, 2000; Scott et al., 2001; Feldman & Nelson, 2004).

Exogenous or iatrogenic hyperglucocorticoidism usually results from the injudicious administration of corticosteroids either given systemically, or given topically and then percutaneously absorbed. However, some dogs are unpredictably exquisitely sensitive to glucocorticoids. Most cases of iatrogenic hyperglucocorticoidism are caused by either injectable or orally administered corticosteroids. However, the parenteral absorption of topical corticosteroid-containing preparations used on the skin or in the ears or eyes may produce clinical signs, especially in dogs weighing less than about 16 lb (7.25 kg). In addition, topically applied or injectable corticosteroids can produce localized effects at the site of application similar to those seen with naturally occurring or iatrogenic hyper-

glucocorticoidism. In other cases, the topical application of high-potency corticosteroids can produce fragile, thin skin with dramatic comedone formation (see Chapter 15).

Characteristic clinical features include bilaterally symmetric alopecia (often sparing the head and distal extremities), thinning and decreased elasticity of the skin, aberrations in pigmentation (changes in coat color, hyperpigmentation, or depigmentation of the skin), bleeding and vascular abnormalities (petechiae, hematomas, phlebectasia), delayed wound healing, scaling, comedones, and calcinosis cutis (see Chapter 15). Hair loss often begins over bony prominences and other areas of friction such as under collars. Diminished cutaneous elasticity may be noted. Thinning of the skin allows enhanced visualization of subcutaneous blood vessels. Thinning of the skin may be especially obvious at the umbilicus and at the site of scarring from prior ovariohysterectomy. Delayed and inadequate wound healing is manifested by the formation of thin scar tissue and striae (stretch marks). Decubital ulcers may occur on pressure points in larger dogs. Comedones (blackheads) are common, and are especially prominent around the nipples and genital region. Large, visually distinctive comedones are seen most frequently with iatrogenic hyperglucocorticoidism resulting from the injudicious use of topical glucocorticoids (see Chapter 15). Phlebectasias appear grossly as erythematous macules or papules on the trunk (Scott, 1985). Secondary pyoderma, especially impetigo (see Chapter 1), commonly results from immune suppression. Secondary *Malassezia* dermatitis also may be seen. Less commonly, secondary localized or generalized demodicosis may occur.

Polydipsia, polyuria, polyphagia, hematologic abnormalities, pendulous abdomen (pot-belly), muscle weakness and atrophy, lethargy, hepatomegaly, and neurologic abnormalities are common nondermatologic signs of hyperglucocorticoidism. The reader is referred to internal medicine texts for further discussion of the noncutaneous manifestations of hyperglucocorticoidism (Feldman, 2000; Feldman & Nelson, 2004).

The Boxer, Boston Terrier, Dachshund, and Miniature Poodle are at increased risk for naturally occurring hyperadrenocorticism (Scott et al., 2001). However, hyperadrenocorticism may be seen in any breed. Hyperadrenocorticism is seen more frequently in older dogs. Definitive sex predilections have not been reported for pituitary-dependent hyperadrenocorticism, but females may be at increased risk for corticosteroid-producing adrenocortical tumors (Scott et al., 2001). Although iatrogenic hyperglucocorticoidism may be seen in any breed, this syndrome should occur more frequently in breeds predisposed to allergic skin disease and immunologic disorders, such as inflammatory bowel disease or immune-mediated arthritides, that are likely to receive prolonged glucocorticoid therapy. In the experience of the authors, English Bulldogs may develop signs of iatrogenic hyperglucocorticoidism, including calcinosis cutis, more readily than other breeds. Age or sex predilections have not been noted with iatrogenic hyperglucocorticoidism.

Clinical differential diagnoses of hyperglucocorticoidism are contingent upon the presenting clinical features. If symmetric alopecia is present, differential diagnoses should include other endocrine dermatoses, as well as follicular dysplasia and acquired pattern alopecia. Nondermatologic signs of hyperglucocorticoidism and laboratory evaluation aid in differentiation. Initial testing includes a complete blood count (CBC), serum biochemical profile, and endocrine testing. The adrenocorticotrophic hormone (ACTH) stimulation test, low-dose dexamethasone screening test, and urine cortisol/creatinine ratio are the most commonly employed screening tests to diagnose canine hyperglucocorticoidism (Feldman & Nelson, 2004). The ACTH stimulation test is the only test that readily identifies iatrogenic hyperglucocorticoidism. Endogenous ACTH and the low-dose dexamethasone suppression tests are used as discrimination tests to differentiate pituitary-dependent hyperadrenocorticism once iatrogenic disease has been ruled out (Feldman, 2000; Feldman & Nelson, 2004). Histopathology also may be useful in the diagnosis of hyperglucocorticoidism.

Biopsy site selection

It is important in all cases of suspected endocrine alopecia to obtain skin biopsy specimens from areas of most advanced hair loss for optimal identification of atrophic follicular changes. Specimens from the junctional zone of normal and alopecic skin commonly are less helpful diagnostically and should be avoided. If firm plaques suggestive of calcinosis cutis are present, they also should be sampled.

Histopathology (Figures 19.7 through 19.9)

In dogs, the epidermis and the epithelium of the follicular infundibulum frequently are atrophic (fewer than three nucleated cell layers); however, random biopsy specimens from affected animals may show normal epithelial thickness. The exception is in specimens from dogs with calcinosis cutis; the epidermis from affected areas is usually acanthotic and may be exudative (see Chapter 15). There may be mild to moderate orthokeratotic hyperkeratosis.

Hair follicles are in hairless telogen phase, and are also truly atrophic. They may be reduced to an exaggerated state of telogen as a single thin cord of epithelium. Sebaceous glands often are moderately to severely atrophic, which is highly diagnostic; however, glands may not be

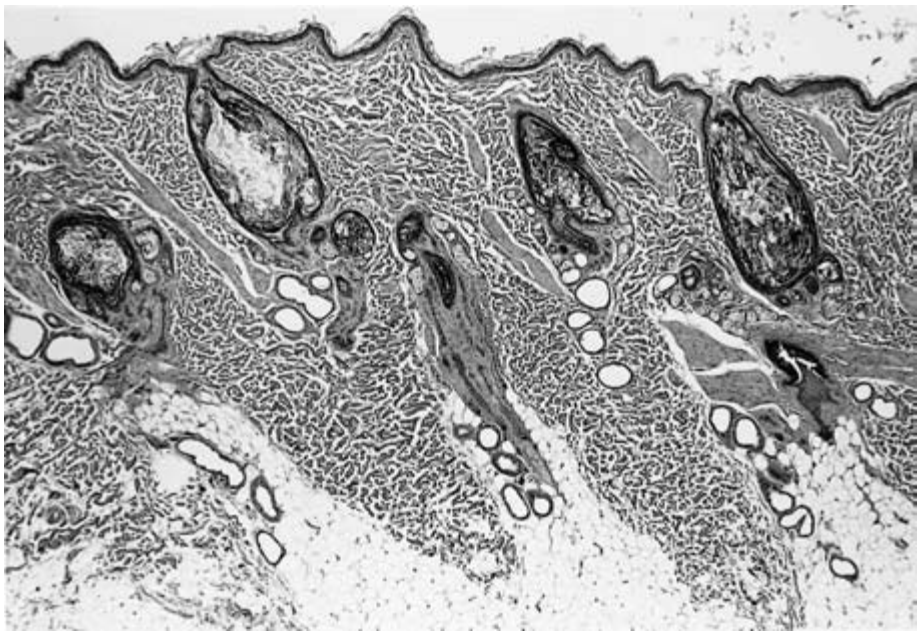


Fig. 19.7 Canine hyperglucocorticoidism showing diffuse follicular keratosis and diffuse follicular atrophy of hairless telogen type.

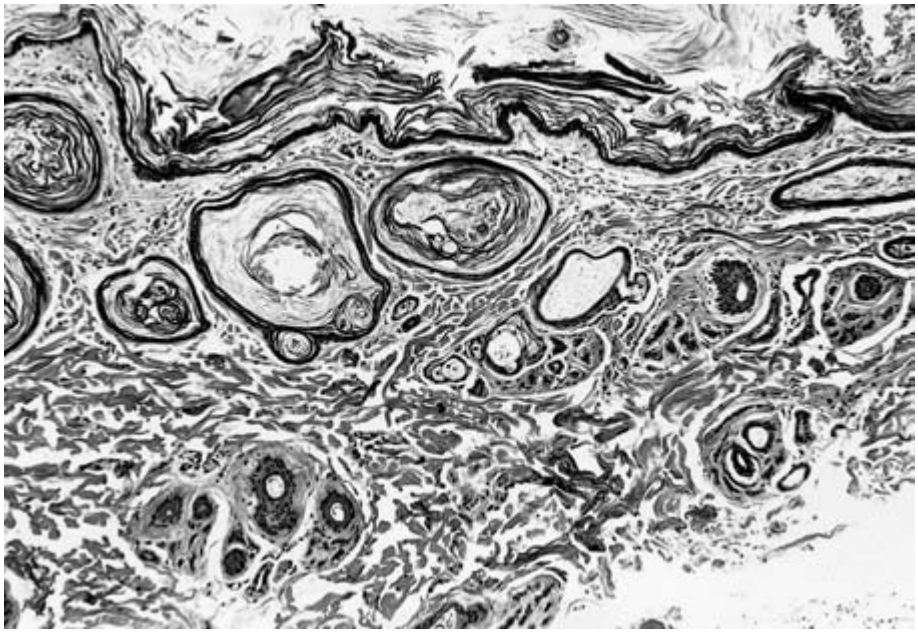


Fig. 19.8 Canine hyperglucocorticoidism demonstrating typical thin-walled follicular comedones, epidermal atrophy, and diffuse follicular atrophy.

uniformly affected in all cases. Flame follicles (see introduction, p. 480) are rare, and are most often featured in plush-coated breeds, such as the Pomeranian. Flame follicles may be a manifestation of an abnormal hair growth cycle in plush-coated dogs, regardless of the type of endocrine stimulus. In some cases, there are occasional 'dysplastic', often primary hair follicles characterized by irregular or wavy outer contours. A recent study has shown that occasional follicular dysplasia is observed in the setting of endocrine follicular disorders (Rothstein et al., 1998).

Follicular hyperkeratosis is moderate to severe. Frank comedone formation is a variable but characteristic feature of canine hyperadrenocorticism. Comedones are characterized by marked accumulation of keratin within thin-walled follicular infundibula. These may approach cystic proportions in some cases. Comedones are often most severe in iatrogenic hyperglucocorticoidism induced by topical application of corticosteroids (see Chapter 15).

Dermal calcinosis cutis may be present (see Chapter 15), and is most common in dogs with iatrogenic hyperglucocorticoidism. Follicular growth cycle arrest and



Fig. 19.9 Higher magnification of canine hyperglucocorticoidism. Note dysplastic appearance of atrophic larger primary hair follicle at left, severely atrophied follicles at bottom, and typical thin-walled comedone at top.

atrophy may not be present in lesions of calcinosis cutis. Although mineralization of the external follicular root sheath is a senile feature found sparingly in normal older dogs (particularly Poodles), extensive external root sheath mineralization also may accompany the dermal calcification of calcinosis cutis (see Chapter 15). Additionally, natural or iatrogenic hyperglucocorticoidism occasionally may result in widespread and prominent mineralization of the external root sheath in the absence of dermal calcinosis.

Phlebectasia occurs in dogs with hyperadrenocorticism (Scott, 1985). Superficial vessels are dilated and congested, and may become proliferative. The epidermis may extend downward and partially enclose the vascular lesion. Phlebectasia is a more consistent and prominent feature of topical corticosteroid reactions in dogs (see Chapter 15).

Histopathologic differential diagnoses principally include other endocrine alopecias or telogen effluvium. When hair growth cycle arrest is observed, all other endocrine-related alopecias must be considered, including hypothyroidism, canine Sertoli cell tumor-associated skin disease, alopecia X, and female hyperestrogenism. Pronounced follicular and sebaceous gland atrophy with epidermal and follicular infundibular atrophy strongly suggests hyperadrenocorticism. Although follicular keratosis is a nonspecific feature of many atrophic (as well as dysplastic) follicular diseases, comedo or keratin cyst formation within a thin-walled follicular infundibulum is generally restricted to hyperglucocorticoidism. Calcinosis cutis, when present, also is diagnostic. Telogen effluvium is characterized by telogen arrest, but true follicular atrophy is not present. Telogen effluvium is uncommon, and hair follicles are often returning to anagen phase by the time of biopsy, in contrast to endocrine alopecias.



Fig. 19.10 Feline hyperglucocorticoidism in a 12-year-old cat. Note the disheveled haircoat and focal areas of secondary infection on the shoulder. (From Feldman, E.C. & Nelson, R.W. (2004) *Canine and Feline Endocrinology and Reproduction,* 3rd edn, pp. 358–93. W.B. Saunders, Philadelphia. Reprinted with permission.)

FELINE HYPERGLUCOCORTICOIDISM

(Synonyms: feline hyperadrenocorticism, feline Cushing's disease)

Clinical features (Figures 19.10 and 19.11)

Hyperglucocorticoidism is a rare disease in the cat. The syndrome can either be endogenous due to hyperadrenocorticism or iatrogenic in association with the injudicious use of corticosteroids. It is difficult to create iatrogenic hyperglucocorticoidism in the cat; frequent use of long-acting, high potency injectable corticosteroids usually is required. Over 75% of cats with hyperadrenocorticism have pituitary-dependent disease, and over 20% have a functioning adrenocortical tumor (Feldman, 2000). The etiopathogenesis of feline hyperglucocorticoidism is beyond the scope of this book. The reader is referred to standard textbooks (Feldman, 2000; Feldman & Nelson, 2004).

The marked association between hyperglucocorticoidism and diabetes mellitus in the cat makes it difficult to differentiate clinical signs attributable to each. Approximately 90% of cats with hyperadrenocorticism are either diabetic or are prediabetic due to the insulin-antagonistic effect of corticosteroids (Scott et al., 2001). Polydipsia, polyuria, and polyphagia are the most common presenting clinical features (Feldman, 2000; Feldman & Nelson, 2004). Weight loss, anorexia, and depression also can occur (Scott et al., 2001). Muscle wasting and the presence of a pendulous abdomen (pot-belly) may be seen (Feldman, 2000).

It is estimated that only 50% of cats with hyperglucocorticoidism display cutaneous signs (Scott et al., 2001).



Fig. 19.11 Ventral view of the cat in Fig. 19.10. The abdomen has been clipped for ultrasound evaluation. The abdomen is hugely distended and superficial blood vessels are prominent due to thinning of the skin. (From Feldman, E.C. & Nelson, R.W. (2004) *Canine and Feline Endocrinology and Reproduction,* 3rd edn, pp. 358–93. W.B. Saunders, Philadelphia. Reprinted with permission.)

Cutaneous signs vary greatly and include alopecia, skin fragility, and easy bruising. Both severity and pattern of hair loss are highly variable (Scott et al., 2001). Poor haircoat quality may be seen. Feline skin fragility syndrome, when present, is the most characteristic clinical dermatologic feature of feline hyperglucocorticoidism, and may occur with endogenous or exogenous disease. Affected skin becomes dramatically thin, appearing translucent, and can be severely damaged by very minor trauma, including careful handling (see Chapter 15). Easy bruiseability may be seen with or without skin fragility.

Breed predilection is not seen with naturally occurring feline hyperglucocorticoidism. Most affected cats are middle-aged or older with an average age of 11 years; 70% are female (Feldman, 2000).

Clinical differential diagnoses are contingent on the presenting cutaneous signs. Differential diagnoses if alopecia is the prime presenting sign include self-traumatic alopecia, telogen effluvium, and early feline paraneoplastic alopecia. Skin fragility, when present, is a highly characteristic clinical feature (see Chapter 15). Inherited defects in cutaneous tensile strength and elasticity such as Ehlers–Danlos syndrome occur from birth, while acquired skin fragility syndrome develops in older adult cats. Skin biopsy is confirmatory for skin fragility due to hyperglucocorticoidism.

Biopsy site selection

Areas of maximum alopecia should be sampled. If the cat presents with feline skin fragility syndrome, skin biopsy is difficult to perform due to the extreme thinness and friability of the skin.

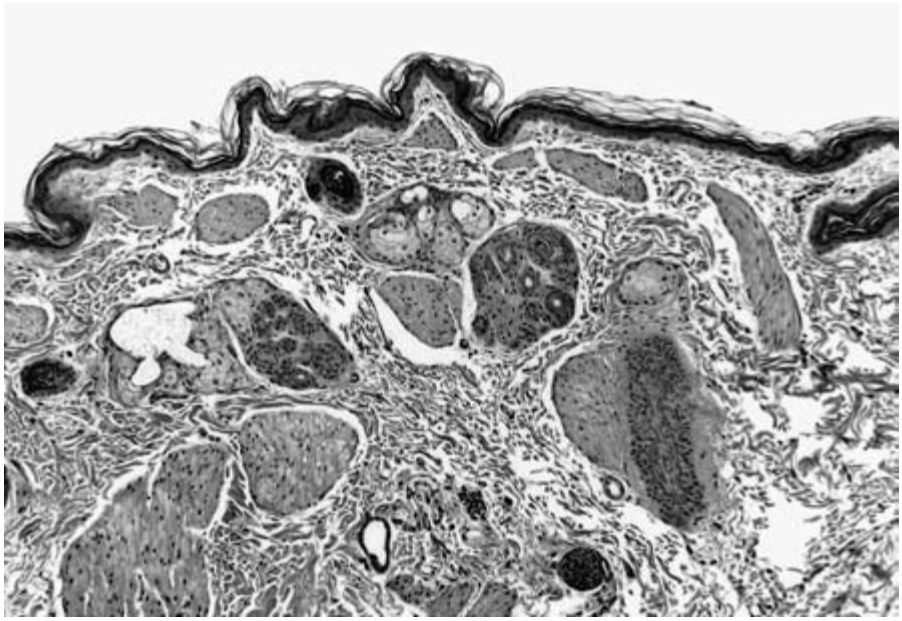


Fig. 19.12 Feline hyperglucocorticoidism demonstrating diffuse follicular atrophy of hairless telogen type; the epidermis is normal.

Histopathology (Figures 19.12 through 19.14)

In cats, feline skin fragility syndrome is the most common cutaneous manifestation of hyperadrenocorticism or iatrogenic hyperglucocorticoidism (see Chapter 15), and may occur with or without obvious follicular atrophy. Lesions from cats with alopecia mirror those of dogs. The epidermis and epithelium of the follicular infundibula are normal to severely atrophic. There is moderate to severe epidermal and follicular orthokeratotic hyperkeratosis. Small comedones may be observed.

Hair growth cycle arrest in telogen phase is accompanied by variable true follicular atrophy, which may be severe in some cases. Hair shafts are often absent (hairless telogen). Sebaceous glands may be mildly to severely atrophic, but are not always affected. There is excessive tricholemmal keratinization, creating a brightly eosinophilic core to the atrophic follicle; this feature is considered highly characteristic of feline hyperglucocorticoidism. There are often very small, round basophilic clusters of secondary hair germ observed at the base of the atrophic hair follicles. Phlebectasia, as seen in dogs

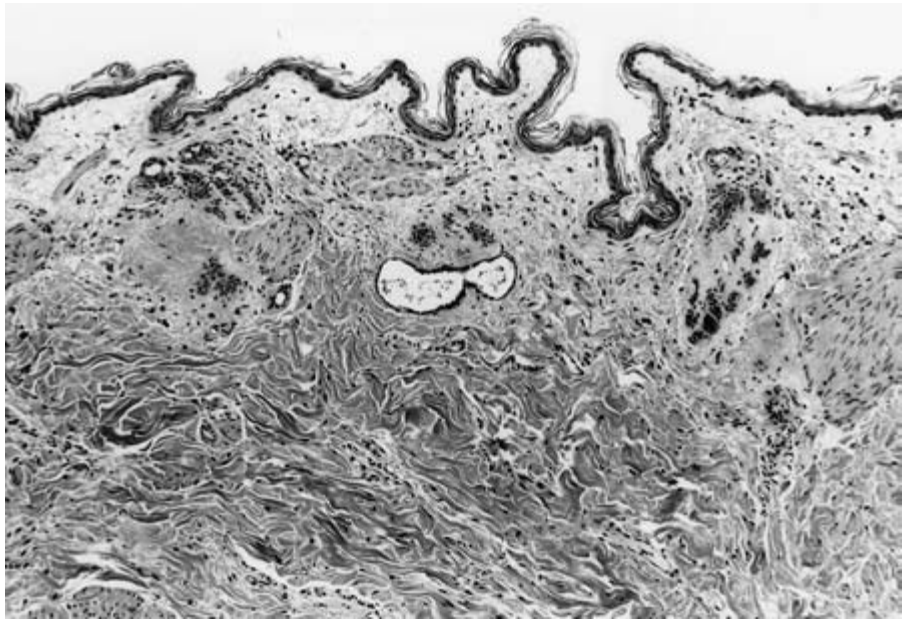


Fig. 19.13 Feline hyperglucocorticoidism featuring severe epidermal, sebaceous gland, and follicular atrophy.

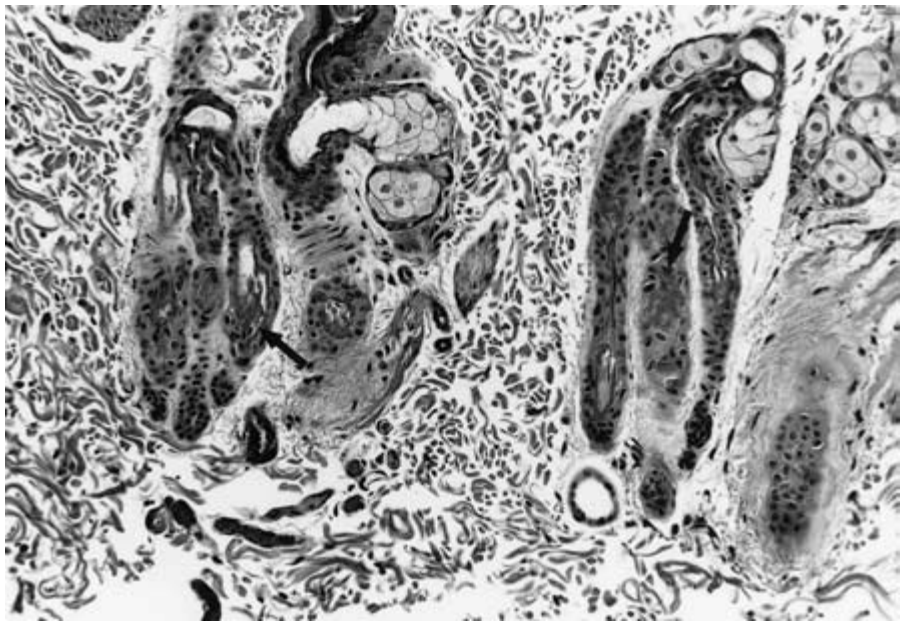


Fig. 19.14 Higher magnification of feline hyperglucocorticoidism. Note prominent tricholemmal keratin within telogen follicles (arrows). Sebaceous glands are mildly atrophic.



Fig. 19.15 Canine Sertoli cell tumor-associated skin disease in a Shetland Sheepdog. Note relative lack of hair ventrally.

(see p. 484), has been described in a cat with iatrogenic hyperglucocorticoidism (Schaer & Ginn, 1999).

The principal differential diagnosis for cats with alopecia (in the absence of skin fragility) is paraneoplastic alopecia. In contrast, paraneoplastic alopecia often features parakeratosis in lesions that have not had the stratum corneum removed by licking. Also, acanthosis may be pronounced in paraneoplastic alopecia. Hair follicles are similarly atrophic, and both conditions feature secondary hair germ clusters; however, increased tricholemmal keratin is a consistent feature of hyperadrenocorticism, but not of paraneoplastic alopecia. Sebaceous glands and dermal collagen are normal in paraneoplastic alopecia, but may be atrophic in feline hyperglucocorticoidism.

CANINE SERTOLI CELL TUMOR-ASSOCIATED SKIN DISEASE

(Synonym: male feminizing syndrome)

Clinical features (Figures 19.15 through 19.17)

Canine Sertoli cell tumor-associated skin disease is an uncommon endocrine skin disease. The syndrome is seen more frequently in regions of the world where canine neutering remains less common. It is seen in conjunction with functional endocrine testicular neoplasia leading to feminization and characteristic skin lesions. Male feminizing syndrome usually is associated with cryptorchidism and Sertoli cell tumor.

Sertoli cell tumors develop from the Sertoli cells of the seminiferous tubules. Approximately 25% of dogs with Sertoli cell tumors develop male feminizing syndrome

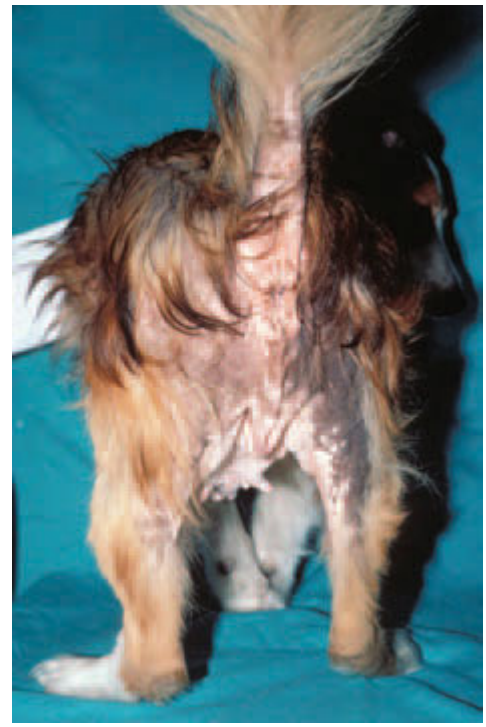


Fig. 19.16 Caudal view of the dog in Fig. 19.15. Bilaterally symmetric alopecia, macular hyperpigmentation, and gynecomastia are present.



Fig. 19.17 Ventral abdomen and prepuce of the dog in Fig. 19.15. Note linear band of erythema and comedones (Griffin's linear preputial erythema) on the prepuce.

(Feldman & Nelson, 2004). Much less commonly, testicular seminomas and interstitial cell tumors are able to initiate male feminizing syndrome and identical skin disease (Scott et al., 2001; Feldman & Nelson, 2004). However, multiple testicular tumors of different origins may be present, and small tumors may not be found. Male

feminization probably results from either increased production of estrogens by the tumor, increased conversion of various male sex hormones to estrogens, or abnormalities in the balance of multiple sex hormones (Feldman & Nelson, 2004). Although it is convenient to view male feminizing syndrome simply as a 'hyperestrogenism', there are conflicting data on estrogen levels; elevated estrogen levels often are not found (Feldman & Nelson, 2004).

Subtle symmetrical alopecia or coat color change in the lateral flanks may be the earliest presenting sign. Bilaterally symmetrical alopecia characteristically begins in the perineal and genital region, and may progress to the abdomen, chest, flanks, and neck. Coat color may lighten, and black or dark brown hairs may develop a fox-red hue, possibly due to prolonged retention of telogen hair. Hyperpigmentation is uncommon in early cases. Focal, macular hyperpigmentation (macular melanosis) commonly begins in the perineal region and on the neck. Diffuse hyperpigmentation may affect the lateral thighs, and in advanced cases the medial thigh and perineal area. Lichenification, always in conjunction with hyperpigmentation and alopecia, may occur in chronic and severe cases, and may be accompanied by greasy keratinous deposits. Secondary superficial pyoderma and *Malassezia* dermatitis may occur in advanced cases, and probably contribute to hyperpigmentation and lichenification. Gynecomastia, nipple enlargement, galactorrhea, and a pendulous prepuce are common. Linear preputial erythema, as described by Griffin (1986), is a well-demarcated linear band of macular erythema with mottled hyperpigmentation or comedones on the ventral prepuce of some dogs, and is an important cutaneous marker of male feminizing syndrome when present. Unlike most endocrinopathies, pruritus can occur in dogs with Sertoli cell tumor-associated skin disease, and may or may not correlate with secondary infections.

Nondermatologic signs of functional endocrine testicular tumors include sexual attraction of other male dogs, urination from a female stance, and prostatitis. Rarely, life-threatening estrogen-induced bone marrow dysfunction may occur.

Male feminizing syndrome occurs most frequently in cryptorchid dogs that develop Sertoli cell tumors. Abdominally-located tumors are more likely than inguinal tumors, and inguinal tumors are more likely than scrotal tumors to produce male feminizing syndrome. Sertoli cell tumors are firm and nodular, and frequently are palpable. Tumor size and duration of tumor presence and function correlate with the severity of clinical signs. Fewer than 10% of Sertoli cell tumors are malignant; metastasis is uncommon.

Boxers, Shetland Sheepdogs, Pekingese, Weimaraners, Cairn Terriers, and Collies may be predisposed (Scott et al., 2001). Male dogs that are either middle-aged or older are most commonly affected.

Clinical differential diagnoses include other endocrinopathies such as hypothyroidism, plus follicular dysplasia and flank alopecia (see Chapter 20). However, the collage of clinical features, including any combination of linear preputial erythema, cryptorchidism, palpable testicular tumors, prostatitis, and the attraction of other male dogs, greatly increases the likelihood of a diagnosis of Sertoli cell tumor-associated skin disease. Histopathologic confirmation of a Sertoli cell tumor and subsequent reversal of cutaneous signs following castration are diagnostic.

Biopsy site selection

It is important in all cases of suspected endocrine alopecia to obtain skin from areas of most advanced hair loss for optimal identification of atrophic follicular changes; skin from the junctional zone between normally haired areas and areas of alopecia should be avoided. Multiple biopsy specimens should be obtained. If lichenified and hyperpigmented areas are present, they should be sampled in addition to areas of maximum alopecia.

Histopathology (Figure 19.18)

The epidermis may demonstrate variable acanthosis, and the follicular infundibula also may be hyperplastic. Not all specimens show acanthosis, and random biopsies may reveal normal epidermal thickness. Increased melanin pigmentation of the epidermis is often observed, and is characterized by deposition of pigment at all viable levels of the epidermis.

There is follicular growth cycle arrest with hairless telogen follicles predominating. True follicular atrophy, as seen in hyperadrenocorticism, is variable and may be absent. Flame follicles (see introduction, p. 480) are rare, but may be featured in affected dogs of plush-coated breeds. Sebaceous glands are generally normal or may be mildly atrophic in some cases. The dermis shows variable inflammation, including mild to moderate, superficial, perivascular to interstitial accumulations of lymphocytes, macrophages, plasma cells, and neutrophils. Inflammation may also extend around adnexal appendages. This inflammation may reflect the presence of secondary superficial pyoderma.

Differential diagnoses principally include other endocrine alopecias. These include hypothyroidism, alopecia X, and hyperadrenocorticism. In particular, the common features of epidermal acanthosis and follicular atrophy may make distinguishing Sertoli cell tumor-associated skin disease from hypothyroidism difficult.

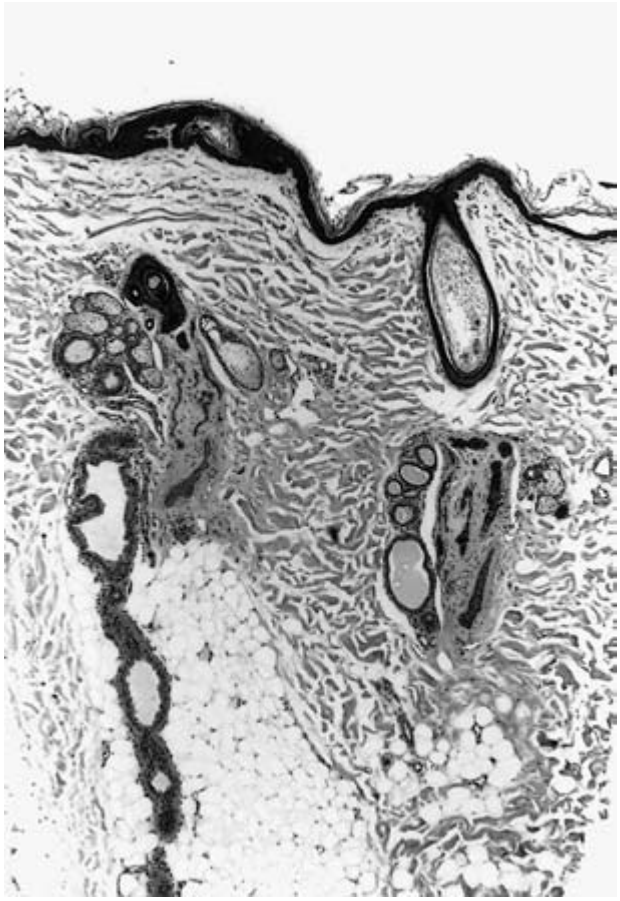


Fig. 19.18 Canine Sertoli cell tumor-associated skin disease. The epidermis is mildly acanthotic; note diffuse follicular atrophy of hairless telogen type. Sebaceous glands are normal.

Hypothyroidism is more common and therefore a more likely diagnosis; however, Sertoli cell tumor-associated skin disease should be suggested by these histopathologic changes in male dogs for which there is no confirmed history of removal of two descended testes, particularly those with gross physical signs of feminization or testicular enlargement.

CANINE FEMALE HYPERESTROGENISM

(Synonym: ovarian imbalance type I)

Clinical features (Figures 19.19 through 19.21)

Canine female hyperestrogenism is a rare endocrine skin disease seen as a consequence of excess estrogens or altered sex hormone ratios. The syndrome is naturally occurring in intact bitches with cystic ovaries or, even more rarely, in conjunction with functional ovarian neoplasms. A physiologically identical disease may be seen in spayed female dogs, induced by estrogen supplementation for urinary incontinence. Both naturally occurring and iatrogenic hyperestrogenism share many features with male feminizing syndrome caused by estrogen-producing testicular tumors (see p. 490).

Bilaterally symmetric alopecia characteristically begins in the perineal–genital region and may progress to the



Fig. 19.19 Naturally occurring canine female hyperestrogenism in a sexually intact adult Miniature Poodle. Bilaterally symmetric alopecia, hyperpigmentation, and lichenification are present in the perineal–genital region and on the abdomen.



Fig. 19.20 Iatrogenic hyperestrogenism in a spayed female Shetland Sheepdog due to administration of diethylstilbesterol. Note hyperpigmented macules in the area of bilaterally symmetric alopecia on the neck.

abdomen, caudal and medial thighs, chest, flanks, and neck. Coat color may lighten, and darker hairs may develop a fox-red hue. Diffuse hyperpigmentation in the areas of alopecia may be seen in advanced cases, especially in naturally occurring disease. Macular hyperpigmentation occurs in both naturally occurring and iatrogenic disease, but may be more common in iatrogenic hyperestrogenism. Increased pigmentation may be accompanied by lichenification and greasy, keratinous, seborrheic deposits, as well as seborrheic odor. Comedones on and surrounding the vulva greatly increase the index of suspicion for hyperestrogenism. Gynecomastia, enlarged nipples, and vulvar enlargement are common. Secondary pyoderma and *Malassezia* dermatitis may contribute to lichenification and hyperpigmentation in a minority of cases. Markedly abnormal estrous cycles characterized by prolonged and frequent estrus, plus false pregnancies, are seen in naturally occurring canine female hyperestrogenism.

Naturally occurring hyperestrogenism may be more frequent in English and French Bulldogs. This syndrome occurs more commonly in older female dogs; these also are more likely to be receiving estrogen supplementation for urinary incontinence.

Clinical differential diagnoses should include other endocrinopathies such as hypothyroidism and hyperadrenocorticism, plus follicular dysplasia. Diagnosis is based on history, clinical findings, laboratory evaluations for other endocrinopathies, histopathology and, occasionally, response to ovariohysterectomy or the termination of estrogen supplementation.



Fig. 19.21 Lateral thorax of the dog in Fig. 19.20, demonstrating symmetric alopecia and macular hyperpigmentation.

Biopsy site selection

It is important in all cases of suspected endocrine skin disease to obtain skin from areas of most advanced hair loss for optimal identification of atrophic follicular changes; skin from the junctional zone between normal and alopecic skin should be avoided. Multiple specimens should be taken and should include areas of lichenification or hyperpigmentation, if present.

Histopathology (Figures 19.22 and 19.23)

Canine female hyperestrogenism resembles Sertoli cell tumor-associated skin disease in male dogs. The epider-

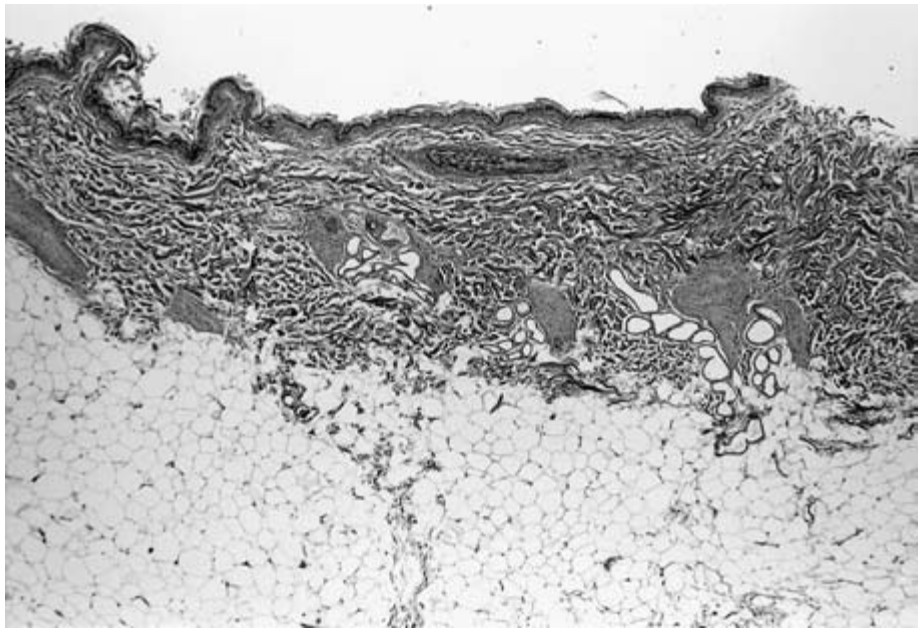


Fig. 19.22 Canine female hyperestrogenism. Diffuse follicular atrophy of hairless telogen type is present. Note normal thickness of epidermis.

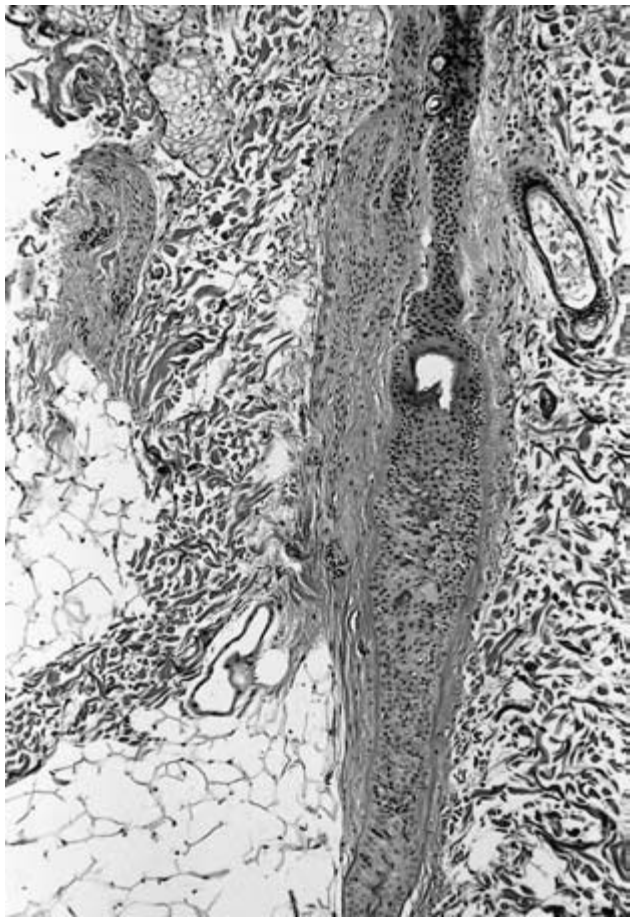


Fig. 19.23 Higher magnification of canine female hyperestrogenism demonstrating follicular atrophy.

mis and superficial follicular epithelium may be moderately acanthotic to slightly atrophic, but are often normal. Acanthosis may be a more prominent feature of naturally occurring hyperestrogenism. Hyperpigmentation may be present and is characterized by deposition of pigment at all viable levels of the epidermis.

Follicles are in growth cycle arrest; hairless telogen follicles predominate. True follicular atrophy, as seen in hyperadrenocorticism, is variable and may be absent. Flame follicles (see introduction, p. 480) are rare, but may be featured in affected dogs of plush-coated breeds. Some cases have mixed inflammation, including neutrophils, lymphocytes, histiocytes, eosinophils, and plasma cells. This inflammation may reflect the presence of secondary pyoderma; in some cases folliculitis is identified (see Chapter 16).

Differentiation of canine female hyperestrogenism from other endocrine alopecias, particularly hypothyroidism, is problematic. Canine female hyperestrogenism is rare, but should be considered in intact females or those known to be on estrogen supplementation.

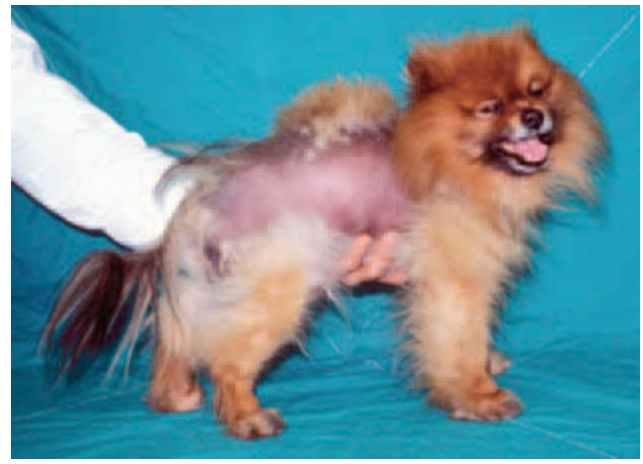


Fig. 19.24 Alopecia X in a male Pomeranian. Note bilaterally symmetric alopecia with hyperpigmentation. The head and distal extremities are spared.



Fig. 19.25 Closer view of the dog in Fig. 19.24. Note 'islands' of normally haired skin within the regions of alopecia and hyperpigmentation.

ALOPECIA X

(Synonyms: adrenal sex hormone imbalance, follicular dysfunction of plush-coated dogs, adrenal hyperplasia-like syndrome, growth hormone/castration-responsive dermatosis)

Clinical features (Figures 19.24 and 19.25)

Alopecia X is an uncommon canine skin disease with distinct breed predilections characterized by progressive, markedly bilaterally symmetric, noninflammatory alopecia with hyperpigmentation. Strong breed predilections suggest heritability. The term, 'alopecia X' was proposed by Olivry in an attempt to underscore that putative endocrine etiologies had not been proven (Olivry, T., per-

sonal communication, 1996). In the past, clinical response to growth hormone supplementation coupled with abnormal growth hormone response test results led to the use of the term 'hyposomatotropism'. However, frequent anomalous growth hormone response test results, lack of response to growth hormone, and response to castration indicate that true hyposomatotropism is likely not present. Some dogs that have initially responded to growth hormone therapy have recrudesced and then responded to castration. Adding to the confusion, mitotane, a derivative of the insecticide DDT that causes necrosis and atrophy of the adrenal cortex and is used for the management of canine Cushing's disease, can cause hair regrowth in dogs with alopecia X, suggesting a role for adrenal hormones. Further, the inflammation created by skin biopsy, trauma, or sunburn is known to cause local regrowth of hair.

Studies by Schmeitzel and Lothrop (1990) indicated that the syndrome, at least in Pomeranians, might be caused by disregulation of adrenal hormone synthesis resulting in adrenal hyperprogestinism and hyperandrogenism, similar to congenital adrenal hyperplasia in humans. It was hypothesized that affected Pomeranians might have a nonclassic, late-onset 21-hydroxylase deficiency leading to progestin and androgen excess at the onset of puberty. Interestingly, clinically unaffected Pomeranians have similar hormonal abnormalities; Schmeitzel and Lothrop (1990) speculated that unaffected Pomeranians have a cryptic form of the same enzyme deficiency. In humans, nonclassic late-onset 21-hydroxylase deficiency and the cryptic form of the enzyme deficiency also are biochemically indistinguishable, despite clinical differentiating features (Schmeitzel & Lothrop, 1990). A recent larger retrospective study examined levels of sex hormones and their intermediates in dogs suspected of having 'alopecia X', but discovered no consistent hormonal abnormality that could explain the alopecia in these dogs (Frank et al., 2003). The authors suspect that this disorder may, in fact, be hormonal, but may derive from abnormalities in local estrogen or other hormone receptors at the level of the hair follicle.

Alopecia X is a slowly progressive disease. Commonly, the initial clinical feature is bilaterally symmetric alopecia originating in frictional areas beneath a collar, on the caudal thighs, or in the perineum. Early lesions may be subtle. Primary hairs are lost, followed by a variable loss of secondary hairs. Lack of hair regrowth after clipping may be noted before frank alopecia. Hyperpigmentation usually develops concomitantly with alopecia in the affected areas, but may be absent, especially in white Poodles. Alopecia and hyperpigmentation gradually progress, resulting in a striking pattern of nearly complete alopecia bordered by normal adjacent hairs. End-stage disease may result in nearly total alopecia of the trunk, neck and proximal legs, sparing the head, distal legs, and distal tail. Islands of apparently normal haircoat and underlying skin occasionally may be present on the thorax. Less commonly, a sparse, wooly coat composed of poor quality secondary hairs remains. Hair may regrow focally at the sites of skin scrapings, biopsy, focal trauma, sunburn, or other inflammatory processes. Affected dogs are otherwise healthy; all available evidence indicates that alopecia X is a cosmetic disease only.

Marked breed predilections have been noted for the Pomeranian, Keeshond, Chow Chow, and Samoyed. Related crossbreeds also may be affected. The syndrome is seen both in male and female dogs, but the preponderance of dogs seen by the authors have been male. Most affected dogs develop alopecia X between 9 months and 2 years of age, often around the onset of puberty. However, dogs as old as 12 years at initial onset of alopecia have been seen. Since clinical signs of alopecia X are more common in Pomeranians bred by successful breeders emphasizing 'plush-coated' dogs, current breeding plans actually may be accentuating the problem (Schmeitzel, L.P., personal communication, 1990).

Clinical differential diagnoses should include endocrinopathies such as hypothyroidism, hyperadrenocorticism, and Sertoli cell tumor-associated skin disease, as well as follicular dysplasia. Breed predilections should increase the index of suspicion. Endocrinologic function tests, serum biochemical profiles, history, clinical course of the alopecia, and histopathology may be helpful in differentiating among these diseases.

Biopsy site selection

It is important in all cases of suspected endocrine disease to obtain skin from areas of most advanced hair loss for optimal identification of atrophic follicular changes. Skin from the junctional zone between normal and alopecic skin should be avoided. Multiple specimens should be obtained.

Histopathology (Figures 19.26 through 19.28)

The epidermis and superficial follicular epithelium generally are of normal thickness; slight atrophy or slight acanthosis may be present. Epidermal hyperpigmentation usually is evident and is characterized by accumulation of pigment in all viable layers of the epidermis.

Hair follicles are diffusely in hair cycle arrest. Telogen hair follicles have prominent tricholemmal keratin in a brush-like pattern and often retain their hair shafts (haired telogen). These follicles do not diverge morphologically from normal telogen follicles of plush-coated dogs. Interspersed are striking 'flame follicles' which may sometimes be diffuse within a biopsy specimen. Interme-

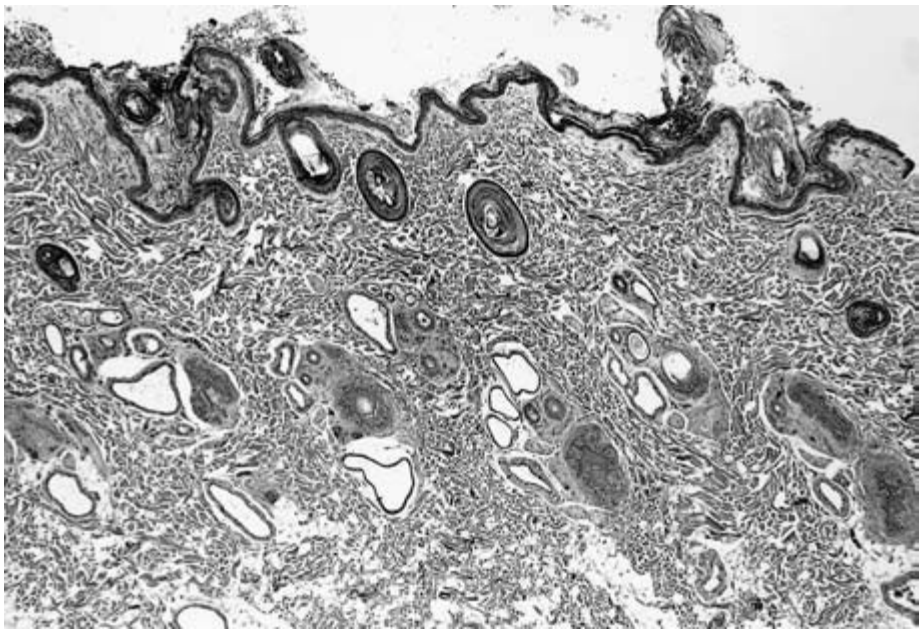


Fig. 19.26 Alopecia X. Diffuse follicular atrophy of catagen type predominates. The epidermis is normal.

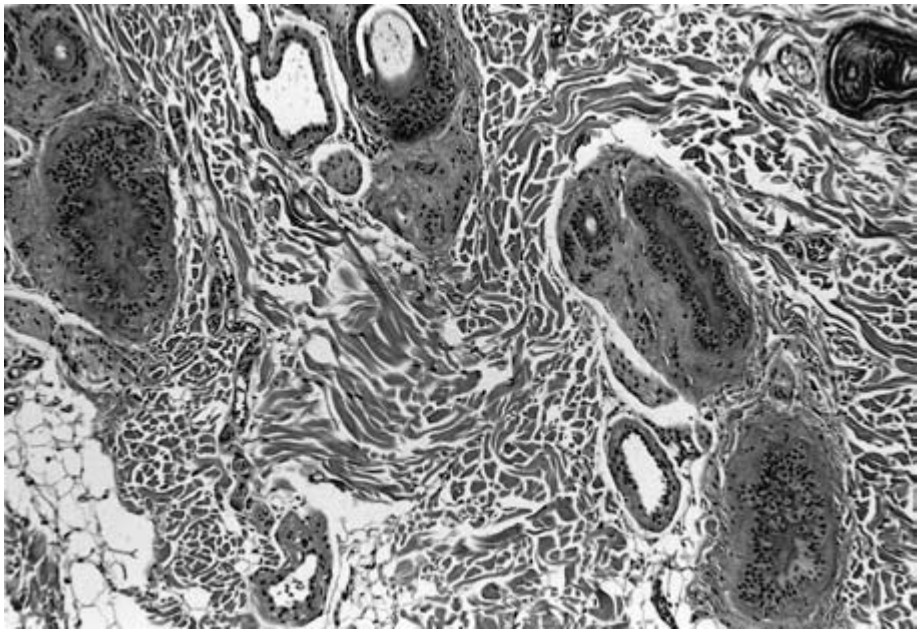


Fig. 19.27 Higher magnification of Fig. 19.26. Arrested hairless telogen follicles demonstrate prominent tricholemmal keratin in a brush-like pattern and are developing the appearance of flame follicles (see Fig. 19.28.).

diate forms (early flame follicles) are common. Flame follicles (see introduction, p. 480) are characterized by large spikes of fused keratin which appear to protrude through the outer root sheath to the vitreous layer, creating a fiery effect. Hair shafts are often, but not exclusively, absent from flame follicles. Flame follicles should not be confused with normal resting telogen hair follicles of plush-coated breeds, which are characterized by prominent tricholemmal keratin and retained hair shafts, as in a recent report (Ordeix et al., 2002).

There also often are dysplastic-appearing follicles characterized by irregular or wavy outer contours. A recent study has shown that occasional follicular dysplasia is observed in the setting of endocrine follicular disorders (Rothstein et al., 1998). Hair follicles are generally of normal size for the stage of the cycle, but may be atrophic in long-standing cases. Sebaceous glands are normal.

When hair growth cycle arrest is observed, all other endocrine-related alopecias must be considered. Among the endocrine alopecias however, prominent and diffuse flame follicle production is most compatible with alopecia X. This may be a self-fulfilling observation, since alopecia X is most common in plush-coated breeds. Flame follicles may be a manifestation of an abnormal hair



Fig. 19.28 High magnification of typical flame follicles. The keratin of this exaggerated telogen follicle is extending through the wall in a fiery pattern.

growth cycle in plush-coated dogs, regardless of type of endocrine or metabolic stimulus. Thus, dogs such as the Chow Chow or Pomeranian can develop flame follicles as a result of other atrophic influences on the hair follicle, such as hyperestrogenism or hyperadrenocorticism. Differentiation amongst endocrine alopecia affecting plush-coated breeds may be made from other features such as acanthosis and inflammation in hypothyroidism, and epidermal atrophy and marked reduction in size of follicles and sebaceous glands in hyperglucocorticoidism.

The prominent tricholemmal keratin of resting telogen hair follicles, as seen in postclipping alopecia (and a normal finding in random biopsy of normal plush-coated dogs), should not be confused with true flame follicle formation. In postclipping alopecia, hair shafts are retained in contrast to most flame follicles; further, the tricholemmal keratin is not as exaggerated as in the flame follicle. The histologic features of follicular dysplasia of the Siberian Husky are very similar to those of alopecia X (see Chapter 20); the significance of this finding is unknown.



Fig. 19.29 Postclipping alopecia in a Keeshond. Hair regrowth has not commenced 4 months after the dorsal lumbosacral area was clipped.

POSTCLIPPING ALOPECIA

Clinical features (Figure 19.29)

Postclipping alopecia is a relatively common syndrome of the dog characterized by lack of hair regrowth following close clipping. Marked breed predilections (sled-dog breeds and other plush-coated breeds) suggest genetic predisposition. Dogs of plush-coated and other breeds commonly have prolonged telogen with retention of hairs (haired telogen); this may be an energy-saving feature to retain the coat without frequent shedding (Credille et al., 2001). In postclipping alopecia, the affected follicles are in synchronous haired telogen; however, these follicles are otherwise normal. This synchrony of haired telogen was not observed by one author (E.J.W.) in the biopsy specimens of 50 plush-coated dogs with non-alopecic conditions. Thus, it is possible that clipping creates synchrony; perhaps by alterations in cutaneous thermoregulation as a result of denuding. Postclipping alopecia is most frequently a sequel to close clipping for venipuncture, surgery, mat removal, wound management, or diagnostic procedures such as myelography.

Clinical features include prolonged lack of hair regrowth after close clipping. The site of clipping looks recently clipped, even months after clipping has occurred. Alopecia usually remains complete, but occasionally a few primary hairs (guard hairs) may regrow. Secondary hair (undercoat) regrowth is not seen. Mild scaling may be seen occasionally. The syndrome occurs most often on well-haired body regions such as the dorsal or lateral trunk, the neck, or the legs. Haircoat may not return for as long as 6 to 12 months after clipping. Newly regrown hair may initially be darker in breeds with 'pointed' haircoat coloring (acromelanism) such as the Siberian Husky and the Alaskan Malamute.

Postclipping alopecia is seen predominantly and most dramatically in plush-coated breeds such as the Siberian Husky, Alaskan Malamute, Samoyed, American Eskimo, Chow Chow, Keeshond, and Pomeranian. The syndrome may occur sporadically in any breed. Age or sex predilections have not been noted.

Clinical differential diagnoses should include failure of hair regrowth after clipping in the context of underlying iatrogenic or endogenous hyperglucocorticoidism, therapy with cytotoxic drugs, hypothyroidism, and alopecia X. Differentiation is based on history, breed affected, supporting clinical or biochemical evidence of specific underlying diseases, and compatible histopathology.

Biopsy site selection

Multiple biopsy specimens should be selected from regions of complete alopecia. Adjacent normal skin can be marked as normal and sampled separately as a comparison.

Histopathology (Figures 19.30 and 19.31)

The epidermis and dermis are usually normal; mild hyperkeratosis may be present. Hair follicles are of normal size, but are diffusely in telogen phase. Hair shafts are retained throughout (haired telogen). Pronounced tricholemmal keratinization may be prominent, as expected in the plush-coated hair follicles, but true flame follicles (see introduction, p. 480) are rare. Small clusters of secondary hair germ may be present at the base of some of the follicles. Occasionally, these are curved, resembling a small blunt 'hook'.

Differential diagnosis is problematic based on histopathology alone, since 'lesions' (other than synchronous haired telogen) do not occur. The diffuse absence of anagen hair follicles is useful diagnostically, but clinical correlation with clipping is required. Alopecia X features striking flame follicles, as well as variable follicular distortion and atrophy. Clinical lesions and history should help to delineate this disorder from alopecia X; however, early signs of the latter may include poor hair regrowth after clipping.

FELINE PARANEOPLASTIC ALOPECIA

(Synonym: pancreatic paraneoplastic alopecia)

Clinical features (Figures 19.32 through 19.34)

Feline paraneoplastic alopecia is a rare and highly characteristic skin disease that is a marker for underlying visceral, usually pancreatic, neoplasia. This syndrome conforms to the criteria recently established for a para-

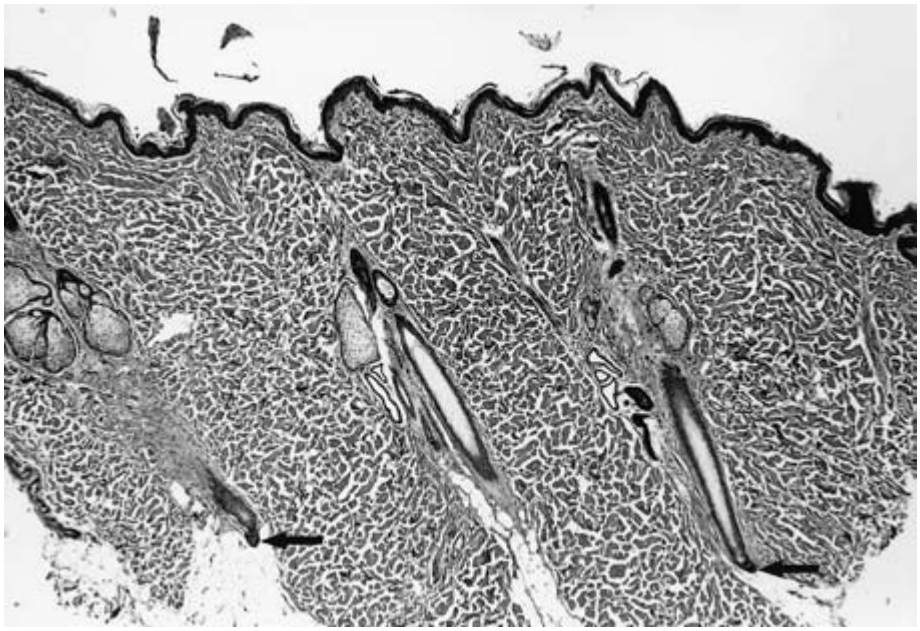


Fig. 19.30 Postclipping alopecia in a dog. Hair follicles are in haired telogen phase. Note small clusters of secondary hair germ at the base of some follicles (arrows).

neoplastic syndrome, i.e. the dermatosis must occur after the development of a malignant tumor, and the skin disease and the tumor must follow a parallel course (McLean & Haynes, 2003). Resolution of feline paraneoplastic alopecia was noted in conjunction with partial pancreatectomy in two cats (Tasker et al., 1999; Scott et al., 2001).

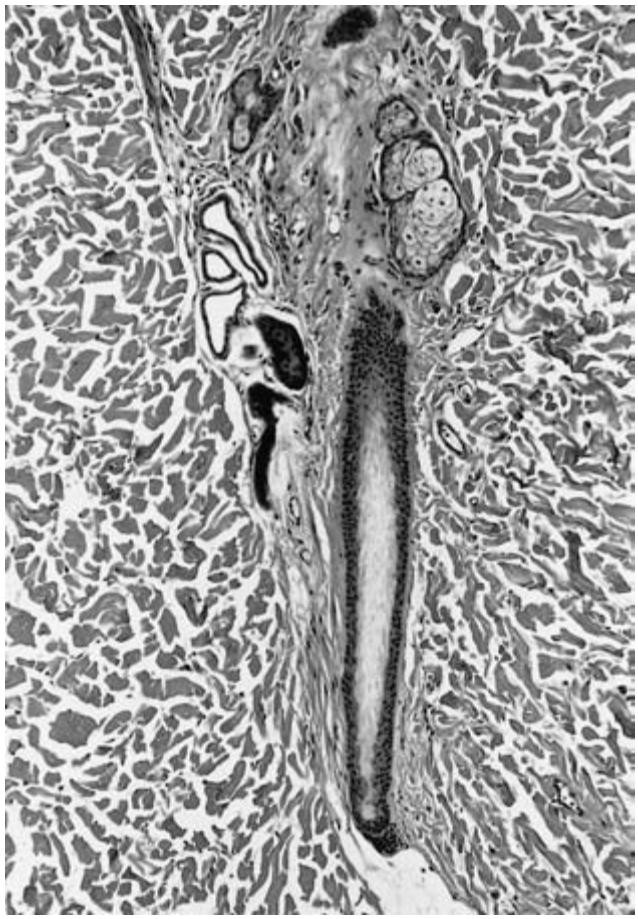


Fig. 19.31 Higher magnification of Fig. 19.30 demonstrating haired telogen follicle. Note slight 'hook' at base.

The great majority of published cases have had neoplasia of pancreatic origin (Brooks et al., 1994; Pascal et al., 1997; Godfrey, 1998; Tasker et al., 1999; Heripret, 2000; Scott et al., 2001; Mauldin et al., 2002). Often, metastatic disease of the liver is present at the time of diagnosis. Although bile duct carcinoma is reported as having induced the syndrome in two cats (Pascal et al., 1997; Scott et al., 2001), the seeming high specificity of induction by pancreatic neoplasia in all other cases calls into question the diagnosis of the triggering tumor in this minority.

Precipitous alopecia is the prime presenting clinical feature. Alopecia usually commences on the ventral abdomen, thorax, and legs, and then generalizes. The pinnae and periorbital regions also may be affected preferentially in some cases. In some cats, excessive grooming also contributes to the alopecia. Remaining hair epilates easily. The regions of alopecia have a peculiar and highly distinctive smooth, shiny, and glistening appearance, even in areas that have not been groomed. There may be adherent crusts or scale in cats that have not groomed. The pawpads are dry, scaly, and shiny, with multiple, concentric, circular rings of scale that give a striking targetoid appearance. Secondary *Malassezia* dermatitis may occur.

Cats commonly excessively self-groom. Some cats experience pawpad pain. Signs of underlying visceral neoplasia include lethargy, inappetence, and weight loss. Constitutional signs may develop in concert with skin disease or may precede it. Lesions generally evolve rapidly over a course of 1 to 3 months. Metastasis of the tumor to the liver or lungs has generally occurred by the time of diagnosis of the skin disease. Most cats die or are euthanized within a month of diagnosis.

Feline paraneoplastic alopecia occurs in older cats. Breed or sex predilections are not available. Clinical differential diagnoses are few, as the syndrome is highly visually distinctive. Endogenous or iatrogenic hyperglucocorticoidism with extensive alopecia may resemble feline paraneoplastic alopecia. Pawpad lesions may be similar to superficial necrolytic dermatitis (SND);



Fig. 19.32 Feline paraneoplastic alopecia in an aged cat. Striking hair loss is evident in the axillae and the ventral abdomen. (From Pascal, A., Olivry, T., Gross, T.L. et al. (1997) Paraneoplastic alopecia associated with internal malignancies in the cat. *Vet Dermatol* **8**, 47–52. Reprinted with permission.)



Fig. 19.33 Closer view of the axilla of the cat in Fig. 19.33. The region of alopecia has a peculiar and distinctive smooth, shiny, glistening appearance. (From Pascal, A., Olivry, T., Gross, T.L. et al. (1997) Paraneoplastic alopecia associated with internal malignancies in the cat. *Vet Dermatol* **8**, 47–52. Reprinted with permission.)



Fig. 19.34 Ventral paw of the cat in Fig. 19.32. Affected pawpads have a dry, scaly, shiny appearance with distinctive targetoid, concentric circular rings of scale. (Photograph courtesy A. Pascal; case material University of California, Davis.)

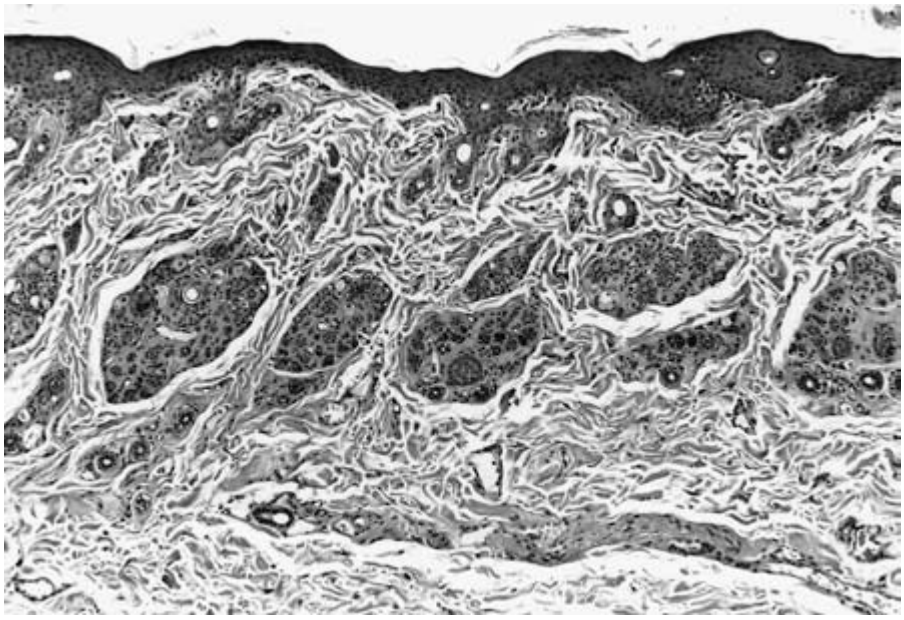


Fig. 19.35 Feline paraneoplastic alopecia. Note contrast between prominent acanthosis and severe diffuse follicular atrophy of hairless telogen type.

however SND is not extensively alopecic. Superficial necrolytic dermatitis has been diagnosed in conjunction with paraneoplastic alopecia in one cat (see Chapter 4). Surprisingly, routine hematology and serum biochemical profiles do not aid in diagnosis. Radiography rarely is useful, but ultrasonography or computed tomography (CT) scanning are of diagnostic benefit. Histopathology confirms the diagnosis.

Biopsy site selection

Regions of maximal alopecia with the characteristic shiny surface should be sampled for histopathology. Pawpad biopsy is not recommended since the lesions are painful, and biopsy results will not alter the grave prognosis.

Histopathology (Figures 19.35 through 19.37)

There is moderate to severe acanthosis. The stratum corneum often is absent, but when found is either diffusely parakeratotic or less often orthokeratotic. The cornified layer is often seen lifting from the underlying epidermal surface. Affected skin of the pawpads may have a fractured or flaky keratin layer. In some cases, erosion and neutrophilic scale/crusting are prominent. There may

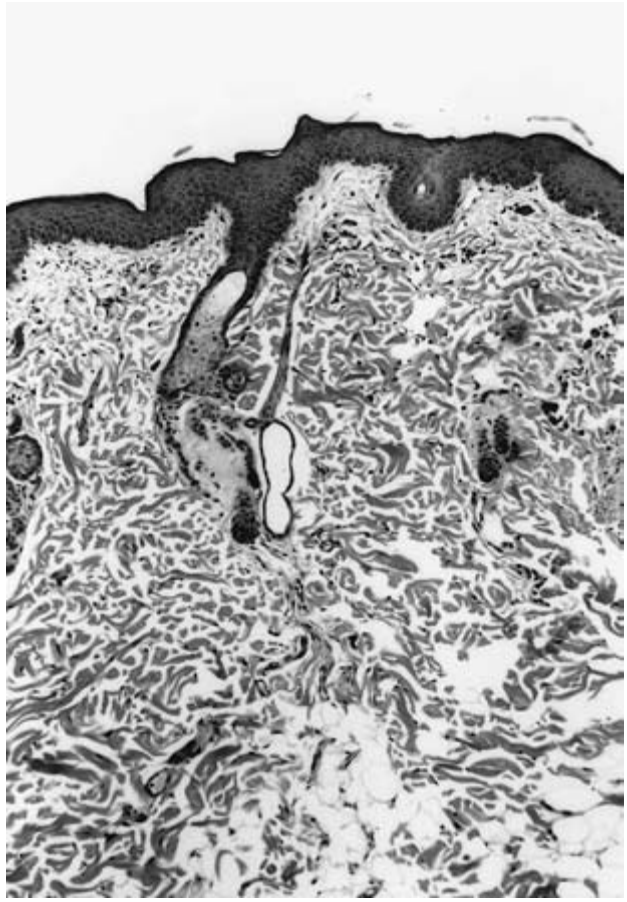


Fig. 19.36 Higher magnification of paraneoplastic alopecia. A normal sebaceous gland lies adjacent to highly attenuated follicles. Note acanthosis and absence of a distinct keratin layer.

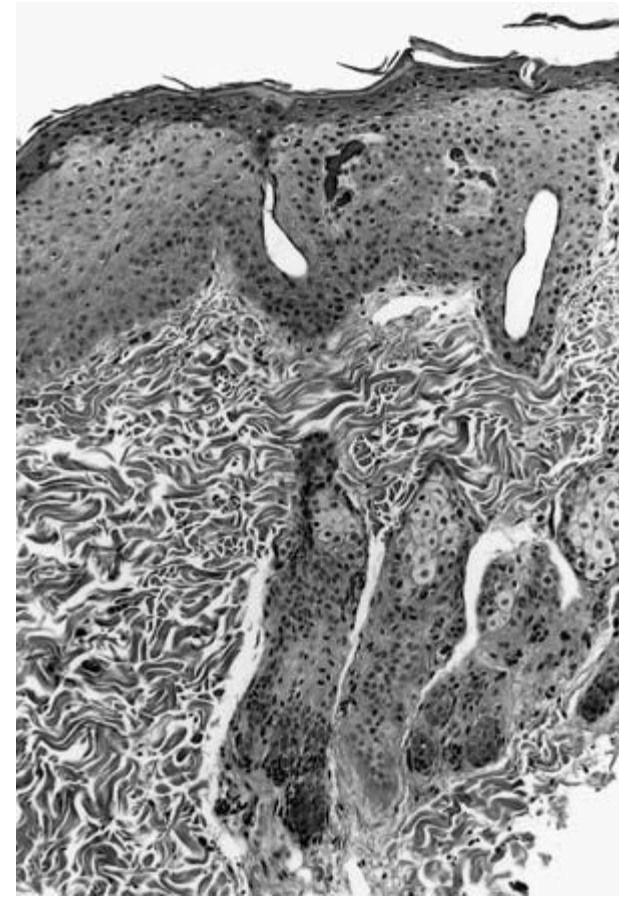


Fig. 19.37 Paraneoplastic alopecia demonstrating parakeratosis and severe acanthosis; note normal sebaceous glands and atrophic hair follicles.

be secondary colonization by *Malassezia* in conjunction with orthokeratotic hyperkeratosis; this association also has been reported (Godfrey, 1998; Mauldin et al., 2002).

Hair follicles are diffusely in telogen and appear miniaturized. Superficial follicles are occasionally plugged with parakeratotic debris. Petite basophilic clusters of secondary hair germ frequently are present at the base of these attenuated follicles. Sebaceous glands usually are unaffected and may appear large in relation to the severe follicular attenuation. Sebaceous atrophy is occasionally observed.

Dermal inflammation is absent to moderate, and is more intense when occurring in conjunction with erosion and crusting. Inflammatory cells include lymphocytes, histiocytes, and fewer neutrophils; the latter are most prominent in areas of erosion and crusting. Mast cells are often numerous.

The principal differential diagnosis for paraneoplastic alopecia is hyperglucocorticoidism. In contrast to hyperglucocorticoidism, paraneoplastic alopecia has pronounced acanthosis, and often features parakeratosis in lesions that have not had this layer removed by licking. Hair follicles are similarly atrophic, and both conditions feature small basophilic clusters of secondary hair germ; however, increased tricholemmal keratin is a consistent feature of hyperadrenocorticism, but not of paraneoplastic alopecia. Sebaceous glands are normal in paraneoplastic alopecia, but may be atrophic in feline hyperglucocorticoidism.

ACQUIRED PATTERN ALOPECIA

(Synonyms: canine pinnal alopecia, pattern baldness, Dachshund pattern baldness)

Clinical features (Figures 19.38 and 19.39)

Acquired pattern alopecia is a relatively common canine skin disease characterized by partially bilaterally symmetric, gradual hair loss. Specific breed predilections



Fig. 19.38 Acquired pattern alopecia in a Dachshund. Note that the pinnae are almost completely alopecic.



Fig. 19.39 Caudal region of the dog in Fig. 19.38. Hair has been lost in a partially bilaterally symmetric pattern.

coupled with both clinical and histopathologic similarities to pattern baldness in humans suggests a genetic basis. Selection for extremely fine haircoats in these breeds may predispose them to this presumptive genetic alopecia (Rest, J., personal communication, 2004). In men, pattern hair loss (male pattern baldness) is hereditary, androgen dependent, and specifically related to dihydrotestosterone metabolism and receptors; the role of androgens is less clear in female pattern hair loss (Olsen, 2003). Similar hormonal associations have not been reported in dogs.

The principal clinical feature of pattern baldness in humans is slowly progressive thinning of the scalp hair coupled with a conversion of normal primary hairs to diminutive, fine vellus hairs (miniaturized hairs that resemble the fine, nonpigmented hair of neonates) (Olsen, 2003). Similarly, the principal clinical feature of acquired pattern alopecia in dogs is slowly progressive thinning of the haircoat in affected areas with conversion of normal primary hairs to vellus-like hairs. Inflammation is not seen clinically. Some hyperpigmentation and mild scaling may occur, especially in long-standing cases. The pinnae and skin just caudal to the pinnae are affected most frequently, but similar hair loss also may be noted on the ventral neck, chest, and abdomen, perianally, and affecting the caudal thighs.

Acquired pattern alopecia is seen most commonly in Dachshunds, but the syndrome also has been identified in a variety of other small dogs with fine haircoats including the Boston Terrier, Chihuahua, Whippet, and Italian Greyhound. The syndrome generally develops in dogs less than 1 year of age. Sex predilections have not been noted.

Acquired pattern alopecia must be differentiated from endocrinopathies such as hypothyroidism, iatrogenic or endogenous hyperadrenocorticism, and sex hormone-associated alopecia. Occurrence in Dachshunds or other small breeds with a lack of other clinical signs should increase the index of suspicion. Differentiation is accomplished by endocrinologic testing and histopathology. Pinnal hair loss also is seen in Dachshunds with canine ear margin seborrhea (see Chapter 8). However, scaling and crusting is the predominant clinical feature of ear margin seborrhea and alopecia is mostly marginal.

Biopsy site selection

Areas of complete alopecia should be selected for biopsy and an additional specimen should be obtained from as normal an area as possible for comparison. This selection technique will allow detection of potentially subtle follicular changes in size and density by comparison with a normal control. If hair loss is present on regions besides the pinnae, sites other than the pinnae should be sampled as pinnal biopsy commonly leads to damaged cartilage, prominent scarring, and distortion.

Histopathology (Figures 19.40 and 19.41)

The epidermis and dermis are normal. Hair follicles are characterized by moderate to occasionally severe diminution in size; overall numbers of adnexal units are not reduced. Follicles are both moderately shorter and thinner than normal, and residual hair shafts present are fine. There is no follicular distortion or irregularity of contour, and arrest of the hair growth cycle is not seen. Small

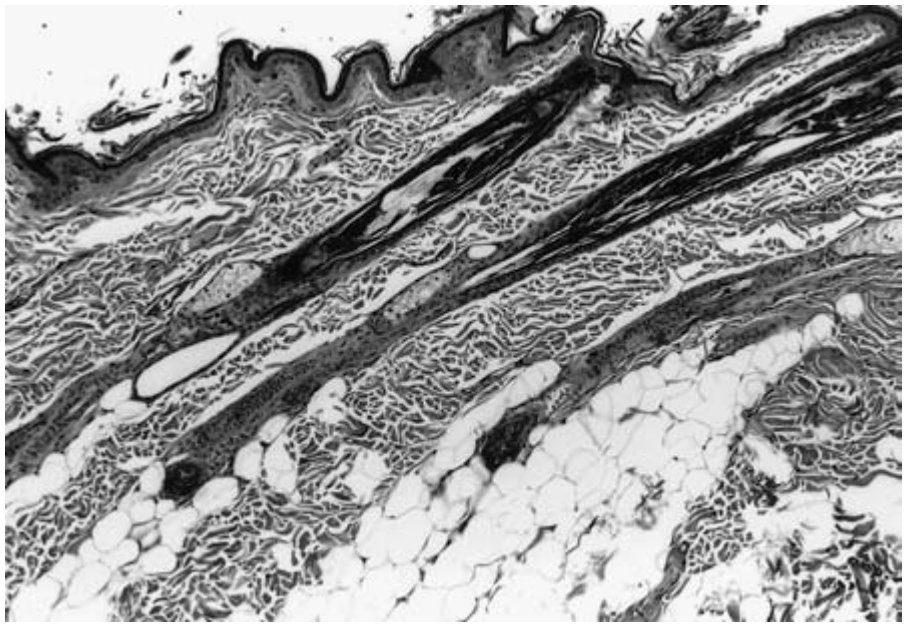


Fig. 19.40 Acquired pattern alopecia in a Dachshund. Note diminution of hair follicles and petite anagen hair bulbs.

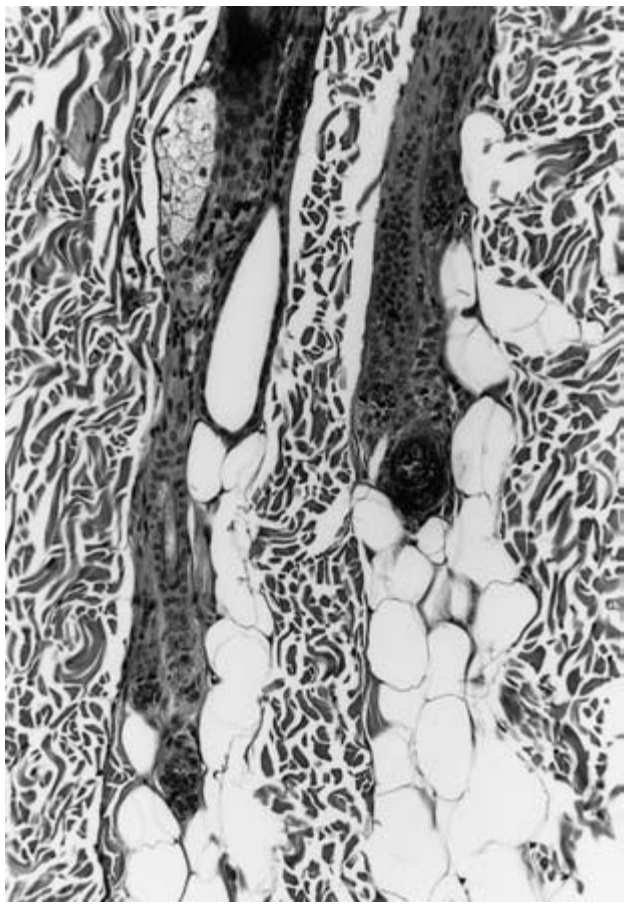


Fig. 19.41 Higher magnification of Fig. 19.40. Note petite anagen hair bulbs.

anagen hair follicles with petite hair bulbs generally are present.

The characteristic histopathologic changes of acquired pattern alopecia should not be confused with endocrine alopecia. Hair follicles are small in acquired pattern alopecia, but are not in growth cycle arrest, as seen in endocrine alopecia. Both petite hair bulbs and retention of fine hair shafts are not features of canine endocrine alopecia. Other specific histologic features of endocrine alopecia, such as epidermal atrophy and comedones in hyperglucocorticoidism, and acanthosis and mucinosis (myxedema) of hypothyroidism, will also allow differentiation.

ISCHEMIC DERMATOPATHY/CANINE DERMATOMYOSITIS

Clinical features (Figures 19.42 and 19.43)

See Chapters 3, 10, and 21.

Biopsy site selection

See Chapter 3, 10, and 21.

Histopathology (Figures 19.44 through 19.46)

Ischemic follicular atrophy occurs most prominently in ischemic dermatopathy/canine dermatomyositis (see Chapter 3) and postrabies vaccination panniculitis (see Chapter 21) and may be most severe in the latter condition. Both of these feature cell poor vasculitis which is



Fig. 19.42 Severe canine dermatomyositis in a Shetland Sheepdog puppy. Note extensive alopecia, erythema, and scaling affecting the face, paws, and tail.



Fig. 19.43 Closer view of the foreleg of the puppy shown in Fig. 19.42. Erythema, alopecia, scaling, and crusted erosions are more severe over bony prominences.

suspected to be the principal cause of the marked adnexal atrophy of these conditions (see Chapter 10). Epidermal and dermal lesions of ischemic dermatopathy have been described in detail (see Chapter 3) and include basal cell degeneration and dermal–epidermal vesiculation, with homogenization and 'smudging' (rarefaction) of dermal collagen. There also is prominent nodular lymphocytic panniculitis in postrabies vaccination panniculitis.

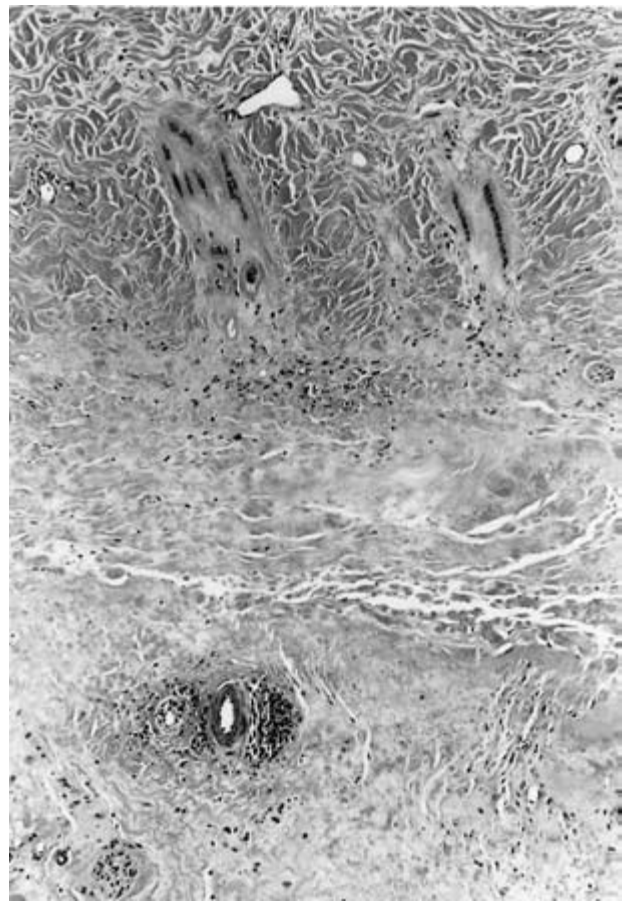


Fig. 19.44 Severe follicular atrophy overlying postrabies vaccination panniculitis. Panniculitis is mild in this view. Hair follicles are remarkably attenuated; note ischemic pallor and smudged appearance of collagen.

Basal cells of the outer root sheath hair follicle have variable and sometimes pronounced vacuolation and apoptosis to the level of the isthmus. This follicular basal cell degeneration is more consistently observed than basal cell lesions of the epidermis (see Chapter 3). Hair follicles typically are moderately to severely atrophic or 'faded.' There is telogen predominance of affected follicles. Secondary hair follicles are often not apparent. Primary hair follicles are devoid of hair shafts and are often small, narrow, and short. In some cases, only a thin shaft of external root sheath remains at the site of a previous follicle. Distortion of the hair follicle to a wavy configuration may be seen. There may be pigmentary incontinence around hair bulbs as well as diffuse distribution of melanophages in the surrounding dermis. Perifollicular mucin may occur. Prominence of the connective tissue of the external root sheath plus smudging and homogenization of surrounding collagen may give the false impression of perifollicular fibrosis; this connective tissue



Fig. 19.45 Canine dermatomyositis with diffuse follicular atrophy accompanied by scant inflammation. Prominent perifollicular pallor and smudging of collagen should not be confused with fibrosis.

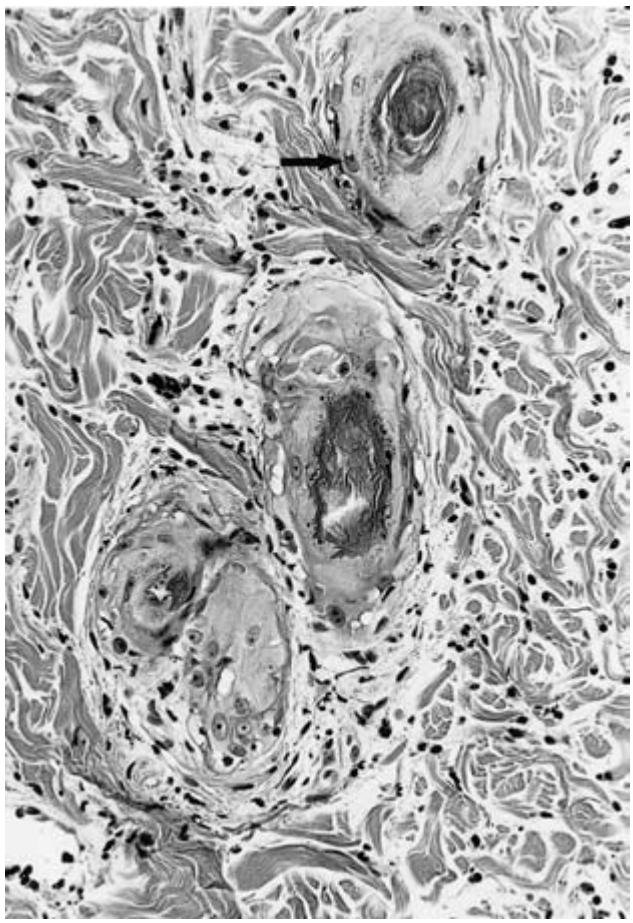


Fig. 19.46 Canine dermatomyositis. Atrophic follicles are surrounded by lymphocytes and macrophages. Note vacuolar degeneration and apoptosis of outer follicular cells (arrow).

layer may appear smudged, pale, or homogenized. Rarely, hair follicles are surrounded by or completely replaced by true fibrosis.

Follicular atrophy similar to the type observed in ischemic dermatopathy and postrabies vaccination panniculitis (see Chapter 21) occasionally has been observed overlying subcutaneous injection reactions from other types of vaccine products or other severe inflammatory lesions of the panniculus (see Chapter 21). Inflammation of the panniculus that disrupts vascular integrity, through immunologic or other mechanisms, may produce morphologically similar ischemic follicular atrophy.

Differential diagnoses for ischemic follicular atrophy are few as lesions are unique and characteristic. Canine traction alopecia shows follicular atrophy and distortion, but may have prominent perifollicular fibrosis, a feature that usually is absent from ischemic follicular atrophy. Accompanying lesions of cell poor vasculopathy (see Chapter 10) and ischemic changes of the dermis (homogenization and 'smudging', see Chapter 3) are not features of traction alopecia.

POST-TRAUMATIC ALOPECIA

Clinical features

Post-traumatic alopecia is a recently recognized syndrome in cats (Noli, 1999; Declercq, 2004). Alopecia occurred within several weeks after pelvic fracture in all four cats reported. The proposed pathogenesis is shearing trauma to highly elastic skin, resulting in partial separation from its underlying blood supply (Declercq, 2004). This type

of trauma may produce changes similar to other ischemic events such as traction alopecia (see p. 507) and ischemic dermatopathy (see Chapter 3). In contrast to those entities which involve low grade impedance of vascular sustenance over time, post-traumatic ischemia is a sudden event and leads to more exaggerated changes accompanied by fibrosis (scarring alopecia). Similar alopecic lesions have not been reported in humans which is likely due to the relative lack of pelage in that species.

As reported by Declercq (2004), cats develop well-demarcated alopecia affecting the lower back. The hair is easily epilated from the margins of affected areas. Hair loss may be defined as 'sudden' by the owners. Newly exposed skin is shiny, and there may be accompanying erosions and crusts. Secondary hyperpigmentation may develop. Partial regrowth of hair at the borders may occur, but central areas of alopecia remain even after many months. Affected cats are otherwise normal.

Breed and sex predilections would not be expected. All four cats were 2 to 3 years of age; this may correlate with lack of experience in younger cats for which the vagaries of the outdoor urban life have not yet taken their toll and produced the wariness so natural to many members of this species.

Biopsy site selection

Specimens should be taken from the centers of alopecic foci. Areas of erosion and crusting should be sampled, if present.

Histopathology (Figures 19.47 and 19.48)

The epidermis is normal to mildly acanthotic; interestingly, the stratum corneum is thin to absent; remnants may flake from the surface. This loss of stratum corneum likely correlates with the shiny appearance reported (Declercq, 2004).

Hair follicles are atrophic, slightly distorted, and invariably in hairless telogen phase. There is a striking linear pattern of perifollicular fibrosis that extends from the superficial isthmus to the depth of the follicle. The arrector pili muscles extend at an angle into these linear fibrous bands and often merge imperceptibly. Sometimes only the follicular infundibulum remains, which ends abruptly at the linear band. Adnexal glands are usually lost; remnants may persist. There is also mild laminar subepidermal fibrosis. Similar laminar fibrosis may be seen at the junction of the dermis and superficial subcutis (panniculus); the latter may be the site of previous separation due to shearing forces. Large and small blood vessels may be surrounded by fibrosis, sometimes strikingly. This perivascular distribution suggests a response to previous vascular trauma. Inflammation is minimal and includes a few diffuse lymphocytes and histiocytes.

The panniculus demonstrates variable degeneration of adipocytes. Adipocytes are variably ruptured to form small cysts; the walls of these cysts appear slightly thickened and may be outlined by macrophages. Macrophages and lymphocytes are clustered among adipocytes. This change of adipocytes is reminiscent of 'lipomembranous change' that has been seen in the

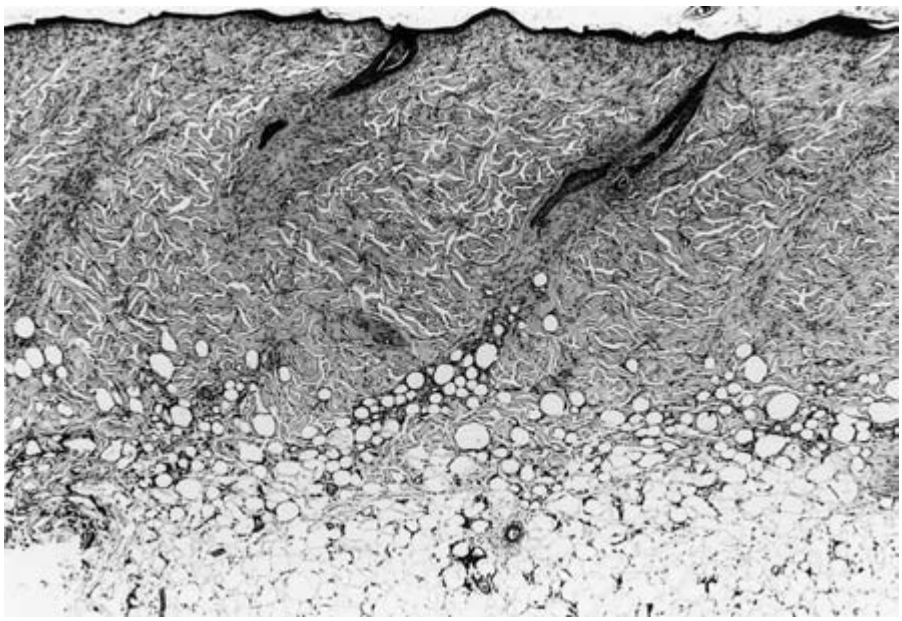


Fig. 19.47 Post-traumatic alopecia in a cat. Severe follicular atrophy is accompanied by linear fibrous bands. Note adipocyte degeneration. (Case material courtesy J. Declercq.)

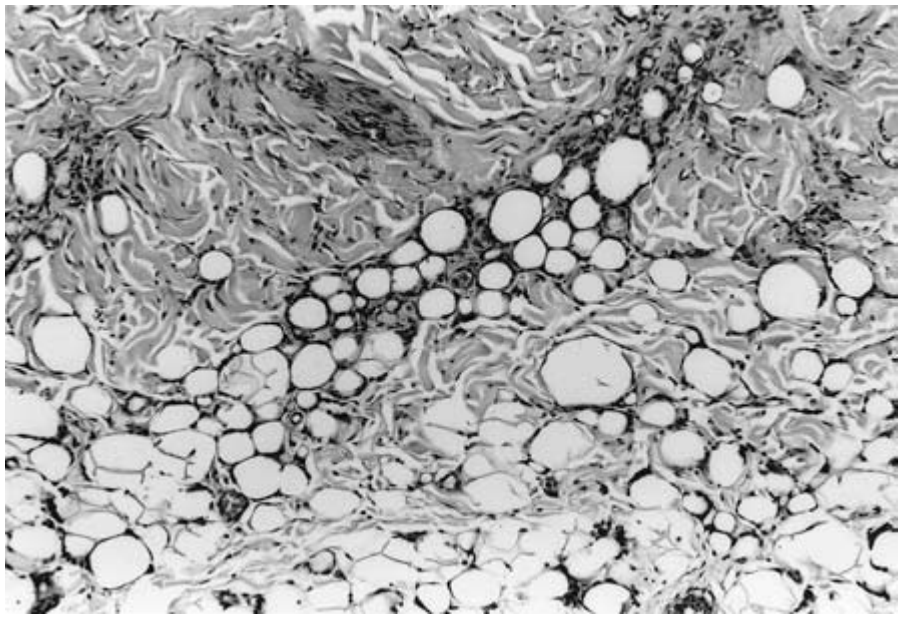


Fig. 19.48 Higher magnification of Fig. 19.47. Note lipomembranous-like change of adipose tissue.

context of ischemia in humans, including in the setting of dermatomyositis (Magro, C., personal communication, 2003). Similar changes have been observed occasionally by one author (T.L.G.) in ischemic dermatopathy/canine dermatomyositis.

Post-traumatic alopecia is visually unique. There may be similarities to ischemic dermatopathy/canine dermatomyositis and to traction alopecia. Post-traumatic alopecia does not feature ischemic dermal changes such as pallor and smudging as seen in ischemic dermatopathy. This may be because the ischemia of ischemic dermatopathy is microangiopathic (see Chapter 10) and therefore more gradual. Ischemic dermatopathy does not include laminar or prominent perivascular fibrosis. Traction alopecia has extreme follicular atrophy, as seen in post-traumatic alopecia, and may feature perifollicular fibrosis. However, the laminar and perivascular fibrosis is lacking in traction alopecia, and ischemic changes of the panniculus have not been observed.



Fig. 19.49 Canine traction alopecia on the temporal region of a Shih Tzu due to chronic tension from a rubber band. (Photograph courtesy A.M. Hargis; case material University of California, Davis.)

TRACTION ALOPECIA

(Synonym: mechanical alopecia)

Clinical features (Figure 19.49)

Traction alopecia is a rare mechanical hair loss associated with grooming procedures that repetitively utilize hair-retaining devices (such as rubber bands or barrettes). Traction alopecia in humans is believed to be due to interference with the blood supply to the hair root (Hantash & Schwartz, 2003). Traction alopecia in humans usually is reversible. Hair regrowth was not seen in dogs with traction alopecia (Rosenkrantz et al., 1989); this permanent type of hair loss is similar to that found in cicatricial alopecia (see Chapter 15). Rosenkrantz et al. (1989) theorized that the difference in prognosis between humans and dogs may be associated with anatomic differences in the perifollicular vascular bed of dogs leading to greater ischemia, coupled with more prolonged and more severe trauma, since dogs cannot communicate that undue hair tension is producing pain. Some of the hair loss seen in animals with traction alopecia also may reflect traumatic damage to hair during repeated removal and replacement of grooming devices. One author (P.J.I.) has seen defects in remaining hairs similar to trichorrhexis nodosa in humans. Trichorrhexis nodosa is a hair shaft defect characterized

by breaching of the cuticle and the separation and fraying of exposed cortical fibers, probably initiated by physical or chemical trauma (Olsen, 2003).

Complete, or almost complete, alopecia is seen in the affected area. Hair follicle ostia dilated with keratotic debris may be observed with a hand lens. Early in the course of damage, an erythematous plaque may be noted at the site of maximum tension. Mild scaling may be present.

The pattern of alopecia is contingent on the device used to apply tension to the hair. Circular rings of alopecia center on the site where the rubber band has entrapped the hair. The lesion may be 'doughnut shaped' with a central area of normal hair growth surrounded by a ring of alopecia, as rubber bands do not apply tension to the center of the ring. Linear bands of alopecia reflect barrette placement. Canine traction alopecia is seen primarily over the temporal region of the head, where devices are used either to keep hair out of the eyes or as decoration.

Alopecia in an unusual 'zebra pattern' may be seen in areas under hair mats in both dogs and cats (Declercq, J., personal communication, 2003); however, this alopecia was not comparable to traction alopecia histologically in the single case examined by one author (T.L.G.). Hair loss in these cases is undoubtedly mechanical, but may involve less severe tension and trauma than in traction alopecia.

Breed predilections correlate with long-haired dog breeds for which rubber bands and barrettes commonly are used. The syndrome is seen predominantly in the Poodle, Maltese, Yorkshire Terrier, Shih Tzu, and Bichon Frise. Recently, the syndrome was reported in an Old English Sheepdog (Ordeix et al., 2001). Age or sex predilections would not be expected.

Traction alopecia associated with grooming devices is visually distinctive. Usually there is historical correlation by the pet owner with the previous use of a rubber band or barrette. If historical information is not available, cicatricial alopecia, alopecia areata, pseudopelade, and other focal atrophic or dysplastic follicular diseases could mimic traction alopecia. Histopathology is useful both to confirm the diagnosis and to offer a prognosis for potential hair regrowth.

Biopsy site selection

Skin biopsy specimens should be obtained from regions of most pronounced and complete hair loss. Such specimens may be of prognostic as well as diagnostic value.

Histopathology (Figure 19.50)

The epidermis is normal. Superficial follicular keratosis is present. Hair follicles are typified by extreme diminution in size and are in exaggerated telogen phase, often characterized by reduction to a single cord of epithelium. There may be follicular drop-out; a thin cord of connective tissue ('stele', after Headington) may be all that remains to mark the location of previous follicles. Less severely atrophic follicles may have trichomalacia, characterized by distorted or fragmented hair shafts within amorphous tricholemmal keratin. The malacic hair shafts may be marked by clumps of melanin. Residual follicles may appear as small cysts. Sebaceous glands are also atrophic. Increased, dense fibrous connective tissue is present around and between atrophic follicles. In some cases, complete cicatricial alopecia is present, characterized by laminar bands of connective tissue which replace all normal dermal structures (see Chapter 15).

Mild mixed mononuclear inflammation may be seen, and melanophages may be present at the site of previous follicles. Occasionally, there is more severe chronic inflammation composed primarily of foamy macrophages and fewer lymphocytes and neutrophils. There may be



Fig. 19.50 Canine traction alopecia. Severe follicular attenuation has reduced deep follicles to a single cord of epithelium. Note mild follicular keratosis.

free lipid vacuoles or 'lipocysts' in the dermis. These changes suggest that entrapment and destruction of sebaceous and apocrine glands by the hair-retaining device has occurred at these sites. Deep focal arteriolitis has been reported (Ordeix et al., 2001).

Cicatricial alopecia is featured in severe late lesions of traction alopecia. Cicatricial alopecia from nontraction causes may be characterized by more severe and complete replacement of the normal dermis by laminar fibrosis than is seen in most cases of traction alopecia; in addition, marked diminution of follicles in the midst of increased dermal fibrosis is more suggestive of traction alopecia than a classical cicatrix.

Differential diagnoses principally include ischemic follicular atrophy of ischemic dermatopathy/canine dermatomyositis and post-traumatic alopecia (see pp. 503 and 505). Ischemic follicular atrophy features similarly severely atrophic follicles as in traction alopecia. However, ischemic follicular atrophy occurs in the context of ischemic dermatopathy/dermatomyositis in which immunologic attack of hair follicles and cell poor vasculopathy occur (see Chapters 3 and 10). Vasculopathic lesions and ischemic changes of the dermis (homogenization and 'smudging') are not features of traction alopecia. Post-traumatic alopecia has consistent laminar and perivascular fibrosis, as well as ischemic changes of the panniculus.

TELOGEN EFFLUVIUM

(Synonym: telogen defluxion)

Clinical features (Figure 19.51)

Telogen effluvium is a rare, or at least rarely diagnosed, reaction pattern seen in dogs and cats characterized by widespread alopecia in response to severe metabolic stress. Mild cases of telogen effluvium probably go undiagnosed. Serious illness, high fever, pregnancy, lactation, anesthesia, surgery, and shock are all potential inducers of telogen effluvium (Scott et al., 2001). One author (P.J.I.) has seen telogen effluvium in conjunction with severe anemia in feline leukemia virus (FeLV)-positive cats. In humans, broad etiologic categories of telogen effluvium include endocrine abnormalities, nutritional deprivation, adverse drug reactions, physical stress (including anemia), and psychological stress (Olsen, 2003). Doxorubicin (Adriamycin^{R}) toxicity probably is the most common drug-induced cause of telogen effluvium in veterinary medicine (see p. 510).



Fig. 19.51 Telogen effluvium due to pregnancy and parturition in a Labrador Retriever. (Photograph courtesy P.B. Vasseur.)

Rapid, premature cessation of anagen growth leads to abrupt synchronization of the follicular cycle such that hair follicles proceed in unison through catagen and telogen. This leads to hair loss of variable severity when old telogen hairs are forced out by new, synchronous anagen hairs. Hair loss usually occurs within 3 to 4 weeks after the insult, but may occur as long as 3 months later. Alopecia resolves spontaneously, if the initiating factor is no longer present, and new anagen hairs grow.

Rapid, progressive alopecia develops over much of the body, partially sparing the face. Hair loss is the only cutaneous abnormality noted. Careful examination of shed hairs reveals characteristics of telogen: uniform shaft diameter, a nonpigmented and slightly clubbed root end, and the absence of an attached root sheath (Scott et al., 2001). Once hair loss begins, it generally continues for less than a week. Systemic signs, if present, reflect the preexistent or coexistent metabolic stress that induced the telogen effluvium.

Breed, age, or sex predilections are not noted. The major differential diagnosis is anagen effluvium, an even rarer syndrome characterized by shedding during anagen arrest secondary to catastrophic disease or high-dose cytotoxic therapy. Anagen effluvium (defluxion) is mentioned in a general reference textbook, but details were not given (Scott et al., 2001). Microscopic examination of hair and histopathology aid in differentiation between anagen and telogen effluvium. Characteristic clinical features linked to a stressful event are requisite for a clinical diagnosis of telogen effluvium.

Biopsy site selection

It is essential to perform a skin biopsy as soon as possible after the hair loss has occurred. If specimens are taken later in the course of the syndrome, histopathology may demonstrate normal anagen hair follicles indicative of the recovery phase. As in other causes of alopecia, regions of maximal hair loss should be sampled.

Histopathology (Figure 19.52)

The epidermis and dermis are normal. Random sampling of affected animals is often done in late stages. Thus, anagen hair follicles often predominate, and signal recovery to active cycling. In early lesions, hair follicles are predominantly in hairless telogen; true atrophy is not present. There is no overall diminution in follicular size. Adnexal glands are unaffected.

Doxorubicin-induced alopecia is a form of telogen effluvium and thus histopathologic differentiation is impossible; clinical differentiation is required. Other differential diagnoses include endocrine alopecia with telogen predominance, notably those in which true atrophy does not occur. Adjunctive features of various endocrine diseases such as acanthosis or atrophy of the epidermis, sebaceous atrophy, or mucinosis (myxedema) should allow differentiation. Also, in some forms of endocrine alopecia there is often true follicular atrophy, i.e. the telogen hair follicles are reduced in size over what is expected for telogen phase. In telogen effluvium, the telogen follicle is of normal size for that phase of the growth cycle. The recovery phase of telogen effluvium is indistinguishable from normal haired skin in anagen growth phase.

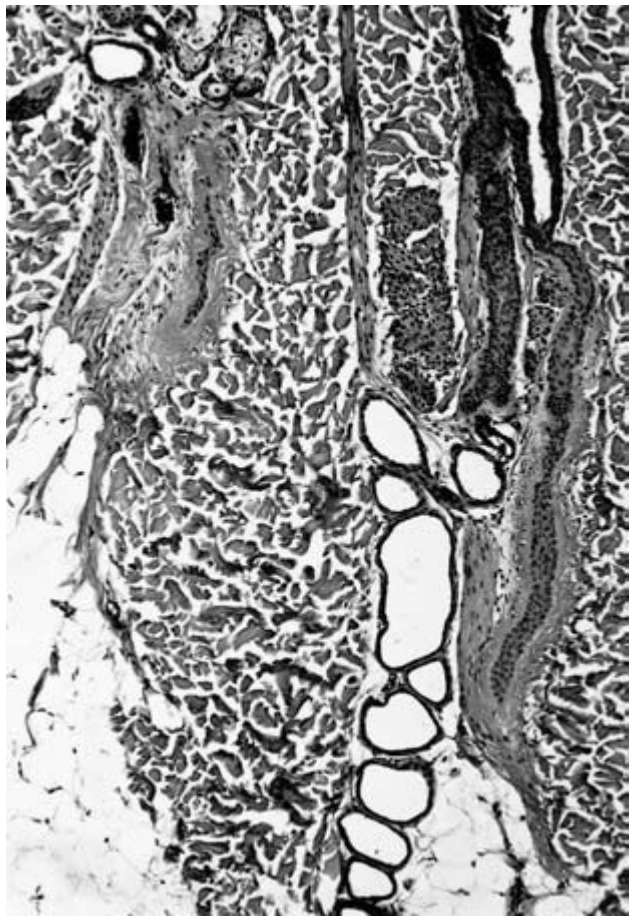


Fig. 19.52 Telogen effluvium. Elongated cords of follicular epithelium characterize the hairless telogen phase.

DOXORUBICIN-INDUCED ALOPECIA

(Synonym: Adriamycin®-induced alopecia)

Clinical features (Figures 19.53 and 19.54)

Doxorubicin-induced alopecia is a common side-effect of the use of Adriamycin® as an anticancer therapeutic agent in humans and dogs. Although alopecia may be seen with a variety of chemotherapeutic agents in dogs, alopecia is



Fig. 19.53 Doxorubicin-induced alopecia in a West Highland White Terrier. The dog has generalized thinning of the haircoat plus regions of more extensive alopecia on the neck, muzzle, and distal extremities. (Photograph courtesy R. Ayl.)



Fig. 19.54 Closer view of the muzzle of the dog in Fig. 19.53. Extensive alopecia with hyperpigmentation is visible on the lateral and ventral muzzle adjacent to the planum nasale and lips. (Photograph courtesy R. Ayl.)

seen much more commonly with doxorubicin-containing protocols than with any other agent (Chun et al., 2001; Kisseberth & MacEwen, 2001). Hair regrowth occurs after the patient has completed the therapeutic protocol and the use of doxorubicin has terminated. Doxorubicin-induced alopecia has long been recognized clinically by veterinary oncologists, but the syndrome rarely is seen by dermatologists and is rarely biopsied. In humans, cyclophosphamide and vincristine are the two other most common inducers of chemotherapy-induced alopecia (Fitzpatrick, 2003).

Doxorubicin has multiple mechanisms of action including intercalation of DNA, which inhibits protein synthesis, increases the formation of free radicals, and causes the inhibition of topoisomerase enzymes (Chun et al., 2001). In humans, chemotherapy-induced alopecia has been studied extensively and primarily is an anagen effluvium due to toxic effects on the rapidly dividing hair matrix cells (Fitzpatrick, 2003). Toxic effect is contingent on agent, dose, schedule and even route of administration; in general, intravenous infusions produce more alopecia than oral medications (Fitzpatrick, 2003).

Data on the cause of doxorubicin-induced alopecia in dogs and cats are sparse. To the authors' knowledge, the histopathology of this syndrome has not been well studied. Current information suggests that, in contrast to the alopecia seen in humans, most cases of doxorubicin-induced alopecia in dogs and cats are examples of drug-induced telogen effluvium. The basis for this discrepancy is not clear, but might relate to marked differences in hair cycle and hair cycle length seen between humans and dogs and cats. Alternatively, differences in hair follicle response to chemotherapeutic agents might relate to the anatomic (and presumed functional) differences in the source of hair follicle regeneration and hair cycle control between the localized follicular 'bulge region' in humans (Cotsarelis et al., 1990) and the more diffuse source of follicular regeneration noted in the dog (Credille et al., 1999).

Doxorubicin-induced alopecia is clinically striking. Hair loss may be complete or may involve just the primary (guard) hairs, resulting in a fuzzy 'puppy' coat consisting exclusively of secondary (undercoat) hairs. Other animals may exhibit a generalized thinning of the haircoat (Kisseberth & MacEwen, 2001). Facial sensory hairs (whiskers) commonly are lost in both dogs and cats (Chun et al., 2001; Kisseberth & MacEwen, 2001). Initial reports indicated that alopecia almost always began on the head and over the site of intravenous injection, with subsequent extension to the ventral neck, thorax, abdomen, and the inner surface of the legs (Van Vleet & Ferrans, 1980). It is now recognized that hair loss may develop in a variety of patterns. Partially bilaterally symmetric alopecia of the face may be visually dramatic. Delayed hair regrowth after clipping also is noted.

Hyperpigmentation of the skin in affected areas in conjunction with alopecia is a singular feature of doxorubicin toxicity (Van Vleet & Ferrans, 1980; Kisseberth & MacEwen, 2001). Hair regrowth after doxorubicin therapy is terminated may be a different color or texture (Kisseberth & MacEwen, 2001); curly haircoats may transform to straight haircoats, and vice versa. Severe and chronic doxorubicin toxicity may cause erythroderma, eventuating in widespread erosions and ulcers within the regions of alopecia (Van Vleet & Ferrans, 1980).

Poodles, Old English Sheepdogs, and terrier breeds are described as being at increased risk (Chun et al., 2001). Other long hair-coated dog breeds with a prolonged anagen hair phase such as Shih Tzus, and various wire-haired terriers probably also are of increased susceptibility to doxorubicin-induced alopecia. Age or sex predilections have not been noted.

Clinical differential diagnoses include telogen effluvium (see p. 509), and endocrinopathies that produce widespread alopecia. Differentiation should not be problematic as affected animals should have a history of doxorubicin administration. Skin biopsy will not determine the specific cause of hair loss; differentiation among various effluviums by clinical or histopathologic features is difficult (Olsen, 2003).

Biopsy site selection

As in other causes of alopecia, regions of maximal hair loss should be sampled. Multiple specimens should be procured to ensure that multiple follicular units can be examined.

Histopathology (Figures 19.55 and 19.56)

The epidermis is of normal thickness. There may be prominent epidermal pigmentation with concentration of melanin in the lower layers of the epidermis.

Hair follicles are in telogen and are devoid of hair shafts (hairless telogen), and thus are identical to those of telogen effluvium (see p. 509). There may be slight distortion of these telogen follicles. True atrophy is not present. An occasional residual anagen hair follicle may be interspersed. Sebaceous glands are not affected. The connective tissue of the external root sheath is relatively prominent and should not be confused with perifollicular fibrosis. Severe ulcerative and suppurative dermatitis also was reported in an experimental study of normal dogs that received high doses and prolonged therapy (Van Vleet & Ferrans, 1980).

Histological changes do not digress from those of other telogen effluviums and differential diagnoses are identical. Clinical differentiation is required.



Fig. 19.55 Doxorubicin-induced alopecia in a dog. Hair follicles are diffusely in hairless telogen.

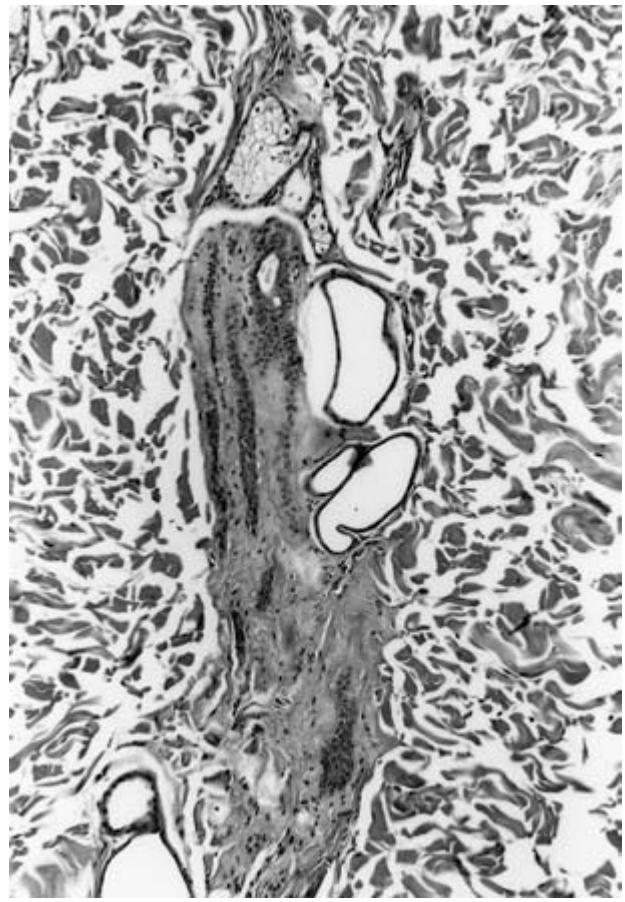


Fig. 19.56 Higher magnification of Fig. 19.55. Typical hairless telogen follicles are surrounded by normal apocrine and sebaceous glands.

EXCESSIVE PHYSIOLOGICAL SHEDDING

Clinical features (Figure 19.57)

Excessive physiological shedding is a very common owner concern that must be differentiated from pathological alopecia. Shedding may be defined as the genetically programmed cyclical and natural loss of telogen hairs. Dogs and cats replace their shed hairs in a continuous, mosaic pattern. Dogs and cats maintained outdoors in parts of the world with well-defined seasons predominantly shed and then replace their haircoat in the spring and the autumn. Domesticated dogs and cats maintained indoors in an environment without marked cyclical changes in photoperiod and temperature tend to shed more continuously year around.

Haircoat loss may be divided into physiological shedding and pathological alopecia. In pathological alopecia, large numbers of hairs can be manually extracted to produce nearly complete alopecia when minimal tension is applied; entire areas may be easily denuded in some



Fig. 19.57 Excessive physiological shedding in a Siberian Husky. Large numbers of telogen undercoat have shed giving the remaining haircoat a sparse flat appearance. (Photograph courtesy J. Declercq.)

cases. Excessive physiological shedding is a normal process; gentle digital extraction should remove some telogen hairs, but leave many remaining hairs firmly rooted in the hair follicles.

Causes of physiological excessive shedding are purported to be photoperiod alteration, temperature alteration, nutritional deficits, and nervousness or hyperexcitability (Scott et al., 2001). In some cases these disruptions may induce a synchronous or sudden shed. Some cases may be idiopathic.

The clinical features of excessive physiological shedding include owner reports of excessive loss of hair into the animal's environment. Excessively plush-coated breeds may preferentially shed their undercoat. Complete alopecia or patterns of frank hair loss should not be features of excessive physiological shedding.

Breed predilections for excessive physiological shedding are controversial. Owner reported concerns of excessive shedding occur most frequently with excessively plush-coated breeds such as northern breeds, Chow Chows, Golden Retrievers, Australian Shepherds, and dogs with short dark hairs such as black Labrador Retrievers and Doberman Pinschers.

Clinical differential diagnoses for excessive physiological shedding include all the atrophic and dysplastic follicular diseases that lead to pathological alopecia. Failure to create alopecia by gently attempting to remove the hair from a defined area should increase suspicion of excessive physiological shedding. Skin biopsy, usually prompted by the owner and not the veterinarian, should reveal normal skin.

Biopsy site selection

If desired, skin biopsies may be obtained from regions where the owner suspects that abnormal shedding has occurred. Multiple specimens should be obtained to increase the likelihood of discovering a cause of pathological alopecia.

Histopathology

Haired skin is generally normal, featuring expected proportions of anagen and telogen hairs, with anagen often predominating. Objective criteria for normal anagen/catagen/telogen ratios in the various breeds are not widely available, so interpretation may be highly subjective. No lesions are observed.

Differential diagnoses principally include the recovery phase of telogen effluvium; however, this condition should have synchronous anagen, so would be more monophasic than a normal coat. Clinical differentiation is required. The definitive diagnosis of a physiologically excessive shed cycle may be one of clinical exclusion.

FELINE PSYCHOGENIC ALOPECIA

(Synonym: self-induced psychogenic feline hair loss)

Clinical features (Figure 19.58)

Feline psychogenic alopecia is a relatively uncommon skin disease characterized by self-traumatic hair removal that is not associated with identifiable underlying causes. It is thought to be an obsessive/compulsive disorder or an anxiety neurosis associated with displacement phenomena in nervous cats. Incriminated precipitating events include competition for social hierarchy, a new environment, change in a cat's 'pecking order', displacement phenomenon such as a new baby or pet in the household, or loss of a favorite owner or other pet. Feline psychogenic alopecia is a diagnosis of exclusion requiring the elimination of pruritic causes of self-traumatic alopecia. Loss of hair is the result of removal by excessive grooming or chewing; damage to the underlying skin does not occur. Since cats may be markedly secretive in this endeavor, owners may be unaware of excessive grooming and thus resistant to the acceptance of this diagnosis.

Well-demarcated, partial or almost complete alopecia is noted in the affected areas. Partial bilateral symmetry is a common feature. Lesions are not found in the exposed skin. Short stubble may be palpable or visible with a hand lens, giving the visual impression of careful clipping or shaving. An examination of feces should show excessive hair, and may aid in proving to the owner that self-grooming is the root of the hair loss.

The distribution of feline psychogenic alopecia is distinctive. Commonly affected sites include the lateral trunk, caudal and medial thighs, abdomen, and dorsal forelegs. Some hair regrowth may occur if the cat abandons a region and refocuses its attention on other



Fig. 19.58 Feline psychogenic alopecia. Markedly bilaterally symmetric alopecia is present on the trunk.

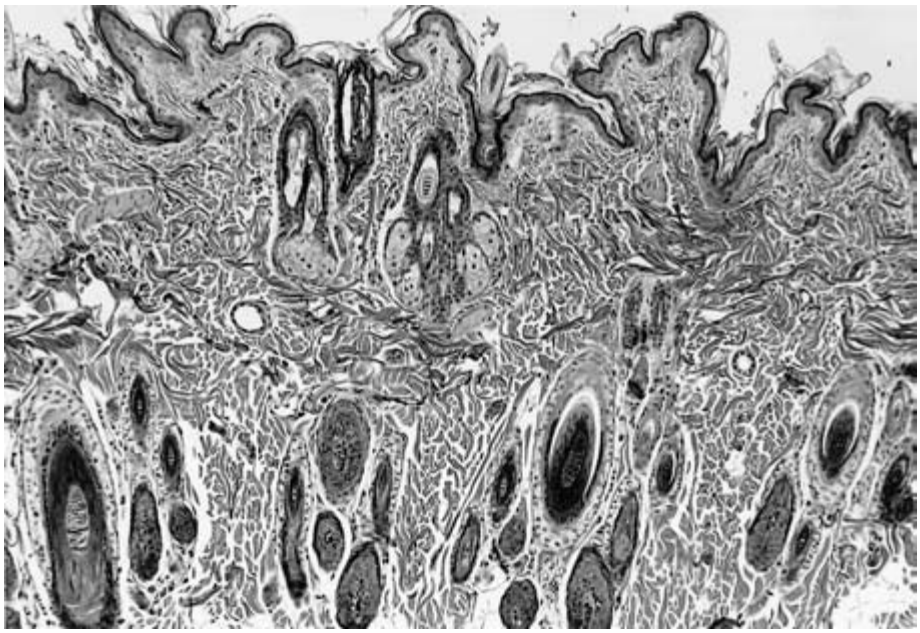


Fig. 19.59 Feline psychogenic alopecia. All skin components, including hair follicles, are normal.

previously unaffected sites. In Siamese cats, new hair growth may be darker in color since heat-labile enzymes that enhance melanization in cool body regions are activated (acromelanism).

Breed predilections have been noted in Siamese and Abyssinian cats, but the syndrome may be seen in any breed. Age or sex predilections have not been reported.

A diagnosis of feline psychogenic alopecia should not be made until all possible pruritic and nonpruritic causes of alopecia have been eliminated from consideration. Alopecia secondary to excessive grooming (due to pruritic or psychogenic causes) is best demonstrated by utilizing an Elizabethan collar; hair will regrow if excessive grooming is prevented by the collar. Underlying pruritic causes of self-induced feline hair loss include flea allergy dermatitis, atopic dermatitis, and food allergy. Self-induced feline hair loss due to low grade allergy may be exceedingly difficult to differentiate from feline psychogenic alopecia. Distribution of self-induced alopecia may offer a clue to etiology. Self-induced feline hair loss due to flea allergy is most likely to involve the caudal abdomen and medial and caudal thighs. Self-induced feline hair loss due to atopic dermatitis and food allergy is more likely to have a more generalized distribution and be less bilaterally symmetric than feline psychogenic alopecia. Stringent flea control, intradermal testing, *in vitro* allergy testing, and elimination diets are useful in documenting an allergic cause for feline self-induced hair loss. Feline demodicosis is an additional rare variably pruritic cause of alopecia in cats; skin scrapings allow differentiation. Histopathology is required to substantiate feline psychogenic alopecia.

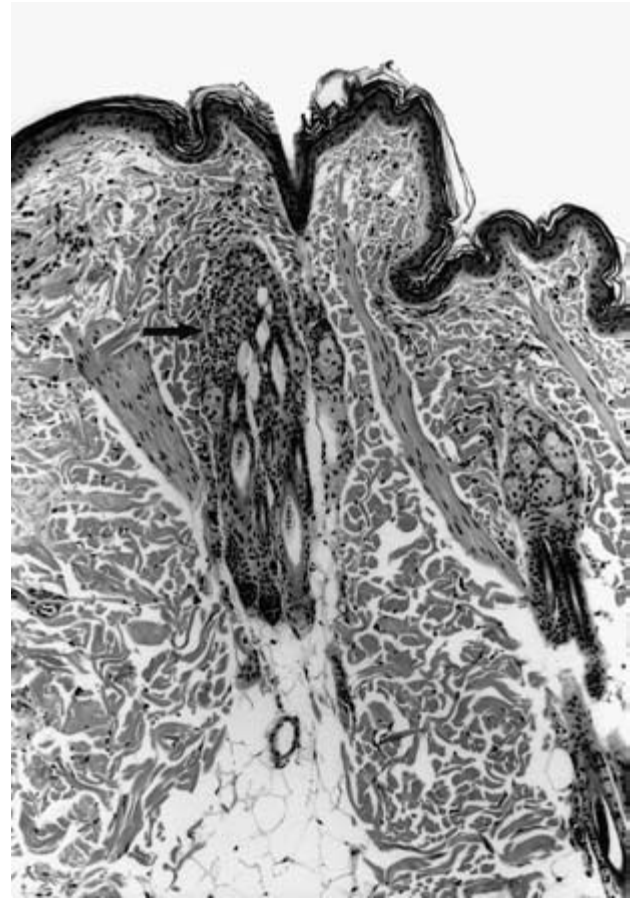


Fig. 19.60 Mild mural folliculitis (arrow) in feline psychogenic alopecia; hair follicles are otherwise normal for the ventral location.

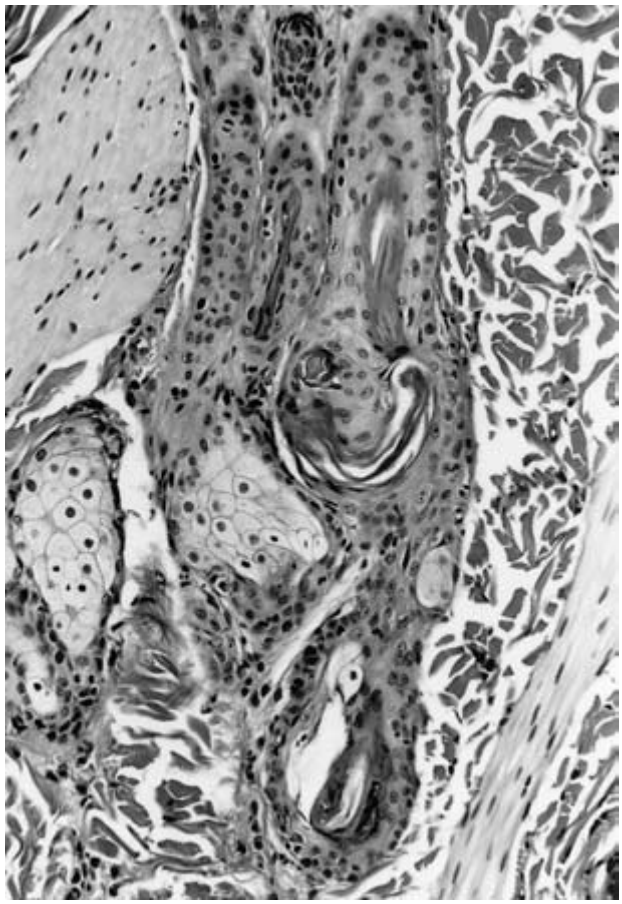


Fig. 19.61 High magnification of 'twanged' hair in feline psychogenic alopecia. The hair has fractured, and there is distorted and prominent tricholemmal keratin in a comma-shaped configuration.

Biopsy site selection

Specimens for biopsy should be obtained from an area of most complete hair loss. Any foci of erythema or crusting also should be sampled in order to rule out the presence of allergy-induced hair removal by the cat.

Histopathology (Figures 19.59 through 19.61)

Notable histopathologic findings usually are not present in feline psychogenic alopecia. Hair follicles usually are normal. Trichomalacia is a prominent feature of some cases, and is characterized by twisted or broken ('twanged') hair shafts within amorphous tricholemmal keratin, sometimes in distorted position within the follicle. Variation in the appearance of the hair shafts may be related to the type of trauma inflicted, i.e. vigorous pulling versus chewing or barbering. Occasionally there may be slightly increased numbers of mast cells or macrophages in the superficial dermis. Rarely, small numbers of lymphocytes or macrophages may encircle and invade the middle portion of widely scattered hair follicles (mural folliculitis) in cases that are dermatophyte culture negative and otherwise clinically compatible with psychogenic alopecia.

Differential diagnosis generally is not problematic for psychogenic alopecia. Normal histology (or trichomalacia) in the clinical setting of alopecia is highly supportive. Differential diagnosis may include mild allergic dermatitis, generally characterized by a superficial lymphohistiocytic and eosinophilic infiltrate. It is important to distinguish mild allergy that is producing excessive grooming from true psychogenic alopecia. In the authors' opinion, even rare eosinophils support allergy-induced excessive grooming in the cat.

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Chapter 20

Dysplastic diseases of the adnexa

Dysplastic diseases of the hair follicle and associated glands are characterized, most broadly, by abnormal growth and development of these structures. Dysplasia in this chapter is not used to define a preneoplastic condition, as in the epidermis for example (see Chapter 22). Considered literally, dysplastic diseases may be acquired; for example, the cycle arrest of the hair follicle in endocrine alopecia technically is a type of abnormal growth (see introduction, Chapter 19). By convention, however, many of the dysplastic adnexal diseases discussed here are of suspected or proven hereditary cause. Thus, these diseases often are breed-specific and have a relatively early onset of expression. Clinical and microscopic features are variable, and reflect the diversity of the affected canine breeds. Microscopic features of dysplasia of adnexal structures include distortion, abnormal deposits, attenuation, absence, proliferation, or degeneration. Dysplastic diseases are manifested usually by permanent and often progressive alteration in adnexal structure and integrity. However, permanence is not a prerequisite; some diseases such as cyclical flank alopecia may be intermittent and discontinuous in expression.

Recognition of individual diseases is often based as much on characteristic clinical features as on diagnostic histopathology. The authors recognize that much of the information currently available for dysplastic diseases is incomplete and that further study is needed.

COLOR DILUTION ALOPECIA AND BLACK HAIR FOLLICULAR DYSPLASIA

(Synonyms: blue dog disease, color mutant alopecia)

Clinical features (Figures 20.1 through 20.3)

Color dilution alopecia (CDA) is a relatively uncommon hereditary skin disease seen in dogs with color-diluted coats, such as 'blue' or 'fawn'. It is characterized by follicular dysplasia, leading to poor hair coat quality and variable alopecia. Black hair follicular dysplasia (BHFD) is a rare canine hereditary skin disease characterized by similar lesions that are restricted to the dark haired areas of light colored dogs with darker spots. Color dilution alopecia shares clinical and histopathologic features with BHFD and in the opinion of the authors, probably represents localized expression of a similar color-related genetic defect. Black hair follicular dysplasia may be viewed simply as localized CDA. Color dilution alopecia also has been seen in blue- or cream-colored cats that express the Maltese dilution gene (Scott et al., 2001). One author (T.L.G.) observed putative CDA in a dilute tortoiseshell-colored cat. Color dilution alopecia and BHFD are discussed separately from other follicular dysplasias as these syndromes are clinically and histopathologically distinctive, and have marked breed predilections.

The relationship between coat color and CDA remains confusing. In general, lighter coat color-dilute animals will develop more severe skin disease than their darker dilute brethren as they age. While Weimaraners have a coat that varies in color between light silver-blue and dark gray, true CDA is extremely rare in this breed. It is not known why most Weimaraners, regardless of color, do not develop color dilution skin disease. Interestingly, follicular dysplasia was recently described in five Weimeraners; the pigmentary abnormalities were similar to CDA but were less severe, as seen in other forms of follicular dysplasia in noncolor-dilute breeds (see p. 522) (Laffort-Dassot et al., 2002).

Color dilution alopecia is associated with a color dilution gene, probably at the D locus (Miller, 1990). Under the influence of coding from multiple genes, 'dilute' hairs form with larger, abnormal pigment granules due to abnormalities in melanin transfer and storage (Scott et al., 2001). This pigment clumping in color-dilute animals leads to unusual 'washed-out' or dilute colors. It is not known if the color dilution gene is directly responsible for initiating the skin disease, or if a linked gene codes for the associated follicular changes (Miller, 1990, 1991). Color dilution alopecia may reflect a defect in follicular maturation that is most severely manifested in the dilute coat color, or alternatively, a multifactorial epithelial maturation defect (Brignac et al., 1988). Attempts to breed for



Fig. 20.1 Color dilution alopecia in a dark blue Doberman Pinscher. Note the diffuse partial loss of hair, especially on the dorsal trunk.



Fig. 20.2 Color dilution alopecia in a light blue Doberman Pinscher. Hair loss is more extensive than in the dark blue dog in Fig. 20.1.



Fig. 20.3 Black hair follicular dysplasia in a Beagle-crossbreed. Hair loss and secondary pyoderma are confined to the darker pigmented area.

color dilution without expression of the associated skin disease have not been successful. Unfortunately these efforts may have produced more tardive onset of clinical disease, thus encouraging continued breeding.

Selmanowitz et al. (1977) speculated that in BHFD, melanocytes might be involved in faulty morphogenetic induction of the follicular appendages in the areas of follicular dysplasia. Breeding studies further suggest that BHFD is due to an autosomal gene with an as yet undetermined dominant or recessive characteristic (Selmanowitz et al., 1977).

Differences in melanin distribution between CDA and BHFD were noted by direct microscopic examination of hair shafts (Hargis et al., 1991). However, variation in melanin distribution among dogs with CDA may be a feature of breed differences (Miller, 1990; Roperto et al., 1995). Thus, to extrapolate, differences between CDA and BHFD may reflect variation in breed expression of a common defect, but not distinct entities.

The initial clinical feature of CDA is the gradual onset of a dry, dull, brittle, poor quality haircoat. Hair shafts fragment and hair regrowth is poor, resulting in a progressive, partial, patchy (motheaten) alopecia and broken stubble that proceeds to more complete hair loss. Hair loss usually is most severe on the trunk, especially dorsally. Hyperpigmentation may occur with chronicity. The alopecia areas become dry and scaly. Follicular papules develop and may progress to frank pustules, indicating secondary bacterial infection. The skin disease is limited to the color-diluted (usually blue) hair with sparing of the differently-colored points, if present. This clinical feature is highly characteristic of CDA. In general, the more color-dilute the dog is clinically, the greater the magnitude of alopecia that develops. Truncal alopecia may be almost complete in lighter colored dogs by 6 years of age. Recurrent secondary pyoderma is common in moderately to severely affected dogs. Secondary pyoderma is less common and more subtle in dogs with mild CDA. Cats with CDA reportedly exhibit varying degrees of symmetric truncal alopecia without evidence of excessive grooming (Scott et al., 2001).

In BHFD, extensive alopecia develops in the affected dark-haired spots. Adjacent white-haired areas are normal. Owners report that darker haired body regions often appear washed out, gray or 'bluish' before hair is lost. Similar to generalized CDA, hairs are lost from affected areas, leaving broken stubble and markedly abnormal remaining hairs with fractured dry, dull shafts. The alopecic areas become dry and scaly. Secondary pyoderma is common in the affected alopecic areas.

Color dilution alopecia is seen most frequently in the blue Doberman Pinscher; hence the original name, 'blue Doberman syndrome'. The syndrome also is seen in other breeds with blue color dilution including the Dachshund,

Great Dane, Whippet, Italian Greyhound, Chow Chow, Standard Poodle, Yorkshire Terrier, Miniature Pinscher, Chihuahua, Bernese Mountain Dog, Shetland Sheepdog, Silky Terrier, Boston Terrier, Saluki, Newfoundland, German Shepherd Dog, Bernese Mountain Dog, Schipperke, plus crossbreed dogs (as compiled by Scott et al., 2001 and Laffort-Dassot et al., 2002). In addition, CDA has been seen in the fawn Doberman Pinscher, fawn Irish Setter, and the red Doberman Pinscher. Color dilution alopecia also has been reported in 'blue and tan' Dachshunds that changed coat color during puppyhood to 'deadleaf' or 'gray and tan' (Beco et al., 1996). Most affected dogs develop the syndrome between 4 months and 3 years of age. However, the authors have seen the syndrome develop as late as 5 to 6 years of age. Sex predilections have not been noted.

Black hair follicular dysplasia was first documented in mongrels (Selmanowitz et al., 1977), but the syndrome also has been seen in many other breeds. Black hair follicular dysplasia is reported to occur in the Bearded Collie, Border Collie, Beagle, Basset Hound, Papillon, Saluki, Jack Russell Terrier, American Cocker Spaniel, Cavalier King Charles Spaniel, Dachshund, Gordon Setter, large Munsterlander, and in pointers (as compiled by Scott et al., 2001). One author (P.J.I.) has seen BHFD most commonly in spotted purebred dogs such as the Beagle and Basset Hound. Skin lesions usually develop within the first few weeks after birth. Sex predilections have not been noted.

In markedly dilute animals the diagnosis of advanced CDA is not difficult. Otherwise, differential diagnoses for CDA may include hypothyroidism, hyperglucocorticoidism, other canine follicular dysplasias (see p. 522), and acquired pattern alopecia. Breed predilections and coat color should increase clinical suspicion. Differentiation is accomplished by clinical history and features, thyroid and adrenal hormone function tests to rule out endocrine disease, and histopathology.

Clinical diagnosis of BHFD usually is not difficult as it is a visually striking disease. Observation of hair loss and haircoat quality changes restricted to the black-haired areas of otherwise light-coated dogs is highly suggestive of BHFD. Differential diagnoses could include other dysplastic follicular diseases. Definitive diagnosis is based upon compatible clinical findings and histopathology.

Biopsy site selection

Specimens should be selected from maximally affected areas with complete alopecia. Papules or pustules, usually indicative of a secondary pyoderma, also may be sampled.

Histopathology (Figures 20.4 through 20.6)

In CDA and BHFD, the epidermis is usually normal, but may be acanthotic if secondary pyoderma is present. Characteristic clumping of melanin in the epidermis indicates color dilution is present.

Atrophy, variable distortion, and abnormal melanin pigmentation characterize hair follicles. Follicles have keratin-plugged infundibula and have varying degrees of dysplasia, characterized by an irregular, misshapen contour. Many follicles are in telogen phase, but anagen hair follicles are usually interspersed, and dominate in some specimens. Hair shafts are often absent or markedly attenuated, and may be fractured, or malacic and fragmented. Clumped melanin pigment accumulation is massive and is present at all levels of the hair follicle, including the bulb, outer root sheath and hair shafts. Pigment is prominent within follicular keratin, and extrusion of pigment from the follicular infundibulum to the



Fig. 20.4 Black hair follicular dysplasia. Follicular atrophy is accompanied by clumped melanin deposition in and around hair follicles. Note similarity to color dilution alopecia (Fig. 20.5).

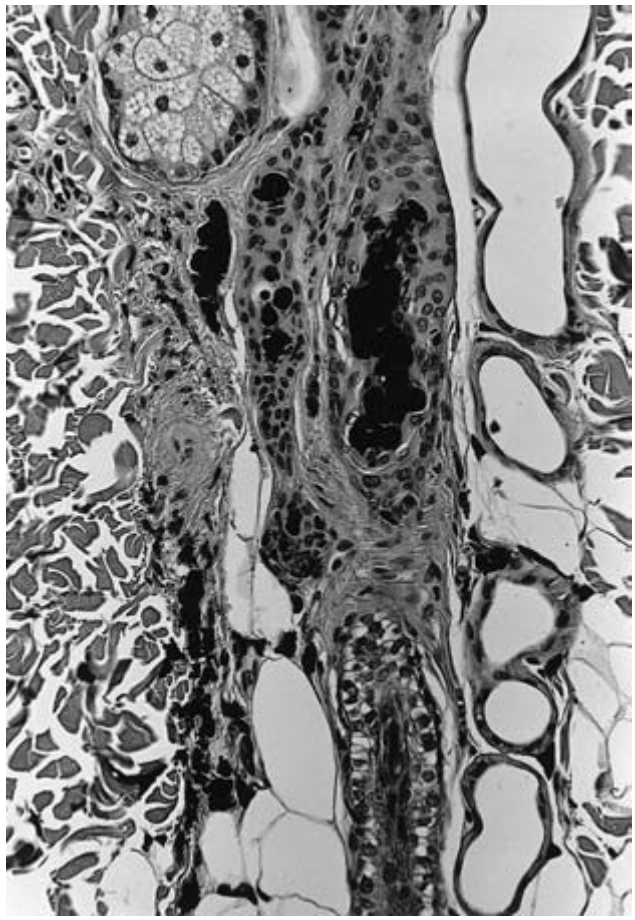


Fig. 20.5 High magnification of color dilution alopecia. Heavily clumped melanin is within distorted hair follicles.

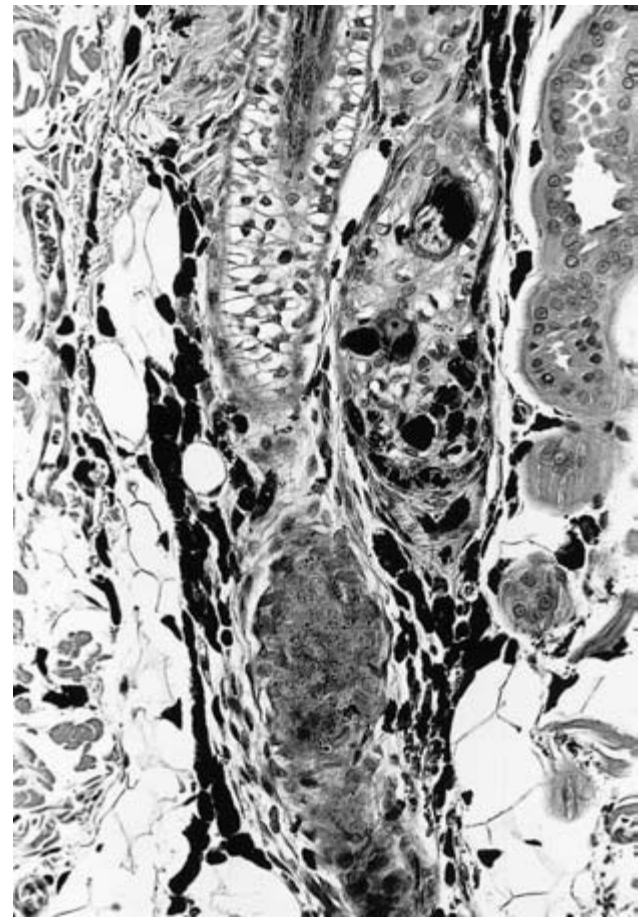


Fig. 20.6 High magnification of black hair follicular dysplasia. Clumped pigment is distributed in and around deep follicles.

surface keratin may be observed. Heavily clumped melanin is present within melanophages around the base of hair follicles. Secondary inflammation, as in chronic pyoderma, consists of neutrophils and plasma cells that surround superficial vessels and hair follicles. Active folliculitis or furunculosis may be present.

Scanning electron microscopy of plucked hairs demonstrates swelling with cuticular ruptures and craters (Guaguère, 1991; Hargis et al., 1991; Roperto et al., 1995; Beco et al., 1996). Fractures have been identified (Guaguère, 1991; Hargis et al., 1991; Roperto et al., 1995). Transmission electron microscopy of hairs reveals large vacuoles containing melanosomes of variable size, including 'macromelanosomes' formed from the fusion of smaller melanosomes (an ultrastructural designation) (Roperto et al., 1995; Beco et al., 1996). The clumped foci of melanin seen with light microscopy are not macromelanosomes, but a collection of melanosomes of varying size accumulating within vacuoles (Beco et al., 1996).

Some of the features of CDA are not of pathologic significance, but instead indicate dilute coat color, specifically melanin clumping in the basilar epidermis, hair bulbs, and hair shafts. These features are less severe in normal color-dilute dogs than in dogs with CDA (Miller, 1990). Clumped melanin is visible in plucked hair shafts of clinically normal color-dilute dogs, but does not form large masses that distort the cuticle (Miller, 1990). Severe accumulations of melanin, particularly within follicular keratin, coupled with follicular dysplasia and fractured hair shafts, are indicative of CDA. Massive melanin clumping within free keratin in CDA may result from fracture of the hair shaft (Miller, 1990).

Black hair follicular dysplasia is considered indistinguishable from CDA histologically. Direct examination of hair shafts showed larger and more numerous melanin granules on light microscopy and more severe cuticular defects on scanning electron microscopy when comparing CDA in a blue Doberman to BHFD in black and white Salukis (Hargis et al., 1991). However, since the lesions



Fig. 20.7 Follicular dysplasia in a Siberian Husky. Most primary hairs are lost from the trunk and secondary hairs appear 'wooly' and reddish-brown or 'rusty'. (Photograph courtesy A.M. Hargis; case material University of California, Davis.)

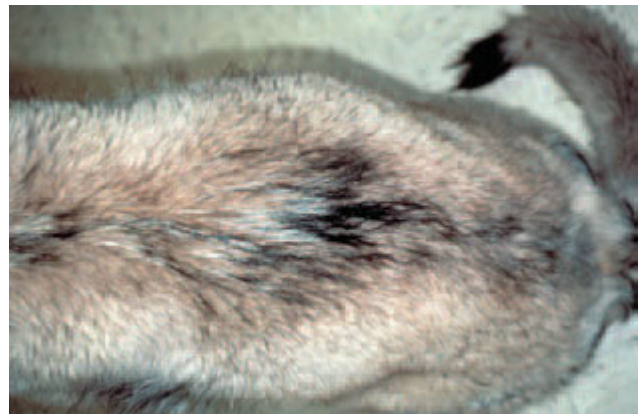


Fig. 20.8 Closer view of the dorsum of the dog in Fig. 20.7. A few primary hairs remain along the midline surrounded by 'wooly' secondary hairs. (Photograph courtesy A.M. Hargis; case material University of California, Davis.)

of these two syndromes are qualitatively the same, there may simply be individual breed variation in the severity of expression of abnormal pigment distribution and hair shaft defects. Alternatively, the expression may be less severe in cases that still retain phenotypically intense (black) pigmentation of the haircoat. In the authors' opinion, differentiation between BHFD from CDA usually is of no consequence except where genetic information is being sought.

One author (T.L.G.) has observed some of the histologic lesions of CDA in an alopecic tortoiseshell cat that was reportedly of dilute color. Clumped melanin within all levels of the follicle (including within keratin), as well as pigmentary incontinence in the perifollicular dermis were observed. However, hair shafts were normal and follicular dysplasia was not observed; thus, the cause of the alopecia could not be directly assigned to color dilution. No further clinical studies were performed.

The differential diagnosis of CDA and BHFD principally includes other forms of follicular dysplasia. Some abnormal clumping of melanin within the hair follicle occurs in the context of other follicular dysplasias (see below). In general, abnormal melanin accumulation is more severe in CDA and BHFD than in other follicular dysplasias.

CANINE FOLLICULAR DYSPLASIA

(Synonym: hair follicle dysplasia)

Clinical features (Figures 20.7 and 20.8)

Canine follicular dysplasia designates a group of uncommon canine skin diseases characterized clinically by altered haircoat quality and varying degrees of alopecia. The clinical features of canine follicular dysplasia vary with the breed affected, but usually are distinctive for that breed. Current breed predilection data are most striking for the Siberian Husky, Irish Water Spaniel, Portuguese Water Dog, and Curly-Coated Retriever. A distinctive and more common follicular dysplasia with marked breed predilections, termed 'cyclical flank alopecia', is discussed separately (see p. 525).

The etiology of canine follicular dysplasia is not known, although marked breed predilections strongly imply hereditary factors. Curiously, abnormalities in steroidogenesis and apparent improvement related to dietary changes were noted in affected Irish Water Spaniels (Cerundolo et al., 2000).

Altered haircoat quality in canine follicular dysplasia relates to both abnormal retention of the haircoat followed by natural environmental damage of retained hairs, as well as structural weakening of putatively dysplastic hairs leading to secondary breakage. Breakage is most prominent in conjunction with aggressive hair grooming practices, the use of harsh shampoos, and presumed friction on the neck under collars (Scott et al., 2001).

The unifying clinical features of canine follicular dysplasia include poor haircoat quality, coat color change, poor hair regrowth after clipping or damage to the hair, and progressive alopecia. In general, primary (guard) hairs are affected more frequently and severely, leading to selective loss of guard hairs and some retention of secondary (undercoat) hairs. Truncal haircoat is affected most prominently and most commonly. Most forms of canine follicular dysplasia reported to date seem to spare the face and distal extremities. Interestingly, this same pattern of alopecia is seen with most endocrine skin diseases and with alopecia X (see Chapter 19); the significance of this finding is not known. Occasionally, partial

hair regrowth may be noted transiently, giving false hope for recovery; however, the syndrome usually is progressive and unremitting.

The syndrome in the Siberian Husky is characterized by loss of primary hairs and a distinctive color change in the remaining secondary hairs to a reddish-brown or 'rusty' color. Secondary hairs are dry, disheveled, damaged, and 'wooly'. Patches of more complete alopecia may be evident in wear areas such as pressure points and under collars. A similar form of canine follicular dysplasia, but usually more tardive in onset, is seen in Malamutes.

Similar clinical features are seen in the Irish Water Spaniel, Portuguese Water Dog, and Curly-Coated Retriever. Variable numbers of primary hairs are lost and the undercoat changes to a dull, lighter color. Some remaining primary hairs on the trunk may be abnormally long. Affected Irish Water Spaniels exhibit a coat color change from reddish brown to grayish brown. The coat color of Portuguese Water Dogs changes from black to reddish brown. Distinctive from most follicular dysplasias, alopecia may be noted in periorbital location in Portuguese Water Dogs (Miller & Scott, 1995). Curious 'islands' of normal hair in areas of almost complete alopecia, similar to that seen in alopecia X (see Chapter 19), are observed in all three of these breeds. Pedigree analysis in four families of Irish Water Spaniels suggests a dominant mode of inheritance (Cerundolo et al., 1999). Interestingly, a well-demarcated patch of marked hairlessness on the throat region plus a comparatively poorly haired 'rat tail' are defined breed standard in the Irish Water Spaniel; breeders may have unwittingly selected for more widespread follicular dysplasia. Clinical distribution of the alopecia may depend on coexistent factors like sex hormone receptor density or function (Miller, 1990).

Data on canine follicular dysplasia is most extensive and convincing for the above-mentioned breeds. Visually similar, progressive, diffuse truncal alopecia due to canine follicular dysplasia has been noted in black and red Doberman Pinschers and in Weimaraners (Miller, 1990; Laffort-Dassot et al., 2002).

Age of onset is variable and somewhat contingent on affected breed. However, the syndrome commonly begins at less than 3 years of age. Sex predilections have not been noted.

Clinical differential diagnoses for canine follicular dysplasia should include endocrinopathies such as hypothyroidism, hyperadrenocorticism, and sex hormone alterations. The marked breed predilections of canine follicular dysplasia, plus endocrinologic evaluation and histopathology will aid in differentiation. The authors have seen Siberian Huskies with alopecic skin disease that seems to blur the lines of differentiation between follicular dysplasia, cyclical flank alopecia, and alopecia X; interestingly, histologic features most closely resemble alopecia X. Similarly, in one report of follicular dysplasia in Irish Water Spaniels, there was both clinical and histopathologic overlap with cyclical flank alopecia (see p. 525; Cerundolo et al., 2000). However, complete hair loss, as observed in alopecia X and flank alopecia, does not occur with follicular dysplasia of the Siberian Husky.

Biopsy site selection

Specimens should be taken from areas of maximum alopecia or haircoat change. It is critical that normally haired skin be obtained for comparison. In breeds other than those mentioned above, control specimens ideally should be obtained from an age-matched dog of the same breed, preferably from the same site as the abnormal specimen. This comparison sampling is integral to characterizing new forms of hereditary alopecia in individual breeds of dogs. Clinicians should exercise caution and restrain from clipping areas adjacent to the most alopecic areas in preparation for skin biopsy, as hair regrowth may not occur.

Histopathology (Figures 20.9 and 20.10)

The canine follicular dysplasias are incompletely characterized. Further histopathologic distinctions amongst the various follicular dysplasias will hopefully emerge through systematic study of large groups of affected animals. Knowledge of the breed affected and distribution of hair loss are crucial in the diagnosis of these conditions.

In general, the epidermis and dermis are usually normal, although variable hyperkeratosis may be present. Follicular infundibular hyperkeratosis is a common feature, as it is in many diseases of abnormal hair follicle growth. Pigmentary incontinence around deep portions of hair follicles may be evident, and there may be mild pigment clumping within follicular structures as well. Hair follicles are variably distorted, and may be truly atrophic and/or in telogen phase without overall reduction in size. Anagen hair follicles also may appear abnormal in size and contour.

In Portuguese Water Dogs, hair follicles are variably affected, often within the same specimen. Affected hair follicles are superficially plugged with orthokeratotic keratin. They may have a wavy or irregular outer contour. Hairs are absent from hair follicles or may appear fragmented and thin. There may be scattered clumps of melanin within follicular keratin and within follicular epithelium. Distorted follicles are generally but not uniformly in telogen phase; misshapen and small anagen hair bulbs are observed. Some deep follicles may exhibit normal anagen morphology but show abnormal hair shafts and melanin accumulation superficially. A large study also reported dissolution of the hair matrix of the

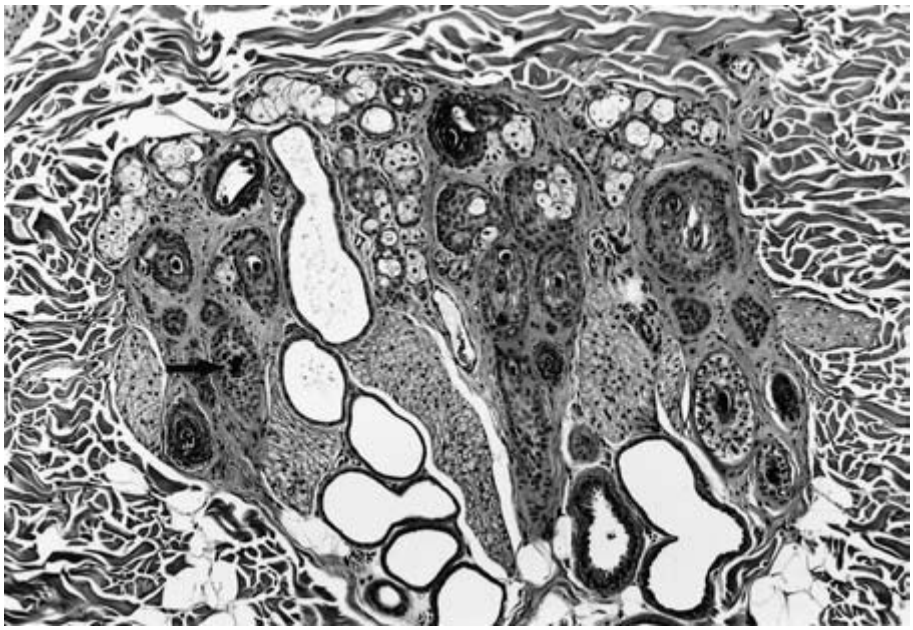


Fig. 20.9 Follicular dysplasia in a Portuguese Water Dog. Hair follicles are atrophic and mildly misshapen in this view; note relative prominence of arrector pili muscles. There is mild intrafollicular clumping of melanin (arrow).



Fig. 20.10 Higher magnification of follicular dysplasia in a Portuguese Water Dog. Note highly distorted hair follicle at center, which contains an abnormal hair shaft.

anagen bulb and vacuolar alteration of the inner root sheath (Miller & Scott, 1995). An occasional abnormal hair follicle may be found in normal coated adults or puppies; these follicles demonstrate intraluminal melanin or dysplastic hair shafts (Miller & Scott, 1995).

As reported in a study of 20 affected dogs, follicular dysplasia of Irish Water Spaniels is manifested in areas of alopecia by atrophy of the lower follicle and dilated hyperkeratotic infundibula. Similar but milder changes are seen in hypotrichotic (partially haired) sites (Cerundolo et al., 2000). Pigment clumping of the hair shaft or hair follicular epithelium and perifollicular pigmentary incontinence are encountered in all affected dogs, even in the normally haired areas; normal dogs of the breed were not examined (Cerundolo et al., 2000). Pigment clumping may be normal for the breed, or may be a feature only of dogs with potential for hair loss.

Follicular dysplasia in adult black and red Doberman Pinschers is characterized by follicular atrophy, follicular infundibular hyperkeratosis, and pigment clumping throughout the hair follicle. Melanin aggregates are observed in hair shafts, hair matrix cells, and intraluminally. There is perifollicular pigmentary incontinence. The pigment abnormalities are reportedly less than seen in color dilution alopecia (Miller, 1990). Similarly, follicular dysplasia of Weimeraners also features pigmentary clumping, but not to the extent or severity of color dilution alopecia (Laffort-Dassot et al., 2002). Since color dilution alopecia is technically also a follicular dysplasia, differentiation may be unimportant.

Interestingly, although the clinical presentation is distinct from alopecia X, the histopathologic features of



Fig. 20.11 Cyclical flank alopecia in a Boxer characterized by partially bilaterally symmetric patches of hair loss and marked hyperpigmentation on the lateral trunk.



Fig. 20.12 Cyclical flank alopecia in a Miniature Schnauzer. A roughly triangular patch of almost complete alopecia with hyperpigmentation is present in the flank region. Hair loss in this dog persisted and was not cyclical.

follicular dysplasia of the Siberian Husky are strikingly similar to that syndrome (see Chapter 19). Flame follicles are diffusely present. Pigment clumping within hair follicles is not seen. The prominent tricholemmal keratin of haired telogen follicles, as seen in post-clipping alopecia (and a normal finding in random biopsy of normal plush-coated dogs), should not be confused with true flame follicle formation.

Differentiation of follicular dysplasia from endocrine alopecia may be required. Individual dysplastic hair follicles are seen in endocrine alopecia, as reported by Rothstein et al. (1998). However, dysplastic follicular changes are more diffuse and severe in follicular dysplasia syndromes than in endocrine alopecia. Clumping of melanin and dysplastic hair shafts are also specific for follicular dysplasia (Rothstein et al., 1998). Follicular dysplasia may also feature abnormalities of the anagen hair follicle, in contrast to endocrine alopecia in which hair cycle arrest in telogen phase occurs.

CYCLICAL FLANK ALOPECIA

(Synonyms: seasonal flank alopecia, recurrent flank alopecia, flank alopecia)

Clinical features (Figures 20.11 through 20.14)

Canine cyclical flank alopecia (CFA) is a visually striking, but relatively uncommon disease, characterized by altered haircoat quality and alopecia, predominantly of the lateral flank folds. Geographic variation in this localized follicular dysplasia is profound. Seasonal hair loss and hair regrowth may be most prominent in regions of the world with well-defined differences in seasons, while cycling may be much less notable or even nonexistent in regions with little seasonal climactic alteration, such as northern California. Thus, the authors also use the term 'flank alopecia', as cyclical hair loss and hair regrowth are not consistent features in some geographic areas.

The etiology of CFA is not known, although marked breed predilections strongly imply hereditary factors. The syndrome is seen most commonly in northern regions of North America giving rise to speculation that photoperiod and seasonal climactic variations heavily influence pathogenesis (Paradis, M., personal communication, 1997; Rosser, E., personal communication, 1997; Scott et al., 2001). Hair loss commonly occurs in late autumn to early spring followed by partial to complete resolution in late spring (Miller & Dunstan, 1993; Scott et al., 2001). Confusingly, a reversed clinical course with hair loss in summer followed by regrowth in winter has been seen in a smaller percentage of cases (Miller & Dunstan, 1993; Scott et al., 2001). Although patterns of alopecia are reminiscent of an endocrinopathy, available data, including thyroid evaluations, do not indicate the presence of endocrine disease (Darminet & Paradis, 2000). Therapeutic response in some cases to either melatonin or increased exposure to light implies the importance of photoperiod and seasonal climactic variations on the pathogenesis of CFA.

The prime clinical feature of CFA is somewhat bilaterally symmetric altered haircoat quality and alopecia. Affected hair may be lighter or darker in color and is dull, dry, and disheveled. Distinctive, serpiginous, well-demarcated borders to the regions of alopecia lend a strikingly geographic image. Both primary and secondary



Fig. 20.13 Closer view of the dog in Fig. 20.13 viewed dorsally. Partially bilaterally symmetric patches of complete alopecia are present on the flanks.



Fig. 20.14 Cyclical flank alopecia in a Chesapeake Bay Retriever. This dog experienced hair loss every winter and regrew hair each summer.

hairs are lost. Hyperpigmentation usually occurs in concert with coat quality change and alopecia. Most lesions are less than 15 cm in maximum diameter. Lesions predominate in the lateral flank folds, but may involve the dorsal midline, cranial ribcage, and axillary regions less commonly. Partial to complete hair regrowth may occur in a cyclical pattern (see above). Regrown hair is often dry, dull, and discolored, and may display alteration in texture. Affected dogs are otherwise normal.

A somewhat different, distinctive, and more generalized clinical pattern of alopecia is seen in the Airedale Terrier. Hair loss is partially symmetric and restricted predominantly to the dorsal and lateral thorax in a distinctive saddle-like or 'H' pattern. Hyperpigmentation is noted. The authors have seen other Airedales with alopecic skin disease that seems to blur the clinical lines of differentiation between follicular dysplasia and alopecia X. In these dogs, hair loss may be profound and affect much of the trunk, with sparing of the head, neck, distal legs, and distal tail. Areas of total alopecia are present with occasional, visually striking, well-demarcated 'islands' of normal hair similar to that seen in alopecia X (see Chapter 19). Cyclical hair regrowth followed by recrudescence may occur seasonally or without apparent seasonality.

Flank alopecia can occur in any breed, but is seen most commonly in the Boxer (Miller & Dunstan, 1993; Scott, 1990; Scott et al., 2001). Breed predilection data is also striking for the English Bulldog, French Bulldog, Miniature Schnauzer, and Airedale Terrier. Other breeds at probable increased risk include the Chesapeake Bay Retriever, Doberman Pinscher, Scottish Terrier, Staffordshire Terrier, German Shorthaired Pointer, German Wirehaired Pointer, Rhodesian Ridgeback, Rottweiler, Kuvasz, and Miniature Poodle. The authors and others (Scott et al., 2001) have seen flank alopecia in many other breeds, including the Bouvier des Flandres, Affenpinscher, Chihuahua, Pekingese, and Shetland Sheepdog.

Clinical differential diagnoses for CFA could include endocrinopathies such as hypothyroidism and sex hormone alterations. However, CFA in most breeds is visually distinctive. Breed predilections, endocrinologic evaluation, and histopathology will facilitate the diagnosis. As stated, CFA in some Airedale Terriers resembles alopecia X (see Chapter 19); histopathology should allow differentiation.

Biopsy site selection

Specimens should be taken from areas of maximum alopecia or haircoat change. Multiple specimens allow the examination of multiple follicular units and enhance the likelihood of achieving a diagnosis.



Fig. 20.15 Cyclical flank alopecia in a Standard Schnauzer. Note massive follicular keratosis and foot-like configuration of keratin above small and distorted lower follicles.

Histopathology (Figures 20.15 through 20.17)

A normal to mildly acanthotic epidermis is often uniformly hypermelanotic throughout all layers, including the stratum corneum. There is variable, often striking follicular plugging with orthokeratotic hyperkeratosis. Abnormal follicles of all stages of the hair cycle (anagen, catagen, and telogen) are present. Both primary and secondary hair follicles are distorted and narrowed, particularly at the base. Often, a widened keratin-filled follicular infundibulum is perched on a truncated follicle with an atrophic base, creating a 'dwarfed' appearance. 'Witch's feet' are due to the appearance of keratin within the dilated infundibula overlying a group of toe-like, shortened, and irregular primary and secondary follicles (Miller & Dunstan, 1993). Hair bulbs, if present, are often greatly misshapen, and may be seen at the base of distorted, sometimes thin and 'dangling' anagen or catagen follicles. Often follicles have a marked wavy or undulating outline. Late stage telogen hair follicles, reduced to a narrow cord of cells, may be prominent in some lesions. Hair shafts are generally absent. There may be rare folliculitis.

Sebaceous glands are diffusely melanized, and apocrine glands are variably pigmented, as reported (Scott, 1990; Miller & Dunstan, 1993). Plugs of melanin form in sebaceous ducts and lie free within the keratin of superficial follicles. Sebaceous gland melanosis reportedly is a nonspecific feature of both endocrine and dysplastic diseases of hair follicles (Bagladi et al., 1996). Also, random and occasional sebaceous gland melanosis may be a normal finding in the skin of dogs (Bagladi et al., 1996).

The microscopic appearance of active lesions of cyclical flank alopecia is distinctive. Some hypothyroid dogs

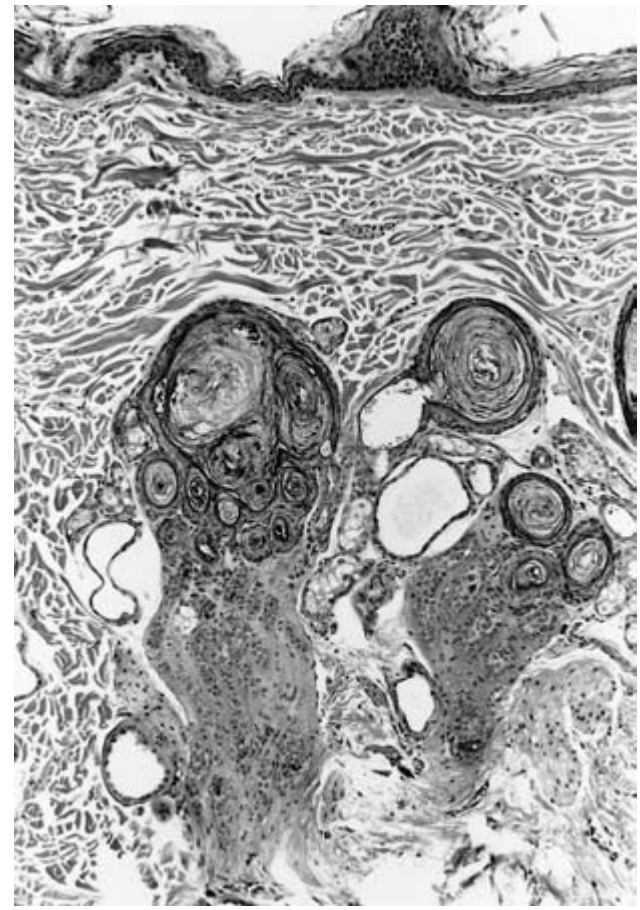


Fig. 20.16 Higher magnification of hair follicles of the dog in Fig. 20.16. A foot-like keratin configuration lies above atrophic irregular deep follicles.

have follicles that taper to an atrophic base, but 'witch's feet' and marked distortion of the follicular contour, as seen in flank alopecia, do not occur. Difficulty in histopathologic diagnosis arises from the cyclical nature of flank alopecia. Thus, depending on the stage in which biopsy specimens are obtained, hair follicles may have a relatively normal appearance and anagen hairs may be prominent. A predominance of normal anagen hairs and more normally contoured hair follicles (within a non-marginal specimen) may herald a return to a cycle of regrowth in affected dogs.



Fig. 20.17 High magnification of hair follicles in cyclical flank alopecia. A primary follicle is markedly distorted (arrow).

CONGENITAL HYPOTRICHOSIS

(Synonym: congenital alopecia)

Clinical features (Figures 20.18 and 20.19)

Congenital hypotrichosis is a lack of adnexa (and therefore hair) in regions of the body where they normally are expected for the species. The so-called 'alopecic breeds' are simply the result of the willful breeding of animals with spontaneously occurring genetic mutations, in order to perpetuate the hairless trait. Consequently, 'alopecic breeds' can be viewed as examples of 'normal' or acceptable congenital hypotrichosis. These breeds include the Mexican Hairless and Chinese Crested dogs, and the Sphinx cat. For clarity, the authors consider hypotrichosis to be any congenital lack of hair. Alopecia signifies loss of pre-existing hair due to a generally acquired pathologic process.

Spontaneously occurring congenital hypotrichosis is a rare disease of the dog and cat that is characterized by varying degrees of hypotrichosis present from birth, or shortly thereafter. Affected animals are born with a diminished number of adnexal structures in affected areas. A spontaneous genetic mutation is believed to be the cause (Scott et al., 2001). Sex-linked inheritance of the genetic trait is suspected for most affected dogs, since most reported cases have been in males. Curiously, animals with congenital hypotrichosis may be born with hair that



Fig. 20.18 Congenital hypotrichosis in four of seven puppies in a litter of Labrador Retrievers. Varying sized patches of complete hair loss are seen on the muzzle and forehead of affected puppies. (Photograph courtesy G.A. Kunkle.)



Fig. 20.19 Generalized congenital hypotrichosis in a young female Rottweiler. Small tufts of hair are present only along the dorsal midline in a pattern similar to the Chinese Crested dog. (From Ihrke, P.J., Mueller, R.S. & Stannard, A.A. (1994) Generalized congenital hypotrichosis in a female Rottweiler. *Vet Dermatol* **4**, 65–9. Reprinted with permission.)

falls out during the first month of life (Scott et al., 2001). Presumably, hair follicle involution occurs after birth in some of these animals.

In congenital hypotrichosis, hairlessness may be the only abnormality noted, or hairlessness may be seen concomitantly with other genetic ectodermal defects such as abnormal dentition and abnormal tear production. The extent of hairlessness may vary from partial to nearly complete. Marked bilateral symmetry commonly is noted. Some dogs may exhibit only focal areas of hairlessness, usually near the dorsal midline. The temporal regions, pinnae, entire ventrum, and caudal dorsum are most frequently affected (as compiled by Scott et al., 2001). The tail also is affected commonly. Facial sensory hairs (vibrissae) may be distorted, curly, or absent. In animals with more generalized hairlessness, remaining hairs most commonly are located on the dorsal midline of the head and thorax, mimicking the pattern seen in alopecic breeds.

Initially, the exposed skin is visually normal in the hairless areas, but subsequently, hyperpigmentation and scaling occur. Mottled hyperpigmentation and hypopigmentation occur as the animal ages. Affected dogs and cats lacking protective pigmentation are at increased risk for solar dermatoses. Secondary bacterial folliculitis and comedones are common, and frequently become more extensive with advancing age.

Congenital hypotrichosis has been reported in many breeds including the Poodle, Basset Hound, Beagle, Labrador Retriever, Bichon Frise, Rottweiler, American Cocker Spaniel, Belgian Shepherd, German Shepherd Dog, Whippet, French Bulldog, Yorkshire Terrier, and Lhasa Apso, as compiled by Scott et al. (2001). Most reports of this syndrome have been in male dogs, with the exceptions of a female Labrador Retriever and a female Rottweiler (Kunkle, 1984; Ihrke et al., 1994). Congenital hypotrichosis is evident at birth, or within the first month thereafter.

Clinical differential diagnoses for congenital hypotrichosis are few if a correlative history is available. Congenital hypotrichosis is not a progressive skin disease. Progression should not be confused with natural enlargement of the area of hairlessness as the animal grows. If history is not available, then congenital hypotrichosis must be differentiated in the adult animal from diseases capable of producing widespread bilaterally symmetric alopecia, including hyperglucocorticoidism, hypothyroidism, sex hormone endocrinopathies, alopecia X, and acquired pattern alopecia. Histopathology is required to confirm the diagnosis.

Biopsy site selection

Multiple areas of complete alopecia should be selected for skin biopsy. An additional specimen should be obtained from as normal an area as possible for comparison. This selection technique will allow detection of subtle follicular changes in cases with only partial alopecia by comparison of follicular size and density with a normal control.

Histopathology (Figure 20.20)

The epidermis and dermis are normal in congenital hypotrichosis. Follicular changes principally include an overall decrease in the density of hair follicles per unit area of dermis; this may be variable case to case. Secondary hair follicles may be markedly reduced in number in the remaining adnexal units. Hair follicles that are present may be small and/or in telogen phase, but usually are not distorted. Follicular distortion was reported in hypotrichotic Birman kittens (Casal et al., 1994). Residual hair shafts, if any, are thin. Follicular keratosis may be present and may be severe, forming comedones, particularly in the Mexican Hairless and other hypotrichotic breeds of dogs. There may be variable reduction in the size of sebaceous glands as well, but they may be normal in size and distribution. Complete absence of hair follicles and adnexal glands has been reported and represents a more extensive ectodermal defect of the skin (Grieshaber et al., 1986; Ihrke et al., 1994). In hairless breeds of dogs with comedone formation, there may be accompanying pyoderma and chronic hyperplastic dermatitis.

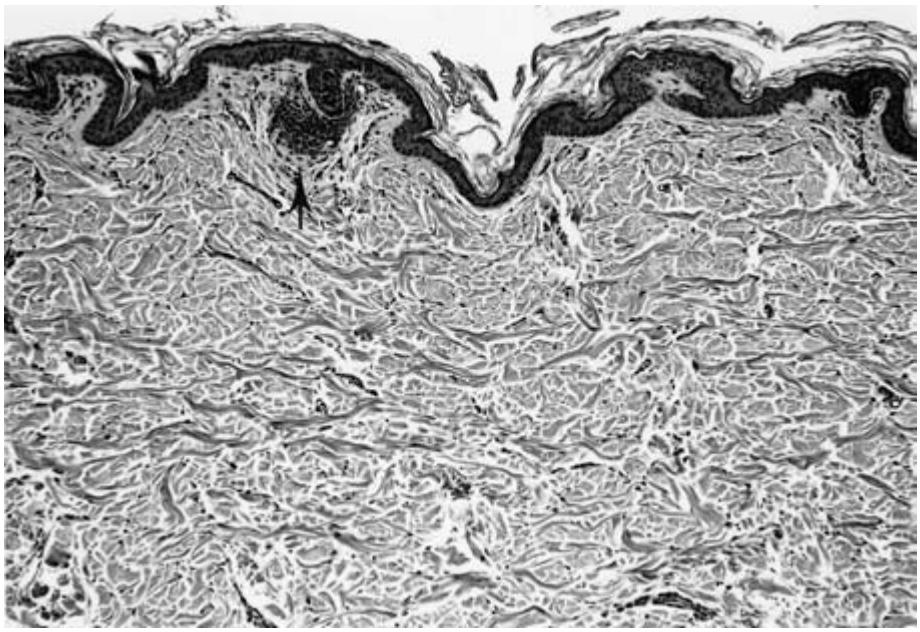


Fig. 20.20 Congenital hypotrichosis in a dog demonstrating nearly complete loss of follicles. A rudimentary follicular remnant remains near the epidermis (arrow).

Differential diagnosis includes acquired pattern baldness for cases of mild hypotrichosis, or follicular dysplasia if follicular distortion is present. The overall density of hair follicles is normal in pattern baldness and follicular dysplasia, and is decreased in hypotrichosis. Clinical differentiation may be required.

FOLLICULAR LIPIDOSIS

Clinical features (Figures 20.21 and 20.22)

Follicular lipidosis is a rare, presumed hereditary follicular dysplasia, published to date in only four Rottweiler puppies. Three dogs were seen in the United States and one dog was seen in Belgium (Gross et al., 1997; Fontaine & Olivry, 1999).

The pathophysiology of this syndrome is not understood. Affected puppies have ballooning of the matrical cells of the hair bulb of primary anagen hair follicles, apparently due to lipid deposition (Gross et al., 1997).

The presenting clinical feature is hair loss affecting only the mahogany or tan points of the face and feet. Diffuse partial alopecia of the affected points is accompanied by subtle loss of normal pigment, leaving the remaining point hairs mouse-gray. Other skin or haircoat abnormalities are not noted. One affected puppy had concomitant chronic renal disease suggestive of atrophic glomerulopathy, a syndrome also reported in Rottweilers, and was found at necropsy to be hypothyroid (Gross et al., 1997). The other three reported dogs with follicular lipidosis had no evidence of systemic disease (Gross et al., 1997; Fontaine & Olivry, 1999).



Fig. 20.21 Follicular lipidosis in a young Rottweiler. Note that diffuse partial alopecia affects only the mahogany points.

Follicular lipidosis has been reported to date only in Rottweilers. Reported puppies were diagnosed as having the disease at 5, 6, 9, and 11 months of age; both male and female dogs were represented (Gross et al., 1997; Fontaine & Olivry, 1999).

Diagnosis of follicular lipidosis in Rottweilers should not be problematic. The authors are aware of no other disease with these clinical features. Histopathology is required to confirm the diagnosis.

Biopsy site selection

Multiple areas exhibiting alopecia and coat-color change should be selected for skin biopsy. Care should be taken



Fig. 20.22 Closer view of the distal forelegs of the dog in Fig. 20.21 demonstrating partial hair loss.

to avoid delicate underlying structures when skin biopsy is performed on the distal extremities of puppies.

Histopathology (Figure 20.23)

The epidermis and dermis of affected mahogany-haired skin are normal. Primary anagen phase hair follicles demonstrate ballooning of the matrical cells of the hair bulb. Secondary anagen hairs are affected less often. Rare vacuoles are seen in hair shafts. Scattered hairs within follicles may appear irregular in contour with a frayed cuticle. Black-haired skin is normal.

In a previous report of three affected dogs, oil-red-O staining of frozen specimens from one dog demonstrated red-staining lipid within the follicular matrical cytoplasm (Gross et al., 1997). Electron microscopy demonstrated intracytoplasmic, homogeneous to granular deposits consistent with lipid.

No known differential diagnoses exist for follicular lipidosis. Although alopecia areata may feature cytoplasmic swelling of matrical cells, lymphocytic inflammation of the bulb and surrounding dermis are differentiating features. Immunohistochemistry for CD3+ T lymphocytes within affected hair bulbs was negative in a reported case of follicular lipidosis (Fontaine & Olivry, 1999).

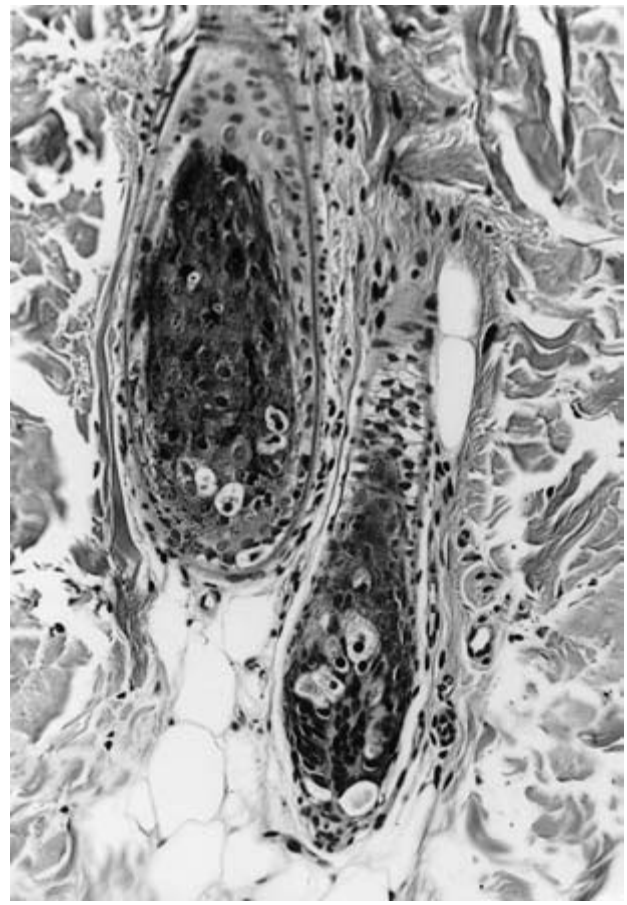


Fig. 20.23 Follicular lipidosis in a Rottweiler. Note ballooning of matrical cells of anagen hair bulb.

SEBACEOUS GLAND HYPERPLASIA

Clinical features

Sebaceous gland hyperplasia is a rare disease of both the dog and the cat. It is characterized clinically by extreme greasiness of the haircoat and underlying skin. Breed predilections are suggestive of a hereditary basis. A genetic basis for this disease also is supported by juvenile onset. The etiopathogenesis of sebaceous gland hyperplasia is not known.

The prime clinical feature of sebaceous gland hyperplasia in both dogs and cats is excessive and relentless greasiness, resulting in clumping of the haircoat. The underlying skin may appear greasy, but scaling or crusting is not present. Severity of disease seems to increase with advancing age. Pruritus has not been noted. Occasionally, secondary *Malassezia* dermatitis may exacerbate the greasiness and initiate pruritus. Affected dogs and cats are otherwise normal.

Border Terriers and Briards may be at increased risk for the development of sebaceous gland hyperplasia as well as Persian cats. One author (P.J.I.) has seen the syndrome in several Golden Retrievers. The syndrome has also been observed in a Devon Rex cat. Others have noted this syndrome in various unspecified dog breeds (Scott et al., 2001). Greasiness is first noted in puppies and kittens at less than 6 months of age. Sex predilections have not been noted.

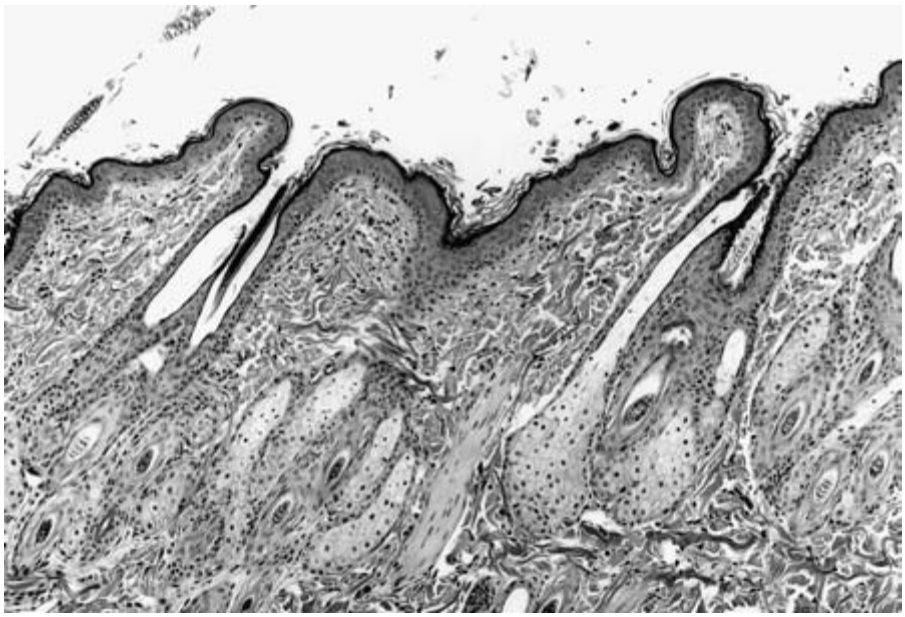


Fig. 20.24 Sebaceous gland hyperplasia in a Persian cat. Sebaceous gland lobules are increased in size but not in number.

Sebaceous gland hyperplasia is clinically striking. Other diseases, such as chronic allergic dermatitis causing greasy haircoats have associated inflammatory changes in the underlying skin. Early age of onset should increase clinical suspicion. Skin biopsy is required to confirm the diagnosis.

Biopsy site selection

Multiple skin biopsy specimens should be acquired from areas of maximal greasiness. If possible, an unaffected region from the same animal should be sampled for comparative purposes.

Histopathology (Figures 20.24 and 20.25)

The epidermis is normal to mildly acanthotic in uninflamed lesions of sebaceous gland hyperplasia. Sebaceous glands are uniformly enlarged. Individual lobules are two to three times larger than expected for location. There may be an increase in the number of sebaceous glands per follicular unit, but this is a not a consistent finding in Persian cats. In a Border Terrier observed by one author (T.L.G.), there was an increase in both the size and number of sebaceous lobules. These extended beyond the hair follicle to the adjacent interfollicular dermis.

Hair follicles are normal in size and distribution. There may be accompanying mild pleocellular dermatitis of superficial and periadnexal distribution, sometimes with increased acanthosis.

No known differential diagnoses exist for sebaceous hyperplasia. Correlation with location may be required as

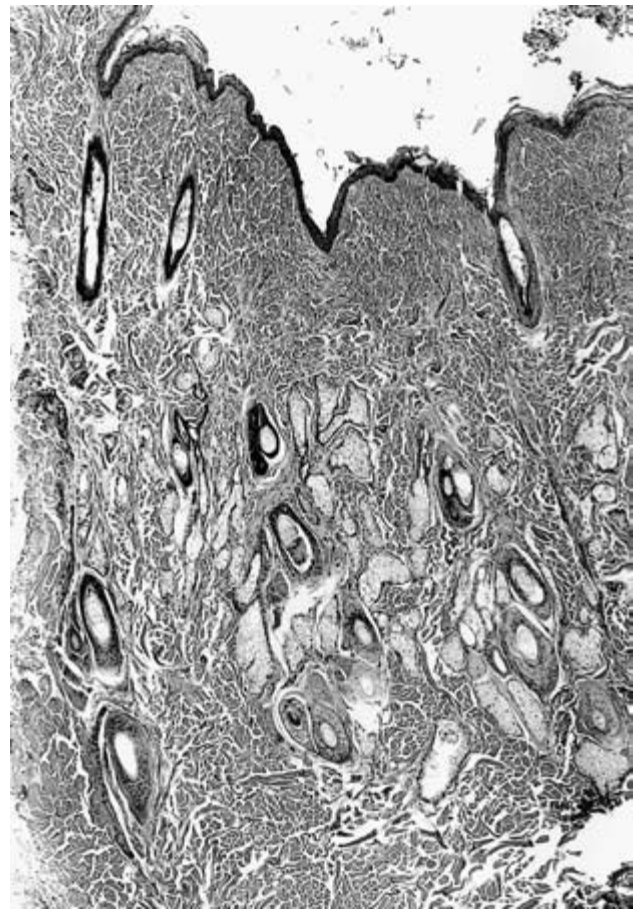


Fig. 20.25 Sebaceous gland hyperplasia in a Border Terrier. Sebaceous gland lobules are increased in size and number; note normal epidermis.



Fig. 20.26 Sebaceous gland dysplasia in a cat. Progressive alopecia, a rough poor quality haircoat, and fine adherent scale are present. (Photograph courtesy L. and S. Hertzel, and S.C. Vandenabeele.)

some sites normally feature large sebaceous glands, notably the chin of cats. Sebaceous hyperplasia may not be obvious in skin that is otherwise normal; gross findings of greasy skin should alert the pathologist to its discovery in tissue. Sebaceous hyperplasia in the setting of inflammatory skin disease is likely reactive. Sebaceous gland hyperplasia may be seen in any long-standing pruritic skin disease of dogs, including atopic dermatitis (see Chapter 9).

SEBACEOUS GLAND DYSPLASIA

Clinical features (Figure 20.26)

Sebaceous gland dysplasia is a rare dysplastic disease of the adnexa seen in both the dog and the cat. Clinically, it is characterized by adherent keratinous debris, and progressive alopecia. A genetic basis for sebaceous gland dysplasia is supported by juvenile onset. It is postulated that a genetic defect causes abnormal sebaceous development. Normal sebaceous gland differentiation and function probably is necessary for normal hair growth (Yager et al., 2003).

The predominant clinical features are adherent scale, a poor quality haircoat, and progressive alopecia. The normal architectural markings of the skin surface may be accentuated, but the skin is not thickened. The haircoat is dull, rough, and dry. The dorsum of the head and dorsal neck may be the initial sites affected. Poor coat quality and alopecia progress to involve much of the animal. In the few cases seen to date, cats seem to develop more severe alopecia with this syndrome than dogs. The preen region on the dorsum of the tail was spared in one observed cat. Pruritus is not a feature of sebaceous gland dysplasia.

Signalment predilections are not available; the syndrome is very rare. Juvenile onset is a prominent feature. Sex predilections have not been noted.

Sebaceous gland dysplasia is clinically distinctive, particularly in the clinical context of juvenile onset. Juvenile hypothyroidism could initiate poor coat quality and alopecia. Skin biopsy is required to confirm diagnosis.

Biopsy site selection

Multiple skin biopsy specimens should be acquired from regions of maximal poor haircoat quality and alopecia. If possible, a relatively unaffected region from the same animal should be sampled for comparative purposes.

Histopathology (Figures 20.27 through 20.29)

There is mild acanthosis accompanied by mild to moderate epidermal and follicular infundibular orthokeratotic hyperkeratosis. In one dog observed, there was patchy parakeratotic and neutrophilic scale/crusting as well.

In cats, sebaceous glands appear to be undergoing premature involution, as there is marked eosinophilia and shrinkage of sebocytes, suggestive of apoptosis. However, complete atrophy does not occur, even in lesions obtained at a later age. Biopsy performed three times in one cat from 4 months to 2 years of age showed similar changes. Sebaceous glands were reduced in size in the final biopsy when compared to the early specimens.

Residual sebocytes, which are variably reduced in size, are outnumbered by epithelial cells of ductular or reserve cell origin. Often, only a small collection of undifferentiated epithelial cells and small sebocytes remains at the site of previous glands. Orderly centripetal progression from reserve cells to mature sebocytes usually is lost. Sebocytes that remain may have irregular cytoplasmic vacuolation; others appear normal except for reduced size.

Early specimens from cats show normal follicular density and appearance. Later biopsy specimens show follicular atrophy and dysplasia. Some normal anagen hair follicles may be observed. Small hair shafts often remain in the atrophic or dysplastic follicles. Some hair follicles show mild perifollicular fibrosis at the isthmus in the vicinity of previous glands, accompanied by distortion of the follicular wall. Occasional trichomalacia is observed. These changes suggest that hair follicles develop abnormally in the face of sebaceous gland dysplasia, but still attempt to cycle. The apparent effect is an overall decrease in the size of adnexal units with time. A few mixed mononuclear cells are present superficially and around hair follicles and occasionally infiltrate the follicular wall (mural folliculitis; see Chapter 18).

In dogs, there is more severe and pervasive follicular dysplasia as compared to cats. Affected follicles have

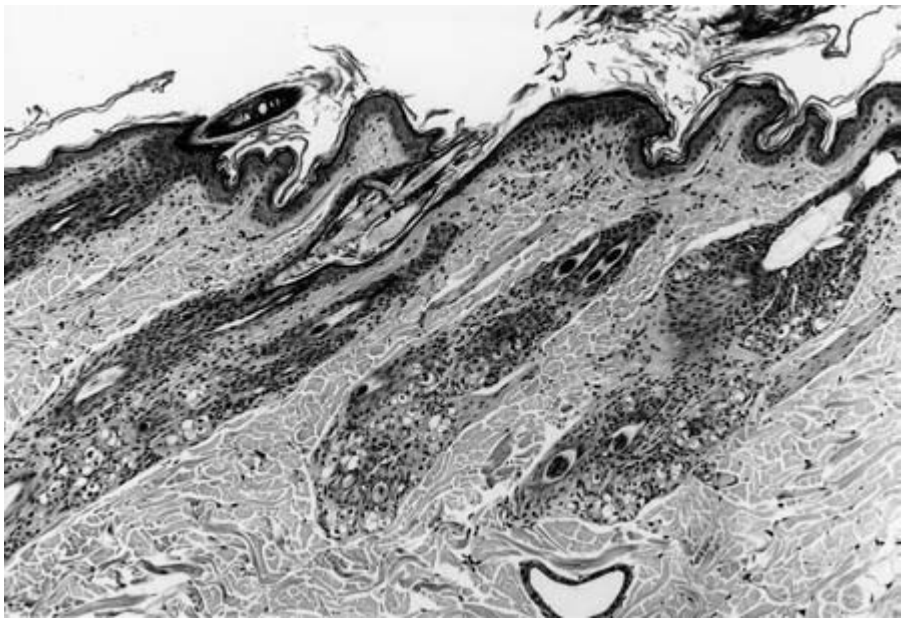


Fig. 20.27 Sebaceous gland dysplasia in a cat. Note diffuse alteration of glands; at this power individual lobules are poorly defined and sebocytes appear small.

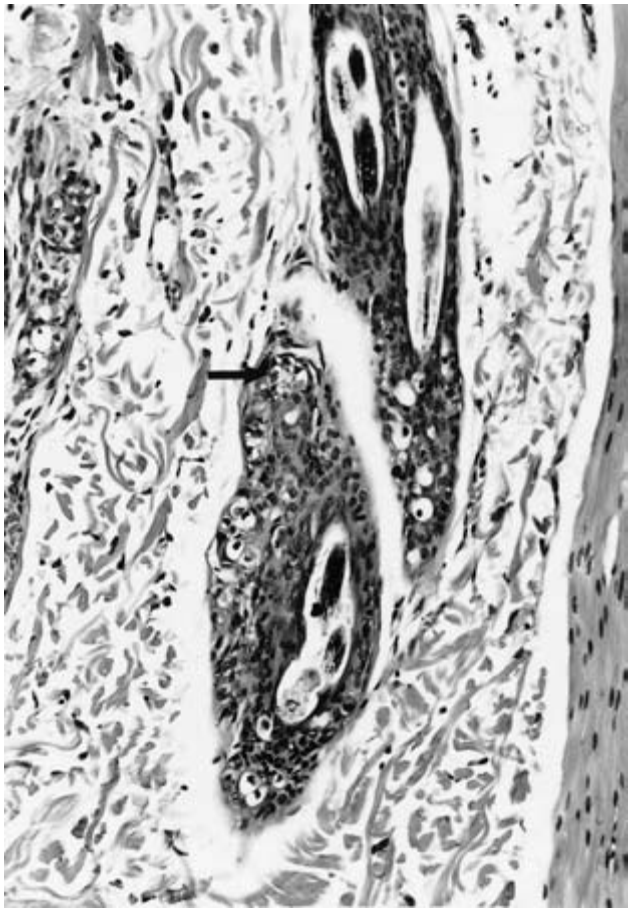


Fig. 20.28 Higher magnification of sebaceous gland dysplasia in a cat, demonstrating residual small numbers of clear sebocytes and increased proportion of small reserve cells; centripetal progression from reserve cells to mature sebocytes is not seen. There is active sebocytic degeneration (arrow).

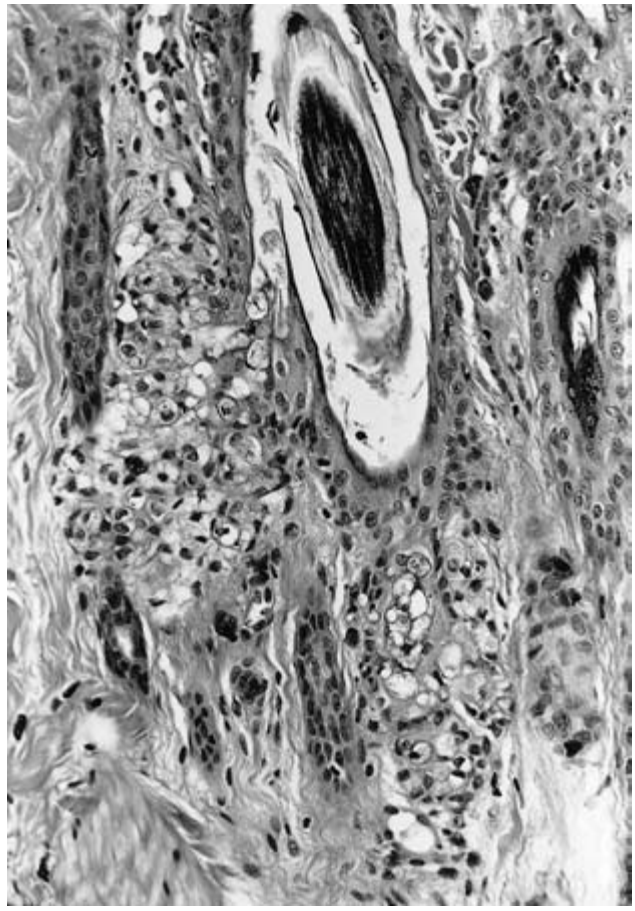


Fig. 20.29 Sebaceous gland dysplasia in a dog. The normal lobular appearance is absent; atypical sebocytes contain variably-sized vacuoles.

irregular, wavy contours and often twisted lower segments. In one dog observed, hair follicles were nearly uniformly in telogen stage, but retained hair shafts. Sebaceous gland degenerative and dysplastic changes are as observed in cats. Mixed inflammation, including lymphocytes, plasma cells, and fewer neutrophils and histiocytes, encircle, and partially infiltrate some follicular walls at the isthmus as well as some of the sebaceous glands. Similar inflammation may extend perivascularly in the superficial dermis. Focal superficial dermal pyogranulomatous inflammation was identified in one dog.

There are no known differential diagnoses for sebaceous gland dysplasia. Late stage lesions might be confused with sebaceous adenitis, but the replacement of normal sebaceous glands by undifferentiated epithelial cells and small sebocytes in sebaceous gland dysplasia allows differentiation. Sebaceous gland vacuolation and atrophy have been observed with hair follicle-predominant erythema multiforme (see Chapter 4); however, apoptosis of sebocytes was not a feature.

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Part IV

Diseases of the Panniculus

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Chapter 21

Diseases of the panniculus

The term 'panniculitis' denotes a group of diseases of multifactorial etiology unified by the localization of the major focus of inflammation to the fat of the subcutis. The panniculus and subcutis are considered to be synonymous in reviews of human panniculitis (Requeña & Sánchez Yus, 2001), and are used interchangeably. The panniculus may also be considered the superficial subcutis, above the panniculus carnosus muscle. Lipocytes, fibrous trabeculae or septa, and blood vessels are the major components of the panniculus. Panniculitis results from direct or indirect damage to these tissues. A wide variety of pathologic processes affect the panniculus. Panniculitis from any cause is enhanced by lipid release from damaged lipocytes, since lipids are vigorous stimulators of inflammation. Once free lipids are liberated into tissue, hydrolysis and saponification occur releasing proinflammatory fatty acids.

Inflammation of the panniculus may be septal and principally involve the interlobular septa that are composed of collagen and vessels, or may be lobular and principally affect the adipocytes. In essence, inflammation of the panniculus shows predominance rather than pure rendering of one pattern; this has been described in humans as 'mostly lobular' or 'mostly septal' panniculitis (Requeña & Sánchez Yus, 2001). 'Mostly lobular' panniculitis is the most common histopathologic subtype of panniculitis observed in the dog and cat, and is characterized by mixed inflammation accompanied by degeneration of adipocytes. 'Mostly septal' panniculitis is considered to be very rare in both species and usually has a vascular component. Panniculitis may be localized or generalized. Localized panniculitis is initiated most commonly by local trauma or injection of foreign material. Generalized or multifocal panniculitis reflects metabolic or systemic disease; some of these remain idiopathic to date.

POSTRABIES VACCINATION PANNICULITIS

Clinical features (Figures 21.1 through 21.3)

Postrabies vaccination panniculitis is a relatively common canine skin disease characterized by focal alopecia with minimal gross inflammation. It is considered to be one of the vasculopathic syndromes under the heading of 'ischemic' dermatopathy/canine dermatomyositis (see Chapters 3 and 10). The syndrome is presumed to be due to an idiosyncratic immunologic reaction to rabies antigen that partially targets vessels. Rabies viral antigen was documented in the walls of dermal blood vessels and in the epithelium of hair follicles via immunofluorescence testing (Wilcock & Yager, 1986). The marked predilection for Toy or Miniature Poodles, as well as other long-haired small breeds, indicates probable enhanced genetic susceptibility for this syndrome, possibly due to the long anagen hair growth cycle in these breeds. It is tempting to speculate that this syndrome may be partially linked to the increased antigenic load per body size, since the same aliquot of rabies vaccine is given to all dogs. In cats, rabies vaccine reactions are those of postinjection panniculitis (see p. 541) and do not resemble those of dogs.

Classically, an alopecic macule or, less commonly, an alopecic plaque develops at the site of prior subcutaneous rabies vaccine deposition. The time interval between vaccination and observation of the lesion usually is 2 to 3 months, but may be longer. Most lesions vary between 2 and 10 cm in diameter. Subtle satellite lesions may be present. A few hairs may remain within the boundaries of the lesion. Erythema and visible inflammation are minimal or absent. Hyperpigmentation may be an occasional sequela, especially in black Miniature Poodles and other breeds that tend to pigment in response to inflammation.

Most lesions develop in the neck and shoulder region near the scapula where most subcutaneous rabies vaccinations are given. Putative gravitational drift can result in the development of lesions ventral to the site of administration; thus the lateral or even the ventral thorax may be affected.

The lesions usually are asymptomatic. A small subgroup of dogs with postrabies vaccination panniculitis display lethargy and depression, and may be febrile. Elevated liver enzymes have been noted. Usually, it is not known if further rabies vaccination has a deleterious



Fig. 21.1 Postrabies vaccination panniculitis in an apricot colored Miniature Poodle. Alopecia and hyperpigmentation have developed at the site of a prior subcutaneous rabies vaccination above the right axillary region. Probable gravitational drift has resulted in extension of the lesions ventrally into the axilla and the triceps region of the right foreleg.

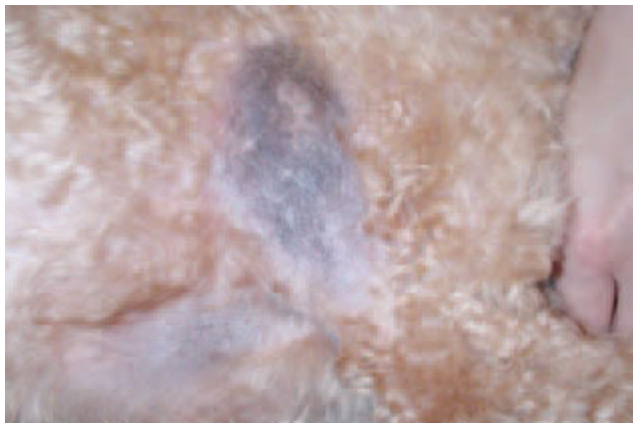


Fig. 21.2 Closer view of the dog in Fig. 21.1. The lesions have extended from the more dorsal vaccination site to the axilla and triceps region.

effect, as most dogs are not revaccinated. However, the authors have observed exacerbation or recrudescence of prior lesions of postrabies vaccination panniculitis by revaccination. Recrudescence occurred concurrently with the induction of new lesions.

In addition to focal vaccine reactions, a small subgroup of dogs develop more severe, widespread alopecia and skin lesions, commonly in conjunction with lethargy and depression. The term 'generalized vaccine-induced ischemic dermatopathy' has been used for these dogs (see Chapter 3). Revaccination with subcutaneous rabies vaccine is not recommended, as the syndrome may exacerbate in response to further antigenic exposure. If alopecia and other ischemic skin lesions begin subtly and gradually, a temporal link with rabies vaccine may not be noted. In these cases, it may not be possible to differentiate postrabies vaccine panniculitis from other forms of ischemic dermatopathy (see Chapter 3).



Fig. 21.3 Postrabies vaccination panniculitis over the left scapula in a black Miniature Poodle. The affected area is nearly totally alopecic.

Chronic rear leg swelling with pitting edema and a temporal association with rabies vaccination has been noted by the authors in a small number of cases. This syndrome may represent another variant of postrabies vaccination-induced immunoreactive disease, as some histologic features are similar (see below).

Postrabies vaccination panniculitis is predominantly a disease of long-haired toy or small breed dogs with long anagen hair cycles. In the opinion of the authors, Poodles and Bichon Frises are at markedly increased risk. Although reports did not note the size of Poodle affected, all affected Poodles seen by the authors have been either Miniature or Toy. The syndrome also has been seen by the authors in the Shih Tzu, Lhasa Apso, Maltese, Silky Terrier, Yorkshire Terrier, Chihuahua, Toy Manchester Terrier, American Eskimo, Poodle crossbreeds, and Miniature Dachshunds. The authors have observed only a single case of postrabies vaccination panniculitis in a large breed dog, a Samoyed. Age or sex predilections have not been noted.

Postrabies vaccination panniculitis is visually distinctive. Clinical differential diagnoses could include other causes of focal, visually noninflammatory alopecia, such as demodicosis and dermatophytosis, alopecia areata, cicatricial alopecia, and erythema ab igne. These must be ruled out by history, clinical presentation, skin scrapings, culture, and histopathology.

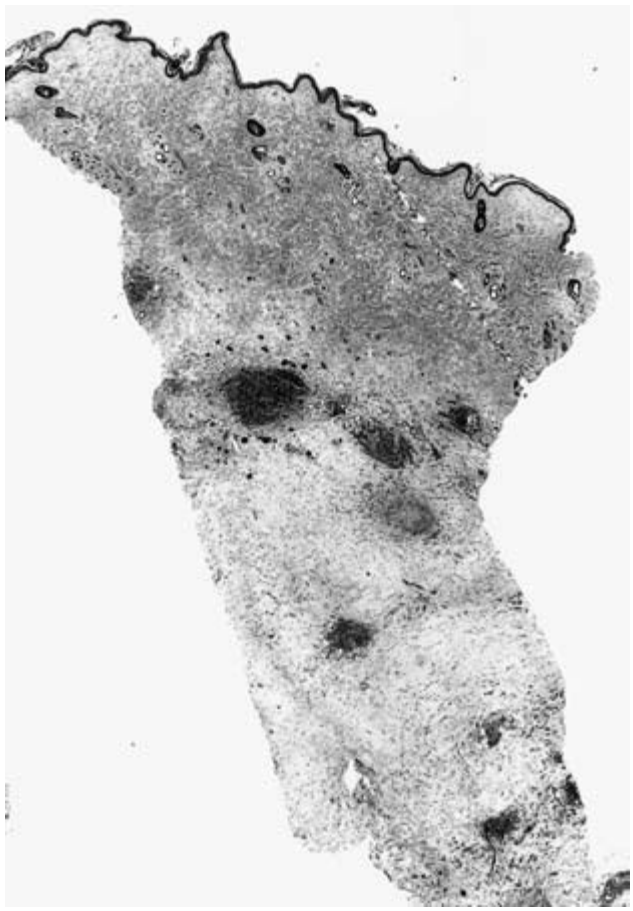


Fig. 21.4 Subgross view of postrabies vaccination panniculitis. Severely atrophic follicles overlie multinodular inflammation of the panniculus.

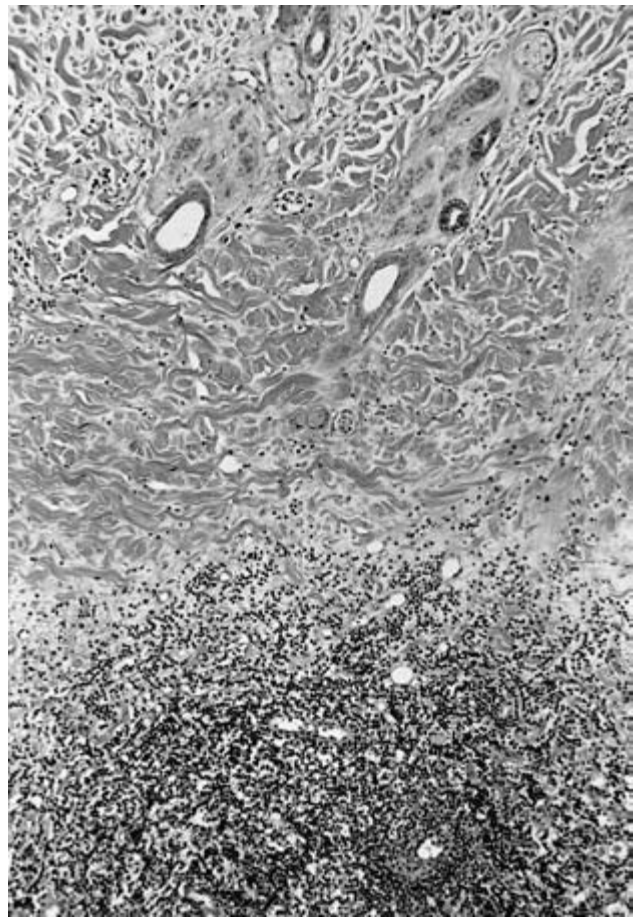


Fig. 21.5 Higher magnification of postrabies vaccination panniculitis. Atrophic follicles are above intense lymphocytic panniculitis. Note the ischemic smudging and pallor of the dermal collagen.

Biopsy site selection

Biopsy specimens should be obtained from affected skin and subcutis just within the outer margin of the plaque or macule. Specimens from near the margin may show more diagnostic histopathologic changes than the central chronic area where typical inflammation may be scant.

Histopathology (Figures 21.4 through 21.6)

The ischemic lesions of the overlying dermis and hair follicles have been discussed, and principally include dermal pallor and smudging, and follicular atrophy (see Chapters 3 and 19). Similar diffuse smudging and pallor of collagen characterize the panniculus. Edema and/or mucin may be prominent.

Moderate to severe, nodular accumulations of lymphocytes, fewer histiocytes, and occasional plasma cells are present in the lower dermis and panniculus, and often tightly surround vessels. There may be amorphous basophilic foreign material presumably constituting vaccine product. Panniculitis may be sparse, most often in advanced lesions. Cell poor vasculitis of small vessels of the panniculus is common and may be subtle (see Chapter 10). Blood vessels may have swollen endothelia, thickened walls, or may be infiltrated by lymphocytes, sometimes heavily. Larger blood vessels may be affected. Variable cell poor vasculitis of the overlying dermis is as seen in ischemic dermatopathy/canine familial dermatomyositis (see Chapter 10). Immunofluorescence testing with antibody to rabies viral antigen revealed deposition in and around vessels as well as in the epithelium of hair follicles (Wilcock & Yager, 1986).

A morphologically similar but more extensive panniculitis occurs in the context of chronic rear leg swelling, and also may represent a putative vaccine reaction. Blood vessels of the deep dermis and panniculus are often cuffed with lymphocytes, histiocytes, and variable plasma cells, as seen in classic postrabies vaccination panniculitis. This inflammation often extends to the deep subcutis, and there is generally severe diffuse edema. Macrophages,

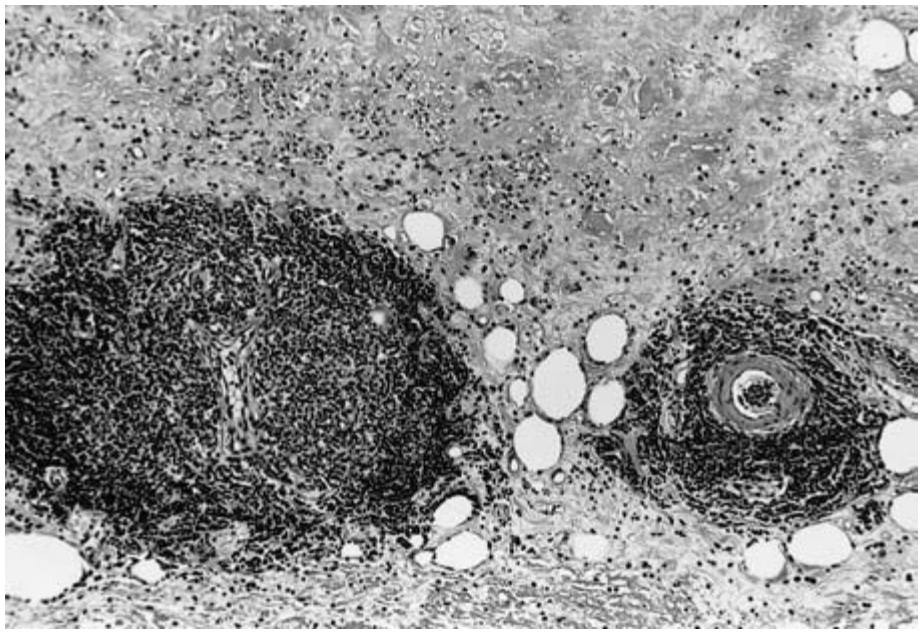


Fig. 21.6 Higher magnification of postrabies vaccination panniculitis. Characteristic nodules of lymphocytes are adjacent to fibrin and other amorphous debris. Note the somewhat hyalinized large vessel at the center of the lymphocytic nodule at right.

with or without lymphocytes, may surround collagen fibers, forming small granulomas. The formation of these granulomas may be striking in some cases and have been observed sporadically in other types of cell poor vasculitis (see Chapter 10), as well as in typical postrabies vaccine panniculitis. This phenomenon is believed to represent an ischemic sequel to localized vascular disease, as described in humans (Magro et al., 1996).

Lesions of postrabies vaccination panniculitis are unique. Eosinophils are usually present in reactions due to other types of vaccines, but are inconspicuous in postrabies vaccination alopecia. Granulomas and pyogranulomas dominate reactions due to many other injected medications. Although follicular atrophy may follow repositol injections (see p. 542), ischemic changes of collagen (smudging and pallor), as seen in postrabies vaccination panniculitis, are not present; further, the inflammatory reaction of repositol injections is overwhelmingly neutrophilic.



Fig. 21.7 Postinjection panniculitis in a dog. A solitary subcutaneous nodule is visible right of center in the clipped region at the putative site of a multivalent vaccine injection. Focal hemorrhage was caused by a subcutaneous injection of lidocaine given in preparation for skin biopsy.

POSTINJECTION PANNICULITIS

Clinical features (Figure 21.7)

Postinjection panniculitis is diagnosed uncommonly in the cat and rarely in the dog (Schmeitzel et al., 1986; Hendrick & Dunagan, 1991). This syndrome probably is underdiagnosed, since lesions may not be obvious clinically or may be deemed inconsequential and hence not worthy of biopsy. Although the etiology has not been proven, the histopathologic pattern suggests a combined foreign body and hypersensitivity reaction. Postinjection panniculitis is caused predominantly by vaccines, and less commonly by other injected medications, including antibiotics such as long-acting benzathine penicillin and tylosin. Potassium bromide may produce similar lesions. Combination vaccines have initiated the reaction in both dogs and cats. Rabies vaccines can induce this reaction pattern in the cat but not, in the authors' experience, in dogs; a separate vasculopathic syndrome of postrabies vaccination panniculitis is seen in dogs (see p. 538).

A solitary subcutaneous nodule, varying in diameter from 5 mm to 3 cm, is noted at the site of a previous subcutaneously administered vaccine or other medication.

Nodules may be either freely moveable or fixed to the overlying dermis, and vary in texture from soft and fluctuant to firm. The overlying skin is normal, but some alopecia may be an occasional feature. Rarely, pain can be elicited on palpation. Systemic signs have not been reported or noted by the authors.

Breed, age, or sex predilections have not been noted. Postinjection panniculitis must be differentiated from other nodular diseases affecting the subcutaneous tissue, such as neoplasms, cysts, sterile abscesses of repositol injections, and traumatic panniculitis. Occurrence at the site of a previous injection increases the index of suspicion. Skin biopsy confirms the diagnosis, and commonly is made after the removal of a suspected neoplasm.

Biopsy site selection

Excisional biopsy of the entire nodule is preferred, as surgical excision also is curative. Wide excision often is performed as cutaneous neoplasia is frequently suspected.

Histopathology (Figure 21.8 through 21.13)

The epidermis and dermis are usually normal. Inflammation may encroach on the deep dermis, depending upon the level of injection. Occasional more superficial dermal lesions may evoke overlying ulceration. Follicular atrophy as seen in postrabies vaccination reactions is rare; however, ischemic alteration of collagen is absent (see p. 538).

The panniculus contains a discrete nodule that often has a necrotic hypocellular center. This center is amorphous and stains lightly eosinophilic or amphophilic; necrotic adipocytes are present. In some cases, smaller grouped central foci of necrosis may be observed. Granular to elongated flecks of basophilic debris often are present in the central zone, particularly in reactions due to vaccines, and are presumably derived from vaccine product (adjuvant or other). Surrounding the core is a layer of macrophages and often giant cells. There may be discrete granulomas or pyogranulomas; in the authors' experience these are more numerous in reactions to non-vaccine medications. The macrophages may be markedly xanthomatous in reactions to lipid-rich medications. A zone of intense lymphocytic and eosinophilic inflammation composes the outer layer; merging of the granulomatous and lymphocytic zones is common. Lymphocytes may be arranged in prominent follicular aggregates along the perimeter of the lesion. The inflammatory pattern suggests a combination of foreign body (granulomatous with giant cells) and hypersensitivity (lymphocytic and eosinophilic) reactions to the deposited vaccine or medication.

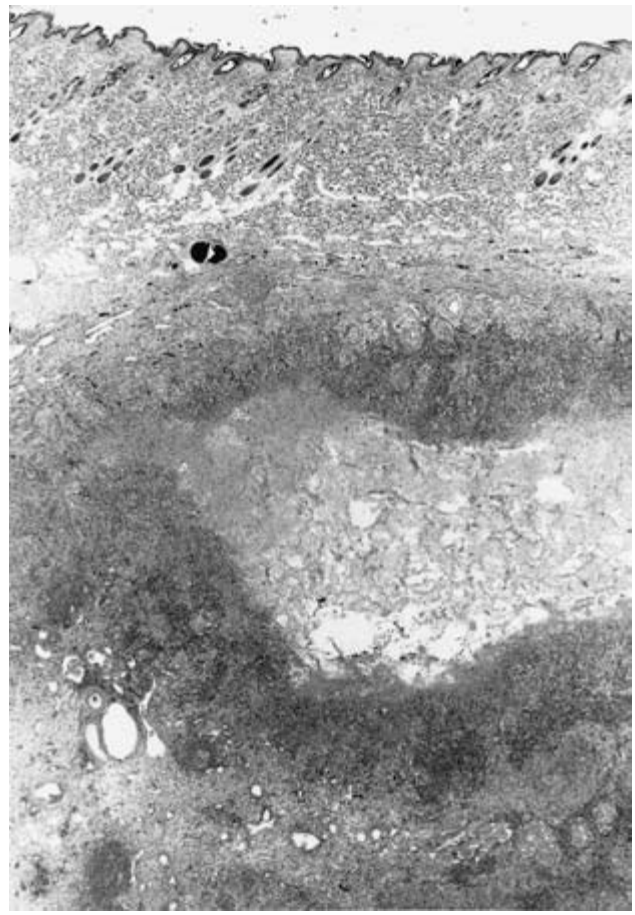


Fig. 21.8 Postinjection panniculitis in a cat due to rabies vaccination. The large pale central zone of necrosis is surrounded by an intense inflammatory cuff.

Differential diagnoses are few, as the reaction pattern of postinjection panniculitis is unique and diagnostic. Postrabies vaccination panniculitis in dogs does not resemble other postinjection reactions, including rabies vaccine reactions in cats. In canine postrabies vaccination panniculitis the lesions are not discrete, the central necrotic zone is absent, and eosinophils are not found. Traumatic panniculitis has necrosis, but generally lacks lymphocytic and eosinophilic inflammation.

STERILE ABSCESS OF REPOSITOL INJECTION

Clinical features (Figure 21.14)

Sterile abscess of repositol injection is a relatively common, likely underdiagnosed syndrome of the dog and cat. Skin lesions have been seen most frequently secondary to repositol corticosteroidpreparations, especially those containing methylprednisolone acetate. To date, the authors have seen this reaction pattern only in response

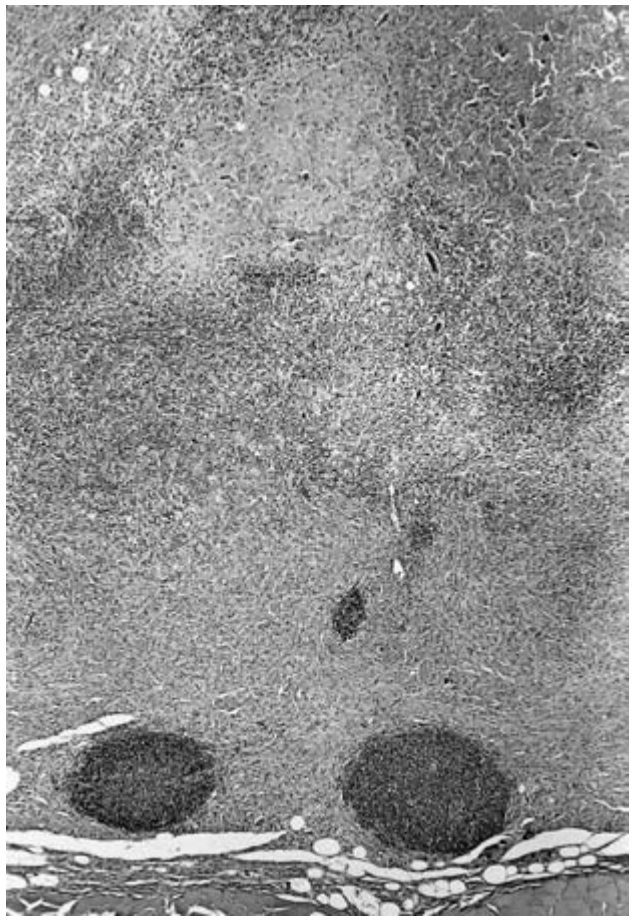


Fig. 21.9 Higher magnification of postinjection panniculitis in a cat. The central pale and amorphous necrotic zone is at top; large lymphoid nodules are at the outer edge at bottom.

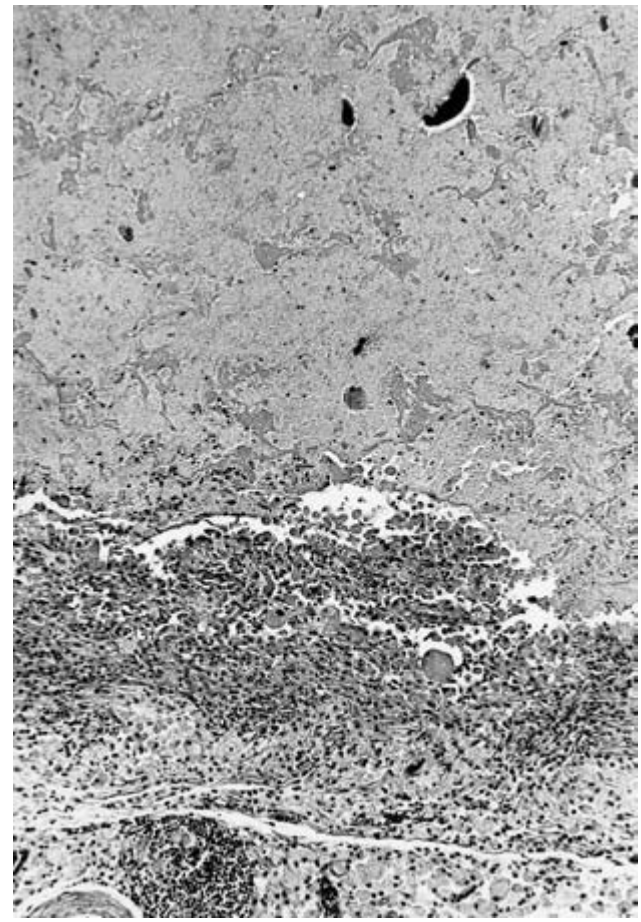


Fig. 21.10 Higher magnification of postinjection panniculitis in a cat, demonstrating necrotic central zone containing characteristic very darkly staining, floccular foreign deposits. Note mixed inflammation with macrophages and lymphoid nodule in outer zone of inflammation at bottom.

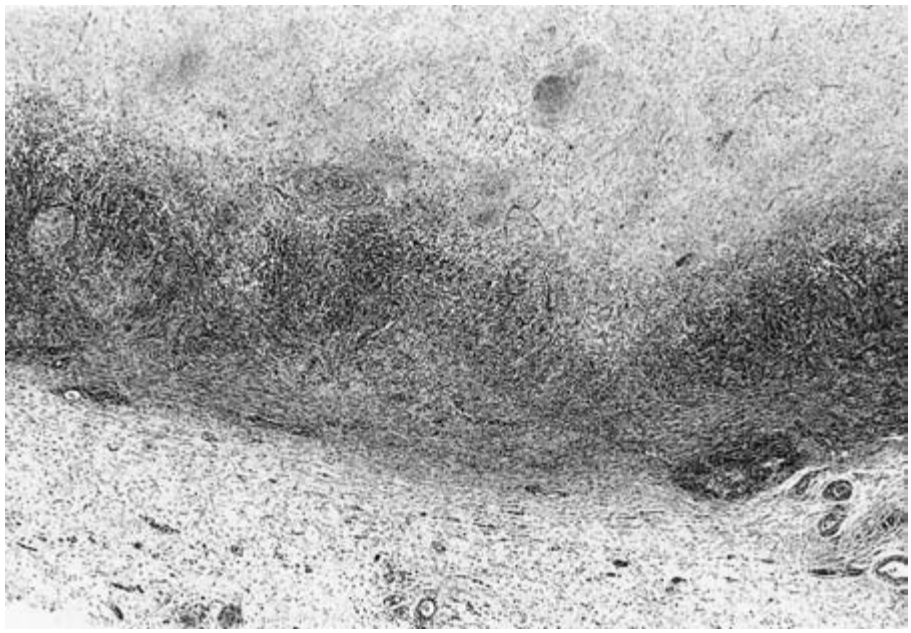


Fig. 21.11 Postinjection panniculitis due to antibiotic in a dog. The central pale necrotic zone at top is outlined by an intense cuff of lymphocyte-rich inflammation, as seen with vaccine reactions.

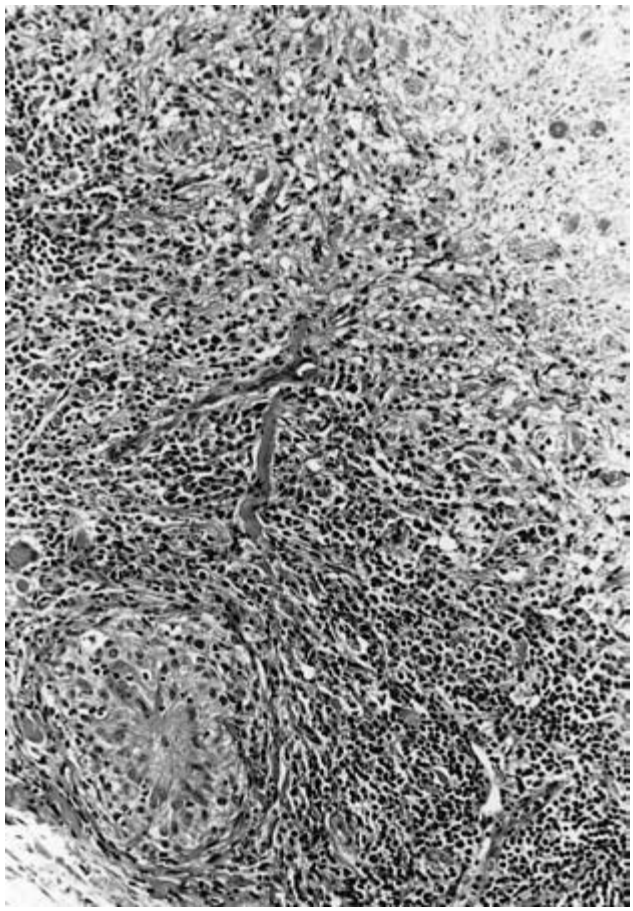


Fig. 21.12 Higher magnification of Fig. 21.11. Note discrete granuloma at lower left.

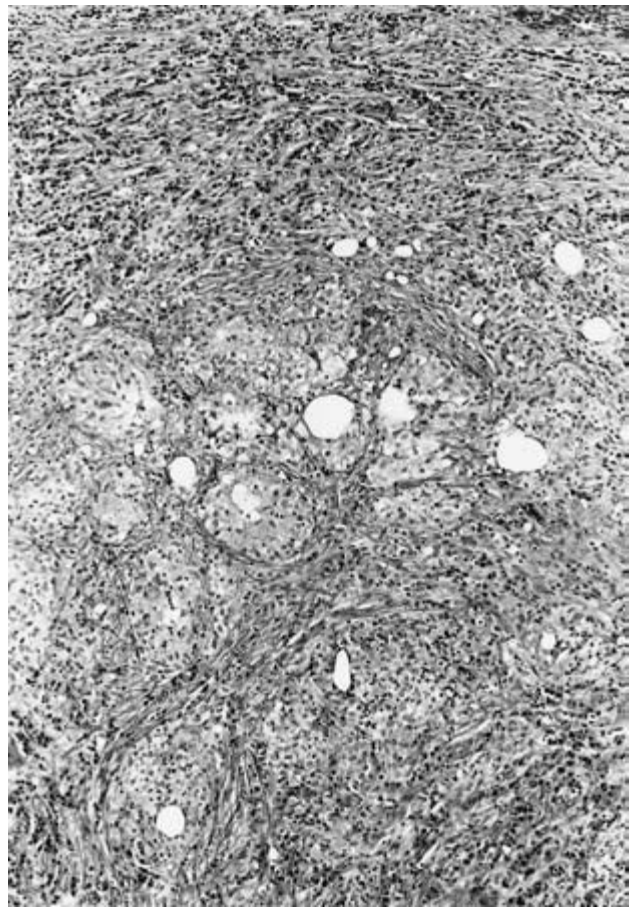


Fig. 21.13 High magnification of postinjection panniculitis due to potassium bromide (KBr). Granulomas and pyogranulomas are abundant.

to repositol injections of corticosteroids or progestational hormones.

Solitary, firm subcutaneous nodules are the most common clinical presentation. Well-demarcated, somewhat circular areas of partial to complete alopecia may occur at the site of injection; however, alopecia is not always present. Occasionally, ventral extensions of a more dorsal circular focus suggest gravitational 'drip configurations'. Most lesions are less than 3 cm in diameter. Careful palpation may reveal that the overlying skin is depressed due to atrophy. The location of these lesions reflects common sites of administered subcutaneous repositol injections, such as the region of the neck between the scapulae or over the lateral thorax.

Information on signalment predilections is not available. However, one author (P.J.I.) suspects that Miniature Poodles may be over-represented.

Clinical differential diagnoses may include other focal panniculitides including postrabies vaccination panniculitis, postinjection panniculitis, traumatic panniculitis, and



Fig. 21.14 Sterile abscess of repositol injection in a white Miniature Poodle. A nodule in the panniculus with a surrounding reasonably well-demarcated area of alopecia has occurred at the site of an injection of a repositol corticosteroid preparation containing methyl prednisolone acetate.

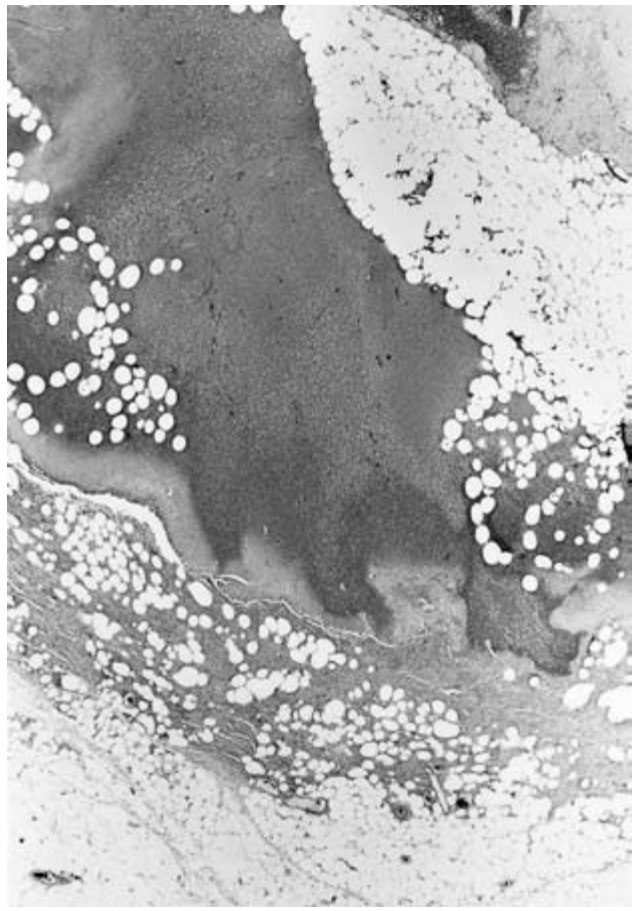


Fig. 21.15 Sterile abscess of repositol injection in a cat. A large dark zone of degenerated neutrophils obliterates the subcutaneous fat. Note fibrous encapsulation encroaching into adjacent adipose tissue along the lower edge of the lesion.

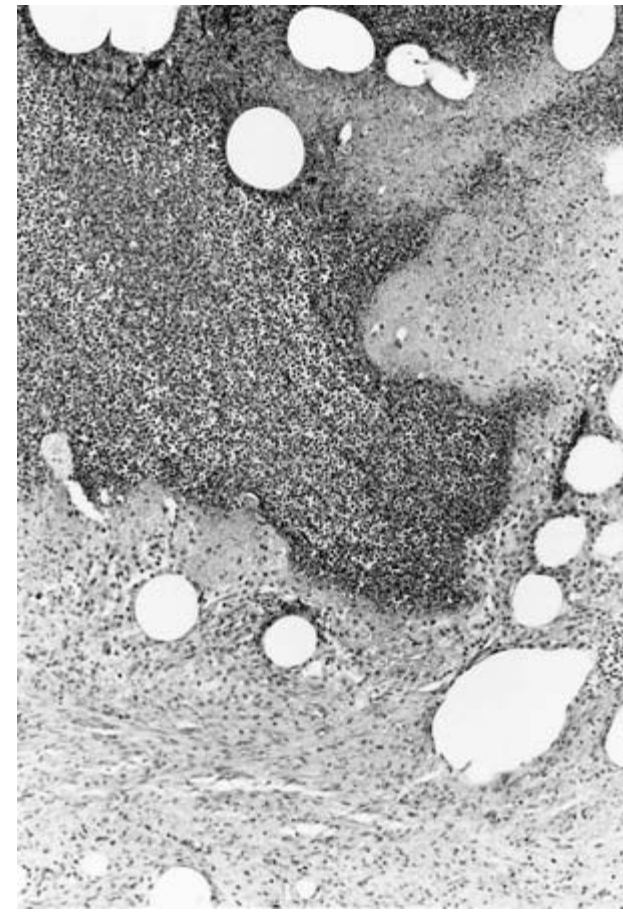


Fig. 21.16 Higher magnification of Fig. 21.15. Note the pale gray amorphous zone of necrosis surrounding a central darker zone of recognizable, degenerated neutrophils. Fibrosis is at bottom.

neoplasia. Differentiation is accomplished by history of type of injection or trauma, as well as skin biopsy.

Biopsy site selection

Excisional biopsy of the lesion is preferred, as surgical excision also is curative. Wide excision often is performed as cutaneous neoplasia may be suspected.

Histopathology (Figures 21.15 and 21.16)

The overlying skin is frequently normal. Occasionally there may be follicular atrophy, resembling that of hyperglucocorticoidism (see Chapter 19). The thickness of the dermis may be reduced; in most cases this is a subjective and thus nondefinitive evaluation, as normal adjacent skin rarely is provided.

There is a relatively discrete nodule in the panniculus that comprises amorphous, uniformly degenerated neutrophils. There may be zones of frank necrosis adjacent to zones of more viable cells. Recognizable adipocytes are not present within the nodule. There is a thin peripheral zone composed of foamy macrophages and there may be variable peripheral fibrosis, forming a thin capsule, which may radiate into surrounding fat.

Repositol injection reactions are unique, and differentiation is not problematic. Clinical inquiries consistently yield a history of repositol injection for these lesions. However, other medications could technically produce a similar reaction pattern.

TRAUMATIC PANNICULITIS

Clinical features

Traumatic panniculitis is a relatively common, but probably underdiagnosed lesion of cats and dogs. Etiologies include focal ischemia caused by blunt trauma, chronic

pressure, or decreased blood supply. The authors speculate that sites overlying bony prominences may be predisposed to blunt trauma creating 'trapping injury' to the adipose tissue overlying bone. Ischemic injury due to decreased blood supply may be more common in obese cats and dogs in which increased fat deposition is accompanied by a disproportionate, lesser increase in vascularity, predisposing to ischemia from slight insult.

The most common presenting clinical feature is a focal, firm subcutaneous nodule. The skin overlying the nodule is normal. Lesions are seen predominantly on the trunk, especially dorsally over the dorsal spinous processes, and over the sternum ventrally. Less commonly, lesions also may be seen over the wing of the ilium, the lumbar eminences in dogs, and over other pressure points. Dorsal lesions have been associated anecdotally with trauma from dog doors and given the informal designation of 'doggie door syndrome'. Lesions are asymptomatic; pain is not noted.

Breed, age, or sex predilections have not been noted. Obese animals probably are predisposed.

Clinical differential diagnoses should include neoplasms, organizing hematomas or seromas, foreign body reactions, infectious granulomas, postinjection panniculitis, and sterile abscess of repositol injections. Foreign body reactions often fistulate and drain, and commonly are painful. Infectious diseases usually are multicentric, inflammation may be obvious, and lesions often are painful. Skin biopsy is required for diagnosis.

Biopsy site selection

Wedge removal of the entire nodule usually is performed, due to suspicion of neoplasia. Occasionally, the ischemic process extends beyond the site of palpable lesion; local recurrence may be prevented by obtaining reasonable margins of normal tissue during procurement, provided that the site is no longer subjected to the trauma that may have initiated it.

Histopathology (Figures 21.17 and 21.18)

The epidermis and dermis are normal, but often are excluded from the specimen submitted for histopathology. The adipose tissue of the panniculus or deep subcutis contains a large central focus of lobular fat necrosis. Adipocytes lack nuclei but retain their normal shape, creating 'ghosts' or 'shells' of fat cells. Ruptured adipocytes form large, cystic spaces. Interspersed and surrounding the devitalized fat cells are foamy macrophages containing lipid debris. Other types of inflammatory cells are rare. Cholesterol clefts may occasionally be observed. There may be accompanying hemorrhage or hemosiderosis. Frequently, marginal fibrosis encroaches upon and interposes among devitalized adipocytes; older lesions may be predominantly fibrotic, and fibrocytes may be markedly proliferative (fibrosing steatitis).

Differential diagnoses are few, as the extensive necrosis and scant inflammation of affected adipose tissue are very characteristic of traumatic panniculitis. Late stage lesions

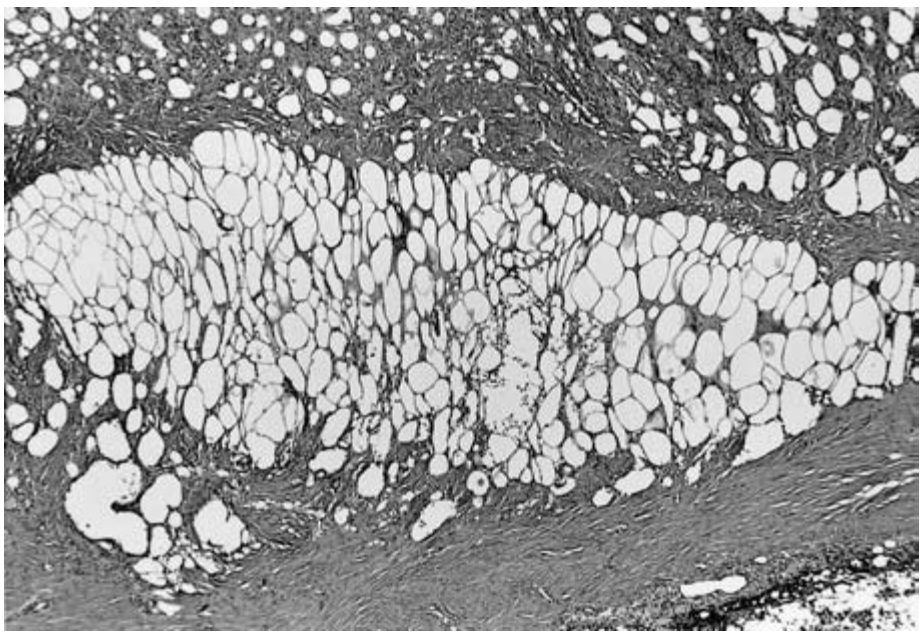


Fig. 21.17 Traumatic panniculitis. A large central zone of necrotic adipose tissue is surrounded by a dense zone of fibrosis.

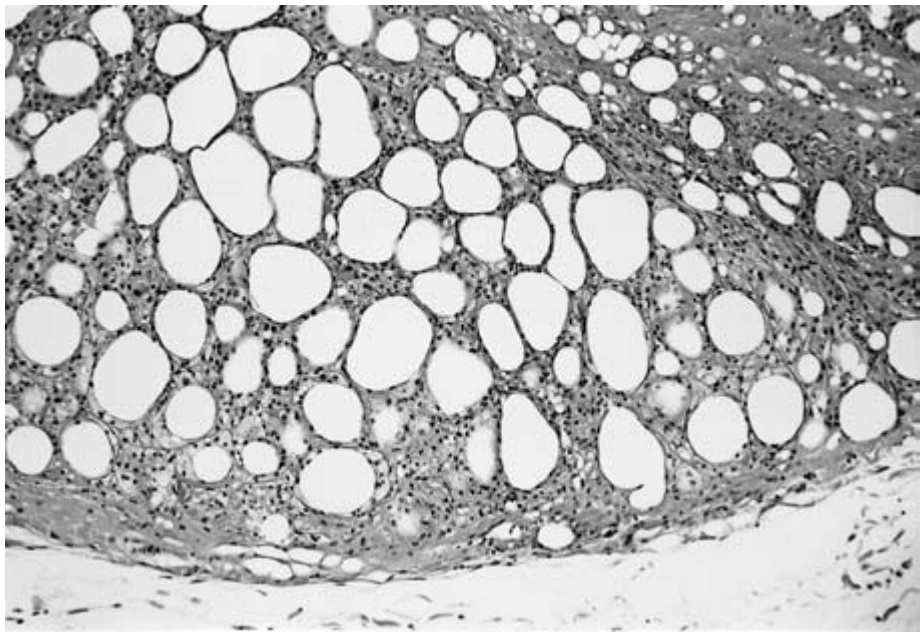


Fig. 21.18 Higher magnification of traumatic panniculitis. Note foamy, lipid-bearing macrophages among ruptured adipocytes.

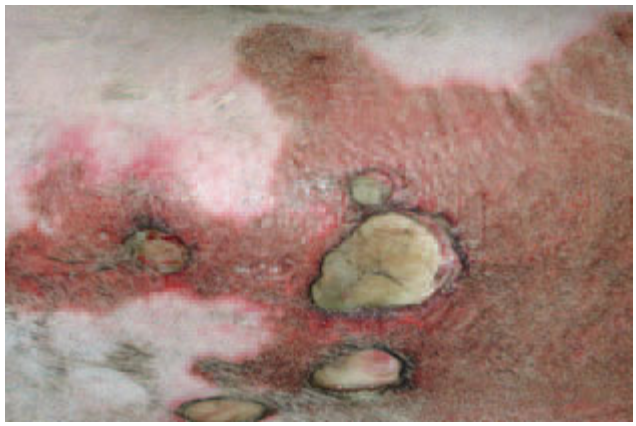


Fig. 21.19 Vasculitic panniculitis of thermal burns in a German Shepherd Dog-crossbreed. Note areas of full thickness necrosis accompanied by widespread hemorrhage and erythema.

with predominant fibrosis may resemble chronic scarring panniculitis of any cause.

VASCULITIC PANNICULITIS OF THERMAL BURNS

Clinical features (Figure 21.19)

See Chapter 4.

Biopsy site selection

See Chapter 4. Deeper biopsy will be required to document involvement of the panniculus.

Histopathology (Figures 21.20 through 21.22)

The overlying dermis and epidermis generally display some degree of coagulation necrosis, as seen in thermal burns (see Chapter 4). In most second degree burns (involving the epidermis and dermis), there are multifocal lesions of the panniculus. Perivascular hemorrhage is accompanied by variable fibrin exudation. Hemorrhage may surround and delineate individual adipocytes in a ring. Neutrophils are intermingled with macrophages and lymphocytes around vessels; foamy macrophages and neutrophils percolate amongst individual adipocytes. Adipocytes are sometimes ruptured. There is rare saponification of adipocytes which creates an amorphous lightly basophilic material within expanded or ruptured cells. Perivascular and septal fibrosis are common in chronic lesions.

Mild to moderate leukocytoclasia (nuclear fragmentation of neutrophils observed in the setting of vascular damage and inflammation) occurs variably in conjunction with perivascular hemorrhage and fibrin. There may be frank fibrinoid degeneration of the wall of small or medium-sized arterioles, as well as occasional fibrin thrombi. Interestingly, similar vascular changes have been described in miniature swine with severe frostbite (Schoning & Hamlet, 1987).

In some lesions vascular walls may appear coagulated; this is most prominent in deeper burns, and thus may be a direct effect of heat. In deep burns, severe secondary inflammation may obscure vascular changes. In some cases, there is diffuse coagulation necrosis of the panniculus, characterized by a diffuse 'washed out' and acellular appearance (third degree burns).

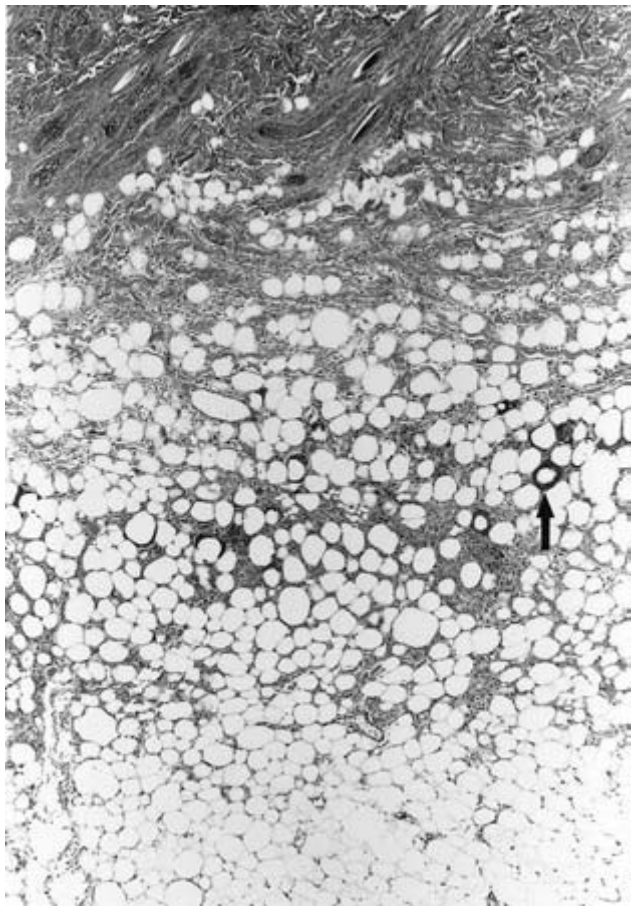


Fig. 21.20 Vasculitic panniculitis of thermal burn in a cat. Coagulated skin overlies inflamed fat of the panniculus. Note ring-shaped hemorrhage (arrow).

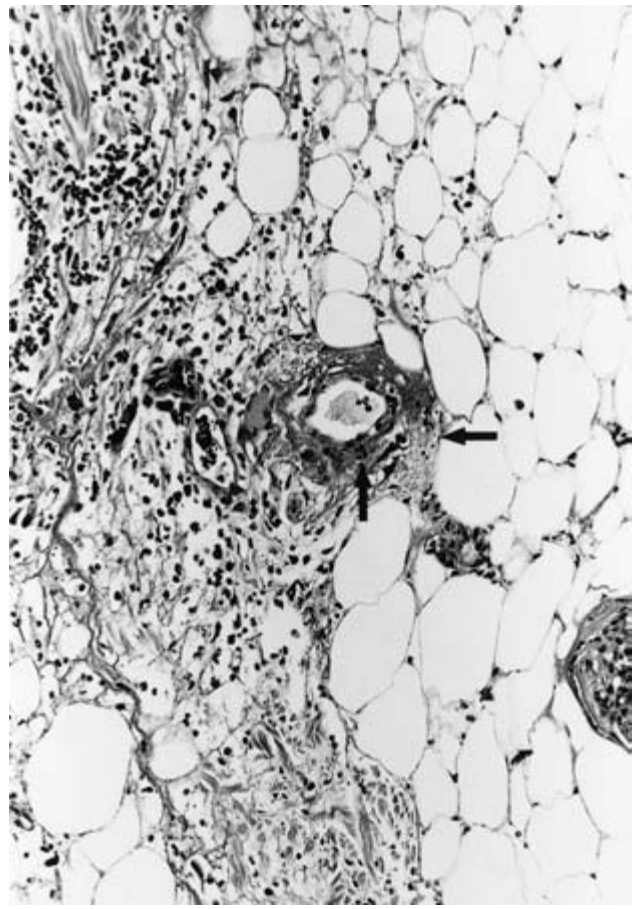


Fig. 21.21 High magnification of vasculitic panniculitis of thermal burn in a dog. A centrally inflamed and degenerated blood vessel is surrounded by fibrin; note leukocytoclasia (arrows).

The vascular lesions of vasculitic septal panniculitis are similar to those of thermal burns. However, vasculitic septal panniculitis is more distinctly septal in pattern, at least in early lesions, in contrast to the random distribution of vasculitic panniculitis of thermal burns. Also, the coagulation necrosis accompanying thermal burns is not present in vasculitic septal panniculitis. Deep septic vasculitis with infarction may resemble vasculitis of thermal burns. However, septic vasculitis sufficient to create tissue damage resembling a burn usually is more severe than vasculitis associated with even the most severe burns. Clinical differentiation may be required; most burn victims remain well in contrast to animals with sepsis.

IDIOPATHIC STERILE NODULAR PANNICULITIS

Clinical features (Figures 21.23 through 21.26)

Idiopathic sterile nodular panniculitis, in its broadest sense, is a descriptive term encompassing all of the sterile inflammatory diseases of the panniculus that are of unknown etiology (Schanley & Miller, 1985). However, popular usage has narrowed the meaning of this term to reflect a more specific disease subgroup (or subgroups) seen rarely in the dog and very rarely in the cat. A marked breed predilection for the Dachshund suggests genetic factors. Although a number of idiopathic panniculitides are seen in human (subcutaneous granuloma annulare, idiopathic lobular panniculitis, erythema nodosum) (Phelps & Shoji, 2001; Camilleri & Su, 2003), none of these diseases share prominent similarities with idiopathic sterile nodular panniculitis.

Multiple firm to fluctuant, deep-seated nodules develop in the panniculus. Nodules may protrude above the surface of the skin. Larger nodules ulcerate or fistulate, draining an oily, clear to yellow-brown liquid. Occasionally, the discharge is hemorrhagic. Well-demarcated ulcers with fistulae, less than 2 cm in diameter, typify the disease. Fistulation or ulceration is accompanied by irregular scarring which fixes the subcutaneous lesion to the overlying dermis. Variable hyperpigmentiation and scarring

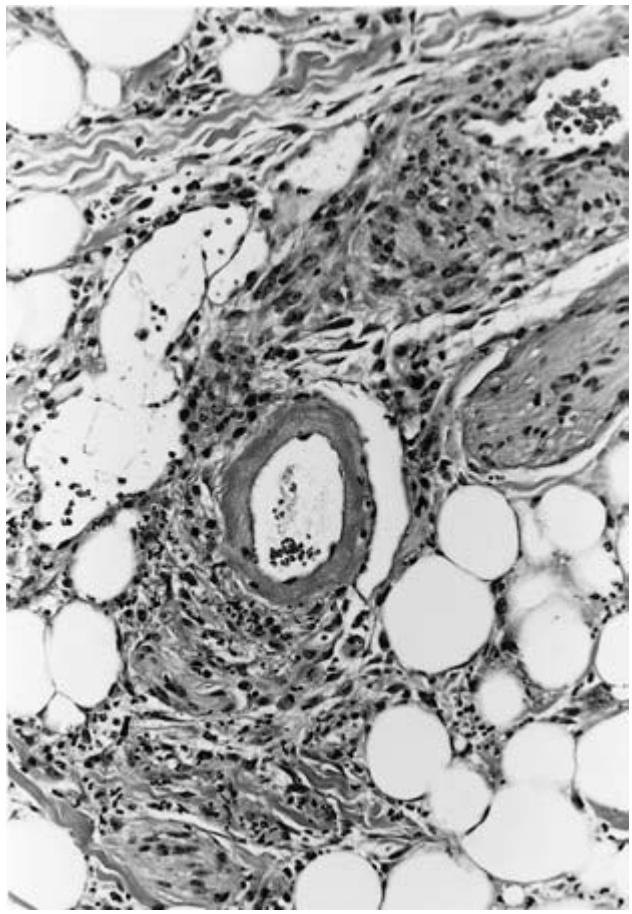


Fig. 21.22 High magnification of vasculitic panniculitis of thermal burn in a cat. Central coagulation of a blood vessel may be the result of direct thermal trauma. Note abundant leukocytoclastic debris.



Fig. 21.23 Idiopathic sterile nodular panniculitis in a Miniature Dachshund. Multiple nodules have ulcerated.

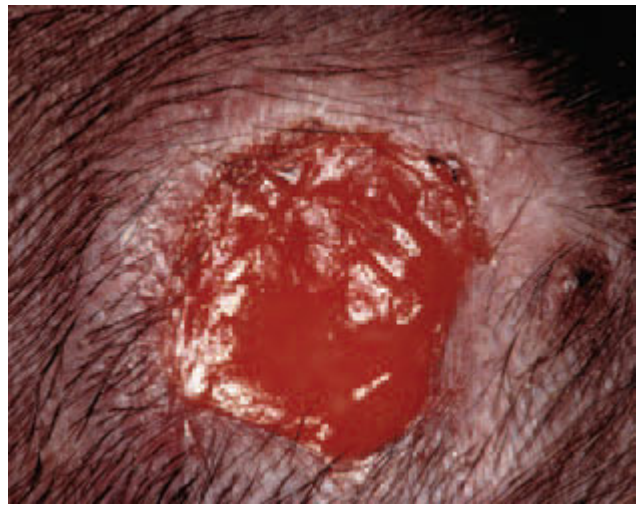


Fig. 21.24 Closer view of the dog in Fig. 21.23. A well-demarcated deep ulcer is seen on the shoulder.

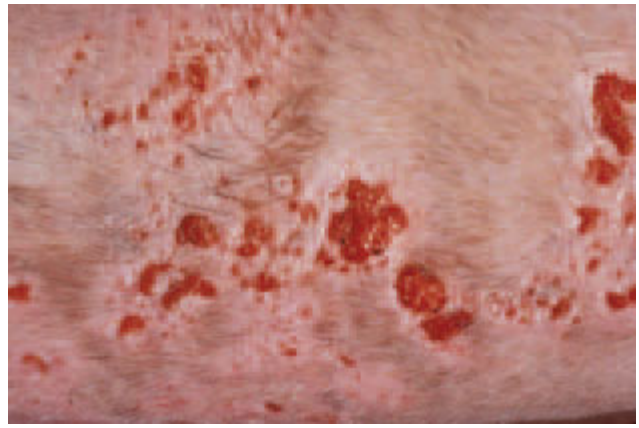


Fig. 21.25 Idiopathic sterile nodular panniculitis in a Collie Dog. Note areas of full thickness necrosis indicative of severe panniculitis.



Fig. 21.26 Idiopathic sterile nodular panniculitis in a cat demonstrating deep exudative ulcers.

alopecia are seen with healing. Chronic lesions may be depressed, irregularly firm, and nodular on palpation. The trunk is most commonly affected, although lesions may occur anywhere.

Systemic signs include fever, anorexia, and general malaise. Commonly, recrudescence occurs in waves, frequently with prodromal systemic signs. An additional very rare subgroup seen by one author (P.J.I.) most typically in the Collie, has a greater propensity towards coalescing ulcerations with extensive drainage, and resembles liquefying panniculitis of humans.

The Dachshund is at increased risk for idiopathic sterile nodular panniculitis. The authors have the impression that the Miniature Poodle and the Collie also probably are over-represented. Age and sex predilections are not noted. Feline idiopathic sterile nodular panniculitis has been seen only in adult cats.

Clinical differential diagnoses should include nodular diseases with cutaneous and subcutaneous involvement, such as opportunistic mycobacterial infections, cutaneous and subcutaneous infections of both systemic and opportunistic fungi, deep bacterial folliculitis and furunculosis, foreign body reactions, and neoplasms. Clinically, foreign body reactions are more likely to be focal or grouped in comparison to the multifocal distribution of sterile nodular panniculitis. Aerobic and anaerobic bacterial cultures, fungal cultures, and histopathology should be performed to rule out infectious causes before a diagnosis of idiopathic sterile nodular panniculitis is made. Fungal culture should not be performed until the systemic mycoses blastomycosis, histoplasmosis, and coccidioidomycosis are ruled out by impression smear and histopathology, since attempted culture may be dangerous (see Chapter 12).

Biopsy site selection

Punch biopsy is not recommended if idiopathic sterile nodular panniculitis is suspected. Large and deep biopsy specimens should be obtained by wedge section to ensure that the sample includes epidermis, dermis, and subcutaneous tissue. Multiple specimens are desirable. Lesions which are cavitated, ulcerated, or necrotic should be avoided if other earlier lesions are present.

Histopathology (Figures 21.27 and 21.28)

The epidermis is normal to acanthotic and may be ulcerated if secondary necrosis and exudation to the surface has occurred. The inflammation of the panniculus is mostly lobular in the early stages, but progresses to diffuse involvement. The deep dermis often is inflamed as lesions expand from the underlying panniculus. Neutrophils and macrophages predominate in initial lesions, and discrete pyogranulomas may be present. Adipocytes may appear necrotic, as ghosts, or may be infiltrated with foamy macrophages. Diffuse inflammation is generally mixed and includes macrophages, neutrophils, lymphocytes, and plasma cells in varying distribution. Special stains for infectious organisms, such as fungi and acid-fast bacteria, are negative. Chronic lesions have scant neu-

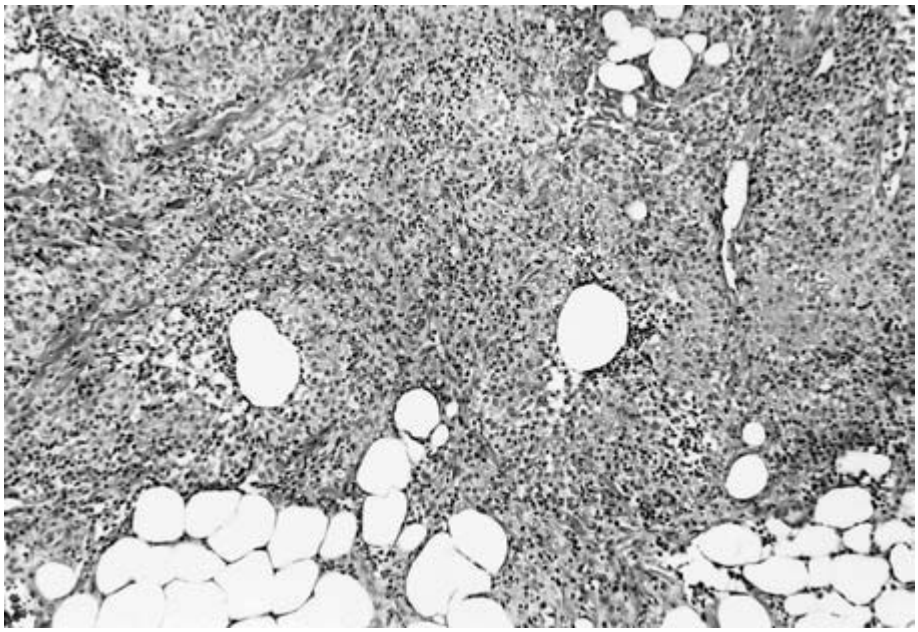


Fig. 21.27 Idiopathic sterile nodular panniculitis in a Poodle. Confluent pyogranulomas and mixed granulomatous inflammation replace adipose tissue of the panniculus.

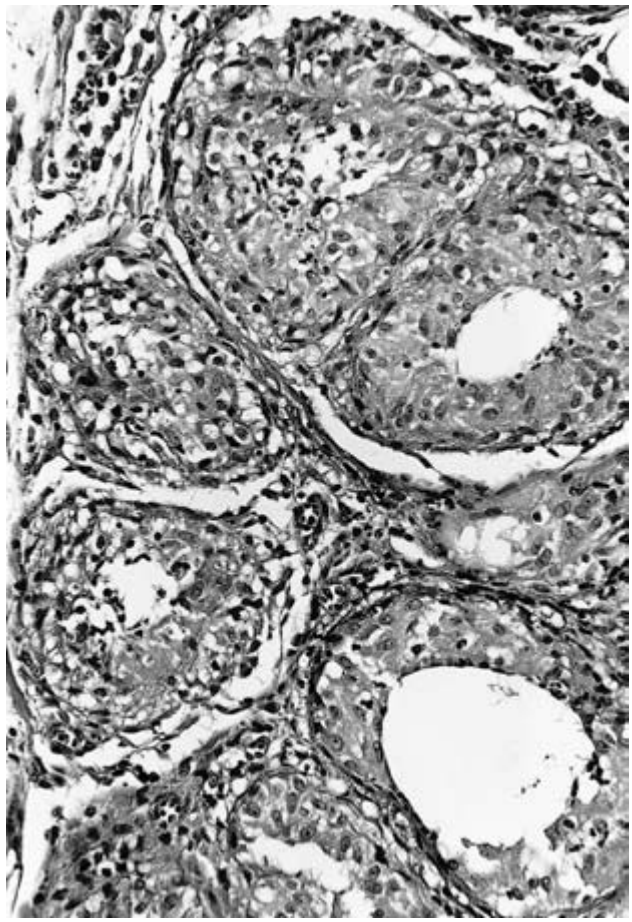


Fig. 21.28 Higher magnification of idiopathic sterile nodular panniculitis in a Dachshund demonstrating discrete pyogranulomas.

trophils and variable fibrosis that replaces the panniculus and often extends to the overlying dermis.

Differential diagnoses for sterile nodular panniculitis include infectious panniculitis, particularly due to opportunistic mycobacteria, and deep lesions of juvenile sterile granulomatous dermatitis and lymphadenitis. As the organisms in some mycobacterial infections may be scant, careful searching using a Fite's modification of an acid-fast stain is warranted. Clinical differentiation may be required. Juvenile sterile granulomatous dermatitis may have accompanying panniculitis that is indistinguishable from sterile nodular panniculitis; however, characteristic periadnexal pyogranulomatous inflammation usually is present. Juvenile sterile granulomatous dermatitis begins in the dermis and extends to the panniculus in severe lesions; the reverse is true for sterile nodular panniculitis. It is of interest that the Dachshund may be predisposed to both diseases.

VASCULITIC SEPTAL PANNICULITIS

(Synonym: subcutaneous leukocytoclastic vasculitis)

Clinical features

Vasculitic septal panniculitis, or subcutaneous leukocytoclastic vasculitis, is a very rare canine skin disease possibly linked to a systemic hypersensitivity reaction. In humans, subcutaneous leukocytoclastic vasculitis presents clinically as erythematous, subcutaneous nodules resembling other inflammatory diseases of the panniculus (Requeña & Sánchez Yus, 2001). Vasculitis is restricted to the panniculus; the mechanism by which subcutaneous leukocytoclastic vasculitis occurs without concomitant vasculitis of the overlying dermis is not known (Requeña & Sánchez Yus, 2001). Withdrawal of medication or treatment of underlying diseases seemingly has initiated resolution in human cases (Requeña & Sánchez Yus, 2001).

Clinical presentation is similar to other forms of panniculitis in that multiple nodules develop in the subcutaneous tissue; these may be quite subtle on palpation. Lesions may be erythematous or, in some cases, hemorrhagic. Fistulation and drainage do not occur. Variable hyperpigmentation is seen with healing. Scarring may fix the subcutaneous lesion to the overlying dermis. Chronic lesions may feel irregularly firm. Fever, joint or muscle pain, and general malaise may accompany skin changes. Breed, age, or sex predilections have not been noted.

Clinical differential diagnoses should include other forms of panniculitis and neoplasms. If vasculitic septal panniculitis is documented histopathologically, the possibility of systemic infection or drug reaction must be evaluated. Vasculitic septal panniculitis must not be deemed idiopathic unless all likely possible causes are investigated.

Biopsy site selection

Punch biopsy is not recommended if vasculitic septal panniculitis is suspected. Wedge section should be used to ensure that the specimen includes epidermis, dermis, and subcutaneous tissue. Multiple specimens are desirable.

Histopathology (Figures 21.29 and 21.30)

The epidermis and dermis generally are normal in most lesions of vasculitic septal panniculitis. In the panniculus, septal hemorrhage and fibrin exudation may be mild to prominent and may extend to lobules in a pattern characterized as 'mostly septal panniculitis' (Requeña & Sánchez Yus, 2001). Septal blood vessels demonstrate variable endothelial swelling, mild fibrinoid change, and

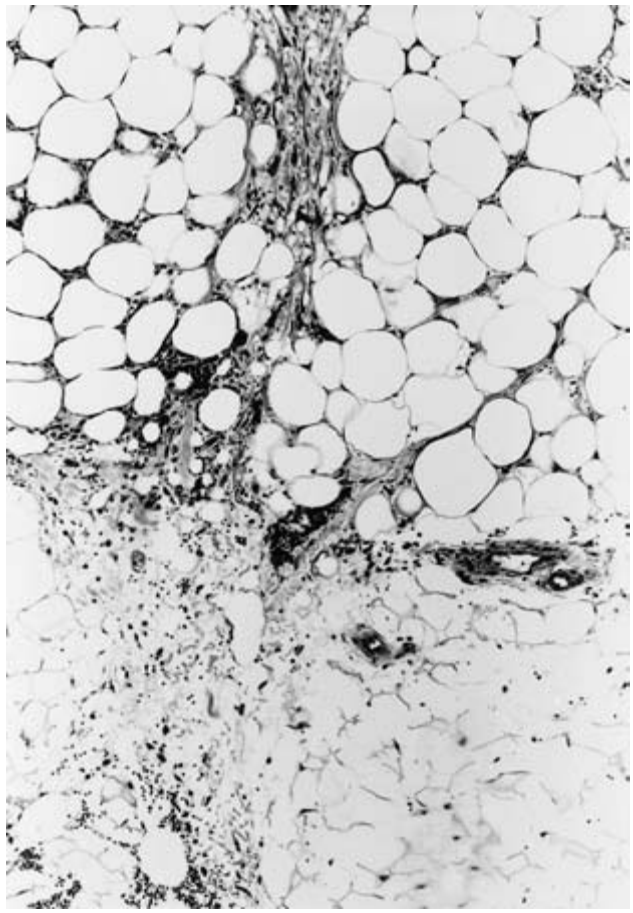


Fig. 21.29 Vasculitic septal panniculitis. Blood vessels are surrounded by hemorrhage and inflammation. Note mild septal fibrosis extending into adjacent fat.

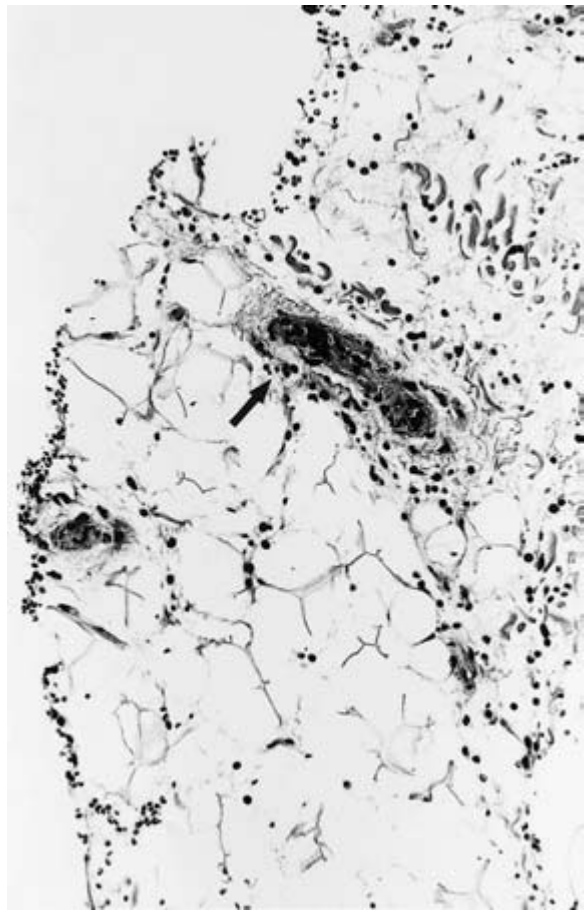


Fig. 21.30 Higher magnification of vasculitic septal panniculitis. A blood vessel is swollen with fibrinoid degeneration; there is perivascular microhemorrhage and fine leukocytoclastic debris (arrow).

occasional thrombosis. Overt inflammation of the vessel walls (true vasculitis) is often subtle or absent. Leukocytoclasia (fragmentation of neutrophils) is generally at least mildly evident, and is indicative of vascular damage and inflammation. The panniculus shows diffuse septal inflammation of neutrophils and mixed mononuclear cells, including macrophages, lymphocytes, and a few plasma cells. Inflammation spreads secondarily to the surrounding lobules. Foamy macrophages percolate amongst lipocytes which may appear devitalized or ruptured. Variable septal and lobular fibrosis occurs in chronic lesions.

Differential diagnosis of early lesions is limited if vascular inflammation or vasculopathic effects (fibrin, hemorrhage) are visualized. Some of the vascular changes are as seen in vasculitic panniculitis of thermal burns. In differentiation, burns generally demonstrate coagulation necrosis of the overlying skin; further, the pattern of vasculitic panniculitis of burns is not as distinctly septal. If vasculitis is not apparent, lesions may not be easily differentiated from chronic panniculitis of any cause.

FELINE PANSTEATITIS

(Synonyms: feline vitamin E deficiency, vitamin E deficiency steatitis)

Clinical features (Figure 21.31)

Feline pansteatitis is a rare nutritional skin disease caused by a severe deficiency of vitamin E and lack of its antioxidant properties (White, 2000). The syndrome is worldwide in distribution, but the frequency is contingent upon feeding practices. Feline pansteatitis is rare in North America and most of Europe.

Vitamin E deficiency and pansteatitis may be caused by the feeding of food deficient in vitamin E, either through natural deficiency or deficient formulation, or food with



Fig. 21.31 Feline pansteatitis in a cat. The area is thickened due to multiple, firm nodules that are present diffusely in the subcutaneous tissue; lesions were also present in the mesenteric fat. (Photograph courtesy S.D. White.)

excess highly unsaturated fatty acids which may destroy vitamin E. Foods with excess highly unsaturated fatty acids are more susceptible to peroxidation during prolonged storage without refrigeration, which causes generation of free radicals and results in depletion of the vitamin. The most commonly reported causes of feline pansteatitis are associated with the feeding of canned red tuna as an exclusive diet or excessive cod liver oil supplementation. Widespread cellular damage results in the deposition of ceroid pigment (a variant of lipofuscin and an intermediate metabolite of various lipids) derived predominantly from cell membranes.

Multiple, irregularly firm nodules of variable density develop diffusely in the subcutis and the abdominal mesenteric fat. Nodules are sensitive to palpation (Koutinas et al., 1993). Fistulation is rare. Firm lumps also can be palpated in the abdominal cavity. Systemic signs include fever, malaise, pain (elicited by palpation), reluctance to move, anorexia, lethargy (sometimes alternating with hyperexcitability), hyperesthesia, and depression (Koutinas et al., 1993). Systemic signs may precede or occur simultaneously with the development of subcutaneous and visceral nodules. Death is a frequent sequela.

All four cats in one report were between 4 and 8 months of age (Koutinas et al., 1993). However, cats of any age may be affected. As would be expected, breed or sex predilections have not been noted.

Feline pansteatitis is a highly characteristic disease clinically. However, clinical differential diagnoses could include other causes of panniculitis as well as neoplasia.

Biopsy site selection

An intact nodule should be removed by wedge section to ensure that the specimen includes epidermis, dermis, and subcutaneous tissue. Index of suspicion for feline pansteatitis is enhanced if yellow, discolored fat is seen during surgical biopsy.

Histopathology

The epidermis and dermis are normal. The fat of the subcutis may demonstrate deposition of yellow or yellow-brown, acid-fast ceroid pigment between and within adipocytes. Ceroid deposits approach the size of a normal fat cell, and similar pigment may also be found within macrophages and giant cells. Ceroid may not be present in biopsy specimens from all cases: one of four previously reported cats with pansteatitis did not demonstrate ceroid microscopically (Koutinas et al., 1993). In early stages of the disease there are infiltrations of neutrophils, but pyogranulomatous or granulomatous inflammation soon predominates. Giant cells may be of the Langhans type (containing a peripheral ring of nuclei). Adipocytes may be necrotic, and there may be saponification and cholesterol cleft formation in some cases. Mineralization has been reported (Koutinas et al., 1993). There may be septal fibrosis.

Differential diagnosis is not difficult if typical ceroid pigment deposition is present. In lesions without ceroid but with saponification and mineralization, differentiation from pancreatic panniculitis may be required. Acid-fast stains may be applied to differentiate acid-fast ceroid from the nonacid-fast hemosiderin seen in some lesions of traumatic panniculitis.

METATARSAL FISTULATION OF THE GERMAN SHEPHERD DOG

(Synonyms: sterile pedal panniculitis of the German Shepherd Dog, deep metatarsal/metacarpal toritis in German Shepherd Dogs)

Clinical features (Figures 21.32 through 21.34)

Metatarsal fistulation of the German Shepherd Dog is an uncommon canine skin disease characterized by well demarcated, frequently symmetric, deep fistulous tracts located dorsal to the midline of single or multiple pawpads (Gross & Ihrke, 1992; Kunkle et al., 1993). The strong breed predilection for the German Shepherd Dog suggests heritability (Gross & Ihrke, 1992; Kunkle et al., 1993; Paterson, 1995; Kristensen, 1997). The etiology is unknown. Antibodies directed against type I and type II collagen have been noted, suggesting a familial disorder

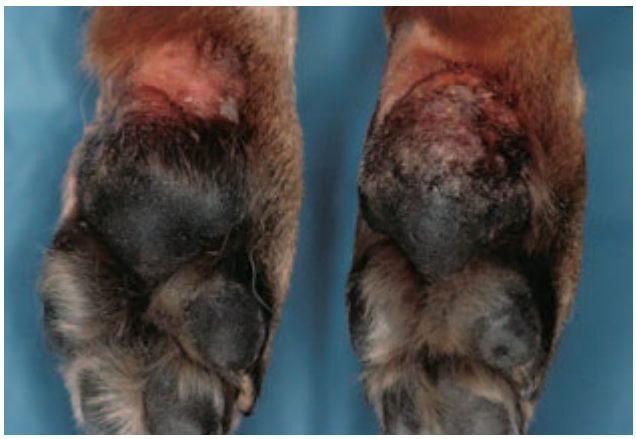


Fig. 21.32 Metatarsal fistulation of the German Shepherd Dog. Fistulous tracts are present dorsal to both carpal pads.

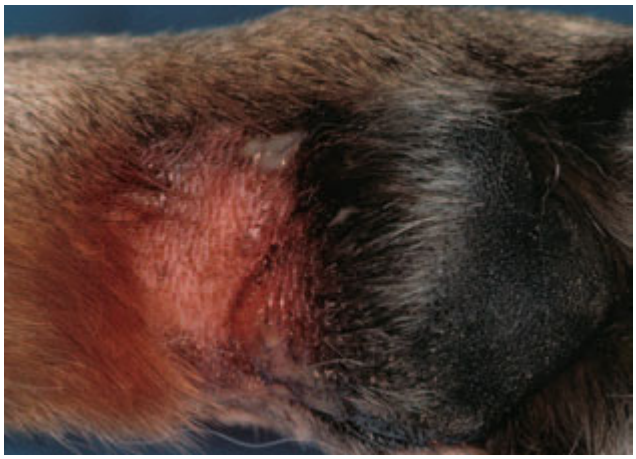


Fig. 21.33 Closer view of the dog in Fig. 21.32. Fistulous tracts exude a milky fluid.

of collagen although details were not given (Scott et al., 2001). German Shepherd Dogs have been bred increasingly for a low, crouching rear stance; the authors speculate that increased strain on soft tissue of the distal extremities (tendons, pawpads, underlying fat pads) may be involved in the pathogenesis.

Some affected dogs have concomitant interdigital bacterial furunculosis, and some have perianal fistulas (Kristensen, 1997); the German Shepherd Dog is predisposed to all three. Genetic linkage between the syndromes may or may not be present.

Focal, deep fistulous tracts with well demarcated, slightly swollen, erythematous borders sparingly exude a serous to milky, viscid fluid. Lesions may be either single or multiple. The most common site is dorsal to the midline of the tarsal pad, but lesions may be dorsal to the carpal pads, and very rarely, other pawpads. Deep palpation elicits pain. Secondary bacterial infection is common. Lymphadenopathy is variable, but usually is mild unless secondary bacterial infection is severe. Scarring is seen with chronicity. Moderately to severely affected dogs are lame.



Fig. 21.34 Metatarsal fistulation of the German Shepherd Dog. Scar tissue deforms the dorsal aspect of the carpal pad.

The syndrome is seen primarily in German Shepherd Dogs; a small number of German Shepherd Dog crossbreeds also have been seen. Some reports suggest a marked predilection for male dogs (Kristensen, 1997; Scott et al., 2001). This suggestion is intriguing, as male dogs usually are heavier and taller, supporting the theory given above regarding increased strain on soft tissue of the distal extremities. Dogs with more direct German ancestry may be over-represented (Scott et al., 2001). Adult dogs between the ages of 2 and 8 years predominate (Scott et al., 2001).

Clinically, this syndrome is quite distinctive; differential diagnosis is not problematic. Fistulous tracts initiated by foreign bodies should be considered; however, sites dorsal to the pawpads, particularly the large tarsal pads, would be atypical for foreign body penetration.

Biopsy site selection

Specimen collection is difficult since the tissue needed is the deep dermis and subcutis directly dorsal to a pawpad. Wedge technique performed under general anesthesia is recommended, since local anesthesia is difficult in this location and hemostasis may be problematic. At least part of the fistula should be included in the specimen. If multiple biopsy specimens are taken, they should be acquired from the same paw to minimize postbiopsy lameness.

Histopathology (Figure 21.35)

The epidermis is moderately to severely acanthotic. If the specimen is obtained from the edge of the fistula, there is a focal area of severe ulceration.

The panniculus is severely inflamed. Inflammation also may extend through the overlying dermis along one edge of the specimen, if the specimen is obtained from the edge of a fistula. In other specimens, the dermis may be relatively uninflamed and overlie cavitation and inflammation of the panniculus. In earlier lesions, neutrophils and macrophages predominate, and discrete pyogranulomas may be observed. In the more commonly received advanced lesions there are diffuse infiltrations of neutrophils, macrophages, plasma cells, and lymphocytes. Inflammation grades into areas of variable peripheral fibrosis, depending on the stage. Fibrosis is generally striking and deep, and often is most severe just beyond the most intense region of inflammation. Fibrous tissue emanates into adjacent areas, where it is accompanied by milder chronic inflammation consisting primarily of plasma cells.



Fig. 21.35 Metatarsal fistulation of the German Shepherd Dog. Note the large central fistula within intense panniculitis.

Differential diagnosis based on histopathology alone is problematic, as the microscopic lesions of metatarsal fistulation are not distinctive. Any foreign body reaction or puncture-induced traumatic lesion that extends to the panniculus may appear similar, as may deep bacterial or fungal infections. Special stains for infectious agents may be required. Knowledge of the breed and site affected are key to the definitive diagnosis of this syndrome.

PANCREATIC PANNICULITIS

Clinical features (Figures 21.36 and 21.37)

Pancreatic panniculitis is a very rare skin disease reported in the dog and cat that is seen in conjunction with underlying pancreatic disease. Judging by publications and the experience of the authors, pancreatic panniculitis is noted



Fig. 21.36 Pancreatic panniculitis in a dog. Multifocal truncal subcutaneous purple nodules ulcerate and drain purulent oily material. (Photograph courtesy C.B. Vitale.)



Fig. 21.37 Closer view of the dog in Fig. 21.36. One large fistulous ulcer is surrounded by devitalized tissue. (Photograph courtesy C.B. Vitale.)

more frequently in the dog (Mason, 1989; Brown et al., 1994; Paterson, 1994; Campbell et al., 2000; Mellanby et al., 2003) than in the cat (Ryan & Howard, 1981; Campbell et al., 2000). A similar very rare and frequently fatal pancreatic panniculitis is seen in humans (Dahl et al., 1995).

In humans, pancreatic panniculitis is caused by the release of the activated pancreatic enzymes lipase, phospholipase, trypsin, and amylase (Phelps & Shoji, 2001). The mechanism by which inactive precursor pancreatic enzymes are activated is not known. However, it has been speculated that increased levels of circulating activated pancreatic enzymes might cause vessel wall damage and increased vessel permeability allowing the active enzymes to escape blood vessels, enter fat lobules, and induce necrosis (Phelps & Shoji, 2001). In humans, pancreatic panniculitis is rare and occurs in only 2% to 3% of all patients with pancreatic disorders (Camilleri & Su, 2003). Similarly, most dogs and cats with either inflammatory or neoplastic pancreatic disease do not exhibit skin lesions.

Pancreatic panniculitis in the dog has been seen in conjunction with pancreatic adenocarcinoma, pancreatic carcinoma, bile duct carcinoma, and pancreatitis (Mason, 1989; Brown et al., 1994; Paterson, 1994; Mellanby et al., 2003). Pancreatic panniculitis in the cat has been reported in conjunction with pancreatitis (Ryan & Howard, 1981). Pancreatic panniculitis in humans usually is seen as a sequela to either pancreatic carcinoma or pancreatitis (Dahl et al., 1995).

Clinically, pancreatic panniculitis in dogs is characterized by either localized subcutaneous nodules or ill-defined soft tissue swellings (Mason, 1989; Brown et al., 1994). Purulent, oily material occasionally discharges from fistulating masses. Lesions predominantly are truncal. However, one author (T.L.G.) has seen two dogs with pancreatic panniculitis causing nodules on the legs and well as the trunk. Lesions may be tender on palpation. Localized subcutaneous nodules that fistulate and drain a milky, oily fluid have been reported in cats (Ryan & Howard, 1981). Both dogs and cats present with depression, vague signs of abdominal distress, pyrexia, pain on palpation, and vomiting (Brown et al., 1994; Campbell et al., 2000).

Interestingly, considering the rareness of the syndrome, four Cocker Spaniels and one Cavalier King Charles Spaniel have been reported (Brown et al., 1994; Mellanby et al., 2003). The authors have seen two other Cocker Spaniels with this syndrome, thus indicating the likelihood of breed predilection. Age or sex predilections have not been noted, but pancreatic neoplasia initiating panniculitis should be seen more frequently in older animals.

Possible clinical differential diagnoses could include infectious diseases with cutaneous and subcutaneous involvement, such as opportunistic mycobacterial infection, cutaneous and subcutaneous infections of both systemic and opportunistic fungi, and other forms of panniculitis. Clinical differentiation is aided by the presence of systemic as well as cutaneous signs of pancreatic panniculitis. Determination of pancreatic enzyme levels (amylase and lipase) and ultrasonographic or magnetic imaging of the pancreas are recommended. Skin biopsy is confirmative.

Biopsy site selection

Large, deep biopsy specimens should be obtained by wedge section to ensure that the sample includes epidermis, dermis, and subcutaneous tissue. Multiple specimens are desirable. Lesions which are cavitated, ulcerated or necrotic should be avoided if other earlier lesions are present.

Histopathology (Figures 21.38 and 21.39)

In dogs with pancreatic panniculitis, the epidermis may be ulcerated in lesions that extend through the dermis.

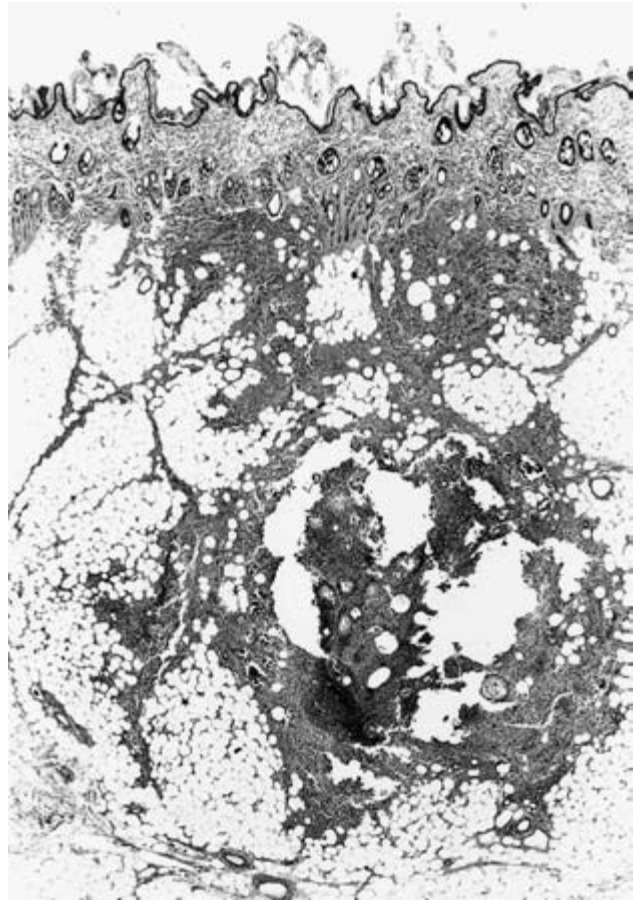


Fig. 21.38 Pancreatic panniculitis in a Cocker Spaniel featuring dense and obliterative inflammation of adipose tissue.

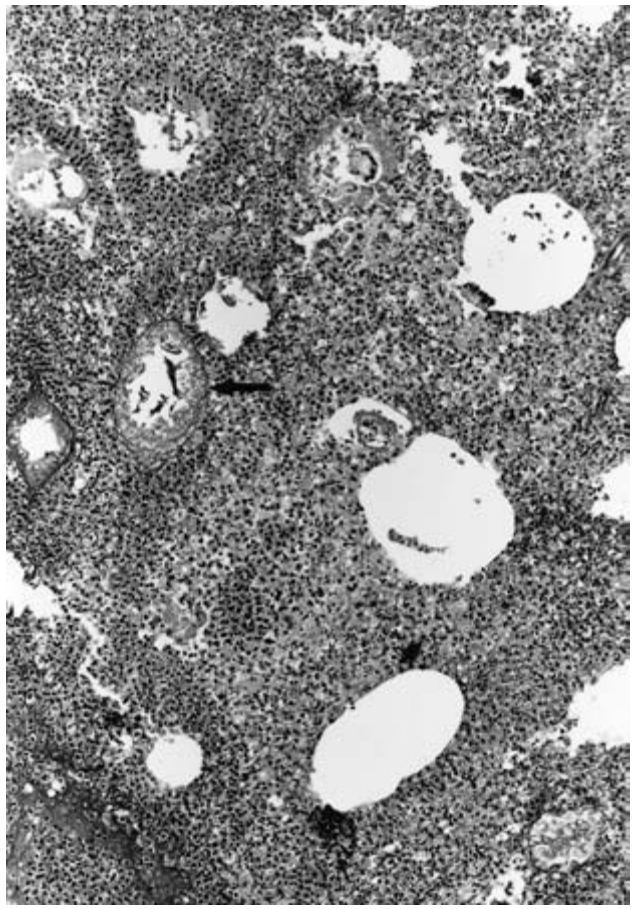


Fig. 21.39 Higher magnification of pancreatic panniculitis in the dog of Fig. 21.38. Diffuse suppurative inflammation is accompanied by saponification of fat (arrow).

The panniculus contains severe, nodular or diffuse suppurative to pyogranulomatous inflammation. There may be severe hemorrhage and fibrin exudation. Adipocytes within these foci are necrotic, sometimes in sharply defined foci, which may be extensive. Necrotic fat often is saponified, which creates an amorphous lightly basophilic material within expanded or ruptured adipocytes. Birefringent saponified fatty acid crystalloids, as seen in fat necrosis of the mesentery of humans, have not been observed in skin lesions in humans (Phelps & Shoji, 2001) or in dogs. Secondary cystic alteration of inflamed and necrotic foci may be seen. Smaller foci of saponification within severely inflamed and hemorrhagic adipose tissue may characterize some lesions. Small foci of deeply basophilic, amorphous mineralization also may be present. Chronic lesions show replacement of inflammatory foci by granulation tissue. Similar lesions have been reported in a cat (Ryan & Howard, 1981).

Affected animals have pancreatic disease of varying causes. Pancreatic lesions, whether neoplastic or inflammatory, uniformly include massive peripancreatic omental fat necrosis, saponification, and inflammation, as seen in the skin.

The lesions of pancreatic panniculitis are striking and highly diagnostic. There are no known differential diagnoses in the dog; the pattern of severe fat necrosis with saponification should warrant a careful search for pancreatic disease. In the cat, lesions of vitamin E deficiency (feline pansteatitis) that do not contain ceroid but have saponification and mineralization may need to be differentiated from pancreatic panniculitis.

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SECTION TWO

NEOPLASMS AND OTHER TUMORS

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Part I

Epithelial Neoplasms and other Tumors

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Chapter 22

Epidermal tumors

CUTANEOUS HORN OF FELINE PAWPAD

Cutaneous horn is a general clinical term describing a circumscribed, conical, or cylindrical mass of acellular keratin in which the height is greater than the diameter. The etiology of the horn cannot be determined without histologic evaluation of the epithelium beneath it. Cutaneous horns are rare in dogs and cats, and may arise from viral papillomas, actinic keratoses, bowenoid *in situ* carcinoma, or invasive squamous cell carcinomas (see pp. 567, 575, 578 and 581), or from dilated pores or infundibular keratinizing acanthomas (see Chapter 23).

Clinical features

Cutaneous horn of feline pawpad is a very rare, specific entity that was first described by Center (Center et al., 1982). The affected cat was feline leukemia virus (FeLV)-positive, and only FeLV was found on viral isolation of the lesions. The lesions recurred despite multiple surgical excisions, and the cat eventually developed similar lesions on nasal planum and eyelids. A group of similar cases has been described (Scott, 1984). There is also one case report of multiple cutaneous horns in FeLV-negative cats (Komori et al., 1998).

The lesions are single or multiple, conical or cylindrical masses of hard keratin up to several millimeters in diameter and up to 2 cm in height. The viral-associated cutaneous horns occur in the centers of digital, central, or metacarpal/metatarsal pawpads. The nonFeLV-associated horns occurred only on digital pads just below the nails (Komori et al., 1998). There is no known age or breed predisposition.

Histopathology (Figures 22.1 and 22.2)

Cutaneous horn of feline pawpad is characterized by a well-demarcated zone of moderate to marked papillomatous hyperplasia of the epidermis from which emanates a column of compact keratin. The shape and homogenous quality of the keratin column resemble a nail. Parakeratotic cells may also be present within the keratin column. Epidermal stratification of the underlying hyperplastic epidermis is well-maintained. FeLV-associated lesions have scattered brightly eosinophilic and shrunken (apoptotic), multinucleated, and/or vacuolated keratinocytes; nonFeLV-associated pawpad horns lack these specific epidermal features (Komori et al., 1998). Atypia or increased mitotic activity is not present. Secondary inflammation may be present, particularly in lesions of long standing that have become fissured.

Cutaneous horn of feline pawpad is clinically and histopathologically distinctive; differential diagnoses are very limited. True viral papillomas have not been described on feline pawpad, but could have similar histologic appearance.

Immunohistochemistry

Immunostaining for FeLV should be performed on pawpad horns, as its presence has significant implications for prognosis and therapy. Papillomavirus immunohistochemistry should also be considered.

PAWPAD KERATOMA

(Synonyms: pawpad corn, callus)

Callus (or callosity) is a general term defined as a localized hyperplasia of the stratum corneum due to chronic pressure or friction. Synonyms include keratoma, keratoderma, tyloma, and tylosis (Anderson, 1994). A corn in human pathology is a callus on the dorsal, lateral, or interdigital aspect of the toes; clavus and heloma are more antiquated names for this common entity. The exuberant stratum corneum of the corn forms a conical mass that protrudes downward toward the dermis. Interestingly, *Dorland's Illustrated Medical Dictionary* (Anderson, 1994) also defines corn as 'a circumscribed hyperkeratosis on the pawpad of dogs, sensitive to pressure'. Corns and calluses in humans are due to inappropriate or



Fig. 22.1 Cutaneous horn of feline pawpad. A column of pale, compact keratin arises from moderately hyperplastic epidermis.

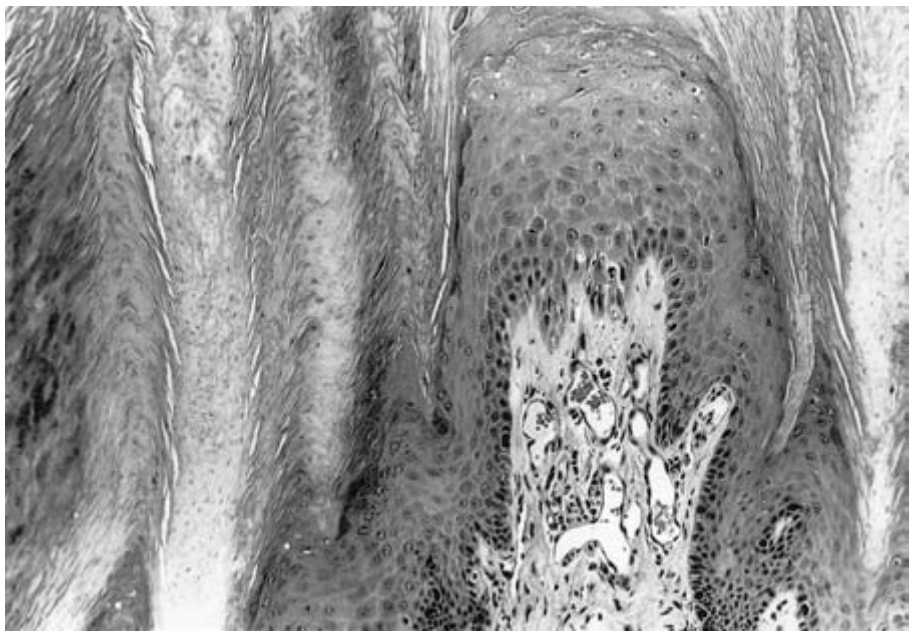


Fig. 22.2 Higher magnification of Fig. 22.1. The epidermis shows papillomatous hyperplasia and mild vacuolation of the stratum granulosum.

poorly-fitting shoes, anatomic deformity resulting in abnormal foot mechanics, or high levels of activity. The lesions usually regress once the abnormal stress has been removed or corrected (Singh et al., 1996; Freeman, 2002). Increased epidermal proliferation and increased corneocyte volume have been demonstrated, indicating that the lesions represent a transient disorder of cornification (Thomas et al., 1985).

Pawpad keratomas occur almost exclusively in racing or retired Greyhounds. Small inorganic foreign bodies (sand, glass) and papillomavirus infection are often mentioned as causes of pawpad keratomas by breeders, trainers, and clinicians (Rosenbaum, M., personal communication, 2002). However, it is more likely that the lesions have a similar etiology to their human counterparts and result from mechanical abnormalities associated

with the physical stresses of racing and subsequent digital osteoarthritis, which exacerbates the problem as a result of altered or uneven gait, and/or misshapen digits.

Clinical features

The exact incidence of pawpad keratomas is difficult to assess, as the majority of lesions are probably not submitted for histologic evaluation. They appear as circular, firm to hard plaques or short cutaneous horns that are less than 1 cm in diameter. They may be solitary or multiple and nonpigmented or deeply pigmented. The majority of keratomas occur on the centers of the digital pads, usually on the areas that bear the most weight. The metacarpal or metatarsal pads may be affected (Rosenbaum, M., personal communication, 2002).

Pawpad keratomas are seen primarily in middle-aged to older racing or retired Greyhounds. Underlying foreign material is rarely found (Bettenay, S., personal communication, 2002). Recurrence after traditional surgical excision is common (Lorch, W., Ness, M. & Rosenbaum, M., personal communications, 2002). Laser surgery (Schick, R., personal communication, 2002) or physical extrusion/curettage of the central keratin core (Bettenay, S. & Olivry, T., personal communications, 2002) may be beneficial.

Histopathology (Figure 22.3)

Pawpad keratomas are characterized by well-defined, dome-shaped, conical, or cylindrical mounds of compact hyperkeratosis that project above the skin surface. Most of the keratin lacks the translucent appearance of normal pawpad stratum corneum. The subjacent epithelium may be mildly hyperplastic with an exaggerated digitated surface configuration. Delicate epidermal papillae may project for a short distance into the keratin mass. Other lesions have mild epidermal atrophy and depression; this is associated with downward expansion of the keratin, forming a discrete core. This endophytic growth pattern may represent a later stage of development. The epidermis does not show viral cytopathology, as in viral papilloma (see p. 567). Inflammation is absent unless there is fissuring or self-trauma. Immunohistochemical staining for papillomavirus is negative (Olivry, T., personal communication, 2002).

Pawpad keratoma with epidermal depression is histologically unique. Pawpad keratomas with papillomatous epidermal hyperplasia are differentiated from viral papillomas by the absence of thick, closely-grouped fronds of hyperplastic epithelium with viral cytopathic effect (see p. 567). In addition, true viral papillomas rarely occur on pawpads, although involvement of haired pedal skin is fairly common. Papillomavirus immunohistochemistry is recommended for equivocal lesions.



Fig. 22.3 Pawpad keratoma (corn) in a Greyhound. Marked, compact hyperkeratosis forms a mass over relatively normal epidermis. At left, the keratin also protrudes downward, forming an epidermal depression.

LINEAR EPIDERMAL HAMARTOMA

(Synonyms: linear epidermal nevus, verrucous epidermal nevus)

Regarding terminology, the current World Health Organization nomenclature avoids the use of 'nevus' entirely (Goldschmidt et al., 1998). Its original definition, from the Latin *naevus*, is a mole or birthmark, implying a congenital melanocytic neoplasm. Although the secondary definition of nevus is 'any congenital malformation of the skin' (Anderson, 1994), confusion is likely unless it is combined with qualifiers, such as sebaceous, apocrine, melanocytic, etc. Benign melanocytic tumors in humans are often referred to only as 'congenital nevi' or 'acquired nevi', depending on age of onset; the latter term is an oxymoron based on either of the foregoing definitions. Additionally, in veterinary medicine, congenital origin is often extremely difficult to confirm, as many owners do

not have their pets from birth. Early lesions may be obscured by pelage or may be assumed to be a normal component of a variegated skin/coat color and not become clinically apparent until later in life.

Hamartoma is defined as 'a benign tumor-like nodule composed of an overgrowth of mature cells and tissues that normally occur in the affected part but with disorganization and often with one element predominating' (Anderson, 1994). Hamartoma is thus a more inclusive term than nevus and is the preferred nomenclature for most lesions that are believed to be malformations, either congenital or acquired.

Linear epidermal 'nevus' is a well documented entity in humans and has localized unilateral, bilateral, and generalized variants. It appears to be analogous to canine linear epidermal hamartoma. Although the majority of human cases are present early in life, some are not clinically apparent until adulthood (Murphy & Elder, 1991).

Clinical features

Linear epidermal hamartoma is a rare lesion in dogs, presenting as scaly or waxy, sometimes coalescent plaques and/or papules forming one or more linear arrays on the trunk or legs (Scott et al., 2001). The lesions may be pigmented. Too few veterinary cases have been reported to determine the typical age of onset; the authors have seen cases in older adult dogs, although the duration of the lesions was unknown. The original case report was in a 2-month-old Schnauzer (Scott et al., 1984). An inflammatory variant also occurs in dogs (see Chapters 7 and 8).

Histopathology (Figure 22.4)

Epidermal hamartomas show an abrupt transition from normal skin to irregular acanthosis that can vary from mild to moderately severe. Epidermal maturation is normal. Epidermolytic hyperkeratosis, as seen in epidermolytic ichthyosis (see Chapter 8), is a feature of many of the more extensive human lesions. This has not been observed by the authors, but is described by Scott et al. (1984) as 'granular degeneration' in some cases. There is marked, laminated hyperkeratosis. The skin surface has a digitated or slightly papillated configuration due to concurrent hyperplasia and keratotic plugging of follicular infundibula. Adnexa are otherwise unremarkable. The dermis is normal.

The clinical appearance of epidermal hamartoma is considerably more distinctive than its histologic picture. Lesions on the legs may need to be distinguished from acral lick dermatitis; the latter has compact hyperkeratosis, epithelial hyperplasia affecting all three segments of the follicle, and 'streaming' dermal fibrosis with vertical orientation of superficial capillaries. Pigmented viral plaque is a differential diagnosis, particularly for lesions on the abdomen. These plaques generally do not form linear arrays and are much more deeply pigmented. Their epidermis is only mildly hyperplastic but has a unique scalloped configuration. Hypergranulosis without granular degeneration is present in pigmented viral plaque, and mild koilocytosis, as seen in viral papilloma (see p. 567), may be detected; koilocytosis could possibly be misinterpreted as early epidermolytic hyperkeratosis. Immunostaining or testing by polymerase chain reaction (PCR) for papillomavirus may be required for definitive diagnosis.

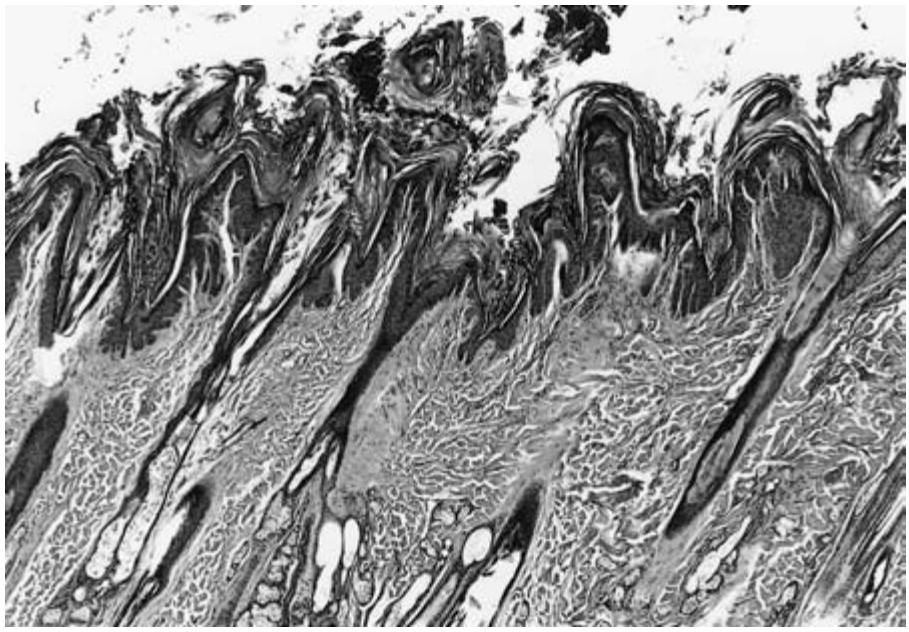


Fig. 22.4 Linear epidermal hamartoma in a dog. Epidermis and follicular infundibula show mild, irregular acanthosis and moderate hyperkeratosis. Note the prominent digitated appearance to the skin surface.

DERMOID CYST

(Synonym: dermoid sinus, pilonidal cyst)

Clinical features

Dermoid cysts are observed rarely in dogs and cats, and are identical to the human lesion with the same name. These cysts are developmental anomalies manifested by focal reduplication of the entire skin structure, including dermis and adnexa. Dermoid cysts are usually solitary and appear clinically similar to follicular cysts. The cysts are dermal or subcutaneous in location and are less than 2 cm in diameter. A small pore often connects the cyst to the skin surface, and hair may protrude through the pore.

As would be predicted by embryology, dermoid cysts often occur along the dorsal midline, which is the site where ectoderm was continuous with neuroectoderm prior to neural tube closure. Lesions occasionally extend into the spinal canal where they are attached to dura mater. However, they may also be found at other anatomic sites, such as the lateral neck or shoulder, particularly in cats.

The Rhodesian Ridgeback has a propensity for development of single or multiple dorsal midline dermoid cysts, which is believed to be inherited via a simple recessive gene (Mann & Stratton, 1966). Boxers and Kerry Blue Terriers also are reported to have an increased incidence (Scott et al., 2001). Because these are congenital anomalies, affected animals are usually young.

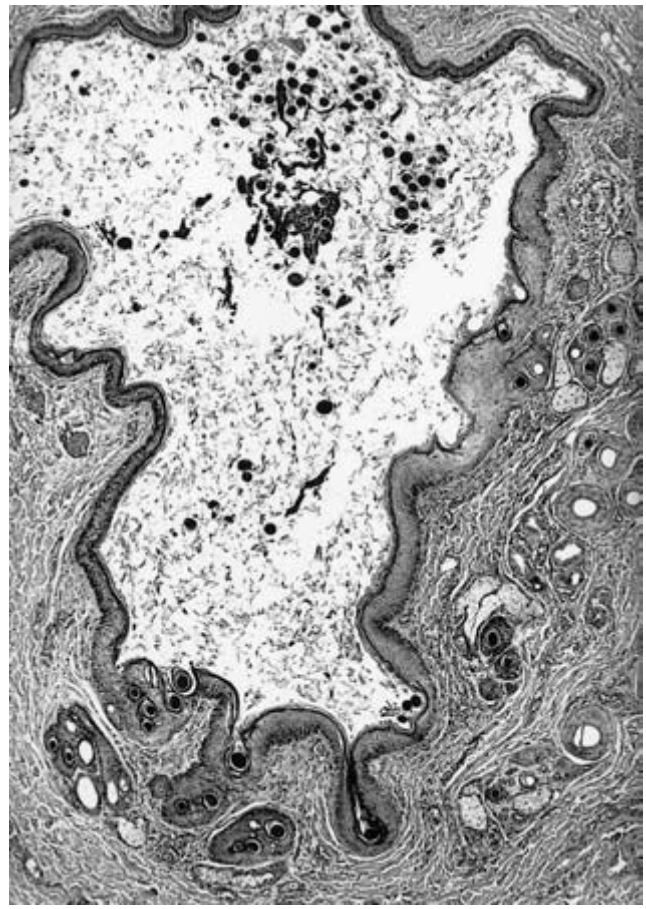


Fig. 22.5 Dermoid cyst in a dog. Small folliculosebaceous units radiate outward from a cyst lined by squamous epithelium with a prominent granular cell layer.

Histopathology (Figure 22.5)

Dermoid cysts have a spherical or tubular central cyst lined by epidermal stratified squamous epithelium, which keratinizes through a prominent granular cell layer. The cyst cavity is often filled with hair in addition to lamellar keratin, and may also contain sebaceous secretions. Dermoid cysts are surrounded by a zone of collagen bundles that tend to parallel the cyst wall; this represents the dermal component of the cutaneous invagination from which a dermoid cyst is derived. Within the dermal collagen surrounding the cyst are well-developed small hair follicles ('folliculettes'), sebaceous glands and, occasionally, apocrine sweat glands; the follicles are attached to and radiate from the cyst wall, resembling the normal relationship of folliculosebaceous units to the epidermis. The hair follicles are usually compound, and delicate hair shafts are often present. The folliculosebaceous units are sparse or moderate in number and tend to be evenly spaced within the dermal collagen.

Differential diagnoses include trichofolliculoma, follicular infundibular cyst, and folliculosebaceous hamartoma. A small dermoid cyst may resemble a trichofolliculoma with predominantly mature secondary follicles, particularly if hair shafts and sebaceous glands are present. The follicles that radiate from the central cyst of a trichofolliculoma are more numerous and also show secondary branching. The central cyst of a trichofolliculoma may contain epithelial segments resembling isthmus and/or matrical portions of a hair follicle, while the central cyst of a dermoid cyst is lined entirely by epidermal-type squamous epithelium. Differentiation of dermoid cyst from infundibular cyst may be problematic. Dermoid cysts have diminutive folliculosebaceous units radiating from the cyst wall and oriented perpendicular to it. Infundibular cysts occasionally have one or two clusters of sebaceous glands attached to the wall; any adjacent hair follicles show a normal perpendicular orientation to the epidermis. Infundibular cysts lack a concentric arrangement of the surrounding collagen. Folliculosebaceous hamartomas almost always have multiple tortuous infundibular cysts with multiple randomly

arranged sebaceous lobules and no anagen follicles, whereas dermoid cysts have a single epithelial cystic structure with a few miniature but complete folliculosebaceous units radiating from it.

SQUAMOUS PAPILLOMA

Clinical features

Papillomatous lesions in which viral cytopathic effects are not evident occur uncommonly in dogs and rarely in cats. They are probably non-neoplastic and may be traumatic in etiology. To avoid confusion, the term 'fibropapilloma', although accurately descriptive, is probably best reserved for the lesion on the penis of bulls that is caused by bovine papillomavirus.

Squamous papillomas are delicate, fimbriated masses that are usually pedunculated. These papillomas are generally smaller than viral warts; they are of the order of 1 to 5 mm in diameter. Lesions are most often observed on the face, eyelids, feet, and conjunctiva. There is no known age or breed predisposition.

Histopathology (Figure 22.6)

The overall architecture of squamous papilloma is similar to viral papilloma (see p. 567). The epithelium forming the papillary projections is moderately hyperplastic, mildly hyperkeratotic, and mature. The collagenous cores of the finger-like projections are bland and delicate. Inflammation is usually minimal or mild. Trauma may result in spongiosis, ulceration, and more severe inflammation. Viral cytopathic effect, such as giant keratohyalin granules, koilocytosis (keratinocytes with clear cytoplasm and pyknotic nuclei), blue-grey cytoplasmic pallor, or inclusion bodies, is not evident.

Differentiation between viral and nonviral squamous papillomas is based largely on the absence of cytopathic effect in the latter. Nonviral squamous papillomas generally have less epithelial proliferation and hyperkeratosis than viral warts. Immunohistochemistry or testing by polymerase chain reaction (PCR) for papillomavirus is indicated for equivocal lesions. Distinction between squamous papilloma and acrochordon (see Chapter 27) is based on the predominance of epithelium in the former and fibrous connective tissue in the latter. However, this distinction may be moot, as the squamous papilloma may actually represent one end of the spectrum of acrochordon in which the ratio of epithelium to connective tissue is unusually high (Murphy & Elder, 1991).

VIRAL PAPILLOMA

(Synonyms: wart, verruca)

Papillomaviruses (PVs) are small, double-stranded DNA viruses that infect many different animal species; they are usually species-specific, and show strong tropism for cutaneous or mucosal squamous epithelium (Sundberg et al., 1994). More than 130 different strains of PVs have been

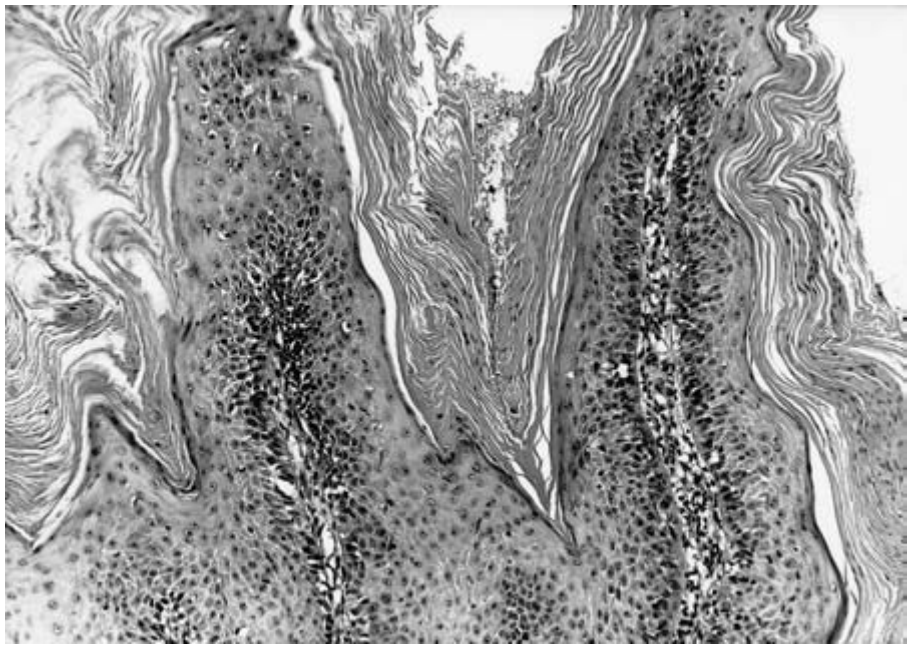


Fig. 22.6 Squamous papilloma in a dog. Hyperplastic, hyperkeratotic epithelium covers papillary projections of fibrous tissue with a mild inflammatory infiltrate. Hypergranulosis and koilocytosis are not present.

identified in humans, but only two genetically distinct PV types have been sequenced thus far in dogs (Nicholls & Stanley, 1999). However, there are at least six different PV syndromes in dogs (Campbell et al., 1988; Nagata et al., 1995; Le Net et al., 1997; Nicholls & Stanley, 1999) and at least three in domestic cats (Carpenter et al., 1987; Carney et al., 1990; Sundberg et al., 2000) that are distinguished by anatomic distribution, histologic features, immunohistochemistry, polymerase chain reaction (PCR) and/or *in situ* DNA hybridization; this suggests that many more strains do exist. Exophytic and inverted viral papillomas are discussed in this section (Carpenter et al., 1987; Campbell et al., 1988; Le Net et al., 1997; Nicholls & Stanley, 1999); canine and feline viral plaques are discussed separately (see pp. 571 and 574) (Carney et al., 1990; Nagata et al., 1995; Sundberg et al., 2000). In humans, the more common PV syndromes are grouped into five categories based on clinical presentation as well as the viral strains that most often cause them: verruca vulgaris or common wart (HPV types 2, 4 and 7), verruca plana or flat wart (HPV type 3), mosaic-type palmoplantar wart (HPV types 2 and 4), deep palmoplantar wart (HPV type 1), and condyloma accuminatum or anogenital wart (HPV types 6, 11, 16, 18, 31, 33, and 51) (Penneys, 1997).

Clinical features

Classic exophytic cutaneous papillomas induced by PV occur uncommonly in dogs and rarely in cats. The reported incidence ranges from less than 1% to 2.5% of all canine skin tumors (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992). One of 444 skin tumors in a large feline survey was a papilloma, and one case of papillomatosis was also cited (Carpenter et al., 1987). Two young cats with multiple lesions were described by Abramo et al. (1997).

Most exophytic papillomas on haired skin are caused by a PV that appears to be different from canine oral papillomavirus (COPV) based on *in situ* DNA hybridization (Campbell et al., 1988). Dogs with COPV-induced mucosal lesions also may have warts that involve the lips, eyelids, or nasal planum. Immunosuppression has been reported to induce extensive COPV lesions on haired skin in a dog with concurrent oral papillomatosis (Sundberg et al., 1994). Oral and cutaneous viral papillomas occurred in the clinical setting of cyclosporine administration in a middle-aged dog (Power, H.T., personal communication, 2003).

Classical, fully-developed, exophytic warts are single or multiple papillated masses that may be sessile or pedunculated. Multiple or numerous lesions are referred to as cutaneous papillomatosis. Lesions are typically less than 1 cm in diameter. They have a fimbriated surface that may appear waxy due to hyperkeratosis. Hyperkeratosis may be severe enough to form a cutaneous horn. Exophytic viral papillomas occur most commonly on the face, ears, and extremities. Although facial mucocutaneous involvement is common, pedal lesions do not involve the pads. Isolated lesions can also occur on other parts of the body.

Exophytic papillomas occur at any age but are most often seen in dogs less than 2 years of age. Many but not all exophytic viral papillomas spontaneously regress over a period of weeks to months. Spontaneous malignant transformation of exophytic viral papillomas is extremely rare; one of the authors (T.L.G.) observed a neoplasm resembling basosquamous carcinoma (see p. 597) arising from a classical papilloma in an 11-year-old Labrador Retriever.

Cutaneous inverted papilloma is a rare endophytic variant in dogs originally described by Campbell et al. (1988); it is very rare in cats. Papillomavirus was detected in these lesions by both electron microscopy and immunohistochemistry. *In situ* DNA hybridization demonstrated that inverted papilloma is also caused by a PV that is distinct from COPV (Campbell et al., 1988).

Inverted papillomas usually appear as multiple, raised, firm, umbilicated masses that are less than 2 cm in diameter. Most cutaneous inverted papillomas arise on the ventral abdomen. In contrast to exophytic papillomas, the inverted lesions do not undergo spontaneous regression.

A single case of pigmented inverted papillomatosis was described in an immunosuppressed Boxer (Le Net et al., 1997). The lesions in this case also had a ventral distribution but were one-tenth the size of the more common inverted papilloma. A unique strain of PV was confirmed by immunohistochemistry and DNA hybridization using Southern blotting (Le Net et al., 1997). A solitary lesion with identical morphology to these distinctive, diminutive papillomas has been observed in a young healthy dog by one of the authors (E.J.W.).

Inverted viral papillomas generally affect dogs less than 3 years of age (Campbell et al., 1988). Whippets, Bernese Mountain Dogs, Irish Setters, Beagles, Great Danes, Cocker Spaniels, and Kerry Blue Terriers are reported to be predisposed to develop viral papillomas (Goldschmidt & Shofer, 1992; Scott et al., 2001; Goldschmidt & Hendrick, 2002).

Histopathology

Exophytic papilloma (Figures 22.7 and 22.8)
These are identical to verruca vulgaris or common warts in humans. Typical viral papillomas comprise multiple finger-like projections of thickened squamous epithelium that generally exhibits normal maturation. The peripheral papillary structures tend to be angled inward at their base; this is referred to as a 'toed-in' configuration. The epithelial fronds are heavily keratinized, and the keratin is

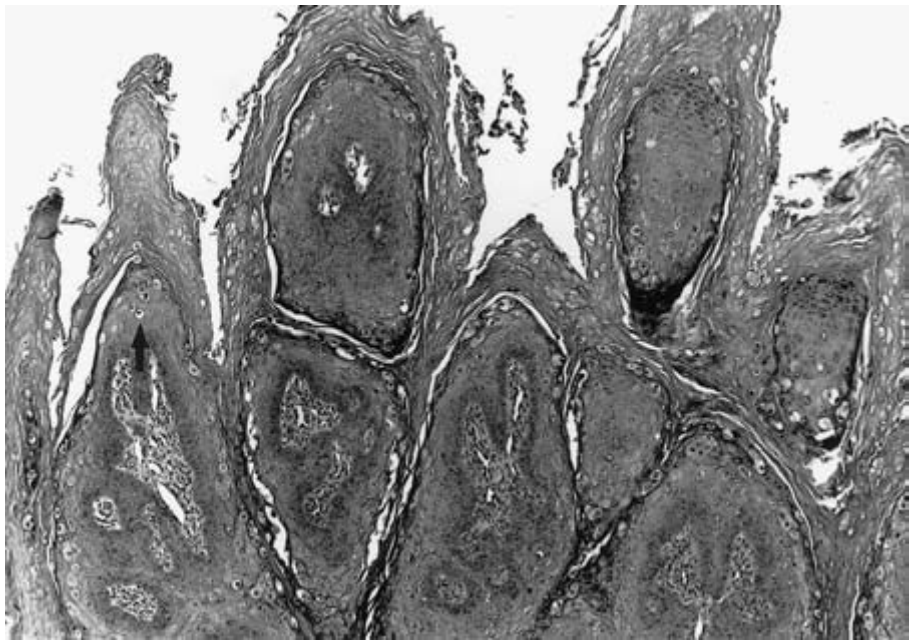


Fig. 22.7 Exophytic viral papilloma in a dog. Hyperplastic, hyperkeratotic epithelium covers closely-grouped papillary projections. Note prominent keratohyalin granules and cells with expanded, pale gray cytoplasm in the stratum granulosum. Scattered koilocytes are evident (arrow).

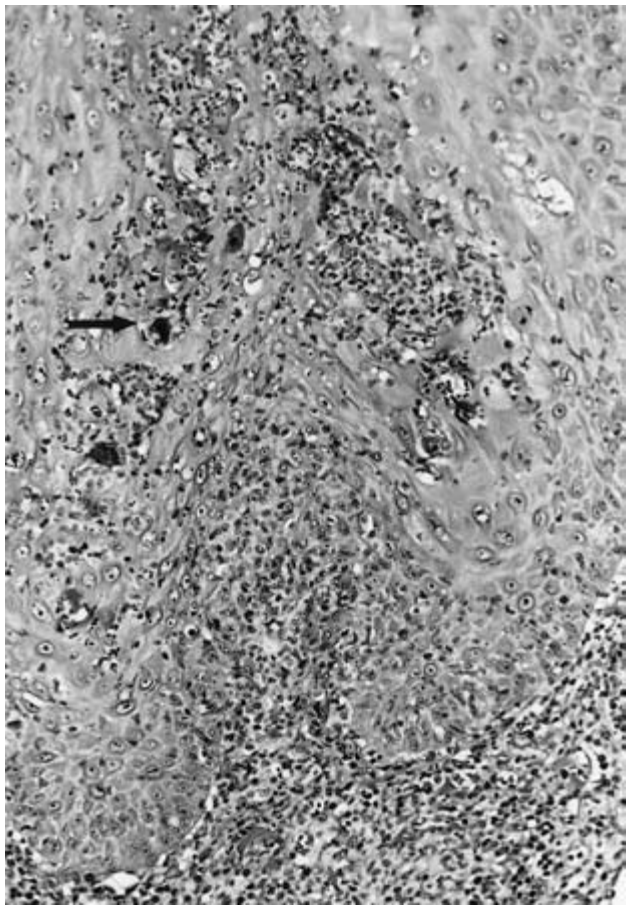


Fig. 22.8 Regressing exophytic viral papilloma in a dog. Marked lichenoid inflammation is associated with keratinocyte apoptosis and lymphocyte satellitosis (arrow).

arranged in peaks and spires. Some lesions have hypertrophy and hyperplasia of basal cells with a concomitant increase in mitotic figures; this most likely represents an early, proliferative phase of the lesion and should not be mistaken for malignant transformation. Ectatic blood vessels and mild to moderate infiltrates of mixed inflammatory cells are generally present in the connective tissue cores of the papillae, and serous or serosanguinous crusts are present at their tips.

Papillomavirus infection is manifested in all species by distinctive changes in the cytoplasm and/or nucleus; these are considered collectively as viral cytopathic effect or cytopathology. The stratum granulosum usually has collections of giant keratohyalin granules with rounded edges. The upper stratum spinosum or stratum granulosum may exhibit koilocytosis. Koilocytes (literally, 'hollow cells') are altered keratinocytes characterized by clear cytoplasm and pyknotic nuclei. More commonly, moderate numbers of superficial keratinocytes have expanded blue-gray cytoplasm and enlarged nuclei with marginated chromatin. Occasionally, pale basophilic intranuclear inclusion bodies can be found at the junction of keratinized and nonkeratinized epithelium.

Regression of exophytic papillomas is manifested by a moderate, interface infiltrate, consisting primarily of lymphocytes. These are known to be T lymphocytes, reflecting a cell-mediated immune response in dogs as well as many other species (Nicholls & Stanley, 1999). There is also progressive individual cell death consistent with apoptosis, manifested by shrinkage, angularity, and increased eosinophilia. Confluent epithelial cell

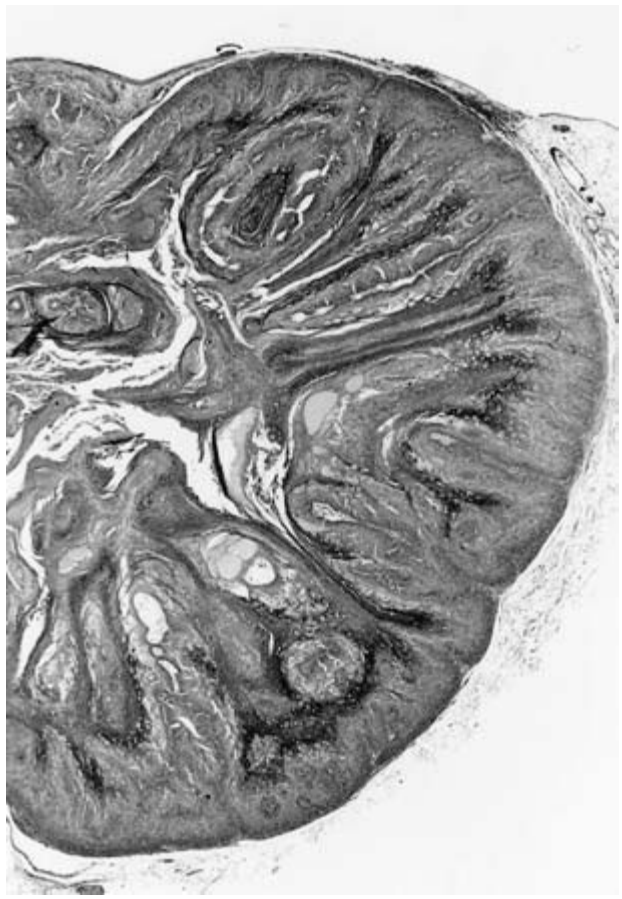


Fig. 22.9 Inverted viral papilloma in a dog. Papillary structures project from a cup-shaped wall of mature squamous epithelium into a keratin core; epidermis is at top.

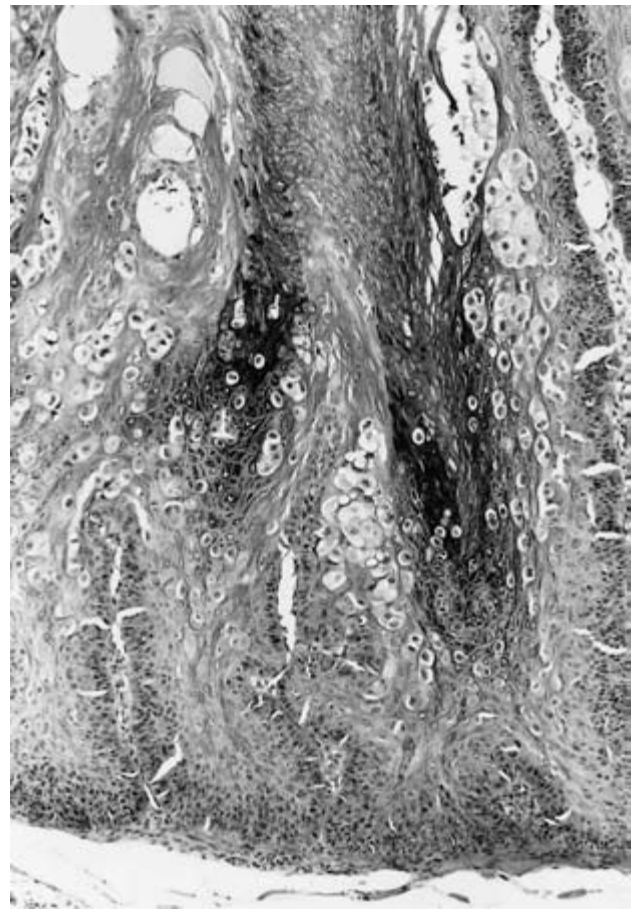


Fig. 22.10 Higher magnification of inverted viral papilloma of Fig. 22.9. Viral cytopathic effect is characterized by multiple clusters of enlarged cells with cytoplasmic pallor. Some giant keratohyalin granules are also present.

death, ulceration, and subacute inflammation are seen occasionally.

Differentiation between viral papillomas and nonviral squamous papillomas is based largely on the absence of cytopathic effect in the latter. Nonviral squamous papillomas generally have less epithelial proliferation and hyperkeratosis than viral warts. Pawpad keratomas in dogs and cutaneous horns on feline pawpads do not have papillary fronds of epithelium, and PV cytopathic effect is absent. Immunohistochemistry (or testing by PCR) or *in situ* hybridization, if available) for PV is indicated for equivocal lesions.

Inverted papilloma (Figures 22.9 through 22.11)
Inverted papillomas are morphologically similar to deep palmoplantar warts in humans (Penneys, 1997), although their clinical distribution is different. They are cup-shaped lesions with a central core of keratin or parakeratotic cells leading to an umbilicated surface. The cup is usually lined by hyperplastic squamous epithelium with centripetal papillary projections. The cells may exhibit either koilocytosis (see above) or blue-gray cytoplasmic pallor. Giant keratohyalin granules and, less frequently, eosinophilic intranuclear inclusions are present.

In the rare pigmented endophytic papillomas in dogs, the endophytic epithelial nodules are very small, hyperpigmented, and lack papillary proliferations (Le Net et al., 1997). Their viral cytopathology is unusual in that it includes large, angular, basophilic intranuclear viral inclusions and deeply eosinophilic, perinuclear inclusions composed of condensed keratin filaments (Le Net et al., 1997).

Inverted papilloma must be differentiated from infundibular keratinizing acanthoma, which is also a cup-shaped, keratin-filled, squamous epithelial mass. Infundibular keratinizing acanthoma has small cysts and anastomosing trabeculae of keratinocytes comprising its epithelial wall, in comparison to the papillary structures of an endophytic wart. Viral-induced inclusion bodies and

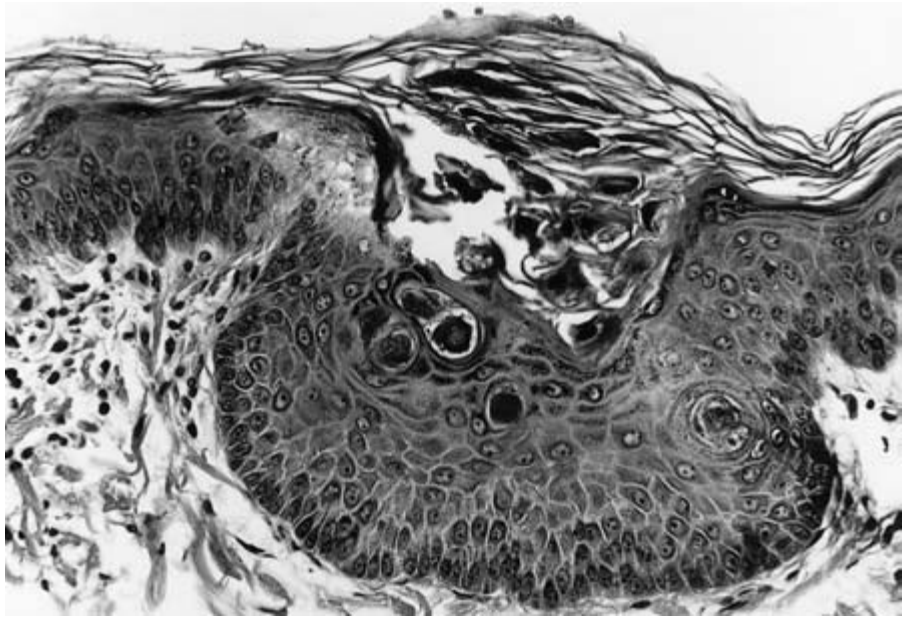


Fig. 22.11 Unusual inverted viral papilloma in a dog, featuring a diminutive cup-shaped structure with large, angular, nuclear and cytoplasmic inclusions in the stratum granulosum.

other viral cytopathic alterations are not present in infundibular acanthoma, and keratohyalin granules are small and sparse.

Immunohistochemistry

Immunostaining can be a useful diagnostic and research tool for lesions of suspected PV etiology in dogs and cats. Bovine PV antibody and other polyclonal anti-PV reagents crossreact with PVs of multiple species and are readily available commercially. Because these antibodies target whole virus, which is assembled in fully-differentiated squamous epithelial cells only, positive reactions are limited to superficial epidermis and stratum corneum. More specific reagents for canine and feline PVs are not yet available.

CANINE PIGMENTED VIRAL PLAQUE

(Synonym: verruca plana)

Canine pigmented viral plaque was not recognized as being of viral etiology until recently (Nagata et al., 1995). In the older veterinary literature, identical lesions were erroneously described as lentigines or lentiginosis profusa (Briggs, 1985) because of their intense hyperpigmentation and multifocal distribution. Some confusion in terminology still exists in current reference texts. In *Veterinary Dermatopathology* (Walder & Gross, 1992) they were reclassified as pigmented epidermal nevi based on certain similarities to verrucous or linear epidermal nevus in humans and the absence of melanocyte hyperplasia, which is a requisite feature of lentigines (see Chapter 34). They are referred to as 'tar spots' in lay terminology.

It has been suggested that canine pigmented viral plaques are analogous to epidermodysplasia verruciformis in humans (see feline viral plaque, p. 574) (Nagata et al., 1995; Walder, 1997). However, despite certain similarities, the authors now believe that there are substantial differences between canine pigmented viral plaques and epidermodysplasia verruciformis. These include facial and extremity distribution, lack of consistent and marked hyperpigmentation, absence of true koilocytosis (keratinocytes with cytoplasmic clearing and pyknotic nuclei), and a much higher rate of malignant transformation in epidermodysplasia verruciformis in contrast to canine pigmented viral plaques (Penneys, 1997; Nuovo & Ishag, 2000). The canine lesions, at least in Pugs, appear to have an autosomal dominant mode of inheritance (Briggs, 1985); the hereditary form of epidermodysplasia verruciformis in humans is autosomal recessive (Penneys, 1997).

The majority of the canine lesions have several features in common with human flat warts (verruca plana); the human lesions can have a familial occurrence, extensive anatomic distribution and hyperpigmentation (Penneys, 1997). However, human flat warts do not undergo malignant transformation.

Papillomavirus-associated carcinogenesis, in general, requires integration of viral genome into host cell DNA. These viral genes, at least in humans, target the *p53* tumor suppressor gene and other host cellular regulatory mechanisms, resulting in a favorable environment for persistent viral replication and destabilization of the host genome (Munger, 2002). Similar events may occur in dogs

with malignant transformation of viral plaques. Further clarification of the relationship between the canine and human disease awaits identification of the specific strain(s) of canine PV responsible for banal versus carcinogenic variants of pigmented viral plaque; two clinically similar but biologically distinct syndromes may exist.

Immunosuppression due to hyperadrenocorticism, hypoglobulinemia, and hypothyroidism, respectively, was suggested as a contributing factor to viral plaque development in three dogs; in one of these, an 8-year-old Pomeranian, the lesions showed malignant transformation (Stokking et al., 2002). Profound immunosuppression in humans, particularly associated with human immunodeficiency virus (HIV) infection or organ transplantation, is associated with an increased incidence of a variety of PV-induced lesions, including epidermodysplasia verruciformis (Penneys, 1997).

Clinical features

Pigmented viral plaques are rare or uncommon lesions of dogs. The actual incidence is difficult to determine, as most are probably not submitted for dermatologic or histologic evaluation. Pigmented viral plaques usually present as multiple, deeply pigmented, ovoid, or circular plaques that are less than 1 cm in diameter. Lesions may be numerous or, occasionally, are solitary. They have scaly, irregular, slightly papillated surfaces. Rarely, the hyperplastic epidermis covers a filiform collagenous protrusion resembling a skin tag. The lesions occur most often on the ventral abdomen, ventral thorax, and medial proximal legs. Involvement may be bilateral or unilateral. Distal legs may also be involved.

Affected animals are usually young adults. There is a strong breed predilection for Pugs and Miniature Schnauzers, supporting a genetic contribution to a cutaneous immunologic milieu that permits persistent PV infection. Boston Terriers and French Bulldogs also have an increased incidence of pigmented viral plaques.

The plaques develop progressively over a period of time and then become stable. The vast majority have no untoward sequelae. In rare instances, pigmented viral plaques undergo malignant transformation to squamous cell carcinoma (Nagata et al., 1995; Walder, 1997); the metastatic potential is unknown. In contrast, 30% to 50% of human patients with epidermodysplasia verruciformis develop *in situ* and invasive squamous cell carcinomas, usually on sun-exposed skin, which may be metastatic and fatal (Kaspar et al., 1991; Penneys, 1997; Nuovo & Ishag, 2000).

Histopathology (Figures 22.12 through 22.14)

Pigmented viral plaques are discrete foci of mild to moderate acanthosis and hyperkeratosis. Keratinocyte maturation is normal. The epidermis has a distinctively scalloped configuration, resulting in widely-spaced, shallow papillations or digitations. The lower layers of the epidermis have moderate to marked hyperpigmenta-

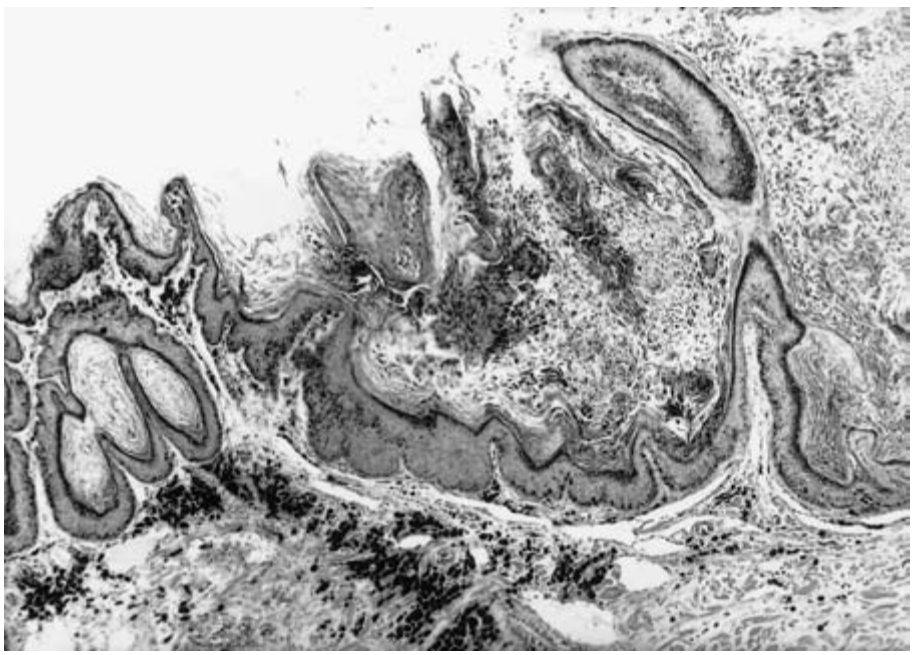


Fig. 22.12 Canine pigmented viral plaque. The epidermis shows acanthosis, marked hyperpigmentation, and hyperkeratosis. Note the distinct, broadly-scalloped architecture.

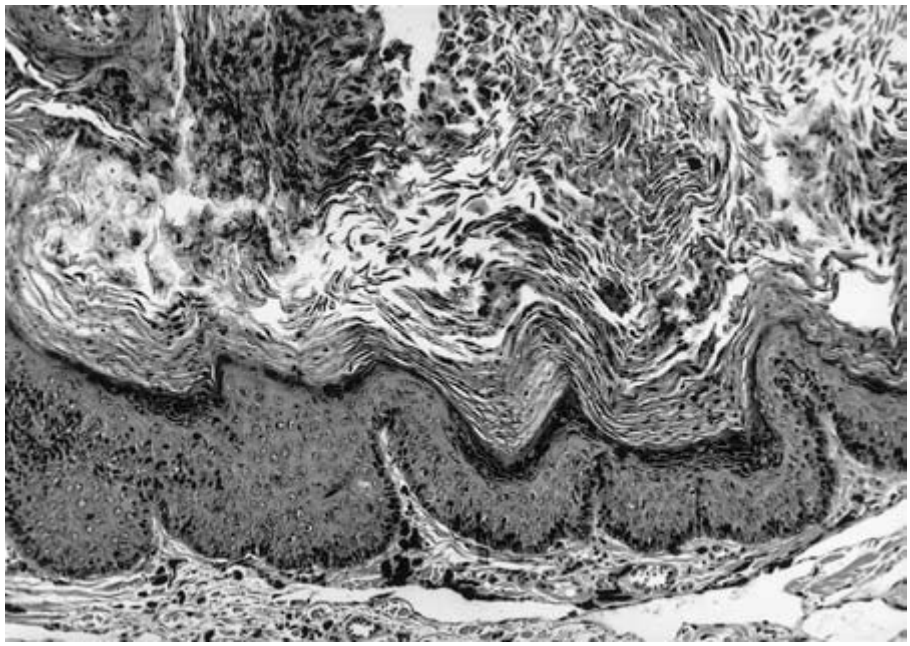


Fig. 22.13 Higher magnification of Fig. 22.12. Viral cytopathology is manifested by an increase in the number and size of keratohyalin granules.

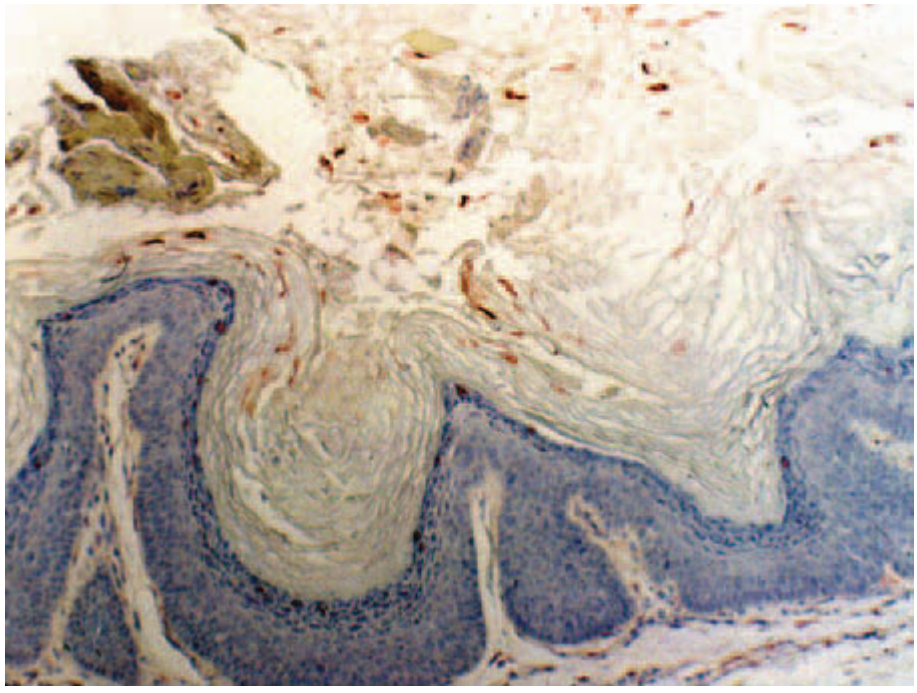


Fig. 22.14 Canine pigmented viral plaque. Papillomavirus immunostain decorates small numbers of nucleated cells in the stratum granulosum and moderate numbers of squames in the stratum corneum (chromogen aminoethylcarbazole [AEC]).

tion, but melanocyte proliferation is not present. Melanin pigment may extend into the upper cell layers of the epidermis including the stratum corneum. Mild to moderate, patchy or diffuse hypergranulosis with enlarged keratohyalin granules is usually present. Small numbers of cells in the stratum spinosum or granulosum may demonstrate papillomavirus-induced koilocytosis, characterized by cytoplasmic clearing and pyknotic nuclei, but this feature is usually subtle. The underlying dermis may contain increased numbers of melanophages, particularly in heavily-pigmented plaques.

Malignant transformation of pigmented viral plaques occurs rarely and is essentially the same as bowenoid or other *in situ* squamous cell carcinoma, with progression

to invasive squamous cell carcinoma; the carcinoma may retain some melanin pigment and may have areas of 'windblown' architecture resembling bowenoid *in situ* carcinoma (see p. 578). Bizarre giant nuclei may be present.

Pigmented viral plaque is distinguished from lentigo clinically by the thickened, slightly irregular, scaly appearance of the former. Histologically, lentigines contain increased numbers of deeply-pigmented, bland melanocytes in the basal cell layer clustered at the tips of elongated rete pegs; these are not present in viral plaques. Lentigines do not have hypergranulosis or koilocytosis. Linear epidermal hamartoma, if melanized, may be a differential diagnosis. Viral plaques generally do not form linear arrays and are much more deeply pigmented. Hypergranulosis without granular degeneration is present in viral plaques, although koilocytosis could be misinterpreted as early epidermolytic hyperkeratosis seen in some lesions of linear epidermal hamartoma. Neither lentigines nor linear epidermal hamartomas exhibit the unique pattern of scalloped epidermal hyperplasia seen in pigmented viral plaques. Immunostaining, or testing by *in situ* DNA hybridization or polymerase chain reaction (PCR) for PV (if available) may be required for definitive diagnosis in equivocal cases.

FELINE VIRAL PLAQUE

(Synonyms: verruca plana, epidermodysplasia verruciformis)

Skin lesions caused by papillomavirus (PV) in cats were documented fairly recently, after immunohistochemical stains for the virus became readily available. These reports were of flat rather than typical exophytic warts and were designated as papillomavirus infection of aged cats (Carney et al., 1990), papillomavirus associated skin lesions (Egberink et al., 1992), and persistent papillomavirus infection (Lozano-Alarcon et al., 1996). Although the specific PV causing these lesions has not been identified, comparative immunostaining using a panel of monoclonal antibodies against various bovine PV epitopes indicates that it is distinct from the PVs causing similar cutaneous lesions in snow leopards, oral papillomas in domestic cats and several different species of wild felids, and canine oral papillomas (Sundberg et al., 2000).

In contrast to canine viral plaques (see p. 571), feline viral plaques are very similar clinically and histopathologically to epidermodysplasia verruciformis in humans. Classical epidermodysplasia verruciformis is a rare hereditary human disorder caused by a specific group of more than 20 different strains of oncogenic human papillomavirus (HPV) in genetically susceptible individuals (Penneys, 1997). An acquired variant of epidermodysplasia verruciformis with identical clinicopathologic and virologic features to classical human epidermodysplasia verruciformis occurs secondary to immunosuppression, particularly due to human immunodeficiency virus (HIV) infection or organ transplantation (Penneys, 1997; Morrison et al., 2002). Similarities between feline viral plaques and epidermodysplasia verruciformis include a clinical and histologic resemblance to verruca plana, a distribution that includes face and extremities, variability of pigmentation, a high rate of malignant transformation to *in situ* and invasive carcinoma, and likely cocarcinogenicity of ultraviolet radiation (Kaspar et al., 1991; Penneys, 1997; Harwood, et al., 1999; Nuovo & Ishag, 2000; Morrison et al., 2002).

The first step in HPV-associated carcinogenesis, in general, is integration of viral genome into host cell DNA. The viral genes that are consistently retained after integration target several important host cellular regulatory mechanisms, such as the *p53* tumor suppressor gene. This results in a favorable environment for persistent viral replication and destabilization of the host genome (Munger, 2002). In humans, specific *in situ* polymerase chain reaction (PCR) technique identifies epidermodysplasia verruciformis-HPV DNA within lesional skin only and can also demonstrate, by a change from diffuse to punctate nuclear staining, integration of viral genome into host DNA; this strongly supports their etiologic and carcinogenic role (Nuovo & Ishag, 2000; Morrison et al., 2002). Similar events are likely occurring in cats with malignant transformation of viral plaques.

Clinical features

The true incidence of feline viral plaques is difficult to estimate; they are most likely uncommon. Lesions that are not on glabrous or sparsely-haired skin are probably not clinically apparent until they undergo malignant transformation to bowenoid or other *in situ* squamous cell carcinoma, invasive squamous cell carcinoma, or basal cell carcinoma.

Feline viral plaques present as multiple, ovoid or elongated, slightly raised lesions that are usually less than 8 mm in greatest dimension. The plaques may be either pigmented or nonpigmented. They have a scaly, slightly irregular surface; gross papillation is not apparent. There is no preferential anatomic distribution.

Three of the four cats in the first case reports were Persians (Carney et al., 1990; Lozano-Alarcon et al., 1996), but this may be coincidence as the majority of infected animals are the common domestic breeds. The reported age range is 7 months to 15 years (Sundberg et al., 2000), but the majority of affected cats are older adults. Immunosuppression may be a contributing factor, as it is in humans; two of the Persian cats in one report had received long-term corticosteroid treatment (Carney et al.,

1990), another reported Persian cat was suspected to have feline infectious peritonitis (FIP) (Lozano-Alarcon et al., 1996), and a domestic cat was seropositive for feline immunodeficiency virus (FIV) (Egberink et al., 1992).

The incidence of carcinogenesis in feline viral plaques is also unknown, but is probably fairly high given the frequency of squamous cell carcinoma in this species. The immunohistochemical identification of PV in 45% of bowenoid *in situ* carcinomas (see p. 578) as reported by Clark (Gross & Affolter, 1998) supports the hypothesis that many of the *in situ* carcinomas arise in pre-existing viral plaques. If, as in human epidermodysplasia verruciformis, multiple strains of feline PV were found to be associated with viral plaques, the prognosis may be dependent upon the relative carcinogenicity of the strain affecting a particular cat.

Histopathology (Figure 22.15)

Feline viral plaques are characterized by mild to moderate acanthosis and laminated hyperkeratosis with an abrupt transition from normal epidermis. The thickened epidermis may have an undulating configuration, but frank papillomatous hyperplasia is not present. Melanin pigment varies from absent in some lesions to abundant in others. The hyperplasia and hyperkeratosis also affect follicular infundibula within the plaques. Keratinocyte maturation is normal; dysplasia or atypia is not present. The granular cell layer is thickened and irregular, and the keratohyalin granules are frequently enlarged. Small numbers of PV-induced koilocytes, characterized by cytoplasmic clearing and pyknotic nuclei, are present in the upper layers of the epidermis. The koilocytes may contain amphophilic pseudoinclusions formed by condensation of keratin fibrils (Carney et al., 1990; Sundberg et al., 2000). Inflammation is not observed.

Malignant transformation of feline viral plaques occurs commonly and generally resembles bowenoid *in situ* carcinoma (see p. 578), but may also have features of actinic keratosis on sun-exposed locations (see below). Early malignant transformation is manifested by increased epidermal thickness, nuclear enlargement and anisokaryosis, variable nucleolar enlargement, and loss of orderly keratinocyte maturation. *In situ* carcinoma may eventuate in invasive squamous cell carcinoma or basal cell carcinoma.

Feline viral plaques are subtle but distinctive lesions. The primary differential diagnosis is nonspecific acanthosis, spongiosis, and/or hypergranulosis secondary to an inflammatory dermatopathy. Papillomavirus immunostaining, polymerase chain reaction (PCR) testing (if available), or electron microscopy is helpful in equivocal cases. If abnormal maturation or atypical keratinocyte morphology is present, a diagnosis of carcinoma *in situ* should be rendered. Definitive histologic diagnosis of feline viral plaques may allow early therapeutic intervention with antiviral compounds, possibly preventing malignant transformation.

ACTINIC KERATOSIS

(Synonyms: actinic carcinoma *in situ*, solar keratosis)

The term 'keratosis' is nonspecific and refers to a 'horny or warty growth or callosity' (Anderson, 1994); actinic

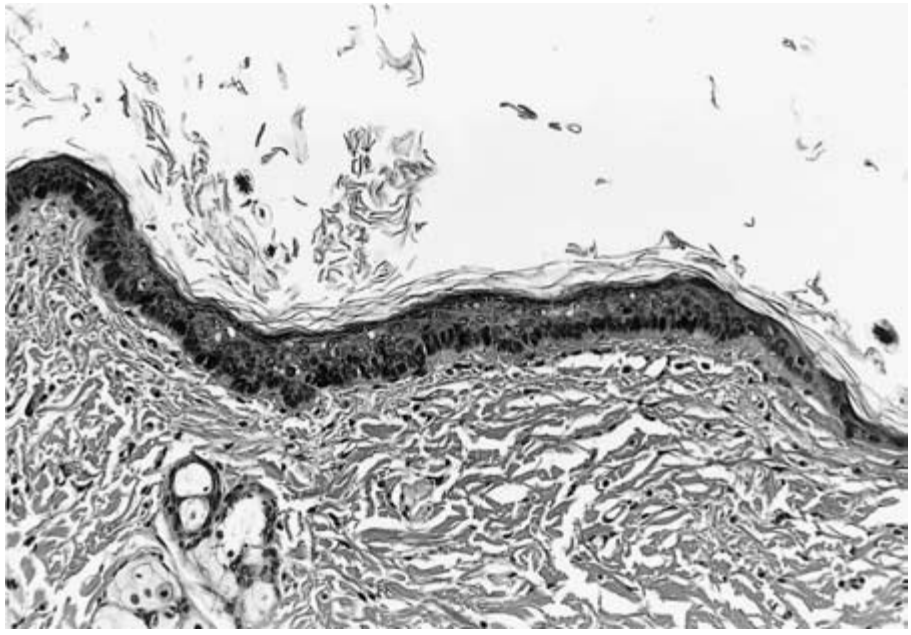


Fig. 22.15 Feline viral plaque. Discrete zone of mildly irregular acanthosis with hyperpigmentation. Note scattered koilocytes (small clear cells) and absence of cytologic atypia.

keratoses are epithelial plaques of solar induction. It is well documented that ultraviolet (UV) radiation causes direct damage to DNA molecules, in addition to indirect damage via free radicals, and those mutations have a specific pattern of C to T and CC to TT nucleotide base substitutions (Dunstan et al., 1998). Ultraviolet radiation-induced mutations in the tumor suppressor gene *p53*, which is critical in inducing apoptosis and controlling cell division, results in clones of altered basal keratinocytes that are resistant to apoptosis and DNA repair (Dunstan et al., 1998). If the mutated keratinocyte population expands sufficiently, an actinic keratosis (AK) will develop. Immunohistochemical detection of abnormal *p53* gene product in feline AK has been recently reported (Albaric et al., 2001).

One study estimated that 0.25% to 1% of AKs per year in humans progress to frank invasive squamous cell carcinoma (Jeffes & Tang, 2000). Another report found that more than 80% of squamous cell carcinomas were either arising directly from or were in close proximity to an AK (Mittelbronn et al., 1998). Similar data do not exist for dogs or cats, although it is common to find AK in the vicinity of squamous cell carcinoma in large biopsy specimens, such as canine inguinal excisions, suggesting that progression of AK to invasive squamous cell carcinoma is likely.

Recent confirmation of numerous genetic and molecular similarities between AK and squamous cell carcinoma (Krunic et al., 1998; Tsukifuji et al., 1999; Ishida et al., 2001; Xu et al., 2001; Hodges & Smoller, 2002; Ashton et al., 2003) have prompted some investigators to suggest abandoning the clinical term 'actinic keratosis' in favor of a more biologically realistic nomenclature such as 'keratinocytic intraepidermal neoplasia', citing the close analogy to the evolution of carcinoma of the human cervix (Yantsos et al., 1999). Others feel that the histological and molecular features are sufficiently alike to confirm that AK represents the earliest recognizable form of cutaneous squamous cell carcinoma (Lober & Lober, 2000). The authors concur that AK is best regarded as one form of squamous cell carcinoma *in situ*, and suggest the term 'actinic carcinoma *in situ*' over actinic keratosis for its superior scientific accuracy. The reluctance to change the terminology may be based not only on historical precedent, but also on the psychological impact for the patient/owner when a diagnosis includes 'carcinoma'.

Clinical features

The only commonly occurring keratosis in dogs and cats is AK. The incidence varies substantially with geographic location, climate, and behavior; lower latitude, higher altitude, arid or semi-arid environment, and prolonged sun exposure are all predisposing factors in both animals and humans. In the colony of Beagle dogs in Colorado in which concurrent solar dermatitis, keratosis, and frank squamous cell carcinoma was first described, approximately 25% of the animals were affected (Hargis et al., 1977).

Actinic keratoses are single or multiple, plaque-like or papillated lesions that are usually 1 cm in diameter or smaller. Lesions have prominent scales, crusts, or scabs; in small numbers of cases, hyperkeratosis is so dramatic that the lesion presents clinically as a cutaneous horn (see p. 562). Actinic keratoses occur most commonly on the pinnae, nose, and eyelids of white-faced cats. In dogs, they are found primarily on the ventral abdomen, ventral flanks, and medial thighs of short-coated, white-haired or piebald breeds. Dalmatians, Pit Bull Terriers, Beagles, Basset Hounds, and other dogs with similar coat characteristics have an increased incidence of AK as well as other solar-induced neoplasia. (Also see Chapter 7 for further clinical discussion of actinic keratoses.)

Histopathology (Figures 22.16 through 22.18)

The epidermis in AK shows irregular hyperplasia that can vary from mild to marked. There is moderate to severe laminated or compact hyperkeratosis and/or parakeratosis. Keratinocyte cytoplasm often stains a paler pink than that of the adjacent epidermis. There is mild to moderate architectural distortion resulting from loss of polarity of variable numbers of keratinocytes in the basal and spinous layers; the earliest changes occur in the basal keratinocytes. Irregular rete ridge formation may be present; these epidermal trabeculae often have angular profiles and are not perpendicular to the skin surface. The basement membrane zone is intact; there is no dermal invasion by atypical squamous epithelial cells unless the lesion progresses to frank squamous cell carcinoma. Mild to moderate nuclear atypia, characterized by nuclear enlargement and pleomorphism, nucleolar prominence, and occasional hyperchromasia is observed. Mitotic activity may be slightly increased, and mitotic figures can occur above the basal cell layer. Scattered brightly eosinophilic and shrunken apoptotic cells may be present. Hyperplasia and dysplasia usually also affect the peripheral layers of superficial hair follicles.

Dermal inflammation and degenerative changes are as previously described for solar elastosis and fibrosis (see Chapter 15), and support the presence of chronic solar damage. Occasionally, there is a dense band of lymphocytes and plasma cells below the AK accompanied by interface damage; these may be referred to as 'lichenoid actinic keratoses', as they are in human dermatopathology (Kirkham, 1997).

An acantholytic variant of AK, which also occurs in humans (Kirkham, 1997), is occasionally observed in cats

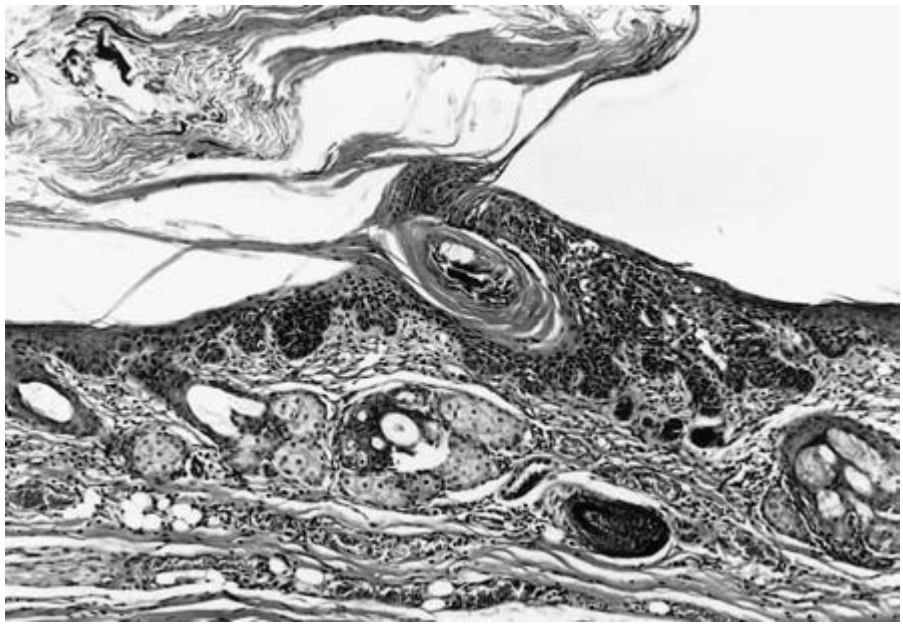


Fig. 22.16 Early actinic keratosis in a cat. Moderately thickened, irregular epidermis and follicular infundibula form a discrete plaque. Note marked hyperkeratosis.

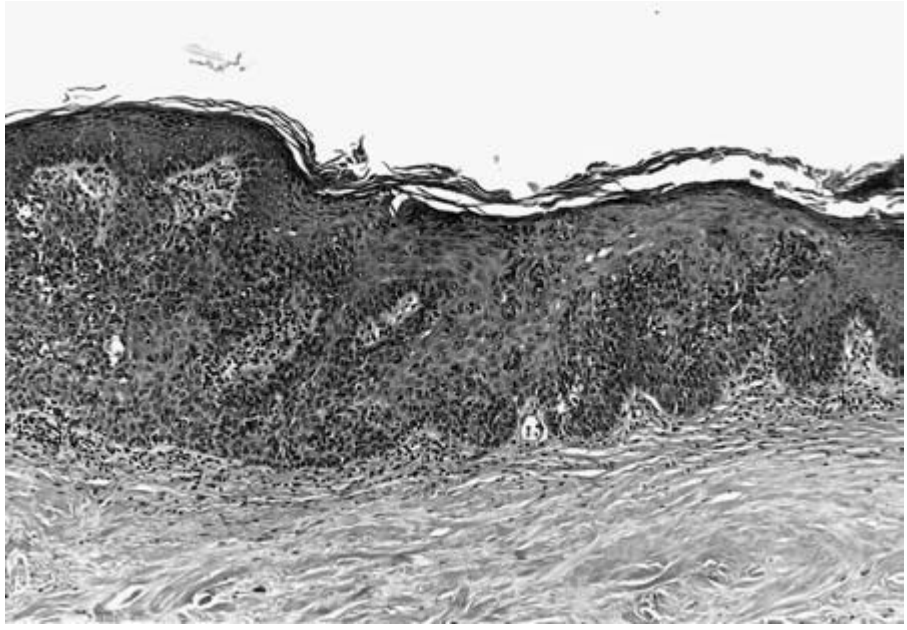


Fig. 22.17 Actinic keratosis on the abdomen of a dog, demonstrating a plaque of moderate, irregular epidermal thickening and keratinocyte dysplasia that starts in the basal cell layer and proceeds upward. Marked, smudgy solar fibrosis is present in the subjacent dermis.

and dogs. Clefts or lacunae develop above dysplastic basal epithelial cells. The clefts contain groups of individualized keratinocytes exhibiting round, brightly eosinophilic cytoplasm and pleomorphic, hyperchromatic nuclei.

Actinic keratosis is differentiated from squamous cell carcinoma by the absence of dermal invasion; serial sections are helpful in ruling out early invasive squamous cell carcinoma. Actinic keratosis needs to be distinguished from lesions of bowenoid *in situ* carcinoma involving sun-exposed, lightly-pigmented areas of the skin; full-thickness epidermal dysplasia, marked nuclear atypia, significant apoptosis, and 'windblown' loss of polarity are most consistent with the latter. Viral cytopathology may also be discernible in bowenoid *in situ* carcinoma (see p. 578) but would be absent in AK. Although the human literature has a subtype called 'bowenoid actinic keratosis' (Kirkham, 1997), it is more likely that these lesions are, in fact, bowenoid *in situ* carcinoma with concurrent AK. Exacerbation of viral-induced DNA damage by UV radiation is well documented in human epidermodysplasia verruciformis (see feline viral plaque, p. 574). The finding of bowenoid features in a lesion that is clinically an AK

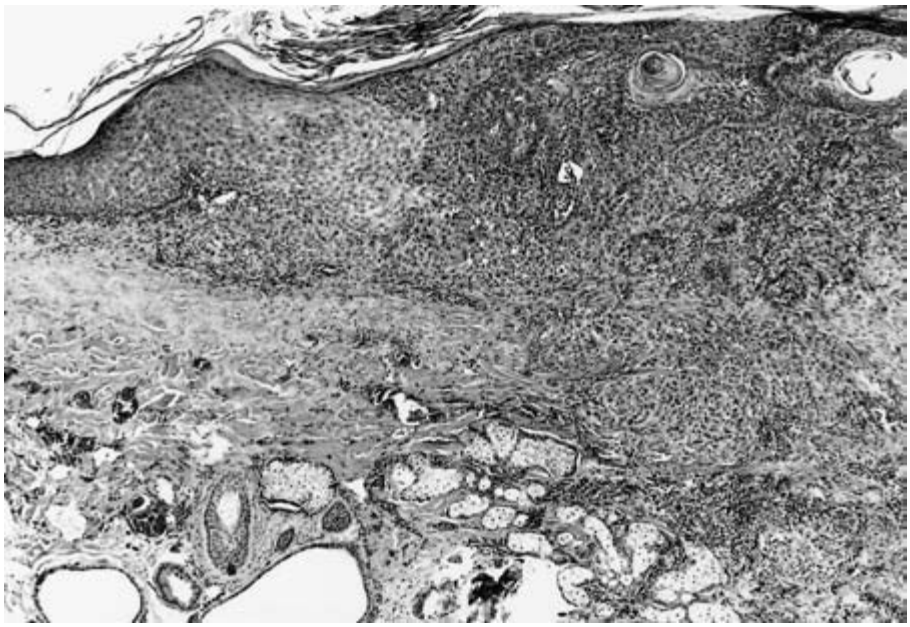


Fig. 22.18 Actinic keratosis progressing to squamous cell carcinoma in a dog. *In situ* carcinoma characterized by thickened epidermis with cytoplasmic pallor and disorderly stratification at left merges into invasive carcinoma at right. Note laminar solar fibrosis and elastosis below the actinic keratosis.

warrants immunohistochemistry for papillomavirus and a search for additional lesions on nonsun-exposed skin, as the therapeutic approach is different.

Acantholytic AK may resemble both pemphigus vulgaris and canine Darier's disease. It is differentiated from pemphigus vulgaris partly on clinical grounds; larger numbers of lesions, bilateral symmetry, and involvement of nonsun-exposed areas are consistent with autoimmune disease. Keratinocyte cytoplasmic pallor; nuclear enlargement, atypia, and loss of polarity, particularly in the basal cell layer; and laminar fibrosis and solar elastosis in the superficial dermis are features of AK that would not occur in either pemphigus vulgaris or canine Darier's disease (see Chapter 2).

BOWENOID *IN SITU* CARCINOMA

(Synonyms: Bowen's disease, multicentric papillomavirus-induced squamous cell carcinoma *in situ*)

This entity in humans was originally reported by Bowen in 1912 as a 'precancerous dermatosis'. It has long been known as Bowen's disease, and the adjective 'bowenoid' is often used to connote the distinctive epithelial features of the lesions. An analogous condition has been documented in the veterinary literature in one dog (Gross & Brimacomb, 1986) and multiple cats (Turrel & Gross, 1991; Miller et al., 1992; Goldschmidt & Shofer, 1992; Baer & Helton, 1993; Rees & Goldschmidt, 1998; Guaguère et al., 1999).

There are some important clinical and etiologic differences between the human and veterinary diseases. Human Bowen's disease is usually a solitary lesion that may occur on sun-exposed or unexposed skin and often affects the anogenital regions (Kirkham, 1997; Penneys, 1997); thus many cases represent a sexually-transmitted disease. Direct animal-to-animal transmission has not been reported. Many of the cases of extragenital Bowen's disease in older literature are due to chronic arsenic exposure from antiquated medications or, more recently, from environmental contamination (Kirkham, 1997). In contrast, no evidence of arsenic exposure was found in the reported canine and feline cases.

It is well-accepted that anogenital Bowen's disease is associated with infection by strains from the mucosal group of human papillomaviruses that cause cervical cancer (Kawashima et al., 1990; Kettler et al., 1990; Collina et al., 1995; Derancourt et al., 2001). Documentation in the literature of any type of papillomavirus infection in extragenital Bowen's disease in humans is inconsistent, even utilizing sophisticated viral identification techniques. Several human studies identified only mucosal papillomavirus strains in approximately one-third of patients tested using *in situ* DNA hybridization and polymerase chain reaction (PCR) (Collina et al., 1995; Deguchi et al., 1998); *in situ* DNA hybridization, Southern blot hybridization, and PCR (Lampert et al., 2000); or *in situ* DNA hybridization alone (Derancourt et al., 2001). All of the lesions in the largest human retrospective study were papillomavirus-negative using *in situ* DNA hybridization and PCR (Lu et al., 1999). Only two reports identified papillomaviruses of the epidermodysplasia verruciformis group in one of three (Tieben et al., 1994) and two of five (de Jong-Tieben et al., 1995)

Bowen's lesions in immunosuppressed human renal transplant patients via a nested PCR technique. In contrast, 28/63 feline cases were found to be immunohistochemically positive for papillomavirus as described by Clark (Gross & Affolter, 1998). Papillomavirus was also confirmed in an identical canine lesion observed by one author (T.L.G.) (Clark, E.G., personal communication 2003). Strain typing of feline and canine papillomaviruses is not yet available, but the common detection of papillomavirus and the extragenital location of the vast majority of bowenoid lesions in these species is more suggestive of an epidermodysplasia verruciformis-type viral etiology (see feline viral plaque, p. 574). Lesions were present on oral and genital mucous membranes in the one reported dog (Gross & Brimacomb, 1986); investigation for papillomavirus was not done in that case, but the mucosal involvement suggests the possibility of a different type of papillomavirus infection from the more typical cases with cutaneous lesions only.

The reported incidence of progression of human Bowen's disease to invasive squamous cell carcinoma ranges from 3% to 11%, but is usually less than 5% (Kirkham, 1997). In contrast, frank squamous cell carcinoma developed in an average of 17% of cats in the above-cited studies. Due to these differences between human and animal lesions, the term 'bowenoid *in situ* carcinoma' (BISC) is preferred by the authors.

Human renal transplant patients develop papillomavirus-associated Bowen's disease due to iatrogenic immunosuppression (Tieben et al., 1994; Collina et al., 1995; de Jong-Tieben et al., 1995; Lampert et al., 2000). Impaired immune surveillance may also be a factor in animals; 22% of the reported feline cases were positive for either feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) (Miller et al., 1992; Baer & Helton, 1993; Guaguère et al., 1999). In one small case series, all of the cats had concurrent demodicosis (Guaguère et al., 1999). Older reports suggested that Bowen's disease may be a marker for internal malignancy in humans, but several more recent large retrospective studies have ruled out any statistically significant link (Chuang et al., 1990; Kovacs et al., 1996; Jaeger et al., 1999). Thus, it is likely that the concurrent myxosarcoma in the canine case report (Gross & Brimacomb, 1986) and the mediastinal lymphoma in one cat in a case series (Baer & Helton, 1993) were incidental.

Clinical features

Bowenoid *in situ* carcinoma is uncommon in cats and very rare in dogs. Lesions of BISC usually present as multifocal, heavily-crusted plaques and verrucous lesions occurring in any location on the body. Solitary lesions are seen infrequently. Sun-exposed and/or nonsun-exposed skin may be affected, and pigmented as well as nonpigmented areas may be involved. Bowenoid *in situ* carcinoma on pigmented skin is often heavily melanized. This phenomenon also occurs occasionally in humans and can confound the clinical diagnosis (Papageorgiou et al., 1998; Krishnan et al., 2001).

Almost all of the animals reported with BISC are 10 years of age or older (Miller et al., 1992; Baer & Helton, 1993; Guaguère et al., 1999); the dog in the single case report was 5 years old (Gross & Brimacomb, 1986). There is no known breed or sex predilection. Bowenoid *in situ* carcinoma lesions may become locally invasive as squamous cell carcinoma; 17% of feline cases and the one canine case described in the literature developed invasive squamous cell carcinoma. That is considerably higher than the incidence in humans, but may reflect the relatively small number of animals reported. The majority of lesions probably remain as *in situ* carcinomas. Metastasis has not been observed. The authors have also seen basal cell carcinomas arise in feline BISC (see p. 589).

Histopathology (Figures 22.19 through 22.21)

Bowenoid *in situ* carcinoma is characterized by a discrete plaque of moderate to severe, irregular epidermal hyperplasia with formation of broad rete ridges; follicular infundibula within the plaque are similarly affected. Moderate to marked hyperkeratosis and/or parakeratosis is present, and serocellular crusting is often observed. Rarely, hyperkeratosis is of sufficient severity to produce a cutaneous horn (Rees & Goldschmidt, 1998). Lesions on pigmented areas typically show marked hyperpigmentation extending into the stratum corneum.

There is full-thickness dysplasia manifested by marked loss of nuclear polarity and disruption of normal epithelial stratification. Dysplastic epithelium frequently descends around follicular infundibula as an irregularly-contoured cuff, or may completely replace superficial follicular epithelium. In the reported cases with concurrent demodicosis, the mites were found in hair follicles within the BISC lesions only (Guaguère et al., 1999). Keratinocyte size and appearance are highly variable and range from small with ovoid, hyperchromatic nuclei to large with pale, glycogenated cytoplasm and bizarre, multilobular nuclei. Multinucleated tumor cells may be present in small numbers. Groups of cells often have dorsoventrally elongated nuclei that are tilted in one direction; this produces the classically described 'windblown' pattern. Occasionally, large atypical keratinocytes are grouped into nests within relatively less dysplastic epidermis.

The nucleoplasm may have a hyalinized, pale basophilic appearance. Nucleoli are variable. Mitotic activity is low to moderate, and mitotic figures may be

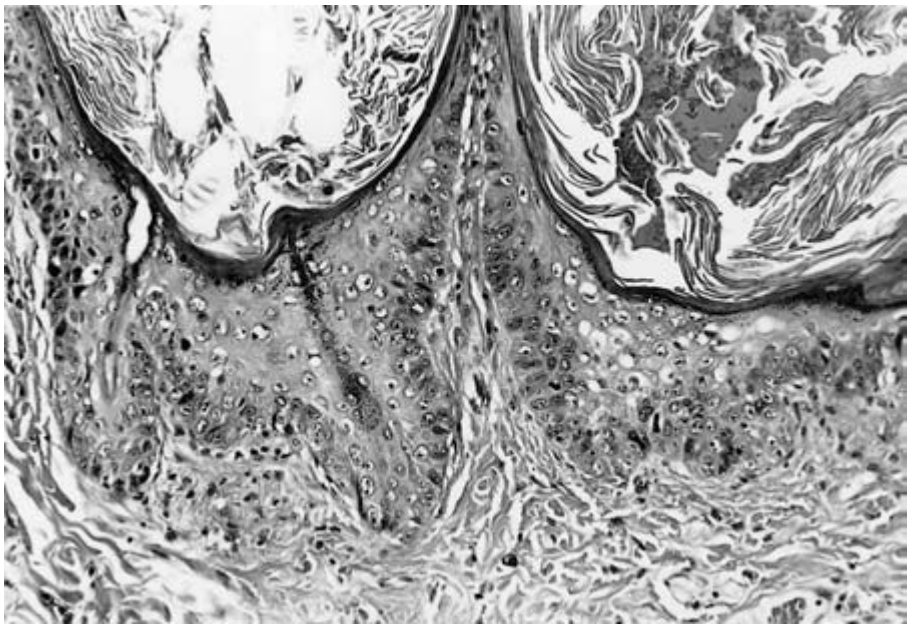


Fig. 22.19 Early bowenoid *in situ* carcinoma in a cat. The epidermis has mild thickening, nuclear enlargement, and some loss of normal stratification. Note the group of koilocytes showing clear cytoplasm and shrunken nuclei in the stratum spinosum.

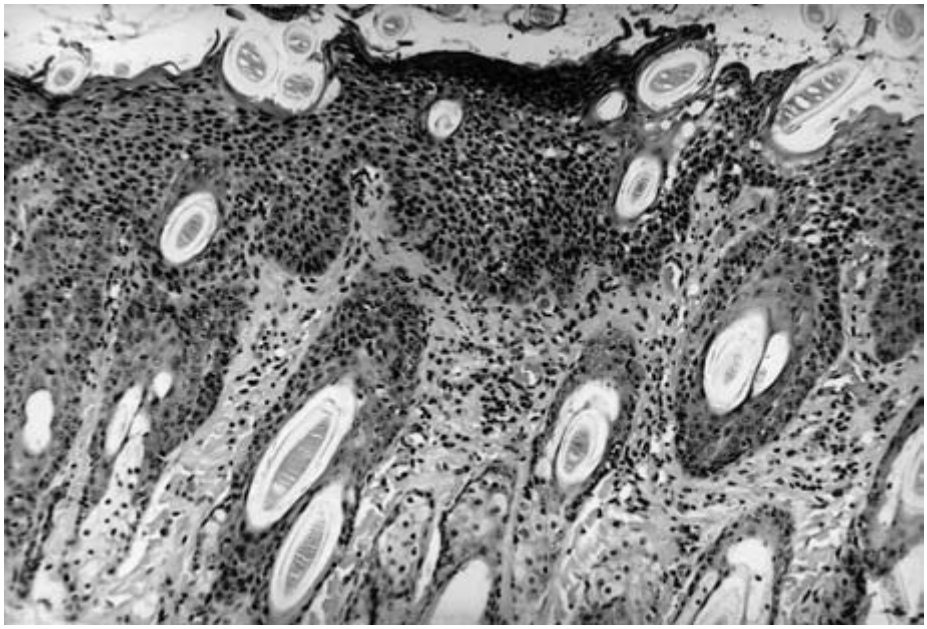


Fig. 22.20 Bowenoid *in situ* carcinoma in a cat. Irregularly thickened epidermis and follicular infundibula have full-thickness disruption of normal stratification and nuclear polarity. Note enlarged, hyperchromatic nuclei.

present in all cell layers. Scattered shrunken, brightly eosinophilic (apoptotic) cells are often seen. Papillomaviral cytopathic effect, manifested by koilocytosis (keratinocytes with clear cytoplasm and pyknotic nuclei) and clusters of large round keratohyalin granules, may be detected within the plaque or in immediately adjacent epidermis. The basement membrane zone is intact until very late in the course of the disease, when frank squamous cell carcinoma or basal cell carcinoma may invade the dermis. The underlying dermis exhibits vascular dilatation and nonspecific perivascular inflammation; solar fibrosis and elastosis may also be seen in sun-exposed lesions (see Chapter 15).

Bowenoid *in situ* carcinoma typically presents with distinctive clinical and histologic features, and diagnosis is straightforward. If lesions are limited to sun-exposed skin in a light-colored animal, differentiation from actinic keratosis may be required. Uncomplicated actinic keratosis

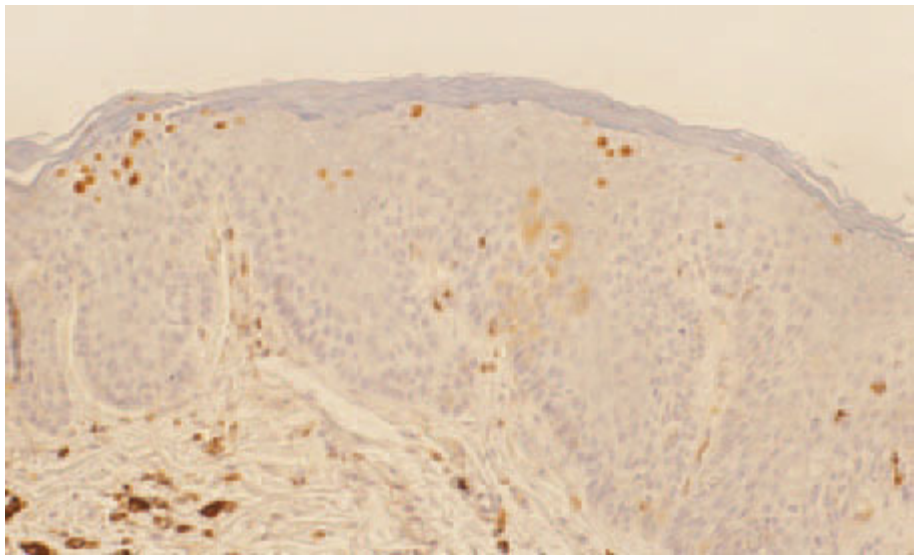


Fig. 22.21 Bowenoid *in situ* carcinoma in a dog. Papillomavirus immunostain colors small numbers of cells in the upper stratum spinosum, stratum granulosum, and cornified layer; pigmented cells in the dermis are melanophages (chromogen diaminobenzidine [DAB]).

has the majority of atypical cells in the basal and lower spinous layers; full-thickness epithelial dysplasia with 'windblown' abnormal nuclear polarity, giant pale keratinocytes, or papillomavirus cytopathology warrant a diagnosis of BISC. The subtype in humans designated 'bowenoid actinic keratosis' is virtually indistinguishable from Bowen's disease (Kirkham, 1997). It is likely that lesions of BISC occurring on sun-exposed skin are complicated by chronic actinic damage, considering that the synergistic oncogenic effect of papillomavirus infection and UV radiation is well-documented in human epidermodysplasia verruciformis (see feline viral plaque, p. 574). Immunohistochemistry for papillomavirus may aid in confirming the etiology.

SQUAMOUS CELL CARCINOMA

Cutaneous squamous cell carcinoma (SCC) is common in humans, and its frequency is increasing worldwide (Wassberg et al., 2001). More than 80% of cutaneous SCCs were found to arise directly from or in close proximity to an actinic keratosis (Mittelbronn et al., 1998); similarly, actinic keratoses and SCCs often coexist in dogs and cats. Thermal injury may also be a predisposing factor as it is in humans; there is a single case report of SCC arising in a burn scar in a dog (Gourley et al., 1982).

The most significant predictive histologic factor for metastasis of SCC in humans is tumor depth; lesions less than 2 mm thick do not metastasize, while those greater than 5 to 6 mm in depth, or invading muscle, cartilage, or bone have an average metastatic potential of 20% based on several retrospective studies (Khanna et al., 2002). Tumors associated with chronic inflammatory or degenerative dermatoses, such as burn scars, as well as those in immunocompromised patients, have a high incidence of metastasis (Kirkham, 1997). Additional prognostic factors include histologic grade, histologic subtype, and perineural invasion (Khanna et al., 2002). In one retrospective study, the 5-year survival dropped from 86% to 50% when perineural invasion was present in SCC and basal cell carcinoma (Williams et al., 2001).

The most common SCCs are usually separated into well-differentiated, moderately-differentiated and poorly-differentiated categories; uncommon subtypes include acantholytic (adenoid, pseudoglandular), clear cell, spindle cell, keratoacanthoma-like, desmoplastic (neurotropic), verrucous, mucin-producing (adenosquamous, mucoepidermoid), and carcinoma arising in Bowen's disease (Nappi et al., 1989; Kirkham, 1997; Petter & Haustein, 2000; Khanna et al., 2002). The well-differentiated, moderately-differentiated, poorly-differentiated, acantholytic, clear cell, spindle cell, and Bowen's-associated types are also seen in dogs and/or cats (Gross & Brimacomb, 1986; Goldschmidt & Shofer, 1992; Miller et al., 1992; Baer & Helton, 1993; Goldschmidt et al., 1998; Scott et al., 2001). Acantholytic, spindle cell, desmoplastic, and mucin-producing variants are reported to be more aggressive than common-type SCC in humans (Nappi et al., 1989; Kirkham, 1997; Petter & Haustein, 2000; Khanna et al., 2002). Similar data are not available in animals. Verrucous SCC has been recognized by the authors and is a new addition to this chapter. As the name implies, it resembles a wart and has an indolent biologic behavior both in humans (Kirkham, 1997) and dogs.

The causal factors and pathogenetic mechanisms for the majority of cutaneous invasive SCC in all mammalian species are very similar to those for actinic keratosis, which represents SCC *in situ* (see p. 575). UV-specific

mutations in the *p53* tumor suppressor gene are well-documented and have been reported in 54% to 75% of SCC in humans (Nagano et al., 1993; Kerschmann et al., 1994; Coulter et al., 1995; Shimizu et al., 1997). In addition, mutation of *p16*, another tumor suppressor gene, was found in 100% of actinic keratoses and cutaneous SCC in one study, but the immunohistochemical staining of the abnormal gene product in the SCC was stronger and more diffuse (Hodges & Smoller, 2002). Mutations in the *p53* tumor suppressor gene, which can be demonstrated immunohistochemically due to overexpression of the abnormal gene product, have been identified in an average of 53% and 32% of cutaneous SCCs in cats and dogs, respectively, although the total case numbers in the three reported studies was small (Teifke & Löhr, 1996; Murakami et al., 2000; Albaric et al., 2001). A variety of cell surface and matrical biochemical changes, such as overexpression of epidermal growth factor receptor or matrix metalloproteinases, have also recently been found to be influential in determining the aggressiveness of SCC in humans (Koseki et al., 1999; Tsukifuji et al., 1999; Shimizu et al., 2001; Xu et al., 2001).

The etiologic role of papillomavirus in human SCC is still controversial. Some studies have found random strains of papillomavirus ubiquitously, suggesting that it is not of pathogenic significance (Harwood et al., 2000; Meyer et al., 2001; Forslund et al., 2003), while other reports have demonstrated an increased frequency of antibodies against specific oncogenic strains in patients with actinic keratosis and SCC, suggesting that it could be a cofactor in tumor development (Bouwes Bavinck et al., 2000; Masini et al., 2003). Papillomavirus was identified by immunohistochemistry in 27 of 100 canine SCCs from various anatomic locations including skin by Schwegler et al. (1997), but no viral antigen was found in a similar study by Sironi et al. (1990). Clark found papillomavirus via immunohistochemistry in four of 17 invasive SCCs arising from feline bowenoid *in situ* carcinoma (Gross & Affolter, 1998). Papillomaviruses have been identified in some cases of verrucous SCC in humans by electron microscopy or *in situ* hybridization (Kirkham, 1997). No papillomavirus was found in canine oral verrucous SCC (Head et al., 2003).

Clinical features

Squamous cell carcinoma is the most common malignant neoplasm of the skin in cats and the second most common in dogs, following mast cell tumor. The reported incidence in cats ranges from 15% to 49% (Burrows et al., 1994; Goldschmidt & Shofer, 1992; Miller et al., 1991) and in dogs from 3% to 20% (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992); these wide variations are largely a reflection of geographic location. Squamous cell carcinoma occurs most frequently in sun-damaged skin and may be preceded by actinic keratosis; the incidence is, therefore, partially dependent upon geography and climate.

Squamous cell carcinomas present as plaque-like, crateriform, papillary, or fungiform masses that vary from several millimeters to several centimeters in diameter. Alopecia, erythema, ulceration, and crusting are present. Lesions may be single or multiple. There is usually a temporal progression from small plaques to larger, ulcerative, or exophytic lesions.

Nasal planum, pinnae, and eyelids are the most common sites in cats. Spindle cell SCC is found most often on the pinnae in cats. In dogs, the most frequently affected areas are ventral abdomen, ventral flanks, and medial stifles. Tumors on canine ventrum are often indurated due to associated solar fibrosis (see Chapter 15). Nonsolar-associated SCC can occur anywhere on the body. Verrucous SCC is more common in the oral cavity. Tumors involving the nasal planum in dogs are rare and may be associated with chronic inflammation rather than chronic solar damage (Rogers et al., 1995; Scott & Miller, 1995). Rarely in humans, SCCs arise in follicular cysts (López-Ríos et al., 1999; Wong et al., 2000). The authors have seen occasional cases in dogs, and there is one report of malignant transformation of multiple cysts in a dog (Scott & Teixeira, 1995).

Cats with white facial or pinnal fur and short-coated dogs with white or piebald ventral coat color have the highest incidence of SCC. The risk for white cats is 13 times higher than for cats of other coat colors (Ruslander et al., 1997). Dalmatians, Pit Bull Terriers, harlequin Great Danes, and Beagles are typical high-risk breeds. Affected cats are usually 5 years of age or older with an average age of 11 (Goldschmidt & Shofer, 1992). Dogs may develop squamous cell carcinoma as early as 3 years of age but the average is 10 years (Goldschmidt & Shofer, 1992).

The tumors may be highly invasive and locally destructive with a gradual loss of tissue of the pinna or nose. Metastasis of SCC is reported in most references as rare or occurring late in the course of disease; however, numeric data are generally not provided. Similarly, statistics on histologic grade or subtype are rarely given in reports on dogs and cats. In the veterinary literature, factors such as perineural invasion and fine gradation of tumor depth have not been addressed; such studies in the future may allow more appropriate prognosis and therapeutic approaches for dogs and cats with SCC. In the original study of solar-associated skin lesions in a Beagle colony in Colorado, two of 18 dogs with invasive SCC had metastases to lymph node or lung (Hargis et al., 1977). Of 15 cats available for necropsy in a large study on nasal planum SCC, seven had regional and one had

distant metastasis (Théon et al., 1995). Thirteen of 61 cats with nasal or pinnal SCC died or were euthanized due to local disease progression; of these, only one had lymph node metastasis (Lana et al., 1997). The majority of dogs with nasal planum SCC were euthanized due to extensive or recurrent local disease, and necropsies were not performed (Rogers et al., 1995; Scott & Miller, 1995). The dog with multicentric SCC in follicular cysts had metastasis to lung and bone (Scott & Teixeira, 1995). These data suggest that late and/or clinically inapparent metastasis may be more prevalent than previously suspected.

Histologic grade *per se* was not found to be of prognostic significance in the study on radiation therapy of feline nasal SCC, although higher proliferative fraction (percentage of nuclei staining immunohistochemically with proliferating cell nuclear antigen (PCNA), which tends to parallel histologic grade) and tumor size did correlate with less favorable outcome (Théon et al., 1995). Unfortunately, the current World Health Organization veterinary staging system has no categories between T_{is} (carcinoma *in situ*) and T_1 (<2 cm), precluding comparison between superficial invasive SCC and those extending into deep dermis.

Histopathology

Well-differentiated squamous cell carcinoma

(Figures 22.22 through 22.24)

This is the most common histologic variant in both dogs and cats; the authors include moderately-differentiated tumors in this category. Well-differentiated tumors are erosive, plaque-like lesions comprising islands and trabeculae of squamous cells that originate from the epidermis and extend into the dermis. The authors have seen rare examples of well-differentiated SCC arising from superficial hair follicles or follicular cysts without involvement of the epidermis. The intact overlying epidermis generally has parakeratosis and crusting; occasionally, marked hyperkeratosis may produce a cutaneous horn. An overlying or adjacent actinic keratosis or, less frequently, viral plaque may be identified.

There is fairly orderly progression from polyhedral, nonkeratinized basal cells at the periphery of the neoplastic epithelial structures to large, polygonal, keratinized cells at the centers. The polyhedral basal cells may be only one layer thick in very well differentiated neoplasms, or they may comprise multiple layers in less well differentiated SCC. Central accumulations of compact laminated keratin, or keratin pearls, are present in variable size and numbers. Large masses of parakeratotic cells may also occur. Keratinization progresses through a granular cell layer as in normal epidermis or follicular infundibulum. The keratinized centers of the lobules may undergo necrosis and become infiltrated by neutrophils.

The cytoplasm of the peripheral basaloid cells is scant and amphophilic; the more central keratinized cells have moderate to abundant, eosinophilic cytoplasm. Some SCCs show moderate to abundant cytoplasmic glycogenation manifested by clear, finely-reticulated cytoplasm; the more extreme examples are analogous to the human clear cell subtype. Nuclei are usually large and vesicular; nucleoli are variable in size and are usually single.

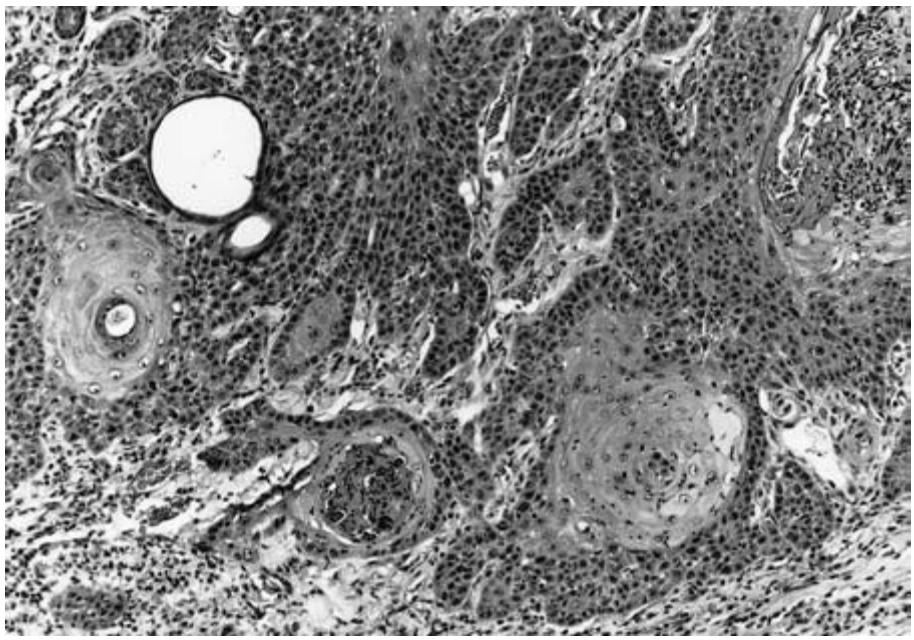


Fig. 22.22 Well-differentiated squamous cell carcinoma in a cat. Islands and trabeculae of squamous epithelium show orderly differentiation from nonkeratinized to keratinized cells. Note central keratin pearls infiltrated by neutrophils.

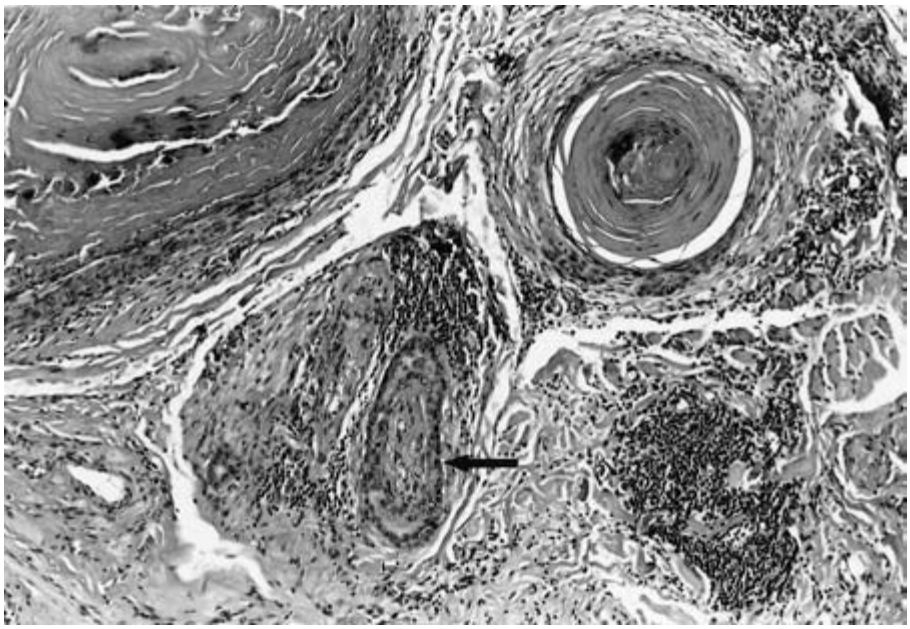


Fig. 22.23 Well-differentiated squamous cell carcinoma with perineural invasion in a cat. A segment of a nerve in the lower center of the field is surrounded by a narrow cuff of neoplastic epithelium (arrow).

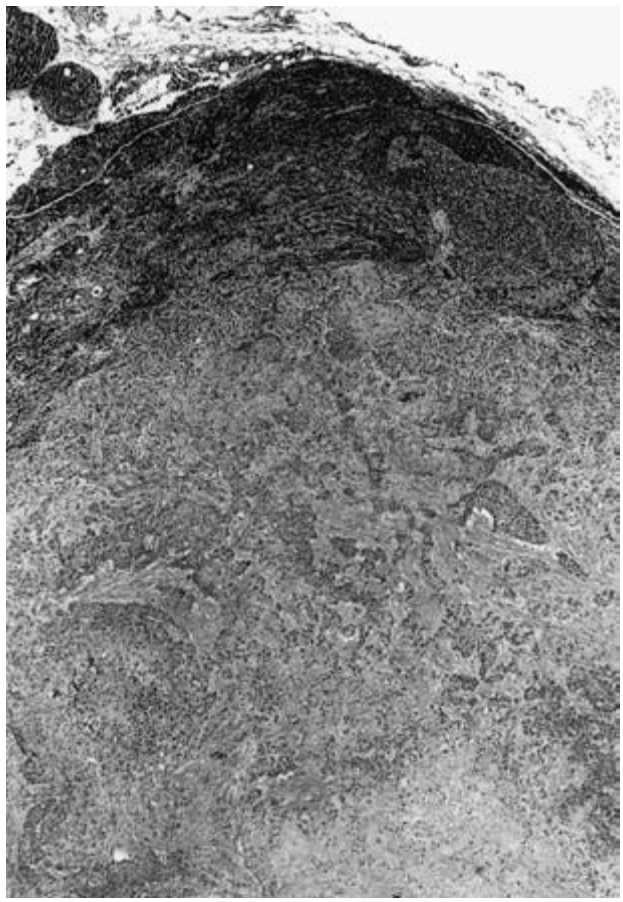


Fig. 22.24 Submandibular lymph node with metastatic well-differentiated squamous cell carcinoma in a cat.

Squamous cell carcinomas occasionally display groups of dorsoventrally elongated nuclei that are tilted in one direction, producing a 'windblown' pattern. Bizarre, multilobular nuclei with smudgy chromatin may also be seen. Neoplasms with these latter two features may be described as 'bowenoid'; this should prompt a search for additional lesions of bowenoid *in situ* carcinoma and viral plaques (see pp. 578, 571, and 574). Mitotic activity ranges from moderately low to moderately high, and is usually higher in dogs than in cats.

Stromal fibroplasia is usually moderate to abundant, and the stroma often contains small clusters and strands of partially-keratinized tumor cells. Stromal infiltration by a variety of inflammatory cells is generally present. Foci of perineural infiltration by small aggregates of neoplastic cells may be identified within or adjacent to the neoplasm; this phenomenon is most commonly observed in feline pinnal and nasal SCC, and may be responsible for local recurrence after apparent complete excision. Lymphatic or vascular invasion is occasionally detected. Diagnosis of well-differentiated SCC should not be problematic.

Poorly-differentiated squamous cell carcinoma

(Figure 22.25)

This is a less common subgroup with similar overall architecture to well-differentiated SCC. Epithelial structures tend to be smaller; cords and nests rather than large islands of squamous epithelial cells often predominate. Alternatively, large sheets of cells may be present. Stromal collagen production is generally less prominent. The majority of the neoplastic cells exhibit amphophilic cyto-

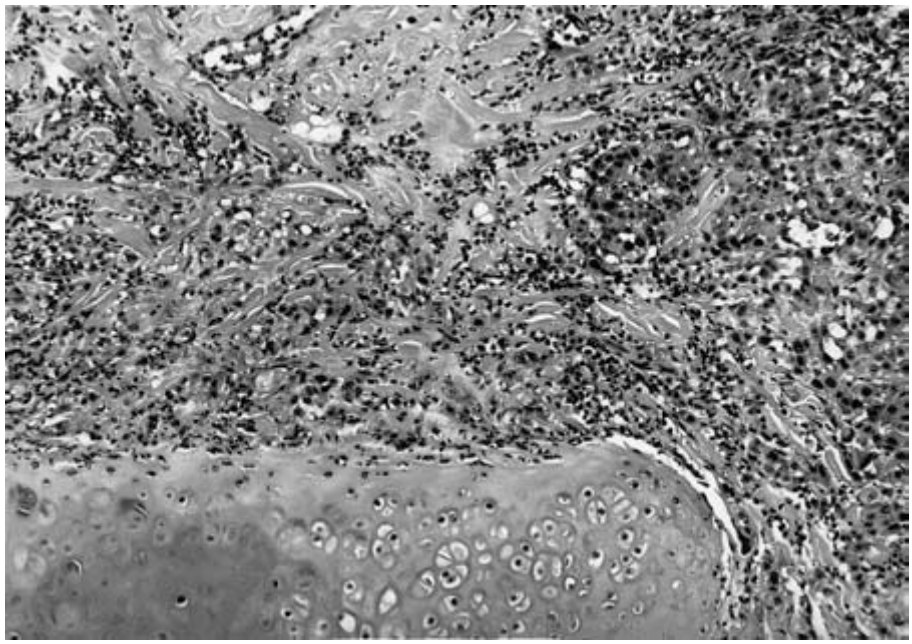


Fig. 22.25 Poorly-differentiated squamous cell carcinoma in a cat. Islands and nests of pleomorphic epithelial cells with haphazard partial keratinization infiltrate an inflammatory stroma. Nasal cartilage is at bottom.

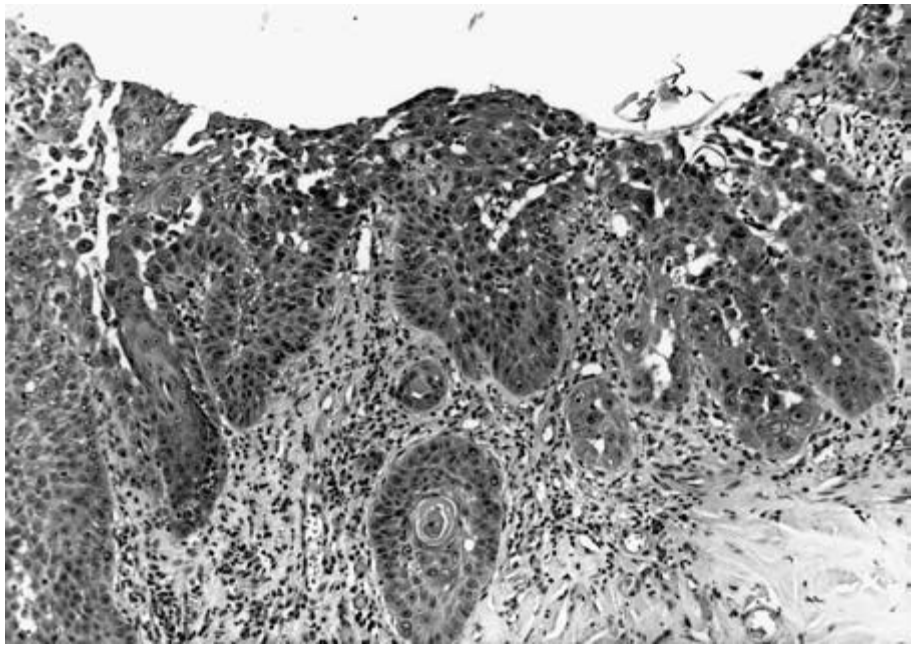


Fig. 22.26 Acantholytic squamous cell carcinoma in a cat. Individualized keratinocytes are present within clefts in the superficial aspects of this plaque-like neoplasm. Orderly maturation and some keratin pearls are still present.

plasm, variably hyperchromatic nuclei, and prominent nucleoli, which may be multiple. There is moderate to high mitotic activity and frequent mitotic atypia. Keratin pearls are not observed, but individual dyskeratotic cells or clusters of partially-keratinized cells may be present.

Poorly-differentiated SCC may be difficult to distinguish from other anaplastic carcinomas, such as those of sebaceous and perianal gland origin, which may show extensive squamous metaplasia. Multifocal contiguity of neoplastic tissue with dysplastic epidermis supports a diagnosis of SCC. Sebaceous carcinomas usually have at least small numbers of cells with smooth-edged vacuoles. Lipid stain, e.g. oil red O, performed on wet tissue would be negative in SCC and positive in sebaceous carcinoma. Immunohistochemistry also may be helpful (see below).

Acantholytic squamous cell carcinoma

(Figures 22.26 through 22.28)

Acantholytic (adenoid, pseudoglandular) SCC is an uncommon variant. Small areas of acantholysis may be

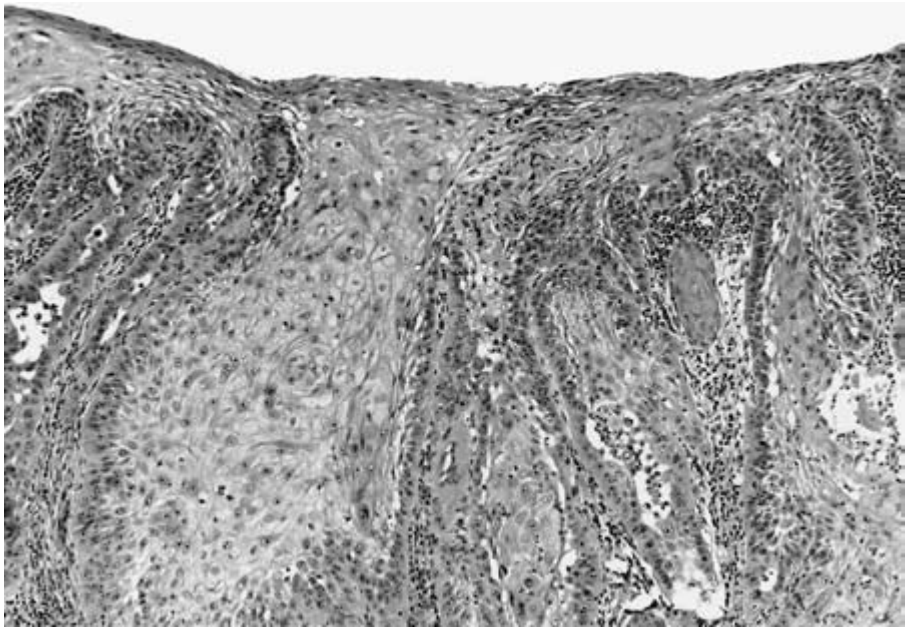


Fig. 22.27 Acantholytic squamous cell carcinoma in a dog. In this example many of the cells have very pale cytoplasm due to glycogen accumulation.

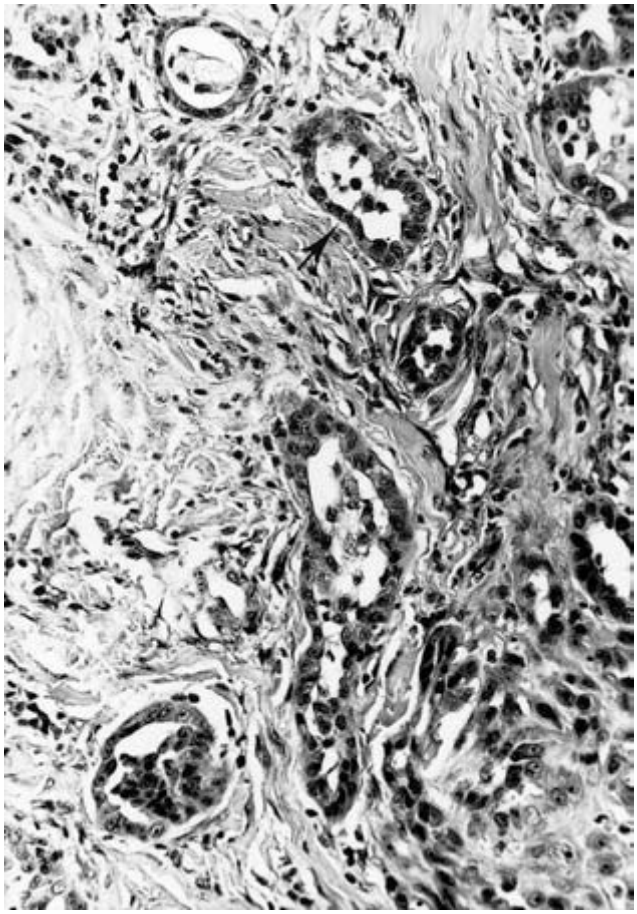


Fig. 22.28 Acantholytic squamous cell carcinoma in a dog. Pseudoglandular structures contain individualized keratinocytes within their lumens. Note that occasional acantholytic cells are still connected by attenuated intercellular bridges (arrow).

present in otherwise banal SCC, but a diagnosis of acantholytic SCC requires that this be the dominant pattern. The pseudoglandular structures are formed by drop-out of partially-keratinized cells from the centers of epithelial islands and trabeculae due to loss of intercellular junctions. Residual keratinized cells float in the pseudolumens or are attached to the peripheral cell layer by elongated intercellular bridges. Foci of well-differentiated SCC are often identifiable in some areas of the neoplasm.

Differentiation of acantholytic SCC from glandular neoplasms, particularly apocrine ductular adenocarcinomas, may be problematic. Absence of classical apocrine decapitation secretion, absence of accumulations of secretory protein, and presence of active acantholysis characterized by individualized keratinized cells within pseudolumens support a diagnosis of SCC. The epidermal contiguity of SCC can be very difficult to distinguish from acrosyringial differentiation and/or follicular contiguity in apocrine ductular adenocarcinoma; adjacent epidermal dysplasia is a useful marker for SCC but is not always present. Immunohistochemistry will allow definitive diagnosis in equivocal cases (see below).

Spindle cell squamous cell carcinoma

(Figures 22.29 and 22.30)

This is a rare variant of poorly-differentiated SCC and is composed of large, pleomorphic spindle and polygonal cells that have abundant, pale or amphophilic cytoplasm. Areas of malignant transformation may be discernible in the overlying epidermis with loss of a distinct basement membrane zone, and atypical spindle cells appear to stream downward from these areas into the dermis. Foci

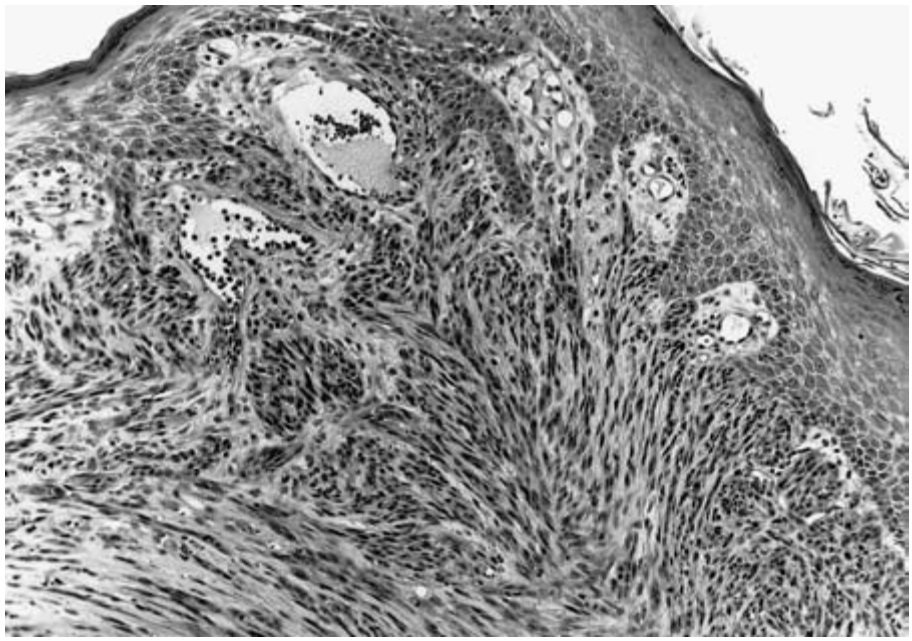


Fig. 22.29 Spindle cell squamous cell carcinoma in a cat. Pleomorphic spindle and polygonal cells are arranged in loose bundles and nests. Note small areas of contiguity with hyperplastic and dysplastic foci of the epidermis.

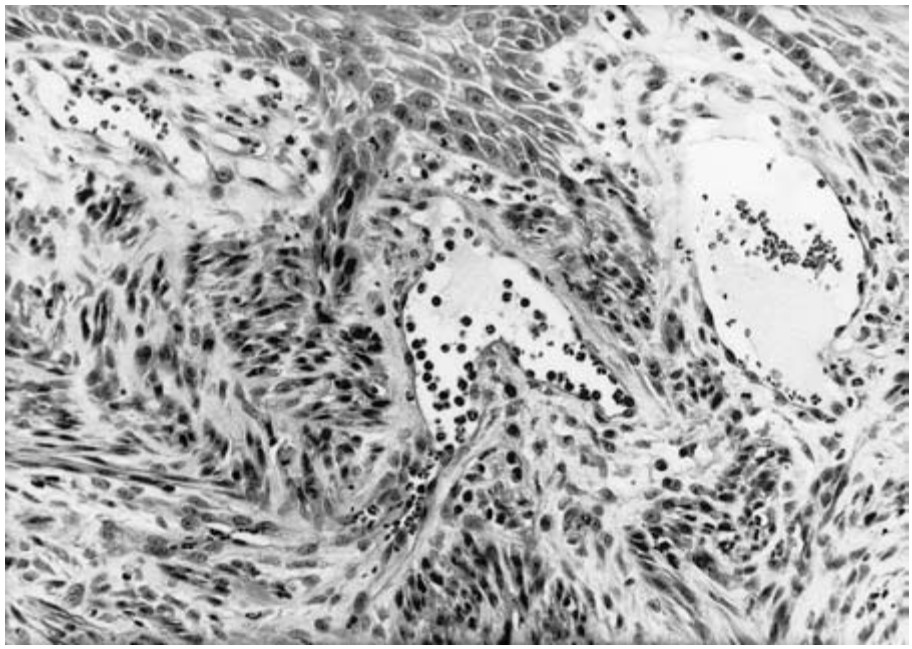


Fig. 22.30 Higher magnification of Fig. 22.29. Spindle cells appear to stream downward from a focus of malignant transformation of keratinocytes.

of partial keratinization characterized by polygonal cells with moderate, glassy, eosinophilic cytoplasm may be present in limited areas of the mass. Nuclei are large and vesicular, and have prominent nucleoli. The mitotic index is high.

Spindle cell SCC must be distinguished from high-grade spindle cell sarcomas; the primary differential diagnosis is amelanotic melanoma. Contiguity with overlying dysplastic epidermis and/or small foci of more typical epithelial morphology confirm a diagnosis of spindle cell SCC; serial sectioning may be required to locate these features. Amelanotic malignant melanomas often abut the dermal–epidermal junction and can have a lentiginous intraepidermal component (multiple individual neoplastic melanocytes infiltrating the basal cell layer) that may be difficult to differentiate from atypical basal keratinocytes. Other mesenchymal tumors, such as leiomyosarcoma and malignant peripheral nerve sheath tumor, usually have a small zone of uninvolved superficial dermis, but this may not be apparent in ulcerated lesions. Definitive

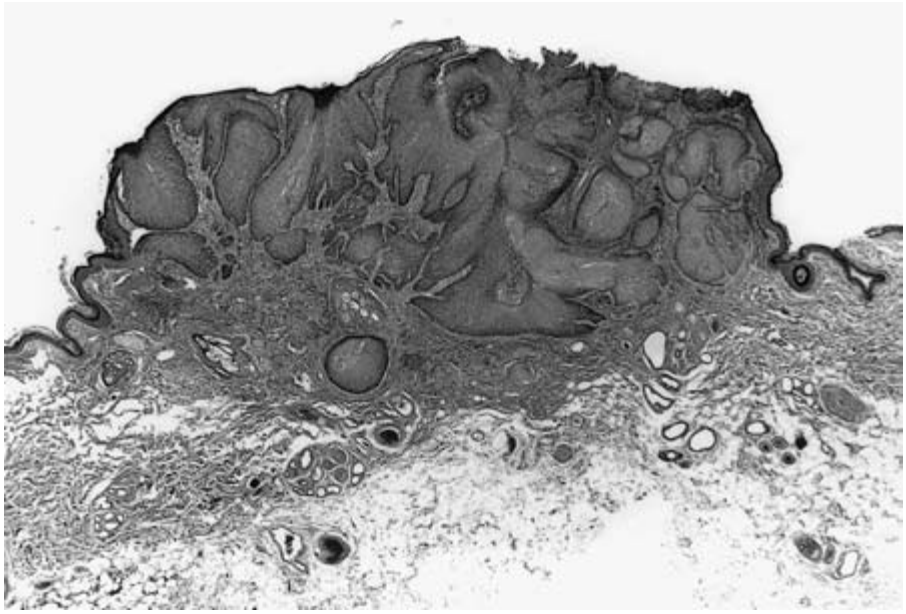


Fig. 22.31 Verrucous squamous cell carcinoma in a dog. The lesion has a papillomatous architecture, but epithelial aggregates are more irregular and mildly invasive at the deep margin.

diagnosis often requires immunohistochemical studies (see below).

Verrucous squamous cell carcinoma

(Figures 22.31 and 22.32)

This rare variant of SCC has been observed by the authors only in dogs; it appears to be closely analogous to human verrucous SCC and is of very low-grade malignancy. Verrucous SCC has both exophytic and endophytic architecture characterized by broad papillary proliferations, trabeculae with rounded ends, and large tubular invaginations. The trabeculae and tubular structures invade downward and anastomose; large lesions may have the appearance of branching tunnels resembling a rabbit warren, giving rise to the antiquated Latin synonym *carcinoma cuniculatum* (Kirkham, 1997). The tumor comprises fairly small, polyhedral keratinocytes, resembling the lower stratum spinosum of the epidermis, and a peripheral basal cell layer. Complete cornification through a granular cell layer does not occur in the endophytic component, and keratin pearls are absent. The tubular invaginations contain sloughed keratinocytes, small amounts of amorphous keratin and inflammatory cells. The cells have scant to moderate, pink cytoplasm. The nuclei are mildly to moderately enlarged, ovoid and vesicular. They generally have small nucleoli that may be multiple. Mitotic activity is low, but atypical mitoses and mitotic figures above the basal cell layer are present. Apoptosis, characterized by shrinkage and hypereosinophilia of individual keratinocytes, may be present and may contribute to the debris in the tunnels.

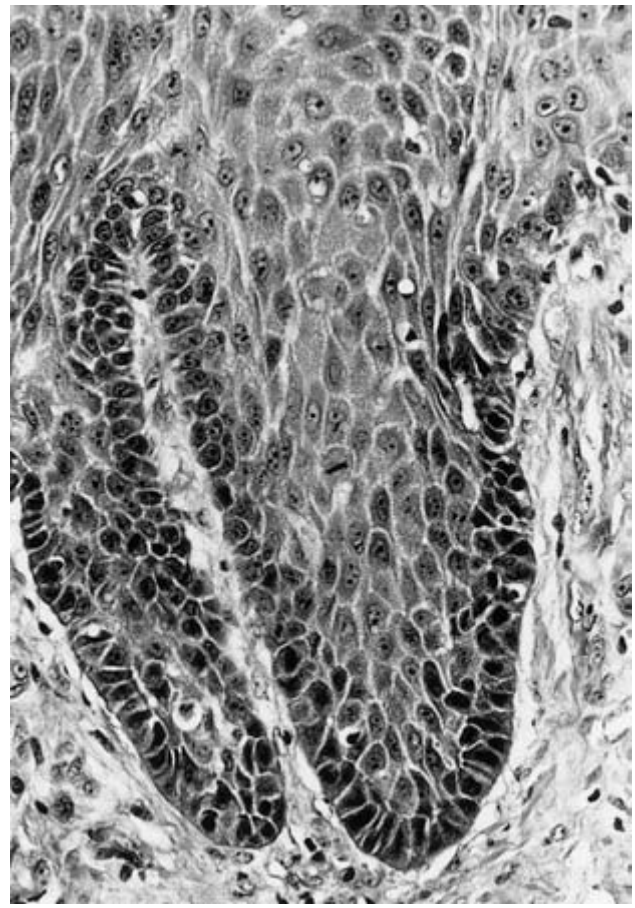


Fig. 22.32 Higher magnification of Fig. 22.31. Epithelial trabeculae with smooth borders have mild nuclear pleomorphism and fairly low mitotic activity that is not confined to the basal cell layer.

Verrucous SCC can be difficult to recognize as a malignancy, and the exophytic component may be confused with squamous papilloma, viral papilloma, or even papillomatous epidermal hyperplasia in small or superficial incisional biopsies. Viral cytopathology (see viral papilloma, p. 567) is absent in verrucous SCC, and the lesions are usually larger than papillomas. Invasion below the basement membrane zone, atypical mitotic figures, and mitotic activity above the basal cell layer support a diagnosis of SCC, but these features may not be present in superficial specimens. If a sample from a nonviral papillomatous epithelial lesion does not contain uninvolved subjacent dermis, it is prudent to request a deeper biopsy. The branching tunnel architecture of the invasive endophytic component of verrucous SCC is distinctive, and identification of atypical mitotic figures and mitotic activity above the basal cell layer confirms the diagnosis.

Immunohistochemistry

The majority of SCCs are positive with any of the commercially available pancytokeratin stains, such as AE1/AE3, as are most other epithelial tumors; however, some spindle-celled SCCs are negative (Sigel et al., 2001). An immunostain for the high molecular weight cytokeratins (CK5/6) has recently become available for formalin-fixed tissue and has been shown to be a sensitive marker for all SCC types (Sigel et al., 2001). Papillomavirus immunostain should be considered if bowenoid features or koilocytosis are present. Distinction of poorly-differentiated SCC from carcinomas of sebaceous/perianal gland origin may be possible with certain immunostaining techniques for certain clones of CD79a, the pan-B lymphocyte marker, but the veracity of this staining reaction is unconfirmed and requires additional investigation (see sebaceous carcinoma, Chapter 24). The utility of immunostains for androgen and/or estrogen receptors in dogs and cats as markers of sebaceous/perianal gland differentiation has yet to be determined. Negative staining for CK8, CK13 or CAM5.2 (CK7/8) readily distinguishes acantholytic SCC from adenocarcinomas. Immunostains for vimentin, S100, microphthalmia transcription factor, melanoma isoform (MITF-M), and smooth muscle actin are useful adjuncts for differentiating spindle cell SCC from melanoma, malignant peripheral nerve sheath tumor, leiomyosarcoma, and sarcomas in general.

BASAL CELL CARCINOMA

(Synonym: basal cell epithelioma)

Basal cell carcinoma (BCC) is the most common malignancy in humans. The major architectural patterns are nodular (noduloulcerative), micronodular, superficial, infiltrative, and morpheaform (fibrosing). Common and uncommon histologic variants, most of which can occur in any of the aforementioned patterns, include but are not limited to pigmented BCC, solid (undifferentiated) BCC, BCC with sebaceous differentiation, BCC with follicular differentiation (keratotic BCC), BCC with matrical differentiation, fibroepithelioma, BCC with amyloid stroma, adenoid BCC, adamantinoid BCC, clear cell BCC, and granular cell BCC (Murphy & Elder, 1991; Kirkham, 1997). Neoplasms corresponding to solid, keratinizing (keratotic), and clear cell BCC are recognized by the authors in dogs and/or cats. The terms nodular, superficial, or infiltrative are generally not applied to canine and feline BCC, although any of these architectural patterns can occur in the context of solid, keratinizing, or clear cell variants. Solid BCC and, rarely, keratinizing BCC may be pigmented.

The exact nature of BCC in humans has been a source of controversy for many years. Architecturally, it appears to originate from the lower layer of the epidermis. Some pathologists before 1980, using only light and electron microscopy, believed BCC to be adnexal rather than epidermal; since the mid 1980s, as primitive follicular neoplasms have become better characterized morphologically and immunohistochemically in humans, benign follicular entities such as desmoplastic trichoepithelioma and trichoblastoma have been culled from the overly-inclusive 'basal cell carcinoma' category (Murphy & Elder, 1991; Kirkham, 1997; Cribier et al., 2000). Similarly in veterinary pathology, trichoblastomas (see Chapter 23) and several ductular sweat gland neoplasms (see Chapter 25) replace most of the old 'basal cell tumor' group, leaving only the small subset that appears to represent true BCC. The majority of the feline lesions described as solid BCC in *Veterinary Dermatopathology* (Walder & Gross, 1992) were erroneously believed to be malignant and have been reclassified as solid-cystic ductular sweat gland adenoma; the remainder comprise both BCC and solid-cystic ductular sweat gland carcinoma (see Chapter 25).

Since the mid 1990s, as increasing numbers of individual keratin markers have become available, multiple studies comparing human BCC to normal hair follicles or benign hair follicle tumors, particularly trichoepithelioma and trichoblastoma, have shown a very similar cytokeratin (CK) profile (Schirren et al., 1997; Yoshikawa et al., 1998; Jih et al., 1999; Kruger et al., 1999; Yamamoto & Asahi, 1999; Kurzen et al., 2001). An overview of these reports reveals that the mutual markers in most cases are cytokeratins 5, 6, 10, 14, 15, 16, 17, and 19 in various combinations. These results point to follicular outer root sheath, possibly the bulge region

where the stem cells are located, as the common differentiation pathway. However, staining of BCCs for some of these cytokeratins, particularly two of the three putative follicular stem cell markers CK15 and CK19, was negative in some studies and limited in distribution in others. It is possible that the negative-staining tumors derive from alternate stem cell populations located in epidermis, sweat glands or sebaceous glands; this may help to explain the wide variety of morphologic variations reported for human BCC (Jih et al., 1999). In addition, the antiapoptotic protein bcl-2 can be immunohistochemically identified in most BCCs, and BerEP4, an epithelial membrane glycopolypeptide antigen, is positive in all BCCs; these two markers also stain many trichoepitheliomas/trichoblastomas to some degree but are virtually negative in squamous cell carcinomas, thus lending support to the follicular nature of BCC (Tellechea et al., 1993; Swanson, et al., 1998).

Although the preponderance of recent evidence in humans suggests that the majority of BCCs are primitive follicular carcinomas, it has been traditional to include them with tumors of epidermal origin in reference texts because of their multifocal connections to the basal cell layer of the epidermis; this may need to be changed in the near future. Based on their close histologic and biologic similarities, there is no reason to suspect that the histogenesis of canine and feline BCC is significantly different from that in humans; however, it is not known which of the more specific immunohistochemical markers will be beneficial in confirming this hypothesis.

As in actinic keratoses and squamous cell carcinomas (see pp. 575 and 581), chronic exposure to ultraviolet (UV) radiation is a key factor in the induction of many BCCs in humans; however, lesions also occur on nonexposed skin. Mutations in the *p53* tumor suppressor gene, usually identified immunohistochemically by overexpression of gene product, are reported in 33% to 56% of human BCCs; mutations with the 'UV signature' of specific DNA pyrimidine base substitutions occurred in 32% to 65% of those (Auepemkiate et al., 2002; Kim et al., 2002; Lacour, 2002; Weihrauch et al., 2002; Bolshakov et al., 2003). An additional highly complex signaling pathway, which is normally involved in embryonic development of hair follicles as well as many other structures, has recently been found to be of primary significance in BCC induction in mice and humans, and its details are still being elucidated (Dahmane et al., 1997; Fan et al., 1997; Parisi & Lin, 1998; Tojo et al., 1999, 2002, 2003; Sheng et al., 2002; Teh et al., 2002; Wetmore, 2003); of import is the identification of UV-signature mutations in one of the genes, known as 'patched', within this pathway in many BCCs (Kim et al., 2002; Lacour, 2002).

A causal relationship between chronic sun exposure and BCCs in dogs and cats has not been established. As in humans, a significant proportion of BCCs in cats coexist with actinic keratoses and squamous cell carcinomas, but others occur in nonsun-exposed locations. Some of these arise from bowenoid *in situ* carcinoma (see p. 578) and are thus likely of papillomaviral etiology. Basal cell carcinomas in dogs are rarely seen in conjunction with other solar lesions, and their pathogenesis is largely unknown.

Clinical features

The authors believe that true BCCs are uncommon in cats and rare in dogs. Regretfully, there is little reliable incidence data in the veterinary literature, as most of these neoplasms have either been included in the old general category of 'basal cell tumor' or have been confused with the solid-cystic variant of apocrine ductular adenoma or carcinoma (see Chapter 25). One source reports that BCCs comprise 1.25% and less than 0.3% of skin tumors in cats and dogs, respectively (Goldschmidt & Shofer, 1992). In the only journal report of BCC in two cats, extremely large, deeply invasive, anaplastic tumors were described; this is a very unusual presentation for BCC and these cases may have represented another type of small cell carcinoma (Day et al., 1994).

The authors recognize three major histopathologic variants of BCC in dogs and cats: solid, keratinizing (keratotic), and clear cell. Solid BCC is the most common variant in cats, and keratinizing BCC is the most frequent in dogs. Pure clear cell BCC has been observed almost exclusively in cats. It is currently controversial whether follicular or any other adnexal differentiation is permissible in neoplasms designated as BCCs in animals. Some authors may choose to place keratinizing BCC in the 'infiltrative' or malignant trichoepithelioma category based on patterns of cornification that resemble these panfollicular tumors (see Chapter 23) (Goldschmidt & Shofer, 1992; Goldschmidt et al., 1998).

Basal cell carcinomas usually present as indurated plaques or umbilicated nodules measuring several millimeters to several centimeters in diameter. Lesions in cats are usually considerably smaller than those in dogs, but are much more likely to be multicentric. The overlying epidermis is commonly alopecic, crusted, and ulcerated. The skin may have a black or blue tint due to melanin pigment within the neoplasm. Feline BCCs occur most commonly on the nose, face, and ears, but may arise in other locations, particularly when associated with bowenoid *in situ* carcinoma. Basal cell carcinomas in dogs are usually truncal, but only occasionally affect glabrous skin. One author (E.J.W.) has seen a single example of BCC in canine nailbed (see Chapter 26).

The average age of cats with 'basal cell tumors', which would include BCCs, was 10 years in several large surveys

(Carpenter et al., 1987; Miller et al., 1991); the tumors reported separately as BCCs occurred in cats from 5 to 17 years old with an average age of 12 years (Goldschmidt & Shofer, 1992). The large majority of BCCs seen by the authors occur in cats at least 10 years old and in dogs at least 8 years old.

The incidence of recurrence and metastasis of BCC in cats is very low; numeric data are not available. The reported rate of metastasis of human BCC to lymph node and/or lung is only 0.003% to 0.55% and usually occurs in chronic tumors that have recurred after excision (Robinson & Dahiya, 2003). Carpenter et al. (1987) reported one instance of lymph node metastasis out of ten feline 'basal cell tumors' that appeared histologically malignant. One of the two putative cases of BCC reported by Day et al. (1994) metastasized to regional lymph node and lung. The lower recurrence rate in comparison to human BCC is most likely a reflection of more aggressive initial surgical excision for animal tumors in general. Metastasis of canine BCC has not been documented.

Histopathology

Solid basal cell carcinoma (Figures 22.33 through 22.37)

Basal cell carcinomas (BCCs) in general are circumscribed but unencapsulated, asymmetrical, superficial dermal masses that have a horizontal orientation. Most lesions have a plaque-like architecture. Larger BCCs extend into the deep dermis and may have a nodular architecture. There is extensive or multifocal contiguity with the lower surface of the epidermis, which is generally eroded or ulcerated. Primarily in cats, the overlying epidermis may also show cytologic changes consistent with viral plaque, actinic keratosis, or bowenoid *in situ* carcinoma (see pp. 574, 575 and 578). Basal cell carcinomas comprise multiple, discrete, epithelial aggregates that vary in size and shape within and among the tumors. The margins of the epithelial aggregates may be smooth, angular, or markedly jagged or spiky. Lesions composed largely of anastomosing or retiform cords of cells, as in human adenoid and fibroepithelioma BCC subtypes, have not been recognized in dogs or cats.

The neoplastic cells of solid BCC resemble basal cells of the epidermis or hair follicles. They are polyhedral or prismatic and have scant, pale cytoplasm without obvious intercellular bridges. Their nuclei are large, ovoid to elongate, and variably hyperchromatic. Mild anisokaryosis may be present, but nuclear pleomorphism is usually not a prominent feature. The high nuclear to cytoplasmic ratio results in a lesion that appears dark blue at scanning magnification. Nucleoli are generally small. Mitotic activity varies from moderately low to high; atypical mitoses may be present. Palisading of cells around the periphery of the epithelial aggregates is present in at least a portion of the neoplasm. Polarity of the internal cells is haphazard. Small areas of spindling may be present. The tumor cells may be melanized by dendritic melanocytes intercalated among them.

Caseation necrosis, sometimes with cystic degeneration, is often present in the centers of larger epithelial islands. Solid BCCs may also have small foci of squamous differentiation characterized by zones of larger, polygonal

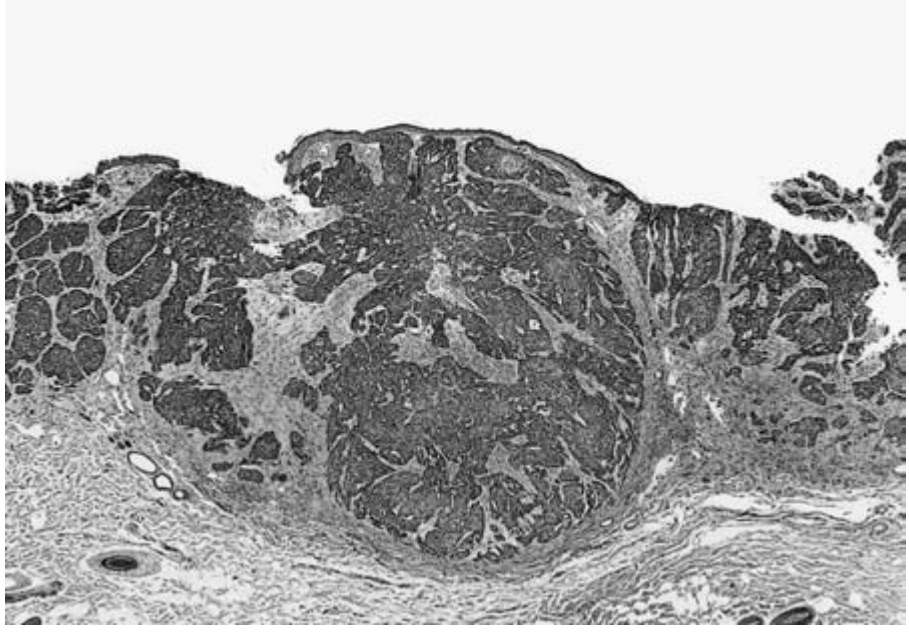


Fig. 22.33 Solid basal cell carcinoma in a cat. This is an irregular, plaque-like neoplasm with multifocal epidermal contiguity and ulceration. Note marked variability in size and shape of the epithelial aggregates.

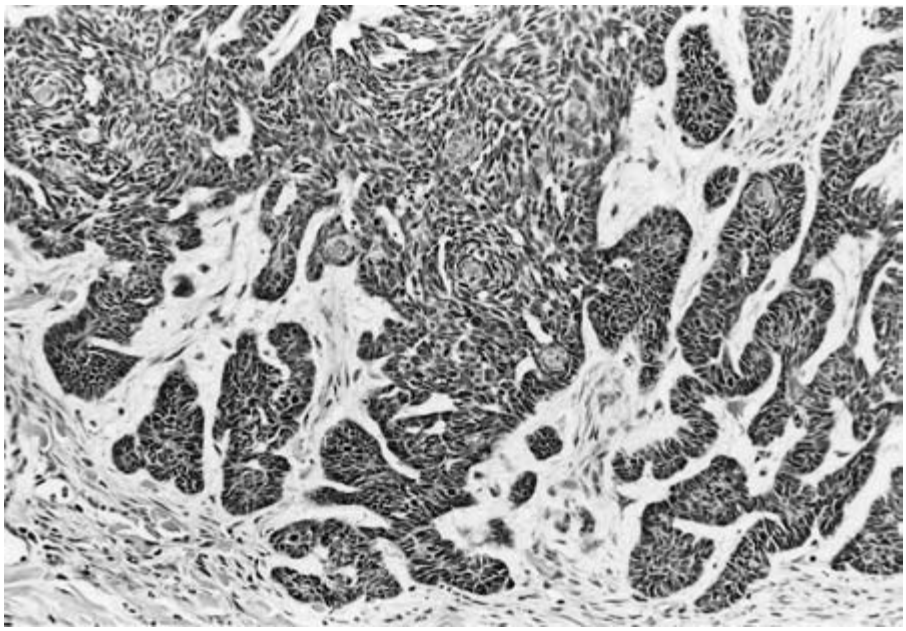


Fig. 22.34 Higher magnification of solid basal cell tumor of Fig. 22.33. The epithelial cells are small and angular with scant, pale cytoplasm and slightly elongated nuclei. Note patchy peripheral palisading.

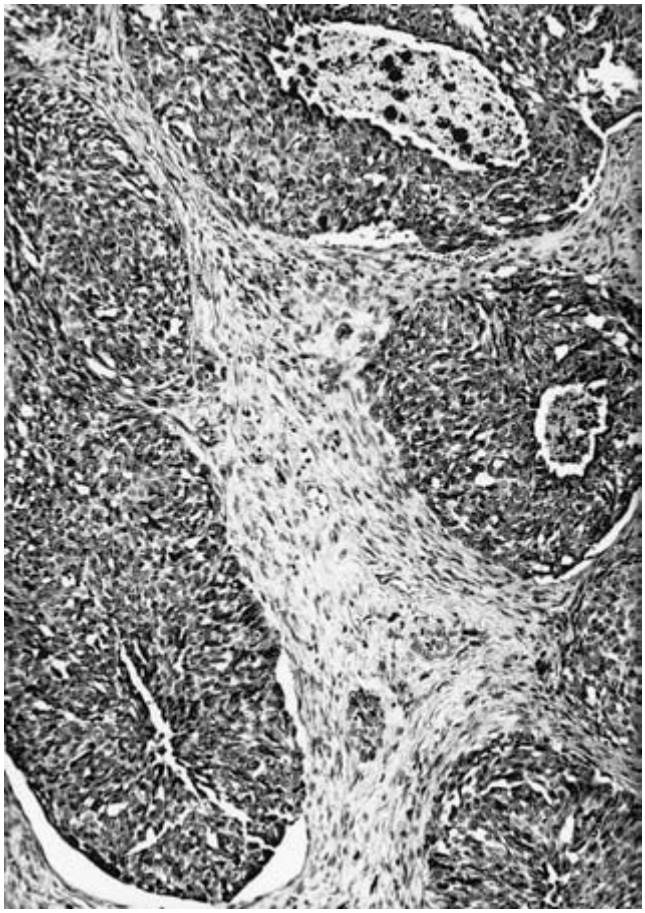


Fig. 22.35 High magnification of solid basal cell carcinoma in a cat. This example is pigmented, and clumps of melanin are present in zones of cystic degeneration. Note prominent clefts between epithelial aggregates and stroma.

cells with more abundant, eosinophilic cytoplasm; their nuclei are large and vesicular and may have prominent nucleoli. Advanced keratinization with frank extracellular keratin production in the squamoid foci is rarely observed.

The epithelial aggregates are embedded in a moderate stroma of fibrous or fibromyxoid tissue of moderate to high cellularity. The stroma generally extends beyond the boundaries of the epithelial component of the neoplasm and is not well demarcated from the adjacent dermis. Stromal infiltrates of lymphocytes and plasma cells are often seen, and melanophages may be present in heavily melanized lesions. Cleft formation between the epithelial aggregates and the stroma is an important diagnostic feature of human BCC, and is generally regarded as post-fixation artifactual retraction secondary to mucin production by tumor cells or stromal fibroblasts. It has also been suggested that these clefts may be due to defective basement membrane production within the neoplasm; loss of collagen XVII (bullous pemphigoid antigen) has been previously reported in human BCC (Kirkham, 1997). Stromal–epithelial clefts can be found in canine and feline BCC; however, this does not appear to be as consistent or specific a phenomenon as it is in humans.

Differential diagnoses for solid BCC comprise other epithelial neoplasms with a small cell-predominant composition; these include solid-cystic ductular sweat gland adenoma and carcinoma, sebaceous epithelioma and epitheliomatous sebaceous carcinoma, and trichoblastoma. Silhouette (the outline of a tumor section viewed with the naked eye or at scanning magnification)

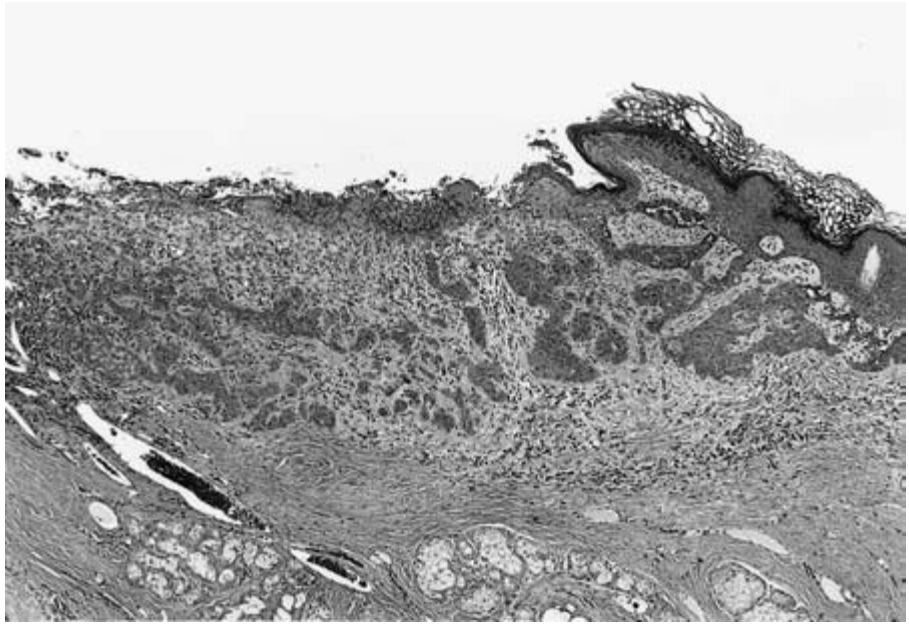


Fig. 22.36 Solid basal cell carcinoma in a dog. Small, markedly irregular aggregates of epithelial cells form an ulcerated, horizontally-oriented mass. Note multifocal contiguity with the basal cell layer of the epidermis at right.

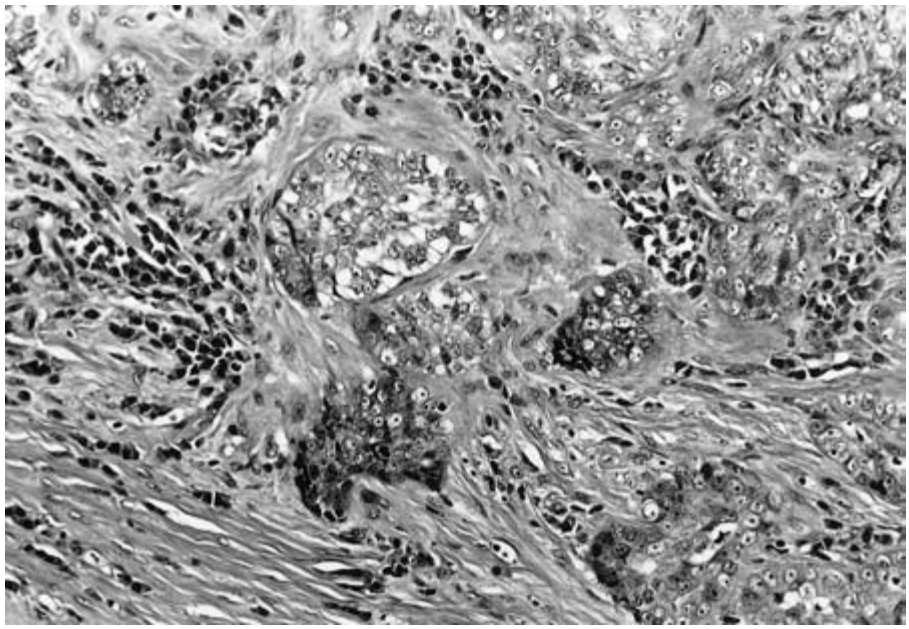


Fig. 22.37 Higher magnification of Fig. 22.36. In this example, some of the epithelial aggregates have prominent cytoplasmic glycogenation resembling clear cell basal cell carcinoma (see Fig. 22.40). Note reactive collagenous stroma with plasmacytic inflammation.

is a key diagnostic feature: BCC is almost always horizontally oriented and irregular, while solid-cystic sweat gland adenoma and trichoblastoma appear smooth, symmetrical, and vertically oriented or round. The racemiform (resembling a bunch of grapes) appearance of solid-cystic ductular sweat gland adenoma, as well as the limited extent of its epidermal contiguity, further distinguish it from BCC at low power. Trichoblastomas infrequently have focal epidermal connections. Sebaceous epitheliomas and carcinomas are irregular, but typically have a fungiform architecture rising above the skin surface. Small or early BCCs are confined to the superficial dermis.

In further differentiation, the cells of solid-cystic ductular sweat gland adenoma are often cuboidal or rounded, in contrast to the polyhedral or prismatic cells of BCC. Short ducts and cells with intracytoplasmic lumens are usually discernible in the sweat gland adenomas, but are absent in BCC. In addition, the stroma of BCC is more abundant and more cellular than that of ductular sweat gland adenoma. The cells of trichoblastoma closely resemble those of BCC, as would be expected in

light of the recent studies indicating a common origin (see above); however, trichoblastomas lack anisokaryosis, nuclear hyperchromasia, frequent mitotic activity, and mitotic atypia, as would be seen in most BCCs. Trichoblastomas often comprise numerous, winding epithelial cords and narrow trabeculae; this pattern is not recognized in canine or feline BCC. In addition, both trichoblastomas and solid-cystic ductular sweat gland carcinomas may show spindling of most of the cells or groups of cells, respectively; this phenomenon is rare in BCC. The stroma of trichoblastomas has minimal to low cellularity and often contains follicular papillary mesenchymal bodies, which are not found in BCC (Brooke et al., 1989).

Sebaceous epitheliomas and epitheliomatous sebaceous carcinomas usually contain at least occasional tumor cells with lipidized cytoplasm. The predominant reserve cells of epitheliomas and epitheliomatous carcinomas are slightly larger and more eosinophilic than those of BCC and do not exhibit peripheral palisading. Oil red O or other lipid stain may be required to differentiate a poorly-differentiated, small cell-predominant, epitheliomatous sebaceous carcinoma from BCC.

Larger solid BCC may not be distinguishable from solid-cystic ductular sweat gland carcinomas based on silhouette or cytologic features. A basaloid malignancy, particularly in a cat, that appears unusually aggressive or has obvious lymphatic invasion warrants a thorough search for small tubular structures or intracytoplasmic lumens consistent with sweat gland origin. Immunohistochemistry often is required for definitive diagnosis (see below).

Keratinizing (keratotic) basal cell carcinoma

(Figures 22.38 and 22.39)

Keratinizing BCC has a similar architecture to solid BCC, but most lesions are thicker plaques greater than 1 cm in diameter. Angular islands and trabeculae predominate in most tumors. The epithelial structures have multifocal contiguity with the epidermis, which is usually ulcerated. Central zones of caseation necrosis are frequently observed, but melanization and cystic degeneration are uncommon. Some tumors may infiltrate into the deep dermis.

The epithelial aggregates are composed predominantly of small polyhedral cells identical to those of solid BCC. Mitotic activity in the small cell population is moderate to high, and mitotic atypia can usually be detected. Patchy melanization of the basal cells is a feature of some tumors. Many of the epithelial islands contain central or peripheral foci of abrupt squamous differentiation with or without extracellular keratin deposition. The patterns of keratinization may be epidermal/infundibular (lamellar keratin via a keratohyalin granular cell layer), isthmus type (compact or amorphous keratin without a granular cell layer), or, less frequently, matrical (direct formation of keratinized 'ghost' or 'shadow' cells without an intervening zone of viable squamous epithelium). The squamous cells have larger, vesicular nuclei with small nucleoli and rare mitotic figures. The stroma is similar to that of solid BCC, and infiltrates of plasma cells, neutrophils, and lymphocytes are common.

Keratinizing BCC must be differentiated from trichoepithelioma, malignant trichoepithelioma, malignant pilomatricoma, and basosquamous carcinoma. Diagnosis

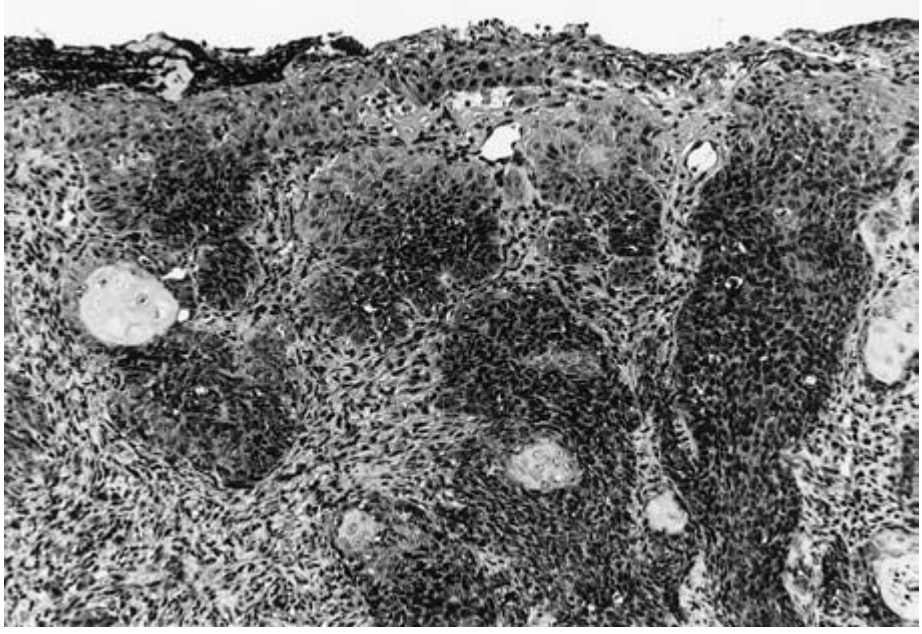


Fig. 22.38 Keratinizing basal cell carcinoma in a dog. Irregular aggregates of predominantly basaloid epithelial cells are intermingled with scattered nests of pale squamous cells. Note multifocal epidermal contiguity and highly cellular collagenous stroma.

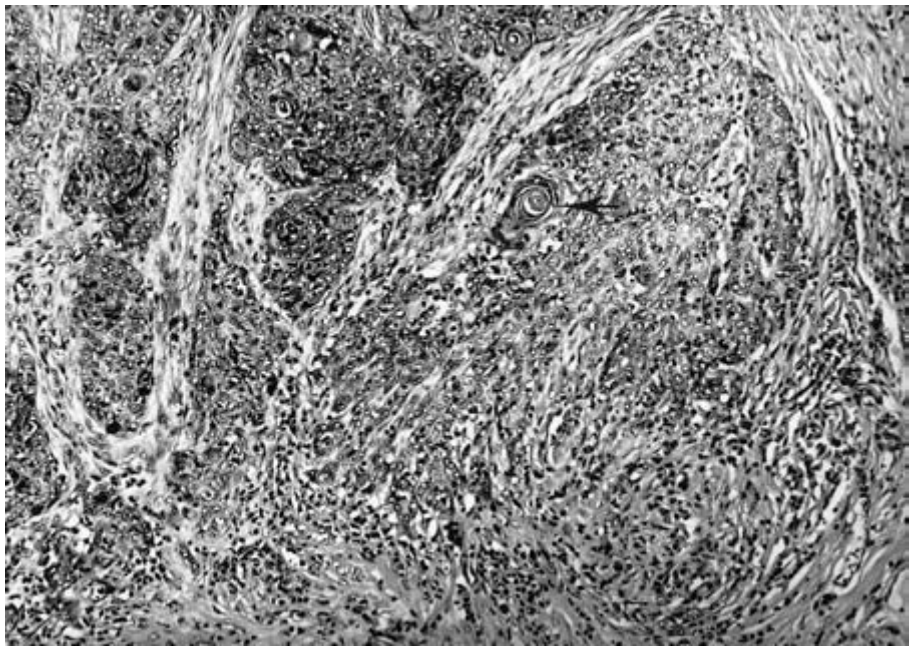


Fig. 22.39 Higher magnification of keratinizing basal cell carcinoma in a dog. The foci of squamous differentiation contain small aggregates of laminated and amorphous keratin (arrow).

of benign trichoepithelioma is usually straightforward; in silhouette, most trichoepitheliomas are nodular and circumscribed, whereas BCCs are generally plaque-like, irregular, and have multifocal epidermal contiguity. Trichoepitheliomas have one or more of the following features that are not seen in keratinizing BCC: discrete cystic structures lined by isthmus or infundibular-type epithelium, cysts filled with keratinized ghost cells, epithelial clusters resembling hair bulbs, and small aggregates of stromal mesenchymal cells resembling follicular papillae. Unlike trichoepitheliomas, keratinizing BCCs have epithelial aggregates with angular margins, multifocal necrosis, moderate to high mitotic activity, and nuclear and mitotic atypia. The stroma of BCC is usually more cellular, and stromal–epithelial clefts may be present.

Distinction from malignant trichoepithelioma is much more problematic, as both are horizontally oriented, infiltrative neoplasms with an admixture of basaloid and squamous cells, and cytologic features of malignancy. The epithelium of malignant trichoepithelioma has features of hair matrix (keratinized ghost cells), inner root sheath (trichohyalin granules and glycogen), outer root sheath (agranular, with or without glycogenation), and infundibulum (keratohyalin granules) in varying proportions. Inner root sheath differentiation is not seen in BCC, and matrical differentiation is limited. Hyalinized collagen cuffs around epithelial aggregates and overt lymphatic invasion are common findings in malignant trichoepithelioma but not in BCC. However, because it has recently been demonstrated that BCCs have a very similar cytokeratin profile to trichoepithelioma and trichoblastoma (see above), one could reasonably argue that keratinizing BCC represents a distinct, low-grade variant of malignant trichoepithelioma.

Keratinizing BCC is differentiated from malignant pilomatricoma primarily by its superficial, plaque-like architecture and multifocal connections to the epidermis. Malignant pilomatricomas are usually larger, deeper neoplasms. Keratinizing basal carcinoma can have small clusters of shadow cells; large, irregular zones of matrical keratinization are a more typical feature of malignant pilomatricoma, and foci of inner root sheath differentiation may also be present. Stromal–epithelial clefts are typical for BCC, but may not be as consistent a feature as they are in human BCC. Basosquamous carcinoma (see p. 597), which was formerly included in the BCC category, is architecturally indistinguishable from keratinizing BCC; however, its squamous epithelial component also has cytologic features of malignancy and resembles squamous cell carcinoma.

Clear cell basal cell carcinoma (Figure 22.40)

This rare variant has an architecture that is identical to solid BCC. Most of the epithelial cells of clear cell BCC are larger than those of solid BCC and have water-clear or finely granular cytoplasm. The nuclei are large, ovoid, and fairly uniform. The nucleoli are small, and mitotic activity varies from low to moderate. Atypical mitoses can usually be detected. Palisading at the periphery of the epithelial aggregates is less consistently present than in solid BCC. Necrosis is a common secondary feature. The stroma of clear cell BCC is often sparser than in the solid or keratinizing variants. Stromal–epithelial clefts are discernible in most lesions.

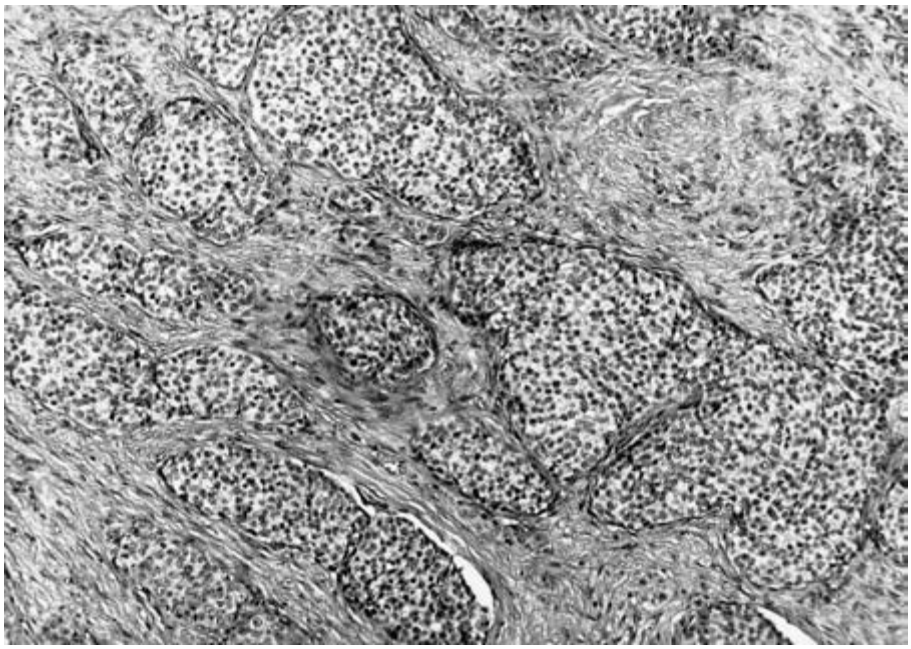


Fig. 22.40 Clear cell basal cell carcinoma in a cat. Irregular epithelial aggregates are composed of larger polygonal cells with clear cytoplasm. Note clefts between epithelium and stroma at bottom.

Differential diagnoses are limited to other neoplasms with marked cytoplasm vacuolation, and include clear cell apocrine ductular carcinoma, balloon cell melanoma, bulb-type tricholemmoma, and sebocytic sebaceous carcinoma. None of these has the irregular, horizontal silhouette of BCC, but epidermal or superficial follicular contiguity is often present in clear cell apocrine ductular carcinoma and sebocytic sebaceous carcinoma. Clear cell BCC is distinguished from both clear cell apocrine ductular carcinoma and balloon cell melanoma by smaller cell size, predominance of angular cell aggregates, and stromal–epithelial clefts. In addition, tubular structures are found only in clear cell apocrine ductular carcinoma, and epidermal contiguity is not seen in balloon cell melanoma or bulb-type tricholemmoma. Clear cell BCC has larger cells and larger cell aggregates than does tricholemmoma and lacks its exaggerated basement membranes; in addition, tricholemmoma is cytologically benign. Most sebocytic sebaceous carcinomas contain at least some cells with multiple round vacuoles or foamy cytoplasm indicative of lipid content; these are usually admixed with squamoid cells and large polyhedral cells in varying proportion. Immunohistochemistry may be required for definitive diagnosis (see below).

Immunohistochemistry

Immunostains for cytokeratins (CKs) 8, 13, and 7/8 (CAM5.2) utilizing routine methodology for formalin-fixed paraffin embedded tissue appear to be quite specific in canine and feline skin biopsies for sweat gland epithelium (see Chapter 25); they are, therefore, important tools for distinguishing solid-cystic ductular sweat gland adenoma and solid-cystic apocrine ductular carcinoma from solid BCC, and for distinguishing clear cell apocrine ductular carcinoma from clear cell BCC. These stains highlight short tubular structures or larger groups of cells in the solid-cystic tumor types and decorate most or all of the cells in clear cell apocrine ductular carcinoma, but are negative in BCC. A panel of multiple poly- and monoclonal CK markers may be required to rule out sebaceous origin; certain clones of CD79a (the pan-B lymphocyte marker) may stain sebocytes, but the veracity of this staining reaction is unconfirmed and requires additional investigation (see sebaceous carcinoma, Chapter 24). A pancytokeratin stain would readily differentiate clear cell BCC from balloon cell melanoma, which is CK negative, vimentin positive, and also positive for more specific markers such as S100a or melanoma isoform of microphthalmia transcription factor (MITF-M). As previously discussed, human BCCs demonstrate CKs 5, 6, 10, 14, 15, 16, 17, and 19; this staining pattern is also found in trichoblastomas and some trichoepitheliomas, so immunohistochemical differentiation from these benign follicular neoplasms may not be possible utilizing cytokeratin profiles in canine and feline tissue. Complete monoclonal keratin profiles have not been established for canine or feline BCC. Neither has the validity of immunostains for the anti-apoptotic protein bcl-2 and the membrane glycopolypeptide BerEP4, which are diagnostically useful for human BCCs, been documented in the veterinary literature; studies in this regard may yield valuable information.

BASOSQUAMOUS CARCINOMA

(Synonym: basal-squamous cell carcinoma)

Cutaneous basosquamous carcinoma (BSCC) is a neoplasm with bimorphic histologic features that has been bounced back and forth between classification as a basal cell carcinoma (BCC) variant ('metatypical basal cell carcinoma') and a squamous cell carcinoma (SCC) variant. It is now regarded as a distinct entity more frequently, although its existence is still not universally accepted (Kirkham, 1997). It is generally considered to be a rare tumor in the skin of humans (Jones et al., 1997; Beer et al., 2000; Martin et al., 2000; Bowman, et al., 2003), but has been reported in older literature to represent 3% to 12% of all BCCs (Kirkham, 1997). The clinical presentation of BSCC in humans is similar to both basal and squamous cell carcinoma, and it most likely shares a common pathogenesis with these entities; however, it is biologically more aggressive than either (Martin et al., 2000; Bowman, et al., 2003).

Basosquamous carcinoma in humans has intermediate histological and immunohistochemical properties of BCC and SCC, and may have a zone of gradual transition between these two types. BerEP4, an epithelial membrane glycopolypeptide that is present in almost all BCCs, was present in at least some areas in 50% to 100% of BSCCs in two studies, while the SCCs were uniformly negative (Jones et al., 1997; Beer et al., 2000). In addition, epithelial membrane antigen was detected in all SCCs, none of the BCCs, and one BSCC (Beer et al., 2000). Staining patterns for the anti-apoptotic protein bcl-2 (identified in most BCCs) was similar in BCC and BSCC (Jones et al., 1997). Similar studies have not been performed in dogs and cats.

Clinical features

Neoplasms that appear analogous to human BSCCs occur rarely in cats and very rarely in dogs. Actual incidence data are not available. In the previous World Health Organization classification system, they were included in the 'basal cell tumor' group, but were described as locally aggressive (Weiss & Frese, 1974). In the current World Health Organization veterinary nomenclature, BSCC has a category all of its own as a malignant tumor of epidermal origin (Goldschmidt et al., 1998). Conroy (1983) also described BSCC as a distinct clinicopathologic entity in dogs that is locally aggressive and has a metastatic capacity approaching that of squamous cell carcinoma, although specific numeric data were not given. The authors believe that the entity described as BSCC in one reference text (Goldschmidt & Shofer, 1992) is most likely an uncommon variant of trichoblastoma that exhibits prominent outer root sheath differentiation (see Chapter 23).

BSCCs are clinically indistinguishable from SCCs and BCCs (see pp. 581 and 589). Site, age and breed predispositions are probably also similar, but too few cases have been seen to draw firm conclusions. The biologic behavior is also unknown.

Histopathology (Figures 22.41 and 22.42)

Basosquamous carcinoma has a similar silhouette to its two close relatives, BCC and SCC. It presents as a horizontally oriented, usually superficial, plaque-like mass

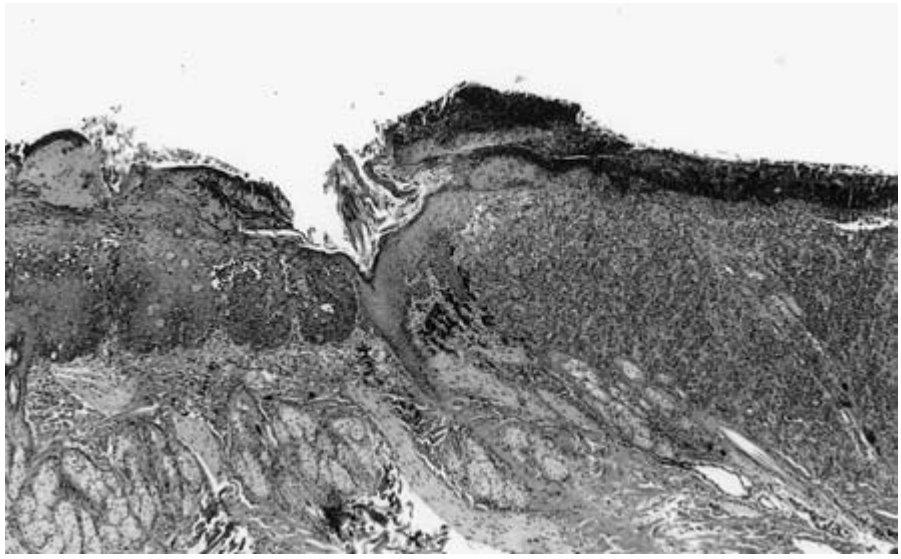


Fig. 22.41 Basosquamous carcinoma in a cat. An ulcerated, plaque-like neoplasm at right is closely associated with bowenoid *in situ* carcinoma at left.

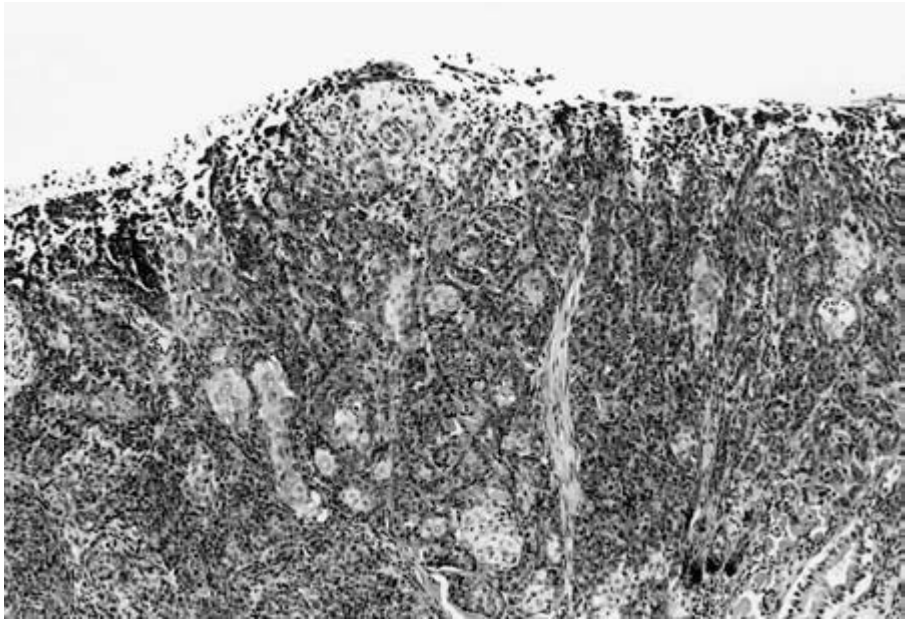


Fig. 22.42 Higher magnification of Fig. 22.41. The neoplasm comprises atypical basaloid and squamous epithelial cells in approximately equal proportions.

that is connected multifocally to the epidermis. Crusting, erosion or ulceration is usually present. The epithelial aggregates comprise islands, trabeculae, and nests that often have angular, irregular profiles. Many epithelial aggregates have typical features of BCC peripherally and well-differentiated SCC centrally; keratin pearls are often present. The tumors may also contain adjacent zones of solid BCC and pure SCC with areas of gradual transition between them. As in both SCC and BCC, a moderate stroma of moderate cellularity surrounds the epithelial structures.

A neoplasm with histologic features virtually identical to BSCC was observed by one of the authors (T.L.G.) invading into the dermis from the deeper aspects of an otherwise classical canine exophytic viral papilloma. The papilloma had an increased proportion of basal and suprabasal keratinocytes, and these exhibited nuclear enlargement, loss of nuclear polarity, and moderately high mitotic activity. The infiltrating epithelial aggregates of the malignant component were relatively small and had basal and squamous components in varying proportions.

The squamous component of BSCC has histologic features of malignancy and does not differentiate toward follicular isthmus or bulb; this distinguishes it from keratinizing BCC as well as follicular neoplasms with combined basaloid (or matrical) and squamous epithelium, in which the squamous component is cytologically bland and shows complete cornification, often with multiple follicular patterns. Solid BCCs may have small foci of squamous metaplasia, whereas the squamous component of BSCC comprises a substantial portion of the tumor. However, since it is likely that these lesions represent a continuum, there may be specific cases that are impossible to assign confidently to either the BCC or BSCC category. Immunohistochemistry studies, which may allow further elucidation, have not yet been undertaken.

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Chapter 23

Follicular tumors

Follicular histology and physiology are highly complex, and a thorough review is beyond the scope of this text. However, since a logical nomenclature of follicular tumors must be based on normal structure, a brief description is included. Hair follicles are divided transversely into three levels. The upper portion, or infundibulum, of the follicle extends from the entrance of the sebaceous duct to the follicular ostium. This segment of the follicle is composed predominantly of outer root sheath epithelium that is continuous with and histologically indistinguishable from the epidermis. The middle portion, or isthmus, of the hair follicle extends from the insertion of the arrector pili muscle to the level of the sebaceous duct. The outer root sheath epithelium of the follicular isthmus comprises smaller keratinocytes that keratinize without a granular cell layer. This tricholemmal pattern of keratinization produces amorphous keratin, in contrast to the lamellar keratin arising via the keratohyalin granular cell layer of infundibular epithelium. The keratinocytes of the isthmus generally have homogeneous, pale pink cytoplasm.

The lower, or inferior, segment of the follicle extends from the mesenchymal papilla to the insertion of the arrector pili muscle. The inferior segment of the follicle during anagen phase contains the outer root sheath, inner root sheath, and hair bulb. The outer root sheath at this level shows marked cytoplasmic glycogenation. The inner root sheath is composed of small cells with clear cytoplasm that keratinize through distinctive, bright red trichohyalin granules. Inner root sheath epithelium produces large plates of keratin that have a laminated appearance in tissue sections. The hair bulb is composed of the multipotential basaloid matrix cells that give rise to the inner root sheath, hair shaft, and lower outer root sheath. Keratinization of matrix cells leaves the cytoplasmic and nuclear membranes intact, producing sheets of 'ghost' or 'shadow' cells. The isthmic outer root sheath becomes the predominant component of the lower half of the follicle during catagen and telogen phases after the hair bulb undergoes involution.

At the base of telogen hair follicles, there is a cluster or column of small adnexal keratinocytes known as secondary hair germ; this is presumably a direct descendant of primary hair germ. Primary hair germ is the epithelial anlage of the folliculosebaceous unit. It appears early in embryonic life as a dense ball of basaloid cells with peripheral palisading that projects downward from the epidermis.

The subsequent growth of both the first hair follicles in the fetus and successive generations of hair follicles throughout life are a result of complex signaling between hair germ epithelium and the subjacent clusters of highly specialized mesenchymal cells known as dermal papillae or follicular papillae. It is now fairly well accepted that a population of multipotential, slow-cycling follicular stem cells resides, at least in humans and mice, in a small area of outer root sheath near the insertion of the arrector pili muscle known as 'the bulge' (Sun et al., 1991). Follicular stem cells in the dog may have a more diffuse distribution (Credille et al., 1999). In an elegant synthesis of recent discoveries in molecular biology and old observations based on light and electron microscopy, Panteleyev et al. (2001) provide convincing evidence for the existence of a second aggregate of follicular stem cells at the base of the outer root sheath adjacent to the hair bulb in mice; these migrate from the bulge cells during anagen and have been dubbed the 'lateral disc'. The lateral disc cells are the secondary hair germ; they become activated at the end of telogen, they are in close contact with follicular papilla, and their progeny form the hair bulb, hair shaft, and inner root sheath. In contrast, the progeny of the bulge region give rise to the outer root sheath (Panteleyev et al., 2001).

Apocrine and sebaceous glands arise embryologically as unilateral protrusions from the upper and mid portion, respectively, of the developing hair peg (Meyer & Görgen, 1986; Panteleyev et al., 2001). Because of this close ontogenetic relationship, it is not surprising that primarily follicular tumors occasionally display foci of divergent differentiation toward adnexal glands, usually sebaceous since their precursor cells are in closer proximity to the putative follicular bulge region. Where this phenomenon

is relatively frequent, the variant has a compound title, such as 'sebaceous trichofolliculoma'. In instances of rare, unclassified divergent differentiation, descriptive nomenclature is appropriate, e.g. 'trichoepithelioma with sebaceous differentiation'.

FOLLICULAR HAMARTOMA

(Synonym: follicular nevus)

Clinical features

Follicular hamartoma is an uncommon, non-neoplastic lesion in dogs. The etiopathogenesis is unknown. Numeric incidence data are not reported. Follicular hamartoma typically presents as multiple, grouped plaques or small nodules. The affected skin has an irregularly thickened texture resembling orange peel. Hairs arising from the hamartoma are thick and brush-like. The number of nodules gradually increases, and the lesion expands over time, sometimes necessitating multiple surgical excisions. Most lesions are several centimeters in size; some may be more extensive and may rarely involve an entire leg or large portions of the trunk. Follicular hamartoma may also present as a single small nodule measuring 0.3 to 1 cm in diameter. There is no known age, breed or site predilection.

Histopathology (Figure 23.1)

Follicular hamartoma contains one or more clusters of architecturally normal anagen hair follicles that are distinctly larger and extend more deeply than adjacent normal follicles. In the majority of cases, all follicles within a cluster are uniform and have the appearance of primary follicles. Hair shafts are proportionately thickened. Follicular infundibular hyperkeratosis, as would be expected in reactive hyperplasia of hair follicles, is not observed. The sebaceous glands within the lesions are slightly enlarged, increased in number, and frequently extend proximally and distally beyond their normal location at the follicular isthmus. Sweat glands maintain their normal anatomic distribution, but are often dilated and occasionally attain cystic proportions. In small numbers of follicular hamartomas, one or several folliculosebaceous units exhibit mild to moderate dysplasia and tortuosity. The follicles are embedded in hyalinized collagen, and a zone of mucin is located peripheral to the vitreous sheaths. The collagenous stroma extends into the hypodermal fat, which may also be increased in depth. The overlying epidermis is mildly hyperplastic and often has an undulating configuration. Hyperpigmentation may be present. Secondary folliculitis is infrequently observed.

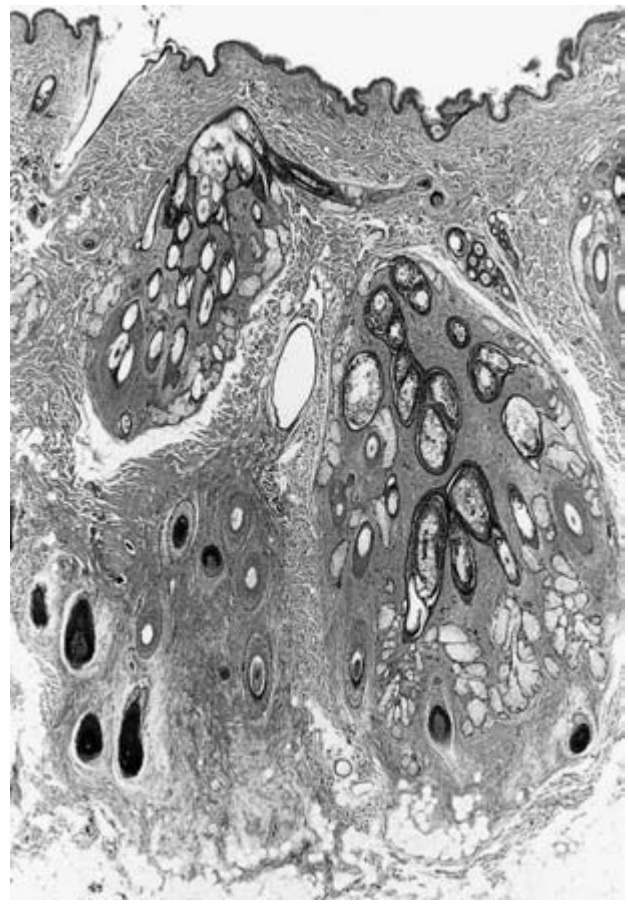


Fig. 23.1 Follicular hamartoma in a dog. Clusters of giant anagen hairs and associated adnexal glands surrounded by increased collagen encroach on the panniculus. Note interspersed normal-sized hair follicles.

Diagnosis of this unique lesion is usually not problematic. If only punch biopsies of lesional tissue are submitted, it may be difficult to appreciate the relative size of the abnormal follicles. Solitary follicular hamartomas are readily distinguished from fibroadnexal hamartoma by the presence of anagen hair bulbs and normal anatomic orientation of the follicles and adnexal glands. When dysplastic changes are present in follicular hamartoma, they are much milder than in fibroadnexal hamartoma.

FIBROADNEXAL HAMARTOMA

(Synonyms: fibroadnexal dysplasia, focal adnexal dysplasia)

Fibroadnexal hamartoma (formerly focal adnexal dysplasia) is a hamartomatous lesion of controversial etiology. Scar tissue formation following the resolution of an inflammatory process could result in entrapment and subsequent distortion of folliculosebaceous units. The

authors frequently see both hyperplasia and significant distortion of hair follicles in areas of reactive dermal fibroplasia, for example in surgical re-excision specimens. Chronic trauma may result in reactive proliferation and distortion of adnexal units with subsequent rupture, inflammation, and scarring. The typical location over pressure points supports this traumatic pathogenesis. However, lesions also occur on the trunk and head. Smaller masses frequently have no evidence of inflammation, but still show marked distortion of adnexal structures. Thus, it is likely that many of these lesions are primary malformations of folliculosebaceous units and, possibly, dermal collagen. In humans, similar lesions have been reported as folliculosebaceous cystic hamartomas (Kimura et al., 1991). A giant variant has also been described (Yamamoto et al., 1994).

Clinical features

Fibroadnexal hamartoma is a common non-neoplastic lesion of adnexal appendages occurring in dogs. It is reported to comprise 2.7% of all canine skin tumors (Goldschmidt & Shofer, 1992). Another survey found an incidence of 1.7% of all canine skin biopsies (Abramo et al., 2003).

Fibroadnexal hamartomas are typically solitary, firm, circumscribed, and dome-shaped to polypoid masses that range from approximately 1 cm to more than 4 cm in diameter. Smaller lesions have partial alopecia. Larger lesions frequently exhibit alopecia and ulceration. Fibroadnexal hamartoma occurs most commonly on the distal legs; pressure points and interdigital areas are frequently affected. The lesions are found less frequently on head and trunk. This anatomic distribution is in agreement with published data (Goldschmidt & Shofer, 1992; Abramo et al., 2003).

Animals are generally middle-aged or older, and a range of 2 to 16 years was recently reported (Abramo et al., 2003). Large breed dogs, particularly Labrador Retrievers, appear to be predisposed (Goldschmidt & Shofer, 1992). Basset Hounds, Maremma Sheepdogs, and Bracco Dogs may also be at increased risk (Abramo et al., 2003).

Histopathology (Figures 23.2 through 23.4)

Fibroadnexal hamartoma is a circumscribed nodule comprising malformed folliculosebaceous units, collagen and, occasionally, apocrine sweat glands. Smaller lesions are confined to the dermis; larger masses extend into subcutis. The hamartomas are usually spherical, although some have a filiform conformation. Superficial ulceration may be present. Intact epidermis covering larger masses is acanthotic, sometimes resembling acral lick dermatitis (see Chapter 7) or an acrochordon (fibroepithelial polyp; see Chapter 27) in severity. The hair follicles are hyperplastic, cystically dilated, and tortuous. Infundibular epithelium predominates; hair bulbs are not found. Orientation of the follicles is severely askew; they often appear to run tangential or parallel to the skin surface. Contiguity of the abnormal follicular structures with overlying epidermis is rare. The follicles are distended with lamellar keratin, and occasional hair shafts are present. Multiple mature sebaceous gland lobules of varying size are distributed haphazardly around the hair follicles, often without obvious ductal connections. Occasionally, lesions contain delicate, arching strands of small keratinocytes interconnecting the follicles to one another or to sebaceous lobules. When apocrine glands are present, they are dilated and abnormally distributed.

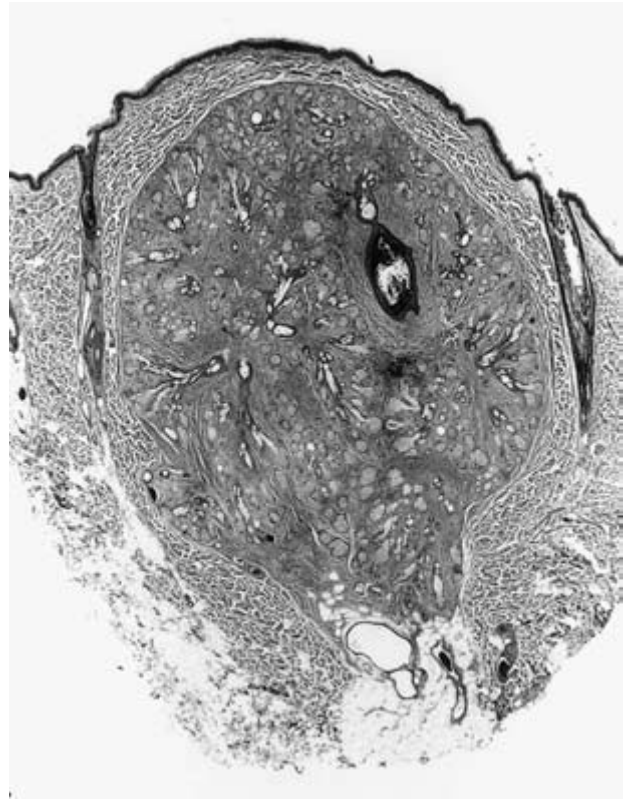


Fig. 23.2 Fibroadnexal hamartoma in a dog. This small dermal nodule comprises multiple distorted folliculosebaceous units surrounded by dense collagen.

The adnexa are surrounded by and interspersed with abundant, mature collagen. The collagen bundles in larger lesions are thick and resemble scar tissue. Some fibroadnexal hamartomas also contain islands of mature adipose tissue admixed with the collagen. The stroma is sharply demarcated from the adjacent dermis or subcutis in uninflamed lesions, but blends into the reactive fibrous tissue around inflamed nodules. Larger lesions frequently have rupture of cystic hair follicles, resulting in severe suppurative or pyogranulomatous inflammation. Patchy,

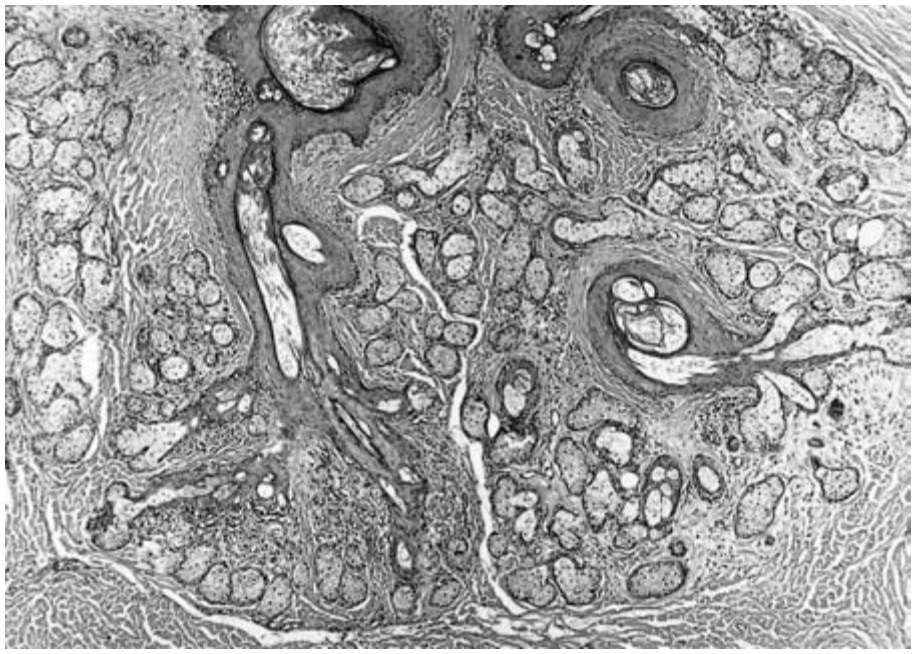


Fig. 23.3 Higher magnification of fibroadnexal hamartoma in a dog. Hair follicles are hyperplastic and markedly tortuous. The sebaceous lobules are distributed haphazardly.



Fig. 23.4 Fibroadnexal hamartoma in a dog. This example has marked hepatoid metaplasia of the sebaceous lobules.

chronic inflammatory infiltrates of plasma cells and macrophages may also be present around the periphery of these lesions regardless of size. Cystic follicles sometimes contain large colonies of staphylococci; *Malassezia* are detected occasionally.

Diagnosis of fibroadnexal hamartoma is generally straightforward. Small fibroadnexal hamartomas are readily distinguished from solitary follicular hamartomas by the absence of anagen hair bulbs and the markedly distorted orientation of the follicles and adnexal glands. Dermoid cysts (see Chapter 22) have a single epithelial cystic structure with a few miniature but complete folliculosebaceous units radiating from it; fibroadnexal hamartomas almost always have multiple tortuous infundibular cysts with multiple randomly arranged sebaceous lobules and no anagen follicles. Trichofolliculoma, a rare lesion in dogs, classically shows a central dilated follicular infundibulum and ostium from which multiple secondary anagen follicles radiate. Trichofolliculoma may have a sebaceous component, and some authors believe that human folliculosebaceous cystic hamartoma (resembling fibroadnexal hamartoma in dogs) is the same entity as trichofolliculoma in a late stage of evolution (Schulz & Hartschuh, 1998). Considering the relative frequency of fibroadnexal hamartoma versus classic trichofolliculoma, this does not appear to be the case in dogs.

FOLLICULAR CYST

A cyst may be defined as a non-neoplastic, simple sac-like structure with an epithelial lining. Classification of cysts depends on identification of the lining epithelium or the

pre-existing structure from which the cyst arose. The majority of cysts in the skin of dogs and cats are of follicular origin and can be further categorized based upon the level of the follicle from which they develop. The categories include infundibular, isthmus, matrical, and hybrid; the last is composed of two or three types of lining epithelium. Because of the histopathologic similarity between infundibular and epidermal keratinization patterns, some cysts are still classified as epidermal cysts or epidermal inclusion cysts in both human and veterinary literature (Goldschmidt & Shofer, 1992; Rosai, 1996; Jones et al., 1997; Kirkham, 1997). This nomenclature suggests that the cysts are formed as a result of traumatic embedding of epidermal fragments or a congenital anomaly of epidermal development, both of which are probably very rare phenomena. Congenital and familial cases of multiple follicular cysts, such as tricholemmal cysts and eruptive vellus cysts, occur in humans (Kirkham, 1997). Multiple follicular cysts are occasionally seen in dogs, although they are usually not numerous, as in the human disorders. The clinical misnomer 'sebaceous cyst' is frequently applied to follicular cysts because of the grumous nature of their keratinaceous contents; this is a holdover from older human and veterinary literature. Sebum is actually a white, milky fluid.

Clinical features

Infundibular and isthmus cysts are common in dogs. In cats, infundibular cysts are fairly common, while isthmus cysts are uncommon. In a large survey, all cysts classified as 'epidermal' or 'follicular' accounted for 3.5% of canine skin tumors and 4.4% of feline skin tumors (Goldschmidt & Shofer, 1992). Exclusively matrical cysts are rare in dogs and cats. Hybrid cysts are common in dogs and rare in cats.

Follicular cysts usually present as solitary, firm, intradermal or, occasionally, subcutaneous nodules ranging from 0.2 to 2 cm in diameter. Larger lesions occur infrequently. Follicular cysts can be multiple either synchronously or metachronously, suggesting a developmental and/or environmental basis for their formation. They are occasionally numerous. The overlying epidermis is intact unless cyst rupture or self-trauma has occurred. The lesions may have a blue, white, or yellow hue depending on the depth of the cyst and color of its contents. Partial or total alopecia may be present. A pore, representing residual follicular ostium, may connect the cyst to the overlying epidermis; this occurs more often in cats. Keratin from the cyst lumen may protrude through the pore, occasionally forming a frank cutaneous horn. The cyst contents have a semisolid, caseous, granular, or doughy consistency; the color may be yellow-white, light brown, or gray.

Breeds of dogs that are reported to be predisposed to develop solitary cysts include Boxers, Shih Tzus, Miniature Schnauzers, and Old English Sheepdogs (Goldschmidt & Shofer, 1992). Clustered follicular cysts of presumed congenital etiology occur on the dorsal midline of the head of young dogs; Boxers and Rhodesian Ridgebacks are predisposed (Goldschmidt & Shofer, 1992). Multiple follicular cysts also develop on pressure points in large breed dogs; these are probably secondary to chronic frictional trauma leading to obstruction of follicular ostia (see callus, Chapter 8). Cysts may also develop in surgical scars secondary to follicular entrapment.

Histopathology

Infundibular cyst (Figures 23.5 and 23.6)
Infundibular cysts are lined by squamous epithelium with an obvious granular cell layer, as in the upper portion of the normal follicle. The keratin contents are laminated and are often concentrically arranged. The keratin may

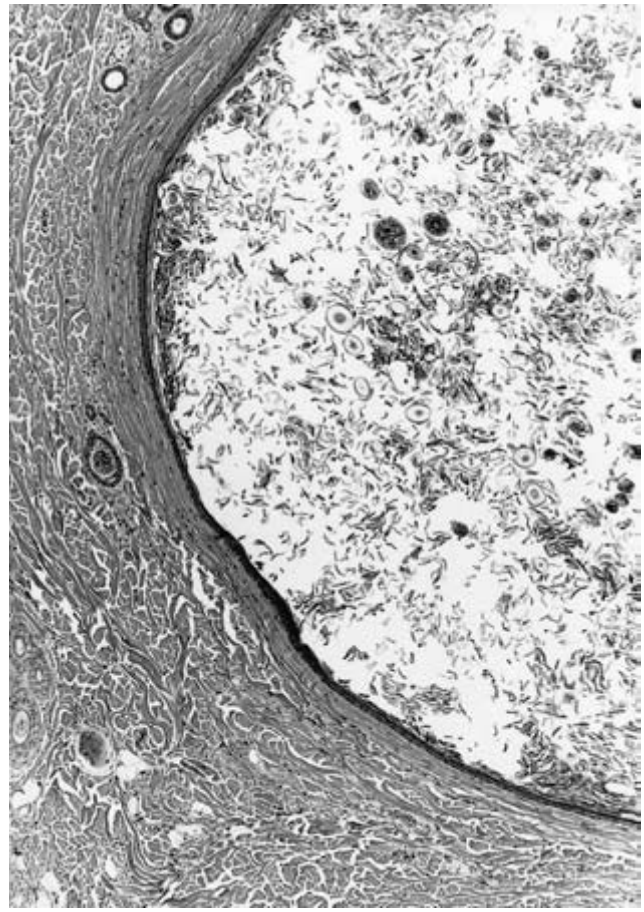


Fig. 23.5 Infundibular cyst from the head of a dog. The cyst is lined by a thin layer of squamous epithelium. The cyst cavity contains flaky keratin and numerous hair fragments.

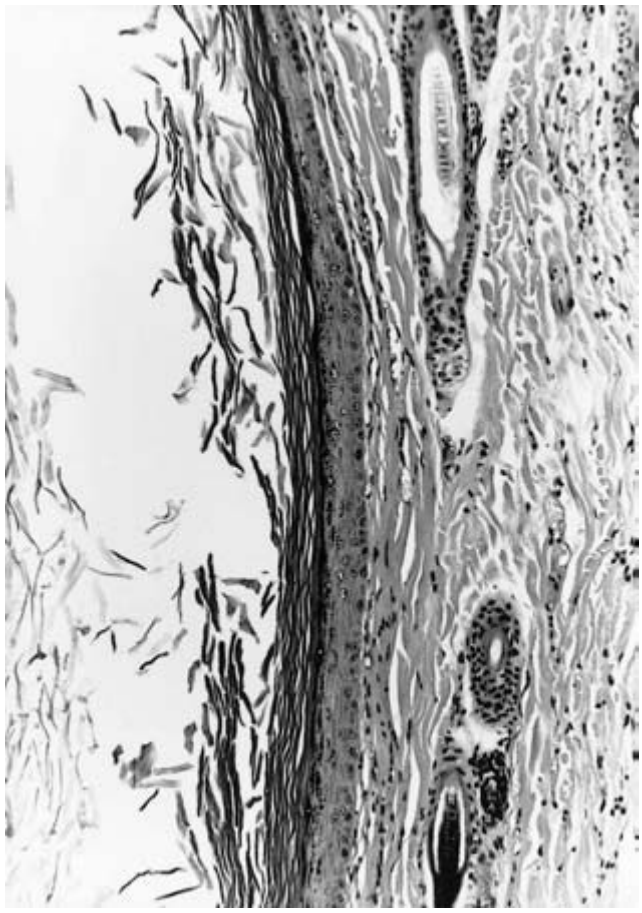


Fig. 23.6 Infundibular cyst in a cat. The cyst wall has a prominent granular cell layer, and the cyst cavity contains lamellar, flaky keratin.

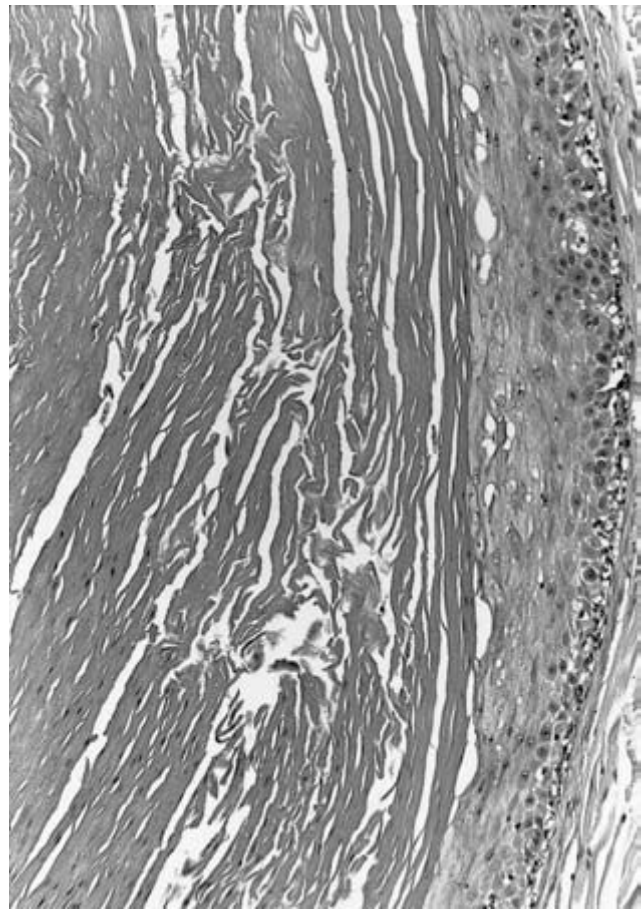


Fig. 23.7 Isthmus cyst in a dog. The epithelium lining the cyst does not have a granular cell layer. Note the keratin contents are paler and more amorphous than in the infundibular cyst (Fig. 23.6).

appear as loose flakes within the cyst lumen. Hair fragments are usually absent in solitary idiopathic cysts, but may be numerous in congenital cysts on the head or in callus cysts. In occasional cysts there may be one or two clusters of sebaceous glands attached to the wall.

Rupture of any type of keratinous cyst results in a marked foreign-body-type inflammatory reaction in the dermis. Free keratin fragments are surrounded by macrophages, neutrophils, plasma cells and multinucleated giant cells. Cholesterol cleft formation is frequently observed. Fibroplasia occurs with eventual encapsulation of the residual cyst wall and keratinous debris. Inflamed lesions may fistulate or ulcerate.

Differentiation of infundibular cyst from dermoid cyst (see Chapter 22) may be problematic, particularly for the occasional infundibular cyst with sebaceous glands. In contrast, dermoid cysts have multiple diminutive follicular sebaceous units radiating from the cyst wall and oriented perpendicular to it. Dermoid cysts and their associated adnexa are surrounded by a broad zone of interlacing collagen bundles that tend to parallel the cyst wall; this represents the dermal component of the cutaneous invagination from which a dermoid cyst is derived. The collagen around infundibular cysts has a normal dermal pattern, although it may be thickened due to chronic pressure or inflammation.

Isthmus cyst (tricholemmal cyst) (Figures 23.7 through 23.9)

The lining epithelium and keratinization pattern of this type of cyst closely resemble the outer root sheath of the middle segment of anagen follicles and the middle and lower portions of catagen phase follicles. These were thus previously described in *Veterinary Dermatopathology* as 'isthmus-catagen cyst' (Walder & Gross, 1992). This name has since been truncated in the current World Health Organization classification (Goldschmidt et al., 1998). Isthmus cysts are lined by epithelium with a sparse or absent granular cell layer. The keratinocytes have pale pink, slightly glassy cytoplasm. Tricholemmal keratiniza-



Fig. 23.8 'Flame follicle' isthmus cyst in a Siberian Husky. The cyst lining is convoluted and agranular, and the cyst cavity is filled with brightly eosinophilic, amorphous keratin (the cracks are processing artifact).



Fig. 23.9 Proliferating isthmus cyst in a dog. Short trabeculae and occasional small horn cysts project outward from the cyst wall. Note the sparse keratohyalin granules and amorphous keratin contents.

tion predominates, and the cyst contents are paler and more homogeneous than in infundibular cysts. Occasional hair fragments may be present.

A rare variant of isthmus cyst observed by the authors resembles a markedly enlarged, exaggerated catagen follicle similar to 'flame follicles' of alopecia X (see Chapter 19) and follicular dysplasia in Siberian Huskies (see Chapter 20). These cysts are relatively small and have epithelium with a wrinkled outline and prominent vitreous membrane. The keratin within the cyst is amorphous and brightly eosinophilic. The cyst contents have a spiked or brush-like perimeter formed by the fusion of the hair cuticle and tricholemmal keratin (flame follicle). These unusual flame follicle cysts have been observed only in Siberian Huskies and may be multiple. Any association between flame follicle cysts and alopecic disorders in this breed is as yet undetermined.

In an uncommon variant of isthmus cyst, the epithelium at the deep aspect of the cyst wall develops short trabecular projections into the surrounding dermis. These are designated 'proliferating isthmus cysts'. Small secondary cysts filled with subtly laminated keratin eventually form. Small numbers of keratohyalin granules are often present. As proliferation continues and cystic structures increase in number, the lesion begins to resemble infundibular keratinizing acanthoma (see p. 619). Weiss and Frese (1974) also proposed that 'follicular cyst with epithelial proliferation' was an early stage of 'intracutaneous cornifying epithelioma'.

Matrical cyst (Figure 23.10)

This type of cyst appears to be derived from the lower or inferior segment of the anagen hair follicle. Matrical cysts

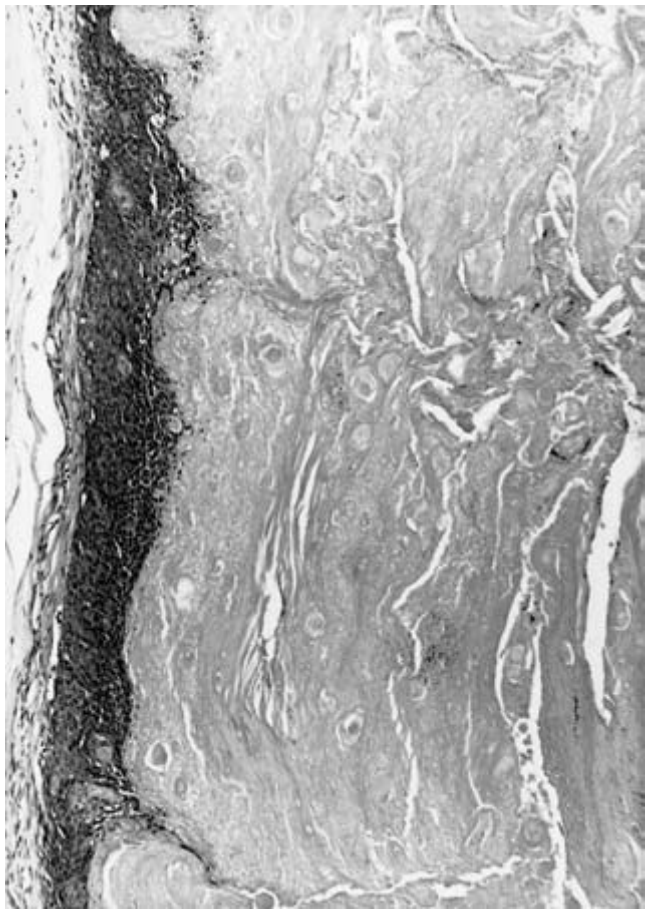


Fig. 23.10 Matrical cyst in a dog. The cyst wall is composed primarily of small, dark, basaloid epithelial cells. Keratinized 'ghost' cells fill the cyst cavity.

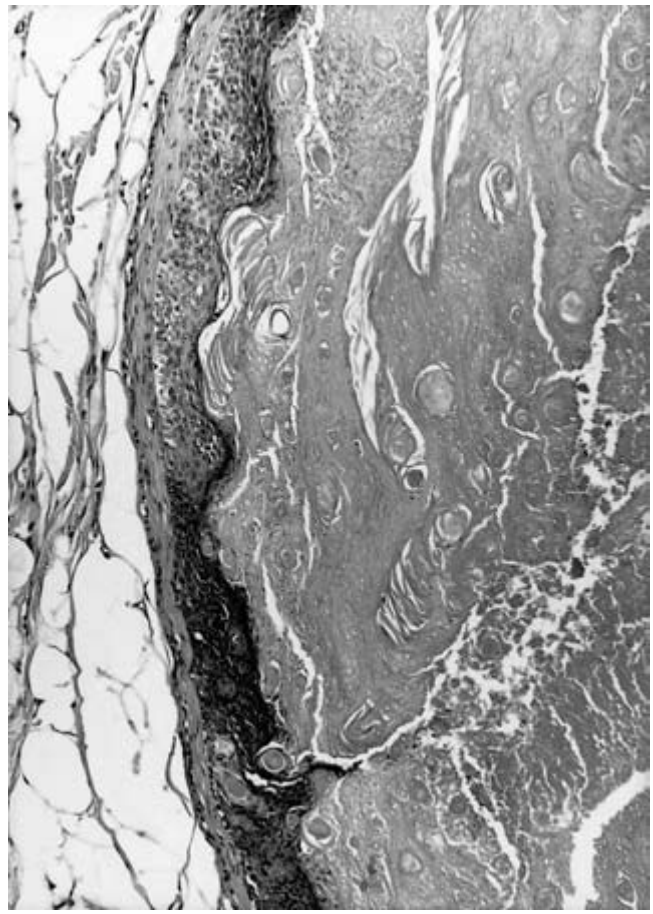


Fig. 23.11 Hybrid cyst in a dog, isthmus–matrical variant. The cyst wall is lined by a mixture of basaloid and agranular squamous epithelial zones. The cyst cavity contains amorphous keratin in addition to 'ghost' cells.

are lined by small basaloid epithelial cells with scant cytoplasm and hyperchromatic nuclei, resulting in a dark blue color to the cyst wall on low power examination. The epithelium keratinizes abruptly, forming 'ghost' or 'shadow' cells. Keratinized ghost cells are pale and refractile and have delicate eosinophilic outlines demarcating cell membranes and nuclear envelopes. Matrical cysts often contain small areas of inner root sheath differentiation characterized by glycogenated cells with trichohyalin granules. This association is not unexpected, as inner root sheath is normally produced by the hair matrix. Interestingly, cysts composed mostly of glycogen-rich, anagen-type, lower segment outer root sheath epithelium do not occur.

Some lesions resembling matrical cysts have a few smaller cystic structures adjacent to the primary cyst; these secondary cysts are lined predominantly by basaloid epithelial cells, but may also contain isthmus- or infundibular-type epithelium. Tumors of this type may be designated as 'proliferating matrical cysts' and may represent precursors to fully developed trichoepithelioma or pilomatricoma (see pp. 616, 624).

Hybrid cyst (Figure 23.11)

As further evidence of the follicular origin of most cutaneous cysts, two or all three levels of follicular epithelium may be represented in a single lesion. The following combinations have been described in humans: infundibular–tricholemmal (isthmic), infundibular–matrical, tricholemmal–matrical, infundibular–sebaceous duct (Requeña & Sánchez Yus, 1991), and matrical–lower outer root sheath (Satoh et al., 1989). The most common combination in dogs as well as humans is infundibular–isthmic. These are lined by infundibular epithelium with a prominent granular cell layer and isthmic outer root sheath epithelium with no granular layer in varying proportions. The infundibular epithelium is usually, but not always, in the superficial aspect of the cyst. The keratin content is a more reliable indicator of cyst origin than its epithelium, which may be severely degenerate or nonrepresentative due to examination of only a single level of sectioning. In addition to the expected laminated and amorphous keratin in cysts of presumed infundibular–isthmic type,

small aggregates of keratinized ghost cells may be found; this indicates that matrical epithelium must also be present somewhere in the cyst wall.

The current World Health Organization nomenclature uses the term 'panfollicular' or 'trichoepitheliomatous' to describe cysts with two or more follicular components (Goldschmidt et al., 1998); however, the authors feel that 'panfollicular' should refer only to lesions with tripartite features, i.e. infundibular, outer root sheath and matrical areas. Panfollicular cysts may also become proliferative and progress to trichoepithelioma (see p. 616). Proliferating panfollicular cysts show small numbers of small secondary cysts budding from the main cystic structure. The secondary cysts are also lined by variable admixtures of matrical, outer root sheath, and infundibular epithelium and contain their respective keratin types.

DILATED PORE

(Synonym: dilated pore of Winer)

Dilated pore is a distinctive proliferative variant of infundibular follicular cyst in the cat that is similar but not identical to dilated pore of Winer in humans (Scott & Flanders, 1984). The lesions in humans are narrower and have a more vertical orientation than those in cats (Murphy & Elder, 1991).

Clinical features

Dilated pore occurs uncommonly in cats. It presents as a solitary, firm mass, less than 1 cm in diameter, with a central dome-shaped protrusion of dense keratin. A frank cutaneous horn is present in some cases. Lesions are most often located on the head and neck. Dilated pore of Winer in humans also has a predilection for the head and neck. Dilated pore occurs primarily in older cats; there is no breed or sex predilection reported (Scott et al., 2001).

Histopathology (Figures 23.12 and 23.13)

Dilated pore is a cup-shaped or pyriform, dilated, follicular infundibulum lined by hyperplastic squamous epithelium. The cyst cavity is filled with compact, laminated keratin which projects above the skin surface through the central pore. The pore is a distended follicular ostium. The epithelium of the cyst wall of a dilated pore has a prominent granular cell layer consistent with infundibular origin. The majority of the cyst wall has marked irregular hyperplasia frequently with a scalloped configuration along its outer edge. The epithelium becomes thinner at the rim of the pore where it merges with adjacent epidermis.

Dilated pores are histologically unique but may be confused with follicular infundibular cysts. Patent follicular ostia are rarely present in routine follicular infundibular cysts.

WARTY DYSKERATOMA

Warty dyskeratoma is an uncommon benign tumor in humans that typically presents as a solitary papule or small nodule, often with an umbilicated center. Multiple lesions occur infrequently (Azuma & Matsukawa, 1993; Griffiths et al., 1997; Kaddu et al., 2002). These tumors have long

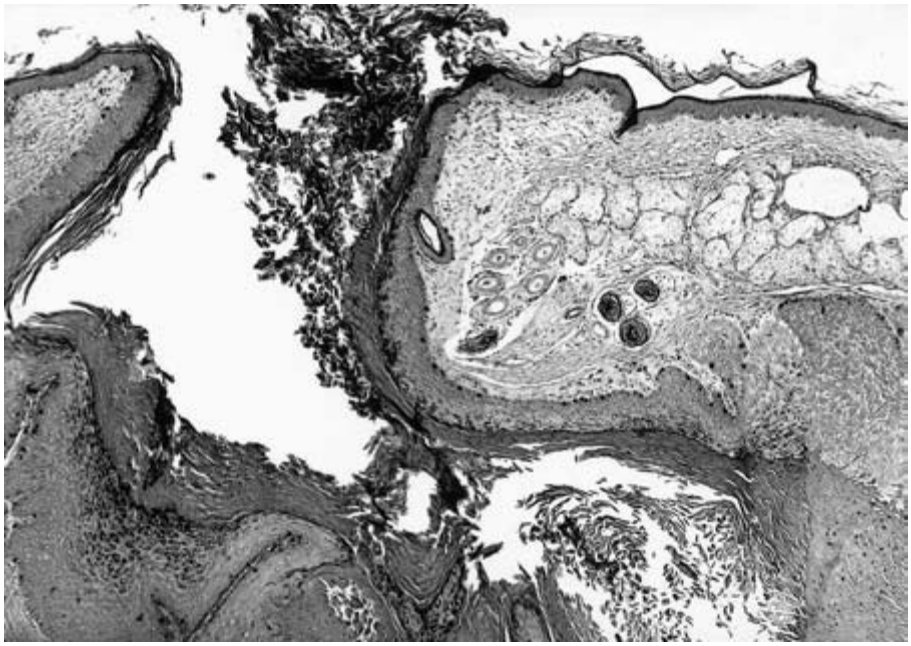


Fig. 23.12 Dilated pore in a cat. Cystically-dilated follicular infundibulum has a keratin-filled central pore that communicates with the skin surface. Note the irregular hyperplasia of the squamous epithelium lining the deeper aspects of the cyst.

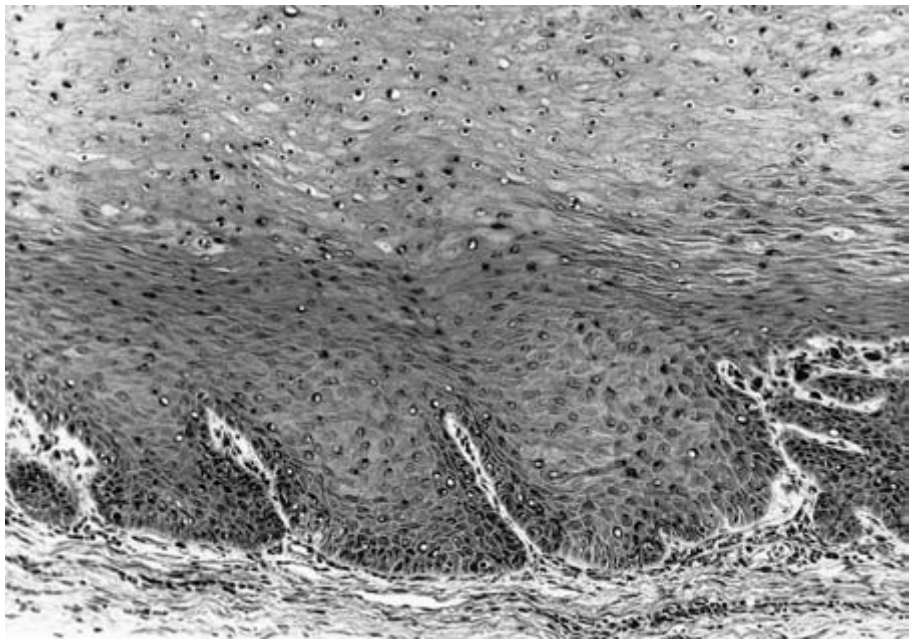


Fig. 23.13 Higher magnification of dilated pore of Fig. 23.12. The squamous epithelium at the base of the cyst is markedly thickened, and the peripheral margin has a scalloped configuration.

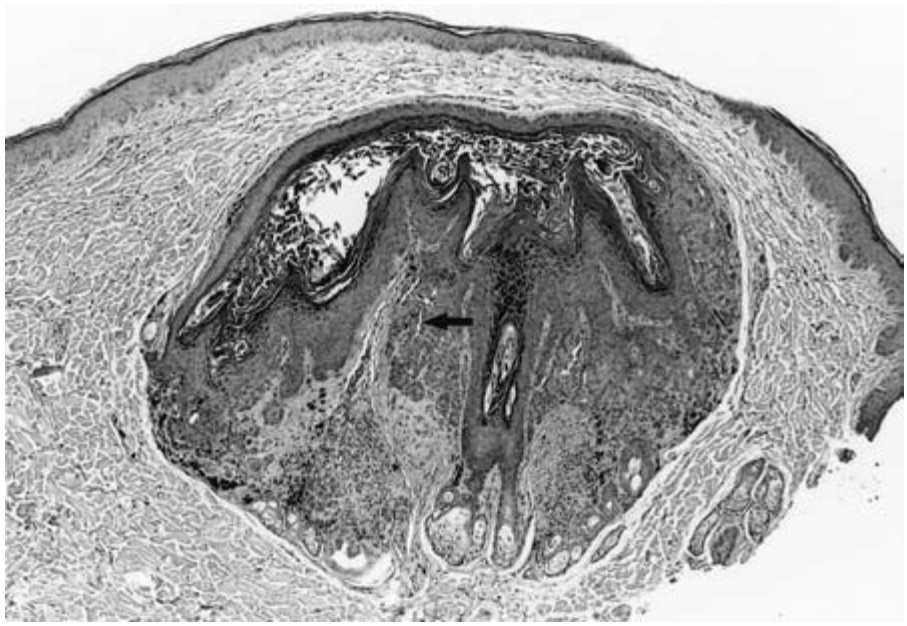


Fig. 23.14 Warty dyskeratoma in a dog. This small, multilocular cystic structure appears to incorporate several follicular infundibula. Note epithelial proliferation and early acantholytic cleft formation along the floor of the cyst (arrow).

been presumed to be of follicular origin based on the architecture of young lesions. Positive immunohistochemical staining of warty dyskeratomas with hair-specific keratins has been reported (Griffiths et al., 1997). The pathogenesis of similar tumors that occur infrequently in the oral cavity in humans is unclear (Harrist et al., 1980).

Clinical features

Warty dyskeratoma is a very rare, benign tumor of dogs that was originally described by Hill (1987). It appears to be identical to the human lesion of the same name. The two cases described in dogs were solitary. Larger lesions comprising clusters of nodules have occasionally been observed by one of the authors (E.J.W.); several of these involved the pinna. Too few cases have been identified to indicate age or breed predilections.

Histopathology (Figures 23.14 through 23.17)

Warty dyskeratoma is a dermal mass with a cup-shaped or cystic architecture. Cup-shaped lesions resemble dis-

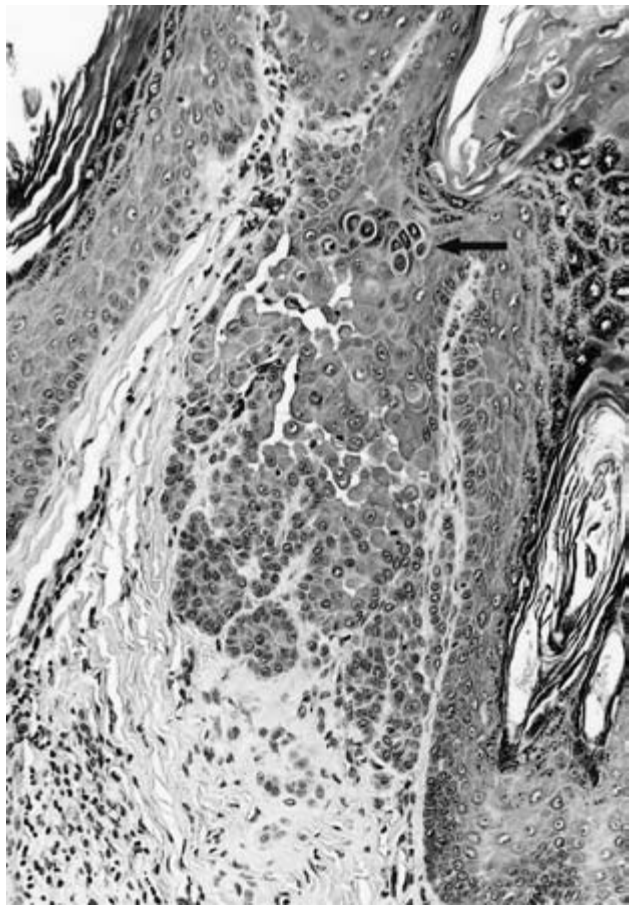


Fig. 23.15 Higher magnification of Fig. 23.14. There is an area of acantholysis with clefts involving hyperplastic stratum spinosum sometimes extending to the stratum basale. Note several shrunken, dyskeratotic cells in overlying stratum granulosum (arrow).

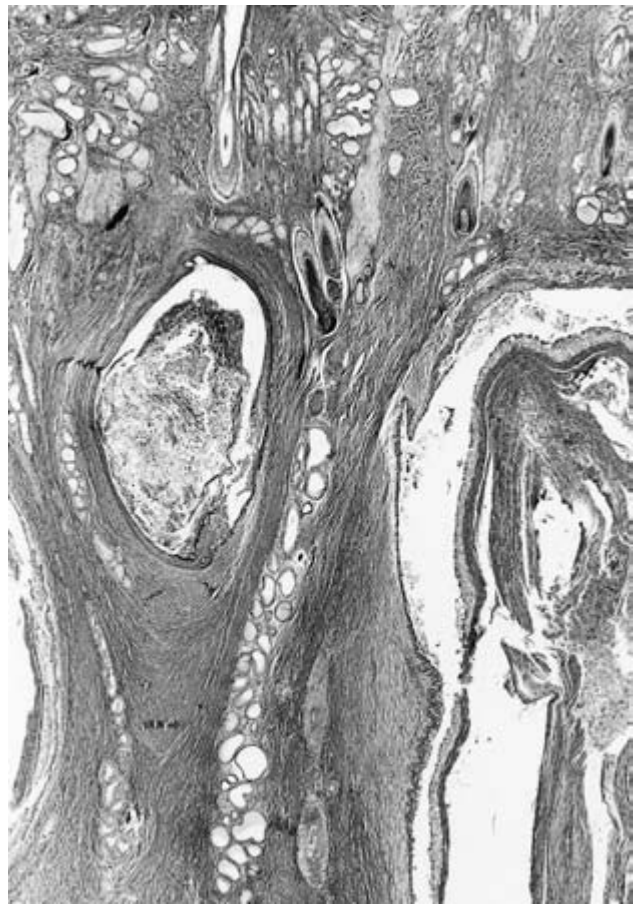


Fig. 23.16 Warty dyskeratoma in a dog. This example comprises large cysts in the deep dermis. Note zones of irregular hyperplasia and large cleft in the wall of the cyst at right.

tended follicular infundibula and open to the skin surface. The superficial portion of the cup or cyst is lined by mature squamous epithelium. The base of the structure has a markedly convoluted lining of stratified squamous epithelium supported by filiform projections of dermal collagen; these are often described as resembling intestinal villi. There is extensive acantholysis of this epithelium, sometimes leaving only the basal cell layer. Individual keratinocyte condensation, representing either apoptosis or dyskeratosis (premature cornification of individual cells), is also observed in the thicker portions of the cyst epithelium. The lumen of the cup or cyst is filled with orthokeratotic and parakeratotic debris, acantholytic keratinocytes, and sloughed apoptotic cells with markedly condensed cytoplasm and nuclei. The viable epithelial cells exhibit moderate nuclear enlargement, variable nucleoli, and low mitotic activity. Cytologic atypia is not present. Inflammation secondary to epithelial degeneration and release of keratin into the dermis may occur.

The architecture of warty dyskeratoma is quite distinctive and differential diagnoses are limited. Differentiation from an acantholytic variant of squamous cell carcinoma arising in a follicular cyst is a potential problem. Infiltration beyond the basement membrane does not occur in warty dyskeratoma, and extensive apoptosis is uncommon in squamous cell carcinoma.

TRICHOFOLLICULOMA

Trichofolliculoma is likely a hamartoma, as it resembles the entire follicular or folliculosebaceous unit and maintains fairly normal interrelationships between the various tissue types. The hamartomatous nature of the human analogue is strongly supported by the occurrence of follicular cycling through anagen, catagen, and telogen phases, as well as a stable population of Merkel cells in the different stages of tumor evolution (Schulz & Hartschuh, 1998; Hartschuh & Schulz, 1999). In human trichofolliculomas, tufts of fluffy hair frequently emerge through a central pore; this does not appear to be a

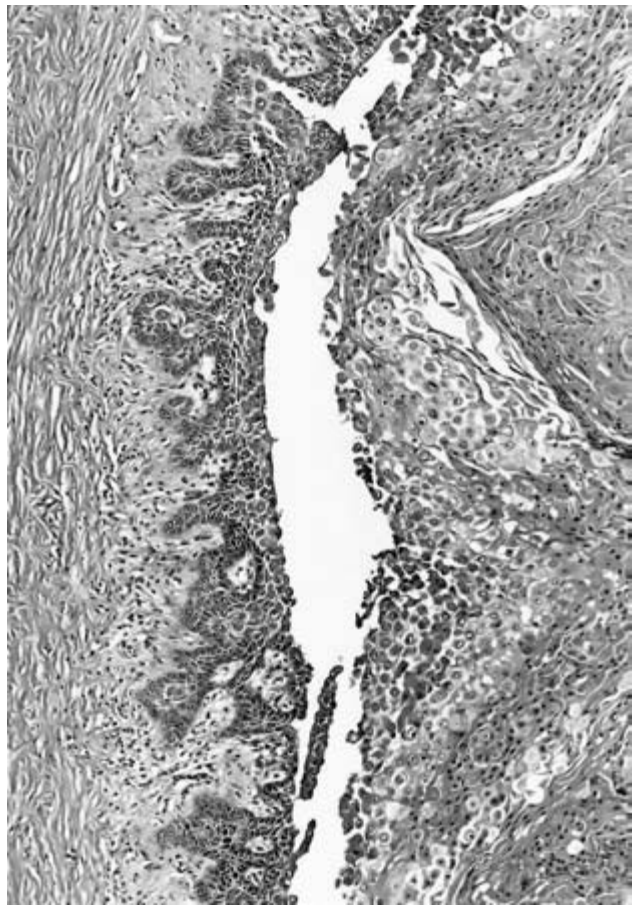


Fig. 23.17 Higher magnification of warty dyskeratoma of Fig. 23.16. The cyst wall shows hyperplasia and dyscohesion, and the cyst lumen is filled with acantholytic keratinocytes that are often condensed or dyskeratotic.

feature of the tumor in dogs or cats. The variant known as sebaceous trichofolliculoma in humans, which contains numerous sebaceous lobules, also occurs in dogs or cats.

Clinical features

Trichofolliculoma is uncommon in dogs and rare in cats. Trichofolliculoma usually presents as a solitary, dome-shaped nodule less than 2 cm in diameter. The overlying epidermis is intact, but there may be a central pore or depression. There is no known age, breed, or site predisposition.

Histopathology (Figures 23.18 and 23.19)

Trichofolliculoma is a well-circumscribed but unencapsulated dermal nodule composed of one or several primary follicles that are large, dilated, and keratinize through a granular cell layer. Hair shafts may also be present. The primary follicles may open onto the skin surface, creating the pores observed clinically. Variable numbers of secondary follicular structures radiate outward from the primary follicles in an arborizing pattern. Lesions may be small and superficial with few secondary follicles, or they may be large and have a complex architecture with numerous secondary follicles. The secondary follicles exhibit various stages of maturation from predominantly basaloid hair germ to fully-developed follicles containing delicate hair shafts. The follicular epithelium may be heavily melanized. The anagen-phase follicles have normal hair bulbs with well-developed mesenchymal papillae. There is a well-demarcated collagenous stroma

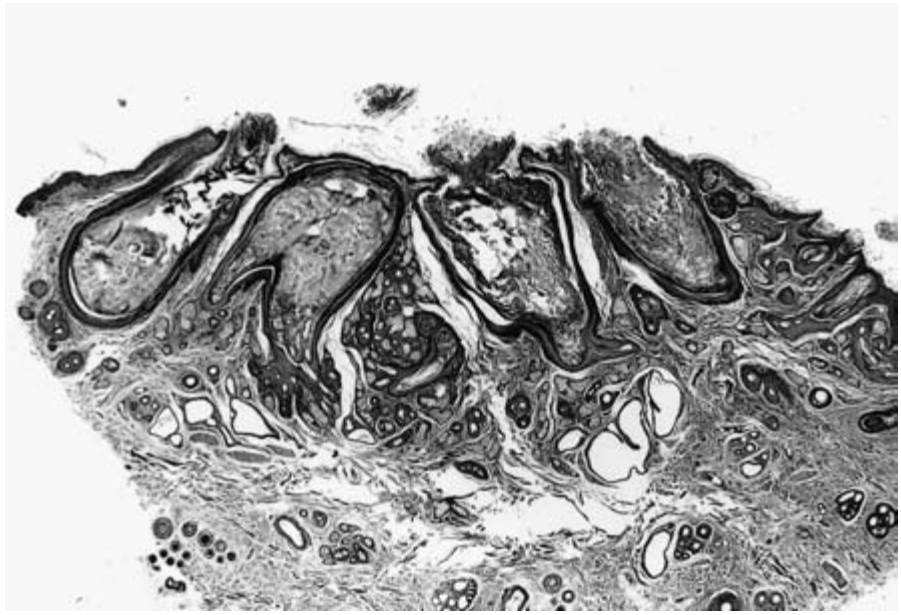


Fig. 23.18 Small, superficial sebaceous trichofolliculoma in a dog. A cluster of keratin-plugged follicles communicates with the skin surface via small pores. Multiple small sebaceous lobules and some small secondary follicles branch from the deep aspects of the dilated follicles.

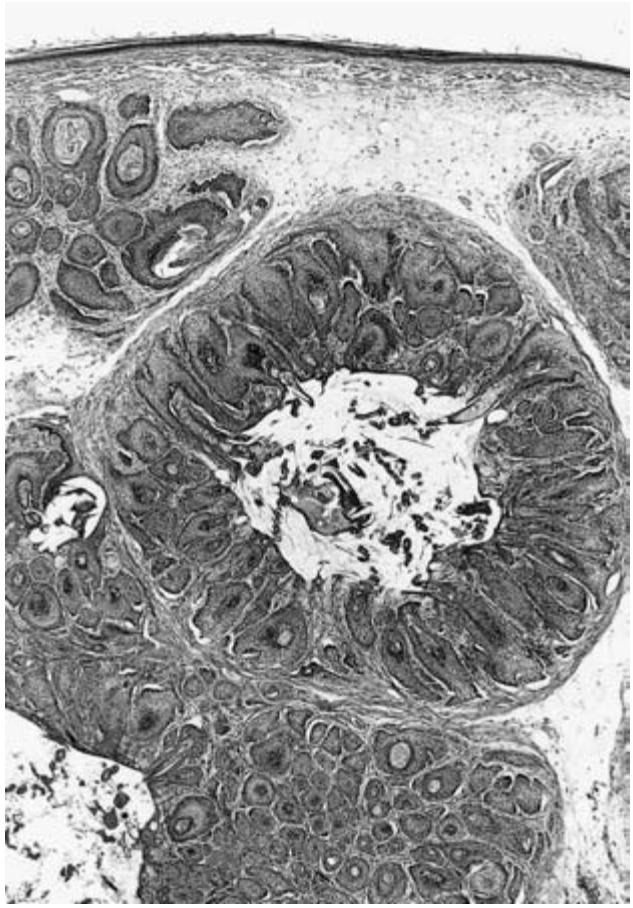


Fig. 23.19 Trichofolliculoma in a cat. Numerous well-differentiated secondary anagen follicles radiate from irregular cystic primary follicles filled with keratin and hair fragments.

of low cellularity separating the mass from adjacent dermis.

Small numbers of sebaceous glands also may be connected to the primary follicles. The glands may be rudimentary or fully developed, and probably parallel the degree of differentiation of the secondary follicles. A trichofolliculoma with dominant sebaceous glands is termed 'sebaceous trichofolliculoma'.

A trichofolliculoma with predominantly mature secondary follicles may resemble a dermoid cyst, particularly if hair shafts and sebaceous glands are present (see Chapter 22). The follicles which radiate from the central cyst of a trichofolliculoma are more numerous, larger, and often show tertiary branching. The central cyst of a trichofolliculoma may contain epithelium resembling isthmus and/or lower segments of a hair follicle, while the central cyst of a dermoid cyst is lined entirely by epidermal-type squamous epithelium. Distinction between trichofolliculoma and fibroadnexal hamartoma may be problematic if the trichofolliculoma is in late telogen stage and has a prominent sebaceous component. It has been proposed, in fact, that late-stage trichofolliculoma and folliculosebaceous cystic hamartoma in humans are one and the same (Schulz & Hartschuh, 1998). Considering the relative frequency of fibroadnexal hamartoma versus classic anagen trichofolliculoma in dogs, this does not seem likely. An arborizing pattern occurs occasionally in trichoepitheliomas, but trichofolliculomas have only one or several primary cysts, and the follicular structures show much more advanced trichogenesis than those of trichoepithelioma.

TRICHOEPITHELIOMA

Clinical features

Trichoepithelioma is a benign neoplasm that is fairly common in dogs and uncommon in cats. It differentiates toward all three segments of the hair follicle (see introduction, p. 604) and is analogous to the human neoplasm of the same name. Incidence estimates range from approximately 0.4% to 4.0% of canine skin tumors (Scott & Anderson, 1991; Goldschmidt & Shofer, 1992; Abramo et al., 1999) and 0.3% to 0.8% of feline skin tumors (Miller et al., 1991; Goldschmidt & Shofer, 1992; Abramo et al., 1999).

Trichoepitheliomas are round to ovoid dermal masses that are usually less than 2 cm in size. Larger masses up to 15 cm occur less frequently. They vary from superficial, dome-shaped nodules to deep dermal and subcutaneous masses. Trichoepitheliomas may be multiple either synchronously or metachronously. There is partial or complete alopecia, and ulceration is common in larger lesions. In dogs, these tumors occur most often on the dorsal trunk and legs, but may affect other parts of the body. Lesions in cats appear to have a predilection for the tail.

There is a breed predisposition for Basset Hounds, Bull Mastiffs, English Springer Spaniels, Golden Retrievers, Gordon Setters, Irish Setters, and Standard Poodles (Goldschmidt & Shofer, 1992). Multiple trichoepitheliomas occur most often in Basset Hounds. Most affected animals are 5 years of age or older.

Histopathology (Figures 23.20 through 23.22)

Trichoepithelioma is usually a well-circumscribed but unencapsulated dermal nodule comprising a random admixture of budding epithelial islands and cystic structures of variable size. Cystic structures may predominate, and some lesions are characterized by a large main cyst and small numbers of progeny cysts around it. Neoplastic epithelium may be focally contiguous with the overlying epidermis or follicular infundibulum. The epithelial aggregates are encompassed in a moderate, well-

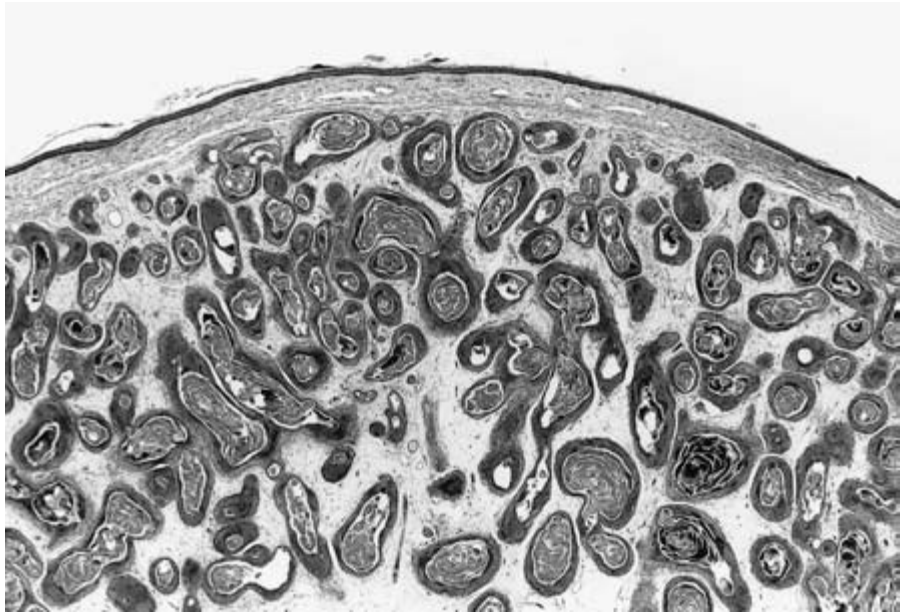


Fig. 23.20 Trichoepithelioma in a dog. This well-circumscribed dermal mass comprises numerous small cystic, tubular, and trabecular epithelial structures within a fibromyxoid stroma.

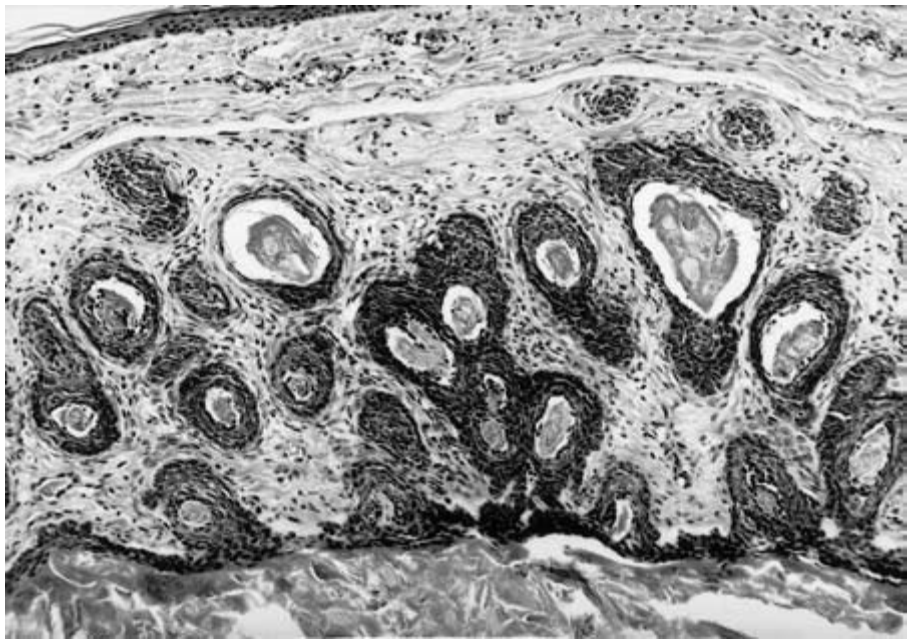


Fig. 23.21 Higher magnification of trichoepithelioma in a dog. Large cystic structure (bottom) and small secondary cysts are lined primarily by matrical epithelium. Cyst lumens contain amorphous keratin and keratinized ghost cells.

demarcated fibrous, fibromyxoid, or myxoid stroma of low cellularity. Mucinosis of the epithelial aggregates has been described in tumors with myxoid stroma (Scott & Anderson, 1991).

The epithelial islands are predominantly composed of basaloid epithelial cells that have prominent peripheral palisading and resemble the matrical cells of follicular bulbs. Advanced trichogenesis (recognizable hair shafts) is uncommon, and papillary mesenchymal bodies (mesenchymal bodies derived from the dermal papillae; also see trichoblastoma, p. 625) are few in number. The epithelial aggregates may be invested by thickened basement membrane zones or vitreous sheaths. The matrical cells have scant, pale cytoplasm and uniform, ovoid, euchromatic nuclei. Nucleoli are small, and mitotic activity is usually low. The cystic structures are partially lined by similar matrical cells and are filled with keratinized 'ghost' or 'shadow' cells. The matrical and shadow cells may be melanized. Mineralization of the keratinized material is rare. The matrical cells transition into zones of larger cells with glycogenated cytoplasm consistent with lower segment outer root sheath. Small foci of inner

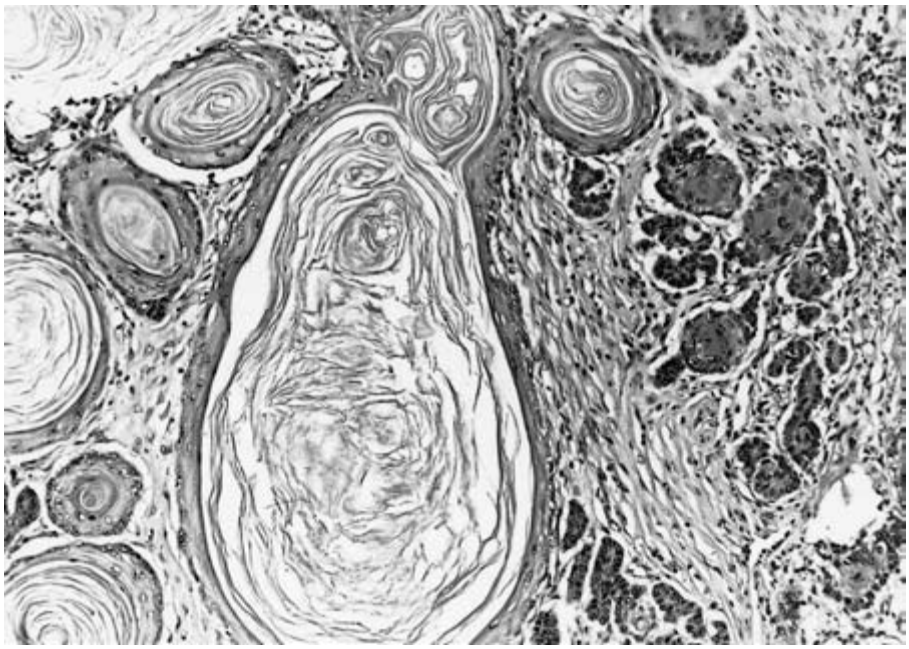


Fig. 23.22 Higher magnification of trichoepithelioma in a dog. Cystic structures of varying size are lined by squamous epithelium showing infundibular and isthmus patterns.

root sheath differentiation with trichohyalin granules may be found. Mitotic activity is not present in the nonbasaloid zones. Cords and trabeculae of small basaloid keratinocytes may radiate outward from cyst walls and may interconnect multiple cysts.

Variable numbers of cysts are partially or fully lined by squamous epithelium with or without a granular cell layer, resembling infundibular and/or isthmus segments of the hair follicle. These are accompanied by their expected patterns of keratinization: infundibular or tricholemmal. The squamous epithelial cells have moderate eosinophilic cytoplasm with round, vesicular nuclei, and small nucleoli. Mitotic activity is also absent in the squamous zones. Cystic structures with combined epithelial features resemble hybrid or panfollicular cysts (see p. 607). Trichoepithelioma with primarily infundibulo-isthmic differentiation is rare.

Secondary inflammatory changes are common in trichoepitheliomas, particularly large lesions of long duration, due to degeneration of cyst epithelium and release of keratin into the stroma. This incites a typical endogenous foreign body reaction with inflammation ranging from suppurative to granulomatous, depending on its duration. Dystrophic calcification of released keratinized material may occur occasionally. Ulceration is often present. Trichoepitheliomas with chronic inflammation frequently exhibit sclerosis, with short cords of small adnexal keratinocytes radiating from cyst walls into stromal collagen; this may mimic an infiltrative growth pattern associated with malignancy. Reactive squamous metaplasia and hyperplasia of epithelium in areas of chronic inflammation also may be misinterpreted as focal malignant transformation. Inflamed trichoepitheliomas often have higher mitotic rates than noninflamed tumors, although no atypical mitoses are present.

Predominantly basaloid trichoepithelioma without significant inflammation may need to be differentiated from pilomatricoma. The cystic structures of pilomatricoma are generally large and fewer in number than in trichoepithelioma. Keratinized ghost cells are present in clusters in trichoepithelioma and in broad sheets in pilomatricoma, often resulting in pressure atrophy of the matrical epithelium. Intracystic calcification and granulomatous inflammation are common in pilomatricoma and rare in trichoepithelioma. Also, the majority of predominantly basaloid trichoepitheliomas will contain occasional small cysts lined by isthmus or infundibular type epithelium, a feature that is absent in pilomatricoma.

Differential diagnoses for predominantly basaloid, inflamed trichoepithelioma include malignant trichoepithelioma and keratinizing basal cell carcinoma. Keratinizing basal cell carcinoma has a superficial, plaque-like configuration, and malignant trichoepithelioma is a poorly-circumscribed, asymmetric neoplasm; both often have multifocal epidermal contiguity and ulceration. Inflamed benign trichoepitheliomas have a more compact, spherical silhouette, and multifocal epidermal contiguity is uncommon. Both basal cell carcinoma and malignant trichoepithelioma have multifocal necrosis, moderate to high mitotic activity, and nuclear and mitotic atypia. Multifocal epithelial necrosis and atypical mitoses are not seen in inflamed benign trichoepithelioma, and areas of

increased proliferative activity and reactive squamous metaplasia are always associated with the inflammatory infiltrate. Discrete large cystic structures are not present in basal cell carcinoma, and the keratin microcysts are usually lined by squamous epithelium, as opposed to matrical epithelium in trichoepitheliomas. However, because it has recently been demonstrated that basal cell carcinomas have an identical cytokeratin profile to trichoepithelioma and trichoblastoma (see Chapter 22), keratinizing basal cell carcinoma may represent a distinct, low-grade variant of malignant trichoepithelioma (see p. 634).

The rare trichoepitheliomas with primarily infundibulo-isthmic differentiation may have an arborizing architecture reminiscent of trichofolliculoma, but trichoepitheliomas have more numerous cysts and less advanced trichogenesis. They are distinguished from deep infundibular keratinizing acanthomas by larger cysts of more variable size. Infundibular keratinizing acanthomas have a predominance of cells with pale, glassy cytoplasm and small keratohyalin granules, in contrast to trichoepitheliomas.

INFUNDIBULAR KERATINIZING ACANTHOMA

(Synonym: intracutaneous cornifying epithelioma)

Infundibular keratinizing acanthoma has had a historically varied nomenclature in the veterinary literature. Although the term 'intracutaneous cornifying epithelioma', proposed in the first World Health Organization classification system (Weiss & Frese, 1974), provides an accurate distillation of the histopathologic features, it gives no indication of the origin of the tumor. In addition, the authors believe that the designation 'epithelioma' should be reserved for neoplasms composed primarily of basaloid reserve cells, such as sebaceous epithelioma (see Chapter 24). The name 'keratoacanthoma' is also inappropriate, as the lesion is significantly different, both biologically and histologically, from keratoacanthoma in humans (see Chapter 26).

A follicular origin for the canine neoplasm was first proposed by Seiler (1981) based on careful observation of histologic features. Although there is no exact human analogue for canine infundibular keratinizing acanthoma (IKA), it bears some resemblance, especially in its early stages, to pilar sheath acanthoma. Human pilar sheath acanthoma is a tubular lesion with a central pore and a fairly simple wall of infundibular and isthmic epithelium (Murphy & Elder, 1991). The etiology of IKA is unknown; immunohistochemical staining for papillomavirus has been consistently negative (Sironi et al., 1990; Schwegler et al., 1997).

Clinical features

Infundibular keratinizing acanthoma is an uncommon, benign follicular neoplasm of dogs. Infundibular keratinizing acanthomas accounted for 1.4% to 2.3% of all canine skin tumors in several surveys (Stannard & Pulley, 1975; Goldschmidt & Shofer, 1992; Abramo et al., 1999).

Infundibular keratinizing acanthomas present as solitary or multiple, partially alopecic nodules ranging from 0.5 to 4.0 cm in diameter. The nodules usually have a central pore or larger opening which is 1 mm to several centimeters in diameter. Larger openings may contain conical or club-shaped, protruding masses of keratin that form cutaneous horns. Some tumors are more deeply located within the dermis and do not open onto the skin surface. Infundibular keratinizing acanthomas are located primarily on the dorsal neck and trunk, although any part of the body can be affected.

The median age of affected animals in the report of Stannard and Pulley (1975) was less than 5 years, while the mean age in the larger survey of Goldschmidt and Shofer (1992) was approximately 7 years. Norwegian Elkhounds, Lhasa Apsos, Pekingese, Yorkshire Terriers, and German Shepherd Dogs have a marked predisposition to develop IKAs (Goldschmidt & Shofer, 1992). Lesions are often multiple in Norwegian Elkhounds and Lhasa Apsos (Goldschmidt & Shofer, 1992) and may also be multiple in German Shepherd Dogs and Old English Sheepdogs (Scott et al., 2001). Spontaneous regression does not occur, in contrast to human keratoacanthoma.

Histopathology (Figures 23.23 through 23.26)

Infundibular keratinizing acanthoma is a well-circumscribed dermal nodule which is oriented around a central cyst filled with laminated keratin. The upper portion of the cyst wall is usually open, forming a C-shaped or cup-shaped structure that connects with the epidermis, creating the central opening observed clinically. Serial sectioning may be required to demonstrate smaller pores histologically. The earliest lesions show broad trabecular projections of epithelium extending downward from a cyst wall that closely resembles follicular infundibulum. Later lesions develop small keratinous cysts within the trabeculae; the cysts become interconnected by delicate cords of epithelial cells. Mature infundibular keratinizing acanthomas have a complex epithelial wall comprising multiple small horn cysts interconnected by a reticular network of cords and trabeculae of small adnexal keratinocytes.

The central cyst and secondary cysts are lined by pale pink, characteristically glassy squamous epithelium that keratinizes through a sparse granular cell layer. The keratin varies from laminated to amorphous. This mor-

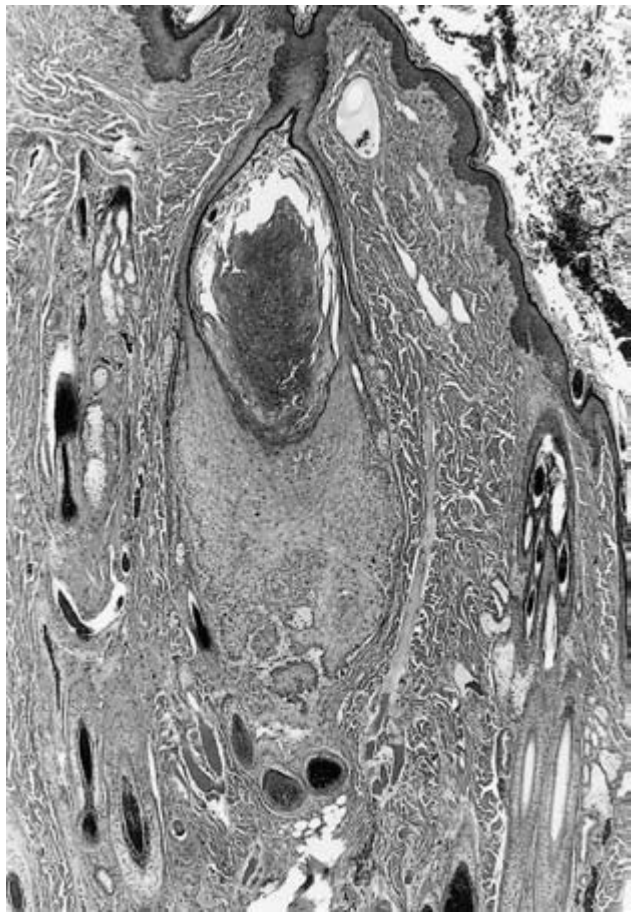


Fig. 23.23 Infundibular keratinizing acanthoma in a dog: very early lesion. Broad trabeculae of pale keratinocytes proliferate downward from the junction of the infundibulum and isthmus.

phology is identical to the lower portion of the normal follicular infundibulum where it joins the isthmus. Nuclei are vesicular and uniform, with inconspicuous nucleoli and minimal mitotic activity. The cords between the secondary cysts generally comprise a double row of uniform basaloid cells. Broader trabeculae contain peripheral basaloid and central squamous cells.

A sparse to moderate stroma is present that contains abundant mucin and few mesenchymal cells, creating a distinctive pale blue background for the epithelial structures. Adjacent dermal collagen is slightly compressed, forming a pseudocapsule. Occasionally, metaplastic cartilage or bone may be found in the stroma. In rare cases, extensive cartilaginous metaplasia results in pressure atrophy of the secondary epithelial structures. Pyogranulomatous or chronic suppurative inflammation secondary to breakdown of cyst epithelium is relatively common.

A small percentage of IKAs show no connection to the epidermis, even when serially sectioned, and are located in the deeper dermis. Architecture and morphology of these lesions are virtually identical to the typical superficial tumors, but the central cyst more closely resembles an isthmus follicular cyst. Proliferating isthmus follicular cyst (see p. 607) probably represents an early form of this deeper type of IKA.

Infundibular keratinizing acanthoma has some similarities to inverted viral papilloma, which is also a cup-shaped, keratin-filled, squamous epithelial mass. Infundibular keratinizing acanthoma has small cysts and anastomosing trabeculae of keratinocytes comprising its epithelial wall, in comparison to the papillary structures of an endophytic wart. Viral-induced inclusion bodies and



Fig. 23.24 Infundibular keratinizing acanthoma in a dog: early lesion. Small horn cysts and short cords and trabeculae of epithelial cells project outward from a central keratin-filled cyst. Note the patchy granular cell layer and well-demarcated tumor margin.

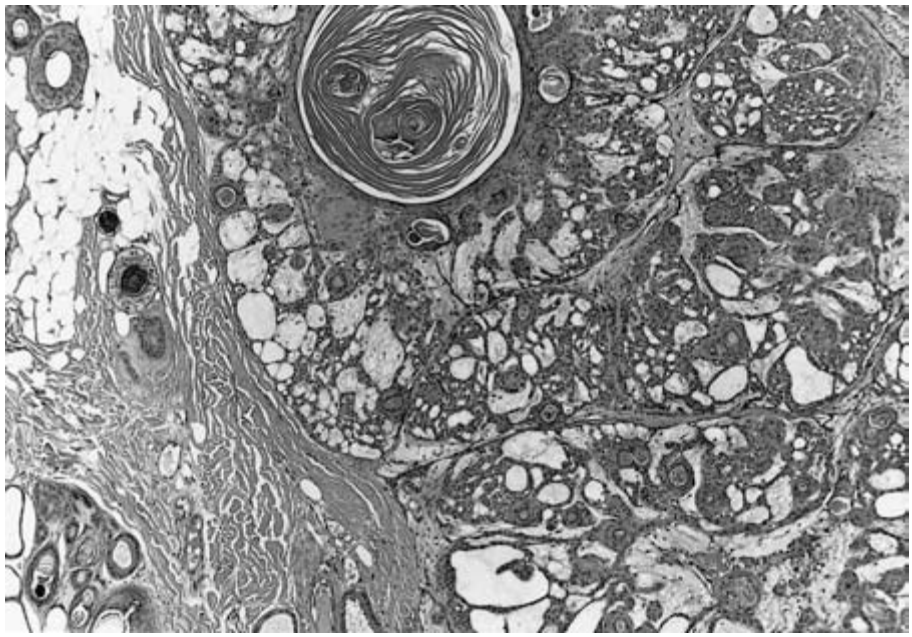


Fig. 23.25 Infundibular keratinizing acanthoma in a dog: mature lesion. Numerous small horn cysts are interconnected by a reticular network of cords of epithelial cells. Note pale, mucinous stroma.

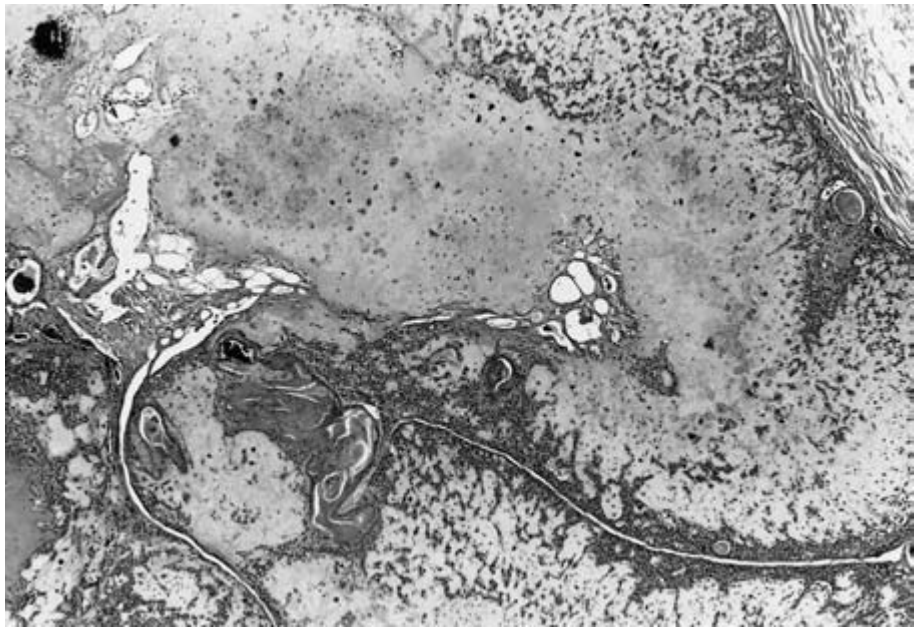


Fig. 23.26 Infundibular keratinizing acanthoma in a dog. This example has marked chondroid metaplasia and expansion of the stroma, resulting in atrophy of the epithelial component.

viral cytoplasmic alterations are not present in infundibular keratinizing acanthoma, and keratohyalin granules are small and sparse.

Infundibular keratinizing acanthomas in which a central pore is not obvious may need to be differentiated from trichoepitheliomas with predominantly squamous epithelium, and from isthmus tricholemmomas. The pale, glassy epithelial cytoplasm, the reticular network of epithelial cords and trabeculae, and the pale blue, mucinous stroma of IKAs are prominent differential features. Trichoepitheliomas have cysts of varied size and show a wider range of follicular epithelial morphology. Isthmus tricholemmomas have few cysts, and the epithelial cells are brighter pink and agranular.

TRICHOLEMMOMA

Clinical features

Tricholemmomas are, by definition, benign neoplasms of the outer root sheath of the hair follicle. Two types have been observed in dogs and one in cats; neither type has

an exact human analogue. The first type recapitulates the inferior segment of the tricholemma, or outer root sheath of the hair bulb and is designated as the 'inferior' or 'bulb type' tricholemmoma. These are rare neoplasms in dogs; the incidence is probably between 0.05% and 0.2% (Abramo et al., 1999). A small number of cases have been described in the literature (Diters & Goldschmidt, 1983; Walsh & Corapi, 1986; Scott & Anderson, 1991). These lesions present as firm, circumscribed nodules, ranging from 1 to 7 cm in diameter, that are most often located on the head and neck. The overlying epidermis is intact and slightly thickened. The average age of affected animals is 10 years, and there does not appear to be any breed predisposition.

A second type of tricholemmoma resembles the outer root sheath of the isthmus segment of the follicle, particularly as it appears during catagen phase. This type of tricholemmoma was originally described in *Veterinary Dermatopathology* as 'isthmus-catagen tricholemmoma' (Walder & Gross, 1992); the name was subsequently altered to 'isthmic tricholemmoma' (Goldschmidt et al., 1998). These tumors are uncommon in dogs and rare in cats. Lesions are dome-shaped alopecic nodules usually less than 2 cm in diameter. Larger lesions may be ulcerated. There is no known age, breed or site predilection.

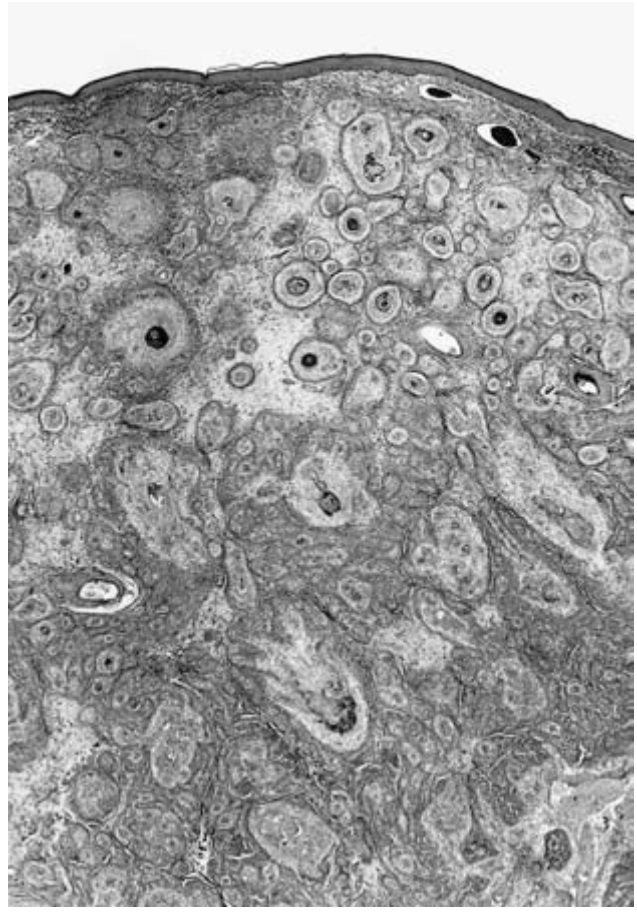


Fig. 23.27 Bulb tricholemmoma in a dog. Islands and nests of very pale epithelial cells form a large dermal mass with a pale fibrous stroma.

Histopathology

Bulb type (inferior) tricholemmoma (Figure 23.27 and 23.28)

Tricholemmomas of this type are well-circumscribed, unencapsulated dermal nodules comprising lobular groupings of small polyhedral cells. Within each lobule epithelial cells are arranged in islands, nests, and delicate trabeculae. There is no contiguity with the overlying epidermis. The epithelial aggregates are cuffed by thick, glassy, basement membrane zones reminiscent of the vitreous sheath of normal hair follicles. There is a sparse to moderate stroma of pale collagen with minimal cellularity. Mucinous stroma may also be present.

The majority of cells have clear cytoplasm, and there is prominent peripheral palisading. The small clear cells are analogous to the glycogen-rich, periodic acid–Schiff (PAS) stain-positive, outer root sheath cells of the hair bulb. The cells in the centers of the islands may have more abundant, eosinophilic cytoplasm, and there may be small foci of keratinization without keratohyalin or trichohyalin granules. Nuclei are small, ovoid, and euchromatic; nucleoli are inconspicuous, and mitotic activity is low.

Differential diagnoses for inferior tricholemmoma are limited, as cutaneous tumors composed predominantly of small clear cells are uncommon. The rare clear cell variant of basal cell carcinoma generally has larger cells and larger cell aggregates than tricholemmoma. Multifocal connection to the epidermis, cytologic features of malignancy, cellular stroma, and stromal–epithelial clefts are usually present in basal cell carcinomas. Granular cell trichoblastoma has more cords and nests than islands and trabeculae, although the granular cells may appear almost clear. The nuclei of tricholemmoma are not peripherally displaced as they are in granular cell trichoblastoma. Tumors that are otherwise typical for ribbon trichoblastoma occasionally have areas resembling bulb tricholemmoma with transition between hair germ and outer root sheath morphology.

Isthmic type tricholemmoma (Figures 23.29 through 23.31)

Isthmus-derived tricholemmomas are well-circumscribed, unencapsulated dermal nodules composed of epithelial

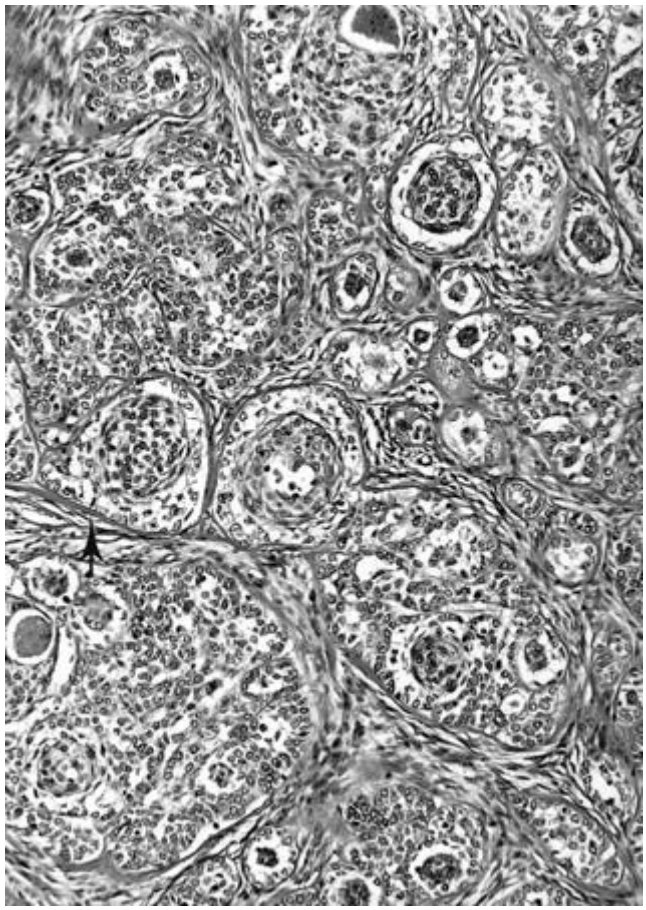


Fig. 23.28 Higher magnification of bulb tricholemmoma in a dog. The small epithelial cells show peripheral palisading and clear cytoplasm. Note prominent basement membranes resembling vitreous sheaths around some of the epithelial aggregates (arrow).

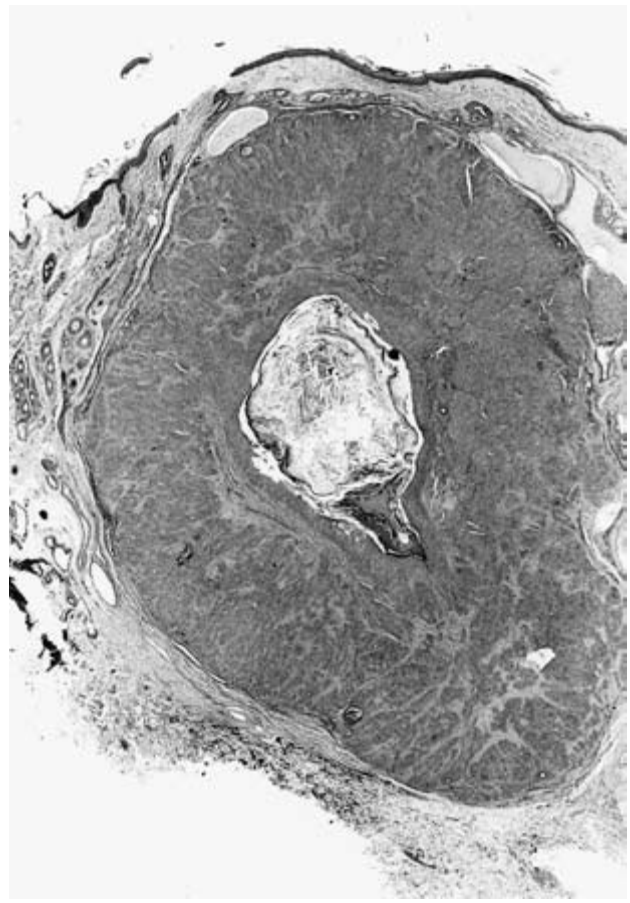


Fig. 23.29 Isthmus tricholemmoma in a dog. Islands and trabeculae of small, pale keratinocytes in a bland fibrous stroma form a well-circumscribed dermal mass. This example is oriented around a central cyst.

aggregates that vary markedly in size and shape. There is usually focal contiguity with the epidermis. Cords and trabeculae of epithelial cells radiate outward from large epithelial islands and often interconnect adjacent islands. The centers of the islands have small foci of tricholemmal-type keratinization (without formation of keratohyalin or trichohyalin granules). Large true keratin cysts are occasionally observed. Larger islands may have a pseudocystic appearance due to drop-out of all of the central keratin. There is a moderate collagenous stroma of low cellularity; small amounts of mucin may be present. The stroma is well-demarcated from adjacent dermis.

Neoplastic cells are fairly small, cuboidal to rounded, and have moderate, pink, often glassy cytoplasm. Nuclei are small, ovoid, and euchromatic with inconspicuous nucleoli and low mitotic activity. Peripheral palisading is not prominent. Scattered shrunken cells with condensed cytoplasm and small hyperchromatic nuclei may be present; these may represent either apoptosis or dyskeratosis (premature cornification of individual cells). Mild melanization of the epithelial cells may be present; occasional lesions are heavily melanized.

Differential diagnoses for isthmic tricholemmoma are limited, as few known tumors are composed almost entirely of small, pink epithelial cells. Infundibular keratinizing acanthoma has some similar features, but is distinguished from isthmic tricholemmoma by the presence of a well-defined central cyst, multiple secondary cysts and abundant stromal mucin. Its cells have paler, glassy cytoplasm than those of isthmic tricholemmoma. Trabecular trichoblastoma may have a similar overall architecture, but is differentiated from isthmic tricholemmoma by the presence of prominent peripheral palisading, some spindling of epithelial cells, and predominance of smaller, prismatic keratinocytes.

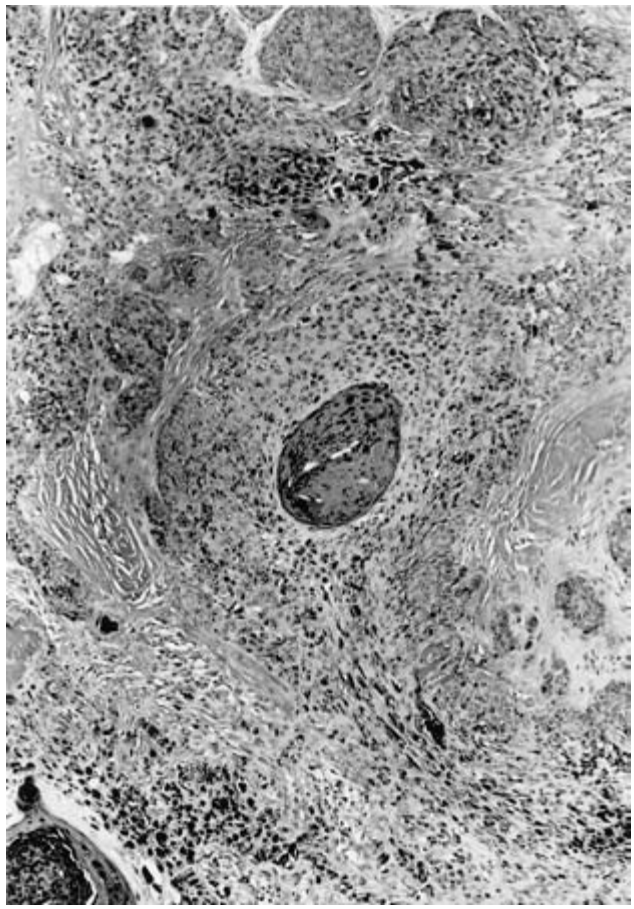


Fig. 23.30 Isthmic tricholemmoma in a dog. Multiple islands of pale keratinocytes contain central cysts filled with amorphous keratin and melanin pigment. Melanophages are present in the stroma.

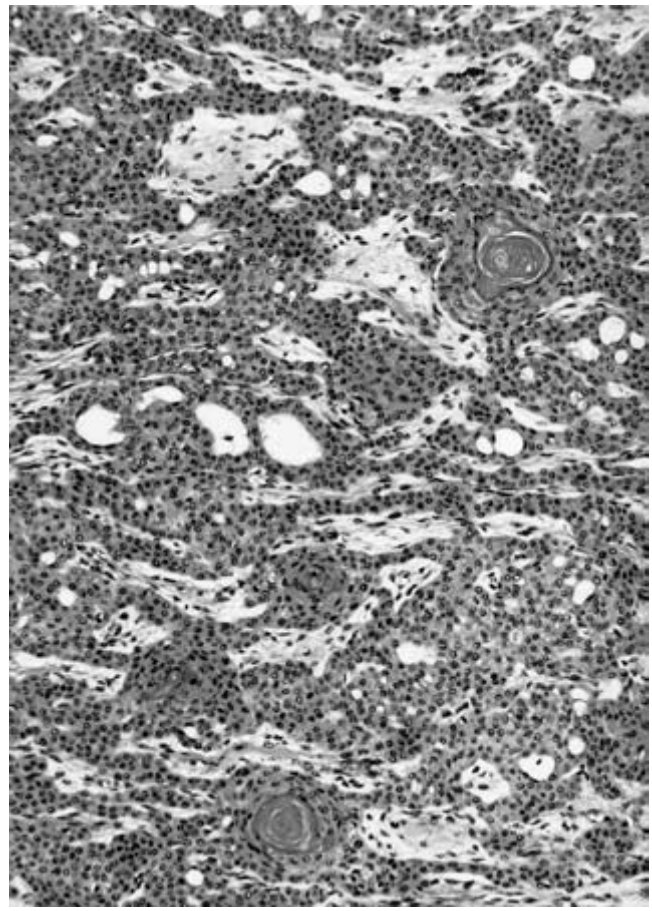


Fig. 23.31 Higher magnification of isthmus tricholemmoma in a dog. Islands and trabeculae are composed of small keratinocytes with glassy cytoplasm. Cystic structures are filled with amorphous, tricholemmal-type keratin. Note that a granular cell layer is absent.

PILOMATRICOMA

(Synonyms: pilomatrixoma, calcifying epithelioma)

Clinical features

Pilomatricoma is an uncommon, benign neoplasm of dogs that arises from the germinative cells of the follicular matrix, or hair bulb. It is the exact analogue of the human tumor of the same name. It represents approximately 1% of all canine skin and subcutaneous tumors (Goldschmidt & Shofer, 1992; Abramo et al., 1999). Pilomatricoma is very rare in cats; single cases are reported in several surveys (Carpenter et al., 1987; Abramo et al., 1999; Scott et al., 2001).

Lesions usually present as solitary, firm to hard, well-circumscribed masses. The tumors are dome-shaped to plaque-like and vary in size from 1 to 10 cm. Some lesions have a gritty or bony consistency and may be chalky when sectioned. The overlying epidermis is often atrophic and alopecic. Pilomatricomas occur most commonly on the proximal legs and dorsal trunk, particularly over the rump and shoulders.

The average age of affected animals is 6 years. Poodles, Kerry Blue Terriers, Old English Sheepdogs, Soft-coated Wheaten Terriers, Airedale Terriers, Bouviers des Flandres, Bichons Frises, Standard Schnauzers, and Basset Hounds were over-represented in a large survey, and tumors may be multiple in some of these breeds (Goldschmidt & Shofer, 1992). The majority of these breeds have in common a continuously-growing coat, which requires greater numbers of mitotically active anagen follicles. Increased hair matrix cell division may provide a larger cell pool for neoplastic transformation in breeds with these coat characteristics.

Histopathology (Figure 23.32)

Pilomatricoma is a well-circumscribed dermal and/or subcutaneous tumor composed of multiple cystic structures

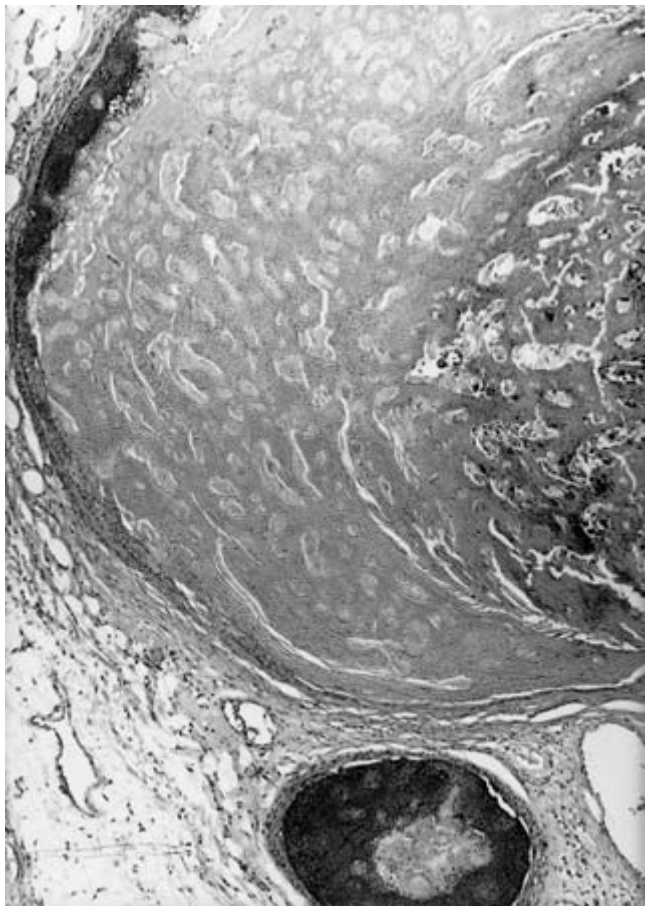


Fig. 23.32 Pilomatricoma in a dog. Large cystic structures are lined predominantly by dark, matrical keratinocytes and are filled with keratinized ghost cells. Note mineralization of cyst contents at right.

of varying size, lined predominantly by small, basaloid keratinocytes which resemble the matrix cells of the anagen hair bulb. The tumor is not contiguous with the overlying epidermis. There is a sparse stroma of collagen and mucin with moderate cellularity.

The basaloid epithelial cells have scant cytoplasm and hyperchromatic, large, ovoid nuclei. Nucleoli are small, and mitotic activity is fairly high. Nuclear or mitotic atypia is not present. The neoplastic cells undergo matrical-type keratinization characterized by abrupt transition to large masses of keratinized 'ghost' or 'shadow' cells that fill the cyst lumens. Small zones of squamous epithelium, with or without a granular cell layer, may also be present. Small foci of inner root sheath differentiation (glycogenated cells with trichohyalin granules) can usually be detected on the inner surface of the cyst lining. Melanization of neoplastic matrix cells and ghost cells may be present, and is sometimes quite prominent.

Ghost cells often become mineralized, and osseous metaplasia may occur, particularly in later stages. Some tumors of chronic duration have a predominance of ghost cells and bone, and little residual epithelium can be identified. Epithelial degeneration and release of keratinized and mineralized material frequently evoke a granulomatous inflammatory response characterized by macrophages, multinucleated giant cells, and formation of cholesterol clefts.

The multilocular architecture of pilomatricoma distinguishes it from simple matrical cyst, which is a unilocular lesion. Proliferating matrical cyst may represent an early form of pilomatricoma, and the division between these two entities may be arbitrary. Differentiation of pilomatricoma from variants of trichoepithelioma in which basaloid cells predominate may be difficult. The cystic structures of pilomatricoma are larger than trichoepithelioma, and zones of nonmatrical squamous epithelium are absent or very limited. Most trichoepitheliomas have at least occasional cysts that are lined primarily by squamous epithelium. Mineralization of cyst contents in trichoepithelioma is rare. The small, basaloid epithelial cells of malignant pilomatricoma, malignant trichoepithelioma, and keratinizing basal cell carcinoma are cytologically similar to those of pilomatricoma, but the carcinomas contain a much higher proportion of cellular areas in comparison to keratinized zones, in contrast to pilomatricoma. In addition, the epithelial aggregates of the carcinomas are more irregular in size and shape, and the borders are infiltrative. Epidermal contiguity, extensive caseation necrosis, nuclear atypia, and mitotic atypia are additional features of these tumors that would be inconsistent with a diagnosis of benign pilomatricoma.

TRICHOBLASTOMA

(Previously: basal cell tumor)

Trichoblastoma refers to a group of neoplasms that are derived from or recapitulate primitive hair germ (see introduction, p. 604). Complicated classification schemes for neoplasms of trichoblastic epithelium in humans were proposed by Headington (Headington & French, 1962; Headington, 1976), to include trichoblastoma, trichogenic trichoblastoma, trichogenic myxoma, and trichogenic fibroma. A broader range of patterns comprised a later scheme of trichoblastomas, to include small nodular, large nodular, cribriform, retiform, racemiform and adenoid cystic types (Ackerman et al. 1993). Recent immunohistochemical studies using highly specific monoclonal antibodies, particularly the three putative stem cell markers cytokeratins 15, 17, and 19, confirm that human trichoblastomas are of follicular stem cell origin (Schirren et al., 1997; Jih et al., 1999; Kanitakis et al., 1999; Yamamoto & Asahi, 1999).

The biologic behavior and histopathologic patterns of these human hair germ tumors conform very closely to

many of the cutaneous neoplasm in dogs and cats that were designated 'basal cell tumors' in older veterinary literature. Unfortunately, although initial immunohistochemical results suggest hair germ origin for canine or feline trichoblastomas, definitive confirmation is not yet possible because the new monoclonal markers for human or murine trichoblasts do not appear to cross-react with canine or feline tissue (Walder & Haines, 1998; Walder, 2000; Goldschmidt et al., 2002) Additional immunostain clones of keratins 15 and 19 are becoming available, and some of these may map to areas of those keratin molecules that are homologous to the same proteins in dog and cat. Despite these technical difficulties, the term 'trichoblastoma' has been given official recognition in the revised World Health Organization classification system (Goldschmidt et al., 1998). Although the majority of trichoblastomas in animals can be separated into several major histologic subtypes (see below), lesions with overlapping patterns are not infrequent, and hair germ tumors with new patterns are likely to be identified in the future.

Clinical features

Trichoblastomas are benign neoplasms that occur commonly in dogs and fairly commonly in cats. The incidence in dogs is probably very close to the total incidence of neoplasms in the old basal cell tumor category; this ranges from 3.7% to 12% in several surveys (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992). The incidence in cats is harder to estimate, as cats develop several different types of neoplasms that are composed predominantly of small basaloid epithelial cells. Tumors which have previously been incorporated in the feline 'basal cell tumor' group include benign and malignant apocrine ductular sweat gland neoplasms, basal cell carcinomas, and trichoblastomas. An incidence of trichoblastomas of 2.6% in dogs and 2% in cats was found in a recent retrospective study (Abramo et al., 1999).

In dogs, trichoblastomas present as solitary, firm, alopecic nodules that are dome-shaped or polypoid. Most tumors are 1 to 2 cm in diameter, but much larger lesions (exceeding 30 cm in rare instances) may occur. Larger masses may be ulcerated. There is a site predilection for the head and neck; the base of the ear is a typical location.

Most affected animals are 6 to 9 years of age. Poodles, Cocker Spaniels, and mixed breed dogs were reported to have an increased frequency of 'basal cell tumor', i.e. trichoblastoma (Bevier & Goldschmidt, 1981); additional strong predispositions have also been found in Kerry Blue Terriers, Bichons Frises, Cockapoos, Shetland Sheepdogs, and Siberian Huskies (Goldschmidt & Shofer, 1992).

The authors recognize an additional rare variant of trichoblastoma in dogs, termed 'trichoblastoma with outer root sheath (ORS) differentiation'. This variant has prominent outer root sheath features but does not resemble either bulb or isthmus tricholemmoma (see p. 621). The entity described as basosquamous carcinoma by Goldschmidt & Shofer (1992) appears to be the same neoplasm. These lesions are usually circumscribed masses on the dorsal trunk that are 1 to 3 cm in diameter. Ulceration is not present. Heavily pigmented lesions may appear gray or blue through overlying skin. Age and breed predilections are as yet undetermined.

In cats, trichoblastomas are usually solitary, dome-shaped, firm nodules less than 2 cm in diameter; larger lesions occur occasionally. Polypoid or pedunculated lesions are uncommon. Alopecia and secondary ulceration are frequent. The lesions are often pigmented and may be confused clinically with melanocytic neoplasms. Tumors occur most often on the head and cranial half of the trunk. There is no known age or breed predilection.

Histopathology

Ribbon type trichoblastoma (Figures 23.33 through 23.38)

The classical canine 'basal cell tumors' have been designated as 'ribbon', 'garland' or 'medusa-head' variants. These tumor subtypes also are mentioned in several surveys of feline skin tumors (Macy & Reynolds, 1981; Carpenter et al., 1987), but in the authors' experience they are rare in cats. Most canine tumors contain a mixture of these patterns with a predominance of ribbon architecture. They are virtually identical to the trichogenic trichoblastoma variant in the original nomenclature of Headington (1976) as well as some variants of trichoblastic fibroma (Requeña et al., 1990).

Ribbon trichoblastomas are well-demarcated dermal nodules that do not have contiguity with the epidermis. Larger tumors may extend into the subcutis. They are composed predominantly of small, basaloid keratinocytes arranged in branching, winding, and radiating columns, generally two cells in width. Islands of cells with radiating columns at their periphery create the 'medusa-head' appearance. The islands sometimes contain microcysts containing amorphous keratin. Occasional small but well-organized hair follicles, rarely containing delicate hair shafts, are detected; these are generally located at the periphery of the neoplasm, but do not appear to represent residual follicles that have been entrapped by the mass.

The epithelial structures are embedded in a paucicellular fibrous stroma that is often hyalinized. In dogs, the stroma is moderate to abundant; in cats, it is sparse. The stroma of most tumors contains small amounts of mucin concentrated around the epithelial columns. Moderate to

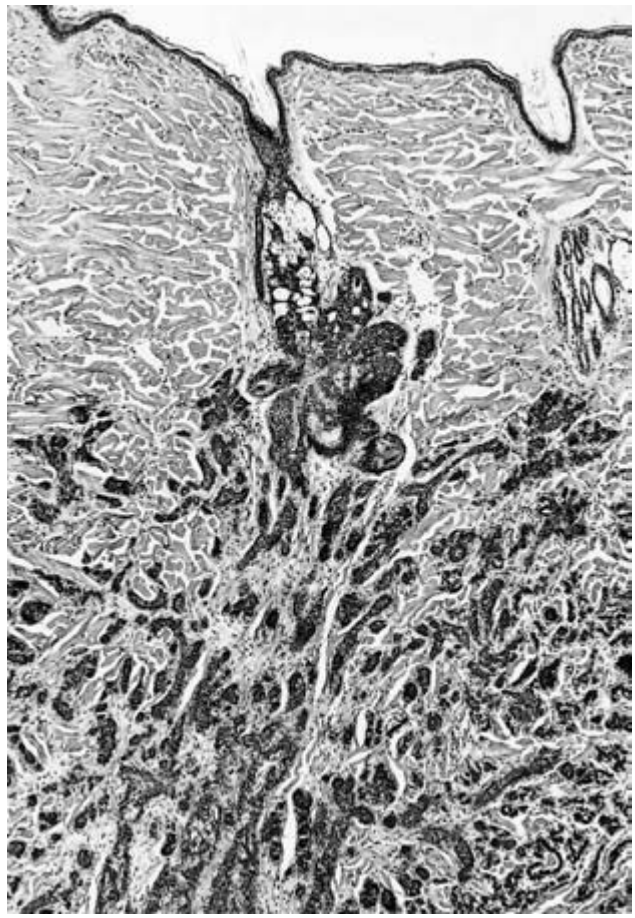


Fig. 23.33 Early ribbon trichoblastoma in a dog. Delicate branching cords and trabeculae of small, basaloid keratinocytes are contiguous with the base of a hair follicle.

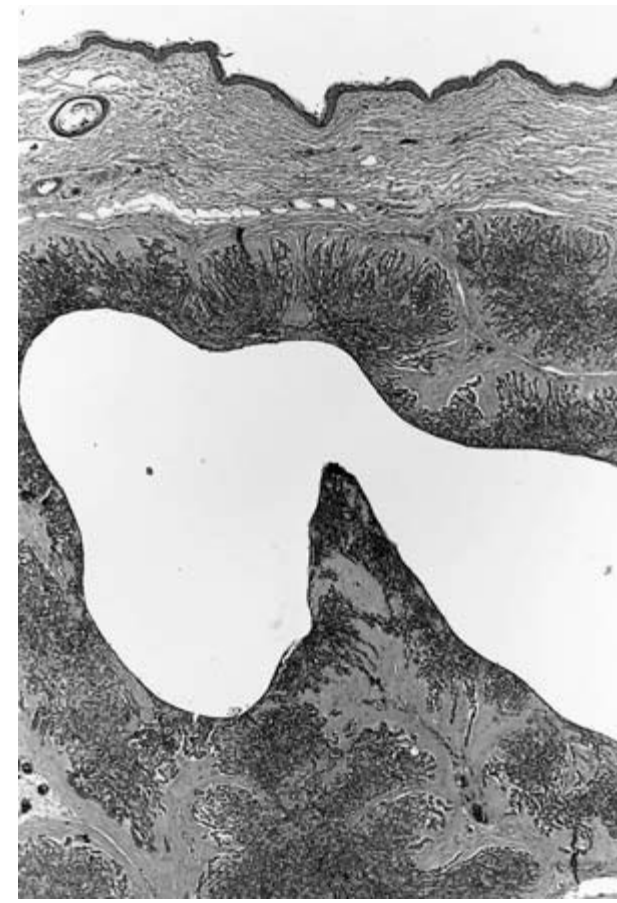


Fig. 23.34 Ribbon trichoblastoma in a dog. This example shows a cavernous cyst and abundant, hyalinized stroma.

abundant mucin may be distributed diffusely through the stroma in canine ribbon trichoblastomas. Scattered tight clusters of small mesenchymal cells are present in the stroma in close association with epithelial aggregates; these represent diminutive follicular papillae (follicular papillary mesenchymal bodies).

The neoplastic trichoblasts have scant, pale eosinophilic cytoplasm with uniform, ovoid, euchromatic nuclei and small nucleoli. Nuclei are oriented perpendicular to the long axis of the columns. Feline ribbon trichoblastomas typically have palisades of spindled cells with elongated nuclei, creating a caterpillar-like appearance in the cell columns. Mitotic figures are usually infrequent, but may be found in moderate numbers in some lesions. Occasional tumors with larger nuclei, moderate mitotic activity, and scattered atypical mitoses occur; it is unknown at the present time if this indicates a potential for aggressive biologic behavior. The medusa-head islands of cells generally have cells with slightly more abundant cytoplasm centrally and one or two layers of basaloid cells peripherally. Melanization is uncommon. Small numbers of canine ribbon trichoblastomas have areas of slightly larger, glycogenated cells that often form nests and islands; these closely resemble bulb tricholemmomas and probably represent foci of maturation of the trichoblasts into outer root sheath epithelium. The follicular papillary mesenchymal bodies in all of the trichoblastoma subtypes are characterized by closely-packed cells with indiscernible cytoplasm. Their nuclei are hyperchromatic and ovoid, teardrop-shaped or slightly spindled. Nucleoli are inconspicuous, and mitotic activity is not present. The diagnosis of ribbon trichoblastoma is straightforward due to its unique architectural pattern.

Trichoblastoma with outer root sheath differentiation (Figures 23.39 and 23.40)

This rare variant of trichoblastoma has extensive ORS differentiation, but the more differentiated areas are distinct from both bulb and isthmus tricholemmomas (see p. 621). The lesions are well-circumscribed dermal masses, often involving the deep dermis and subcutis, with multi-



Fig. 23.35 Ribbon trichoblastoma in a dog. This unusual variant has arcuate cords of trichoblasts and trabeculae of larger keratinocytes enmeshed in a loose fibrous stroma resembling follicular fibrous sheaths.

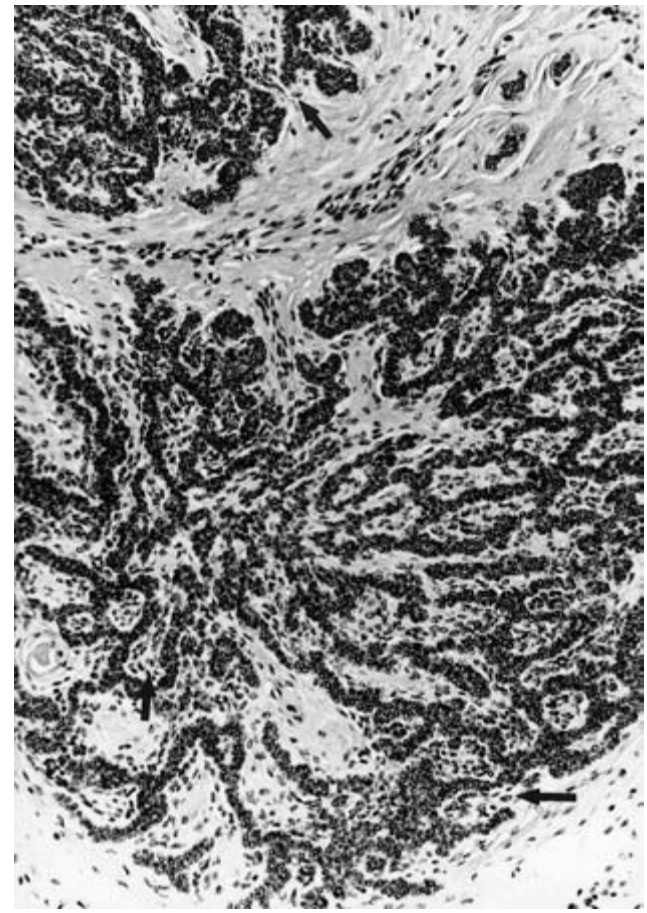


Fig. 23.36 Higher magnification of classic ribbon trichoblastoma in a dog. Double rows of trichoblasts are arranged in branching and winding patterns. Note the groups of small mesenchymal cells, resembling primitive dermal papillae (follicular papillary bodies) (arrows), within the fibromyxoid stroma.

lobular and trabecular architecture, and large areas of cystic degeneration. Epidermal contiguity or ulceration is not seen. The tumor margins are smooth and noninvasive. The epithelial aggregates contain small, polyhedral epithelial cells (trichoblasts) in anastomosing cords similar to classic ribbon trichoblastoma; these merge into small islands of cells with markedly glycogenated cytoplasm, resembling anagen suprabulbar ORS, or broad trabeculae of pale pink, isthmic-type keratinocytes that line the cystic zones. The glycogenated cells do not show peripheral palisading, and no trichohyalin granules are present. The isthmic-type areas have moderate apoptosis manifested by individual cells with discrete, condensed cytoplasm and nuclei; other cells in these areas appear truly dyskeratotic and are characterized by discrete, brightly eosinophilic cytoplasm and viable nuclei. The cystic zones appear to be a result of apoptosis, acantholysis, and keratinocyte drop-out. The stroma is similar to classic ribbon trichoblastoma. The trichoblasts are frequently melanized, but otherwise have similar cytologic features to those in common ribbon trichoblastoma. Nuclei in all of the epithelial cells are larger than those of typical trichoblastomas; they are ovoid, vesicular and have small nucleoli. Mitotic activity varies from moderately low to moderately high.

The primary differential diagnosis for trichoblastoma with ORS differentiation is canine apocrine ductular adenoma, which is also a fairly large, deep dermal adnexal neoplasm that may have brisk mitotic activity. The small epithelial cells of ductular adenoma form tubular structures lined by double rows of cells, whereas the small cells of trichoblastoma form anastomosing cords. The foci of squamous differentiation in ductular adenoma produce keratin deposits via a granular cell layer; neither keratohyalin granules nor keratin lakes are found in trichoblastoma with ORS differentiation. Neither bulb tricholemmoma nor isthmus tricholemmoma has a significant population of small, trichoblastic

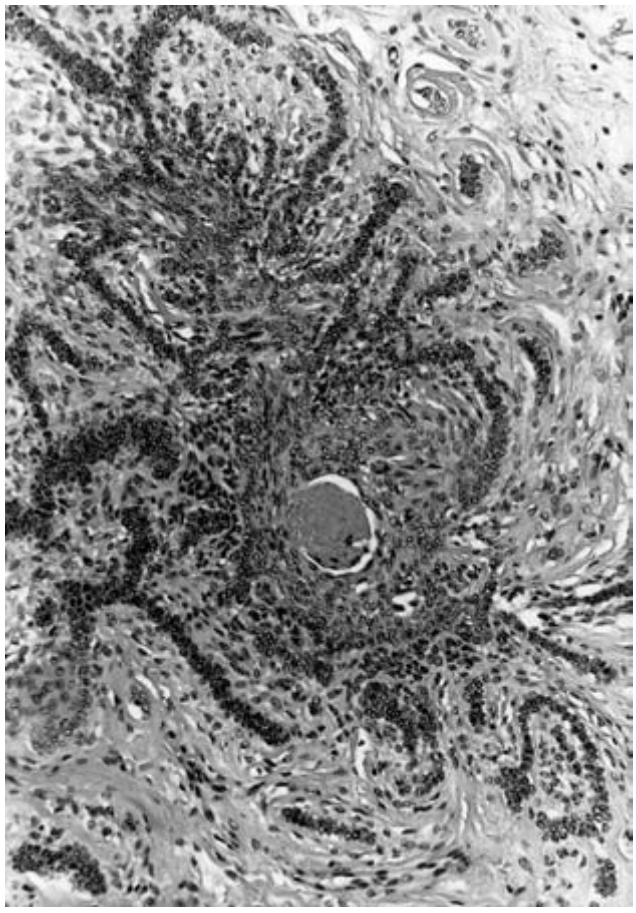


Fig. 23.37 Higher magnification of ribbon trichoblastoma in a dog. A medusoid island is composed of slightly larger keratinocytes. Note small central cyst exhibiting tricholemmal keratinization.

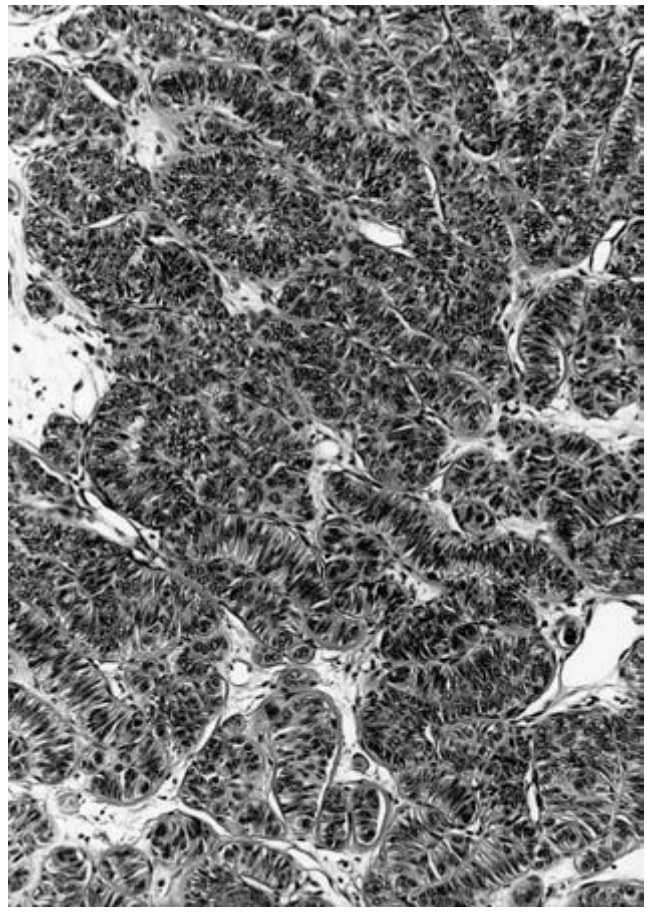


Fig. 23.38 High magnification of ribbon trichoblastoma in a cat. Winding cords of spindled cells with elongate nuclei create a palisaded appearance resembling caterpillars.

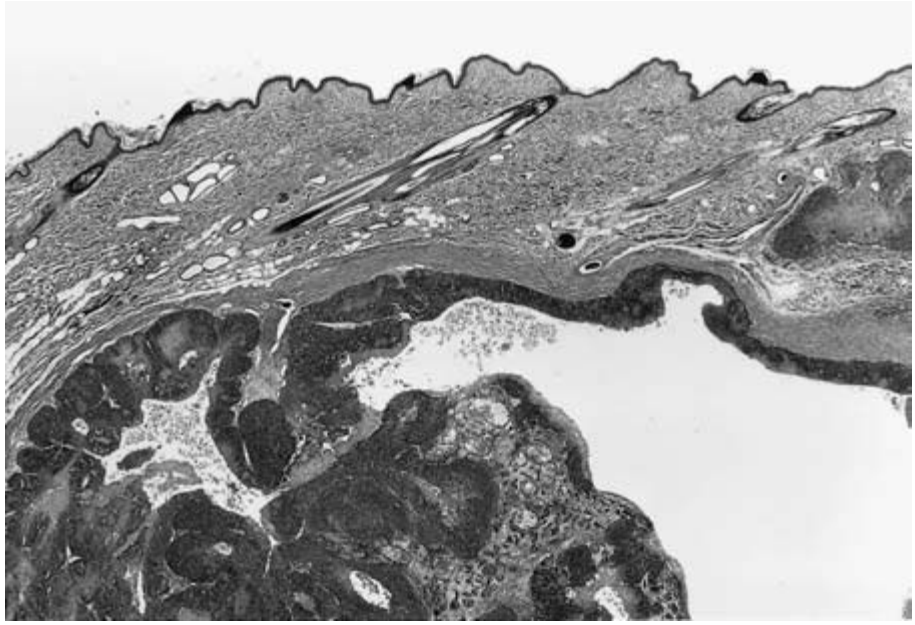


Fig. 23.39 Trichoblastoma with outer root sheath differentiation in a dog comprised of a circumscribed mass of small keratinocytes forming lobules and trabeculae. Note large areas of cystic degeneration.

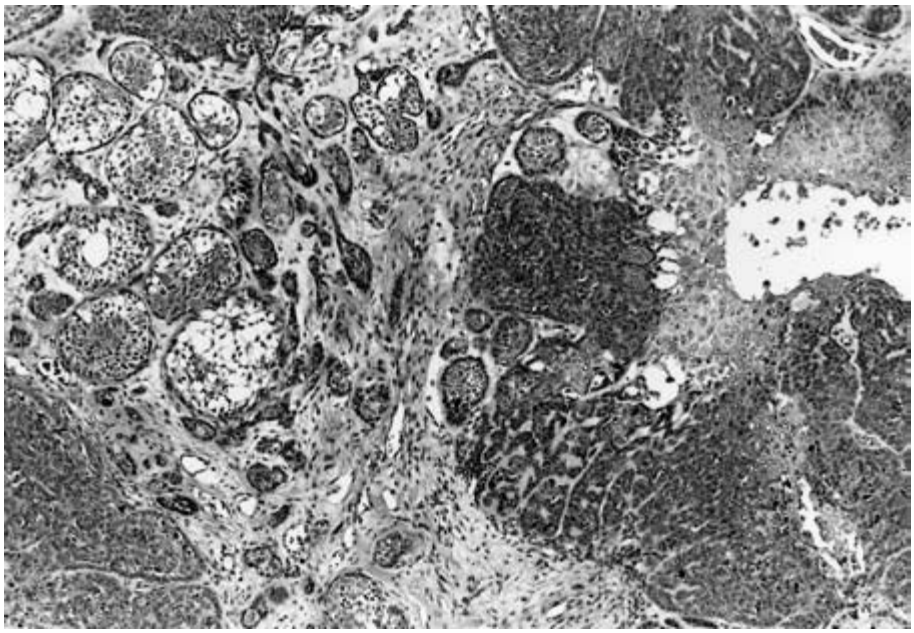


Fig. 23.40 Higher magnification of trichoblastoma of Fig. 23.39. The epithelial aggregates comprise typical trichoblasts in serpiginous cords that merge into small islands of cells with markedly glycogenated cytoplasm (left) or broad trabeculae of pale glassy, isthmic-type keratinocytes that line the cysts (right).

epithelial cells. The absence of multiple keratin-filled cysts distinguishes trichoblastoma with ORS differentiation from trichoepithelioma and pilomatricoma.

Trabecular type trichoblastoma (Figures 23.41 and 23.42)

The most common variant of trichoblastoma in cats appears analogous to the simple trichoblastoma of Headington (1976). This type of trichoblastoma also occurs occasionally in dogs. These are well-circumscribed dermal nodules comprising islands and broad trabeculae of small keratinocytes with prominent peripheral palisading. Connection to the overlying epidermis is focal or absent. Keratin microcysts may be present; advanced trichogenesis is not observed. There is a sparse stroma of pale collagen and mucin with low cellularity. Follicular papillary mesenchymal bodies (see ribbon type trichoblastoma, above) can be readily detected in the stroma of most lesions. The peripheral cell layer of the epithelial structures shows scant, pale cytoplasm with uniform, ovoid, euchromatic nuclei and low mitotic activity. The internal cells have slightly more abundant, pale eosinophilic cytoplasm, and nuclei are often more elongate. Spindling of keratinocytes is often a prominent feature in feline tumors. The epithelial cells of trabecular trichoblastoma may be mildly or moderately melanized; the pigmentation usually has a patchy distribution.

Trabecular trichoblastoma is differentiated from isthmic tricholemmoma by the presence of prominent peripheral palisading, absence of foci of tricholemmal keratinization, and a paucity of plump, glassy, pink, isthmus-type keratinocytes.

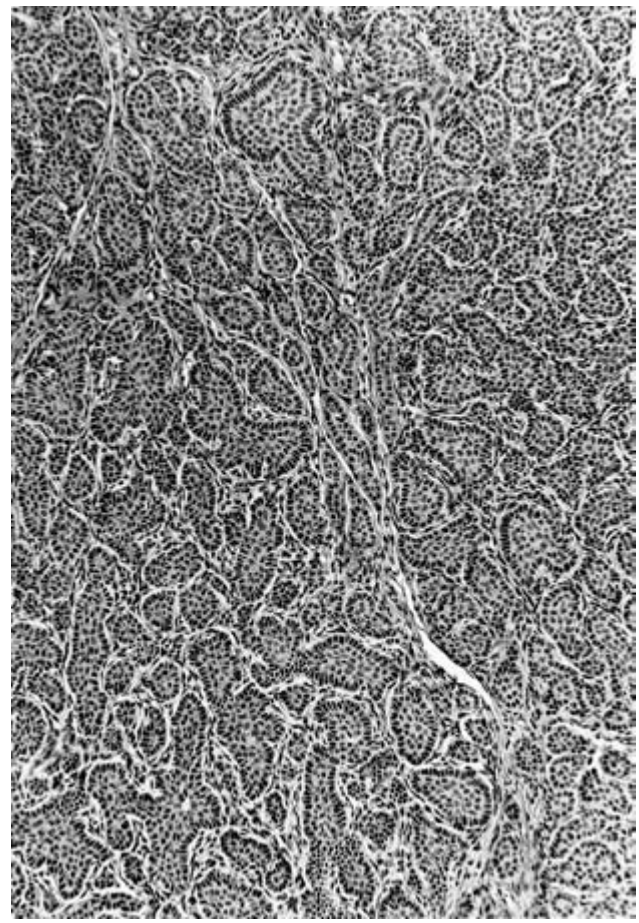


Fig. 23.41 Trabecular trichoblastoma in a cat. Small islands and branching trabeculae are composed of small, polyhedral keratinocytes with prominent peripheral palisading.

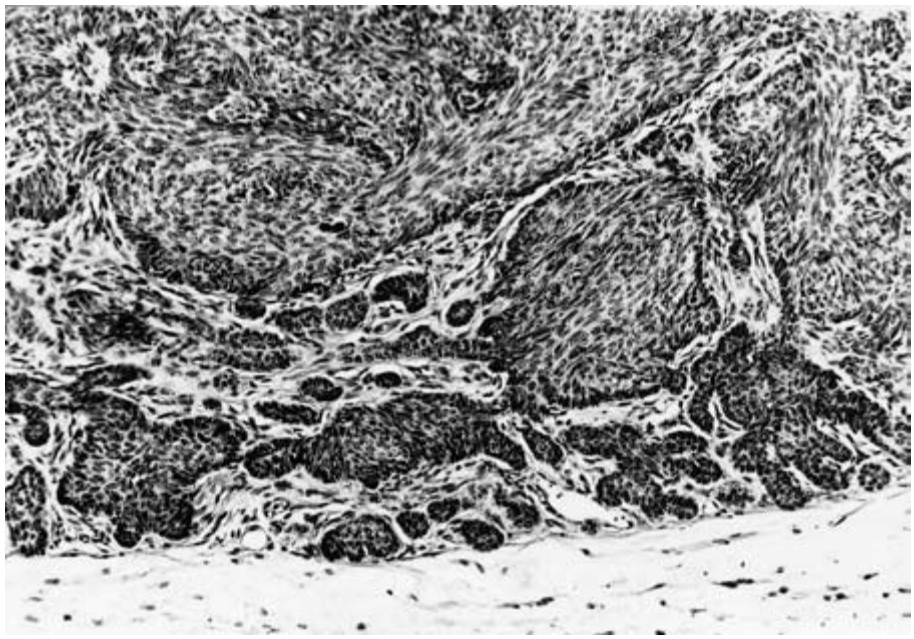


Fig. 23.42 Trabecular trichoblastoma in a cat. Spindling of some of the epithelial cells is prominent. Note sparse, slightly cellular stroma and well-demarcated tumor margins.

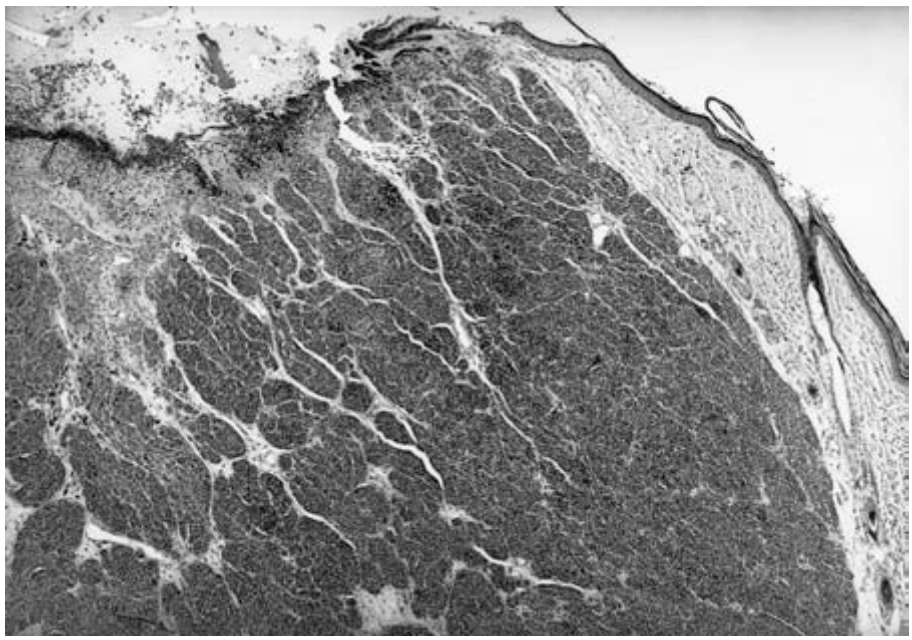


Fig. 23.43 Spindle cell trichoblastoma in a cat characterized by a well-circumscribed dermal mass with a sparse, fibromyxoid stroma and shallow crateriform ulcer. Small, basaloid cells are grouped into islands and trabeculae; spindled morphology is not obvious at low magnification.

Spindle cell type trichoblastoma (Figures 23.43 through 23.46)

Spindle cell trichoblastoma was provisionally designated 'benign feline basal tumor' in *Veterinary Dermatopathology* (Walder & Gross, 1992). As implied by the old nomenclature, this subtype is seen only in cats. Transitional lesions with ribbon or trabecular morphology adjacent to typical spindle cell zones have been recognized, indicating that this is yet another variant of hair germ tumor. Immunostaining patterns, using markers available thus far, are identical to other trichoblastomas (Walder, 2000; Goldschmidt et al., 2002) (see below).

Spindle cell trichoblastoma is a well-circumscribed dermal nodule that generally has a fairly broad zone of connection to the overlying epidermis. Ulceration is common. The tumor frequently has a lima-bean-shaped silhouette with the central indentation at the tumor surface. The neoplasm is composed of basaloid epithelial cells arranged in islands, nests, and short trabeculae

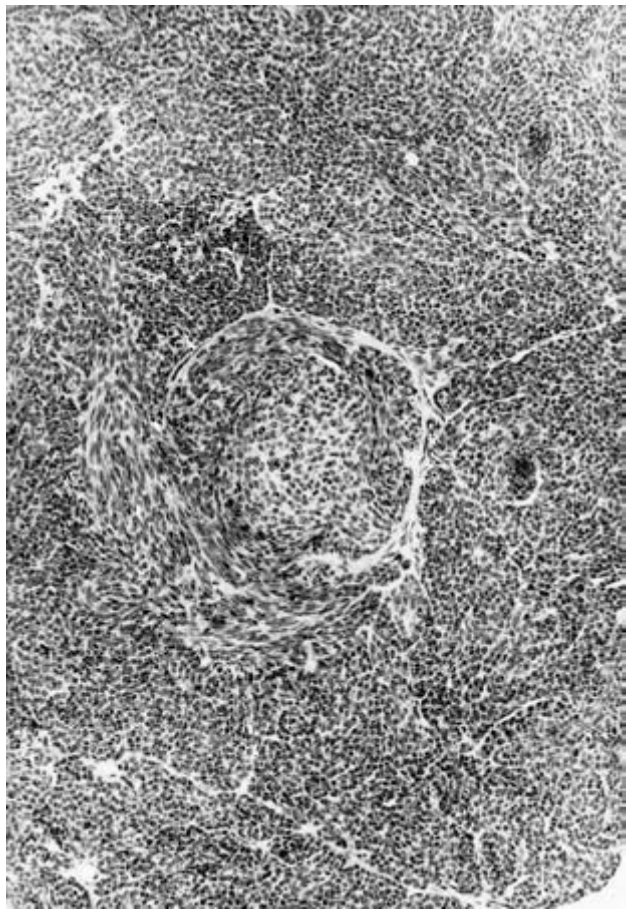


Fig. 23.44 Higher magnification of spindle cell trichoblastoma in a cat. Aggregates of elongated trichoblasts often have a whorled configuration, and peripheral palisading is not evident. Note the two small follicular papillary mesenchymal bodies at right center and top right.

without prominent peripheral palisading. Larger islands may have central foci of caseation necrosis. There is a sparse collagenous stroma of low cellularity; moderate amounts of stromal mucin are often present at the center of the neoplasm.

The epithelial cells have scant, pale cytoplasm and bland nuclei. Nucleoli are inconspicuous, and mitotic activity is low. There are large zones of spindling characterized by elongation of cytoplasm and nuclei, producing a whorled configuration that often affects entire epithelial aggregates. Squamous differentiation or keratinization is infrequently observed. Many spindle cell trichoblastomas have mild to moderate melanization of the epithelial cells, and stromal melanophages may be present. Follicular papillary mesenchymal bodies (see ribbon type trichoblastoma, above) are present in small numbers, often at the periphery of the tumor in association with aggregates of more typical trichoblasts.

Differential diagnoses for spindle cell trichoblastoma include basal cell carcinoma and solid-cystic ductular sweat gland adenoma, both of which have similar epidermal contiguity and may be pigmented. Epithelial cell spindling may occur in basal cell carcinoma and solid-cystic sweat gland adenoma, but is rarely as extensive as in spindle cell trichoblastoma. Basal cell carcinoma generally has an asymmetrical, irregular silhouette and a plaque-like architecture. The stroma of basal cell carcinoma is more abundant, more cellular, and generally extends beyond the boundaries of the epithelial component. Mitotic activity is usually higher, and atypical mitoses are present. Solid-cystic ductular sweat gland adenoma typically has a small central focus of epidermal contiguity that is not umbilicated, cystic degeneration is

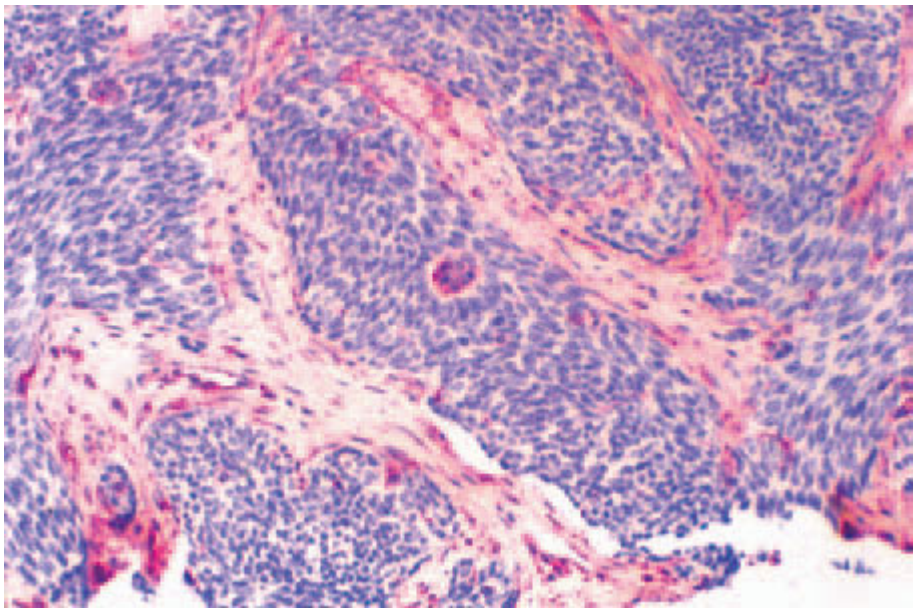


Fig. 23.45 Spindle cell trichoblastoma in a cat. Vimentin immunostain highlights the follicular papillary mesenchymal bodies, noted particularly at center and upper left (chromogen new fuchsin).

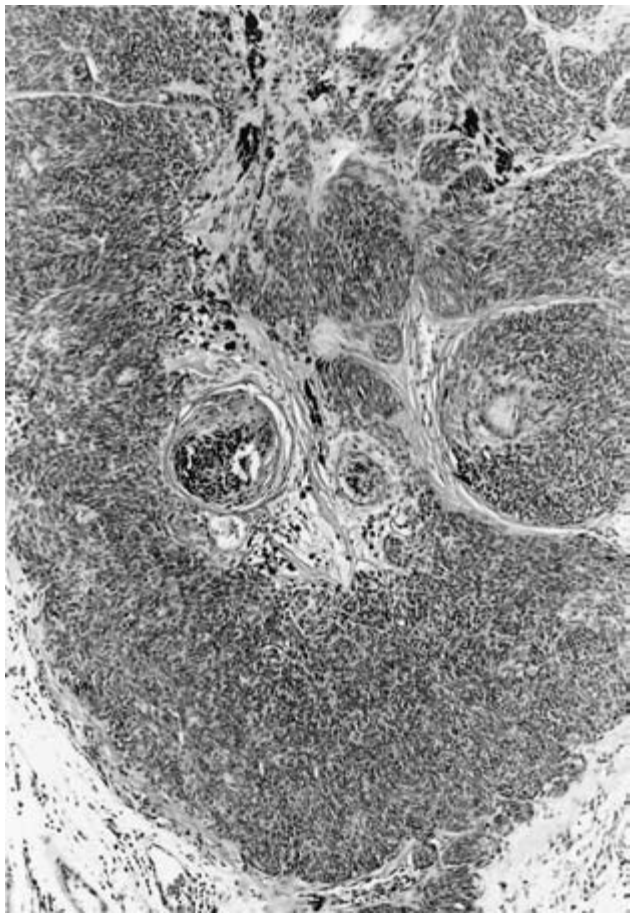


Fig. 23.46 Spindle cell trichoblastoma in a cat. This variant is melanized and contains squamous epithelial cysts with pigmented keratin pearls.

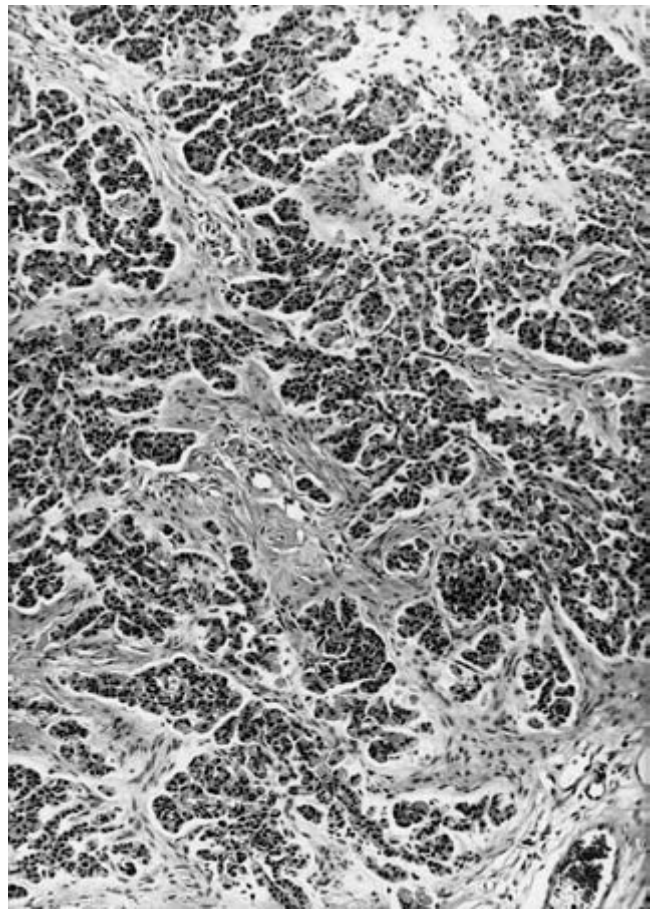


Fig. 23.47 Granular cell trichoblastoma in a dog. The overall architecture is identical to classic ribbon trichoblastoma.

common and often extensive, and small ducts or intracellular lumina can usually be identified.

Granular cell type trichoblastoma (Figures 23.47 and 23.48)

This rare variant of hair germ tumor in dogs was first reported by Seiler (1981) as a subtype of basal cell tumor. Histopathologically, the architecture is identical to the canine ribbon-type trichoblastoma described above, but some or all of the epithelial aggregates are composed entirely of larger cells with abundant, finely granular or vacuolated cytoplasm. Nuclei of the granular cells are small, angular, and eccentric.

Ultrastructurally, the granules are lysosomes containing numerous intact and fragmented vesicles of undetermined origin. Similar degenerative changes may also be observed in granular cell schwannoma, granular cell ameloblastoma, and granular cell basal cell carcinoma; the latter two entities have been reported in humans only (Barr & Graham, 1979).

Granular cell trichoblastoma is distinguished from granular cell basal cell carcinoma by its ribbon-like architecture, absence of epidermal contiguity and lack of cytologic features of malignancy. The cells of granular cell trichoblastoma may appear almost clear, requiring differentiation from bulb type tricholemmoma. Tricholemmoma has more islands and trabeculae than cords and nests, and the nuclei of tricholemmoma are not peripherally displaced as they are in granular cell trichoblastoma.

Immunohistochemistry

Although immunostains for cytokeratins (CK) would rarely be required in a practical sense in the diagnosis of trichoblastomas, they have been utilized to investigate the origin of these neoplasms and are occasionally of benefit in differential diagnosis. Canine and feline ribbon and trabecular trichoblastomas were found to have strong, diffuse staining with the polyclonal reagent 34βE12 (CKs 1, 5, 10, 11) and fairly strong, patchy staining with the

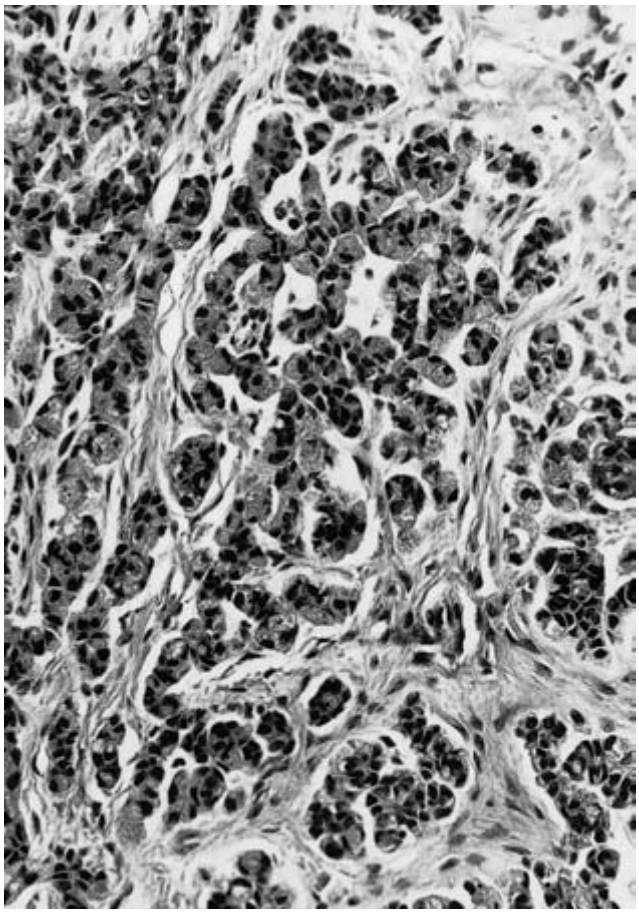


Fig. 23.48 Higher magnification of Fig. 23.47. The cells have more abundant, granular cytoplasm and eccentric, angular nuclei.

monoclonal marker CK14; both of these markers were also positive in, but not limited to, secondary hair germ of telogen follicles in control tissue (Walder & Haines, 1998). CAM5.2 (CK7/8) was negative in these tumors (Walder & Haines, 1998). All trichoblastomas, including the spindle cell type, were diffusely and strongly stained with CK5/6 and were negative with CK13 (Walder, 2000). Additional polyclonal preparations that uniformly stained trichoblastomas are AE1 (CKs 1–8) and LP34 (CKs 1, 5, 6, 8, 10, 14, 18) (Goldschmidt et al., 2002). Immunostaining for the mesenchymal intermediate filament vimentin highlights follicular papillary mesenchymal bodies in the stroma (Walder, 2000).

In problematic cases of spindle cell trichoblastoma, immunostaining with CAM5.2 or CK13 can be used to exclude sweat gland origin. All sweat gland neoplasms evaluated to date have at least some areas of strong CAM5.2 or CK13 positivity, and staining with CK5/6 is patchy (Walder, 2000). Immunohistochemistry does not appear to be beneficial in distinguishing trichoblastomas from basal cell carcinomas, at least in humans, as both neoplasms have a similar cytokeratin profile that includes CKs 15, 17 and 19, the putative follicular stem cell markers. Only limited monoclonal CK panels have been performed on these tumor types in animals.

MALIGNANT TRICHOEPITHELIOMA

(Synonym: matrical carcinoma)

Trichoepitheliomas with biologic or histologic features of malignancy are briefly described in two reference texts (Goldschmidt & Shofer, 1992; Goldschmidt & Hendrick, 2002) and are included in the current World Health Organization classification (Goldschmidt et al., 1998). Malignant trichoepithelioma is not a formally recognized category in human dermatopathology, although a single case report exists (Hunt & Abell, 1991). Malignant trichoepitheliomas are defined in the current World Health Organization classification system as malignant tumors with only matrical and inner root sheath features. However, the authors believe that these tumors should meet the nosological requirements of their benign counterparts, i.e. infundibular, isthmus and matrical segments of the hair follicle should be represented. Distinction from malignant pilomatricoma (see p. 637) may not always be possible. Until more cases are documented and consistent clinicopathologic parameters become established, it may be prudent to use a more general term, such as matrical carcinoma or follicular carcinoma.

Clinical features

Malignant trichoepitheliomas are rare and have been described in dogs only (Goldschmidt & Hendrick, 2002); neither have the authors seen any feline examples. Clinical features have not been documented in the literature. Based on a small number of cases, malignant trichoepitheliomas tend to be larger and less well-circumscribed than their benign counterparts. The tumors are often ulcerated and may have an irregular, plaque-like configuration. The dorsal trunk appears to be a common location. Age distribution and breed predilection are unknown.

Local recurrence and lymphatic metastasis may occur. The cases originally described by Goldschmidt and Shofer (1992) had lymphatic invasion and disseminated metastasis; less aggressive subsets of malignant trichoepithelioma probably also exist. The entity designated as 'infiltrative trichoepithelioma' (Goldschmidt & Shofer, 1992; Goldschmidt et al., 1998) is histologically nearly identical to malignant trichoepithelioma and is reported to recur in 10% of cases; the authors believe this is consistent with a low-grade malignancy.

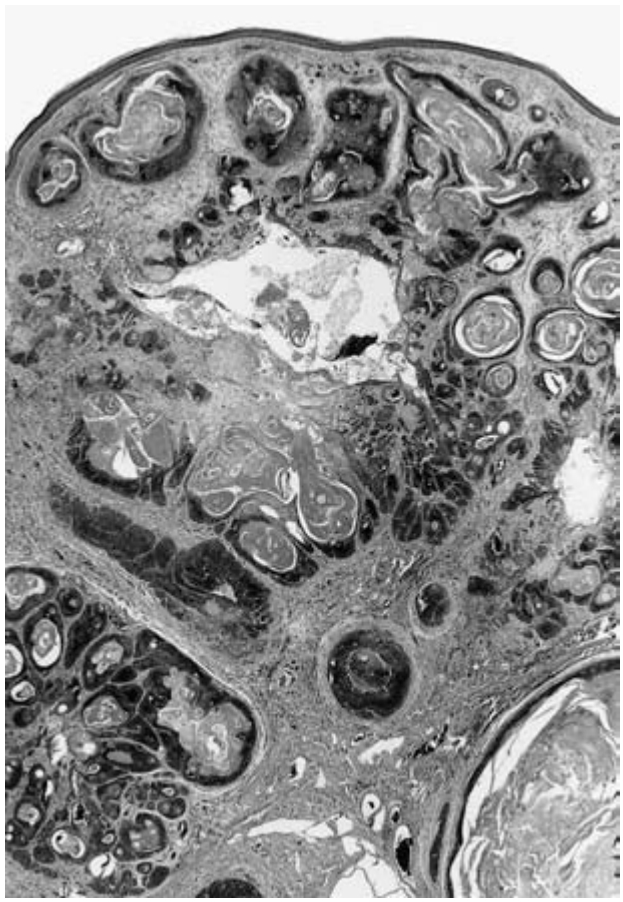


Fig. 23.49 Well-differentiated malignant trichoepithelioma in a dog. Architecture is similar to benign trichoepithelioma (Fig. 23.20), but epithelial aggregates are more irregular in size and shape, margins are ill-defined, and zones of necrosis are present.



Fig. 23.50 Higher magnification of well-differentiated malignant trichoepithelioma in a dog. Irregular cysts, trabeculae, and nests of basaloid and squamous epithelium represent matrical, root sheath, and infundibular differentiation. Note large, hyperchromatic nuclei and multiple patterns of keratinization.

Histopathology (Figures 23.49 through 23.52)

Malignant trichoepitheliomas are asymmetrical, poorly-circumscribed, nodular, or plaque-like dermal masses that may extend into subcutis. Focal or multifocal contiguity with epidermis or follicular epithelium is often observed. The tumors comprise islands of variable epithelial aggregates, including trabeculae, cords, and nests of basaloid matrical keratinocytes with sparse to moderate transition to squamous epithelium. The islands exhibit variable size, shape, and circumscription. The squamous epithelium has features of inner root sheath (trichohyalin granules and glycogen), outer root sheath (agranular, with or without glycogenation), and infundibulum (keratohyalin granules) in varying proportions. Complete keratinization is usually present in some of the epithelial aggregates, but is not as extensive as in benign trichoepitheliomas. Frank cysts are usually present but infrequent. The islands of matrical cells often have central caseation necrosis in lieu of or in addition to sheets of keratinized ghost cells.

The matrical cells have scant cytoplasm, large ovoid nuclei, one or more nuclei, and moderate to high mitotic activity. Nucleoli are usually small, but nuclear hyperchromatism may be present. Atypical mitotic figures can usually be identified. Peripheral palisading is often observed in the larger epithelial aggregates. The foci of inner root sheath, outer root sheath, and infundibular differentiation lack cytologic features of malignancy.

There is a moderate to abundant collagenous stroma with moderate cellularity. The epithelial aggregates often have cuffs of hyalinized collagen. Nests of tumor cells may be found within stromal lymphatic vessels. Secondary inflammation is often present due to ulceration or release of keratin from degenerate epithelial aggregates. Malignant trichoepitheliomas with a minimal squamous component and relatively small islands of matrical epithelium widely spaced through the stroma appear to be more commonly associated with lymphatic invasion; this is the pattern originally illustrated by Goldschmidt and Shofer

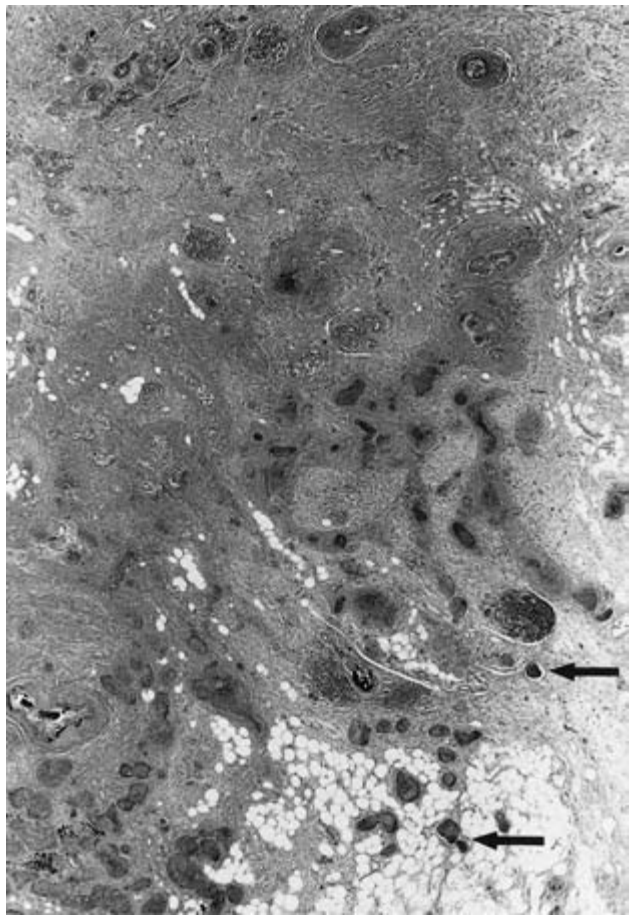


Fig. 23.51 Poorly-differentiated malignant trichoepithelioma in a dog. Small, irregular epithelial aggregates separated by an abundant stroma infiltrate deeply into the subcutis. Note foci of lymphatic invasion at bottom right (arrows).

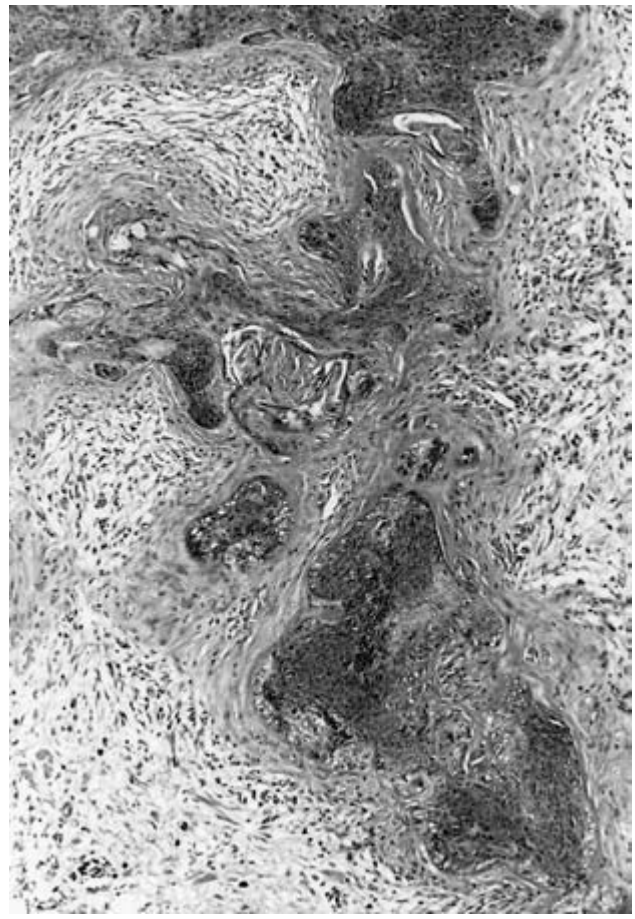


Fig. 23.52 Higher magnification of poorly-differentiated malignant trichoepithelioma in a dog. Neoplastic epithelial cells show primarily matrical and outer root sheath features with limited keratinization. Note highly cellular stroma forming dense cuffs around the tumor aggregates.

(1992). Other malignant trichoepitheliomas show larger areas of advanced trichogenesis and have less intervening stroma between islands and trabeculae of epithelium; these are architecturally similar to benign trichoepitheliomas and appear to be less aggressive; however, long-term retrospective studies are required to substantiate this.

Differential diagnoses for malignant trichoepithelioma include inflamed benign trichoepithelioma, malignant pilomatricoma, and keratinizing basal cell carcinoma. Inflamed benign trichoepitheliomas have a more compact, spherical silhouette, and multifocal epidermal contiguity is uncommon. Areas of increased proliferative activity and reactive squamous metaplasia are always associated with the inflammatory infiltrate. Multifocal epithelial necrosis and atypical mitoses are not seen in benign trichoepithelioma. Differentiation between malignant trichoepithelioma and malignant pilomatricoma is problematic and sometimes impossible; malignant pilomatricomas usually have a marked predominance of atypical matrical cells and large zones of keratinized ghost cells, but foci of squamous epithelium and keratin pearls, occasionally with features of malignancy, are described in most of the reports in human and veterinary literature. The epithelial aggregates of malignant pilomatricoma are usually larger than those of malignant trichoepithelioma. The more general term 'matrical carcinoma' may be preferable for borderline lesions. Keratinizing basal cell carcinomas have a superficial, plaque-like configuration with multifocal epidermal contiguity and ulceration. Their margins are angular and show an infiltrative growth pattern. Discrete large cystic structures are not present, and keratin microcysts, if present, are usually lined by bland squamous epithelium. Inner root sheath differentiation is not expected in keratinizing basal cell carcinoma. Stromal–epithelial clefts are often present in basal cell carcinoma, but may not be as consistent a feature as they are in human basal cell carcinoma. However, because it has recently been demonstrated that basal cell carcinomas have a very similar cytokeratin profile to trichoepithe-

lioma and trichoblastoma (see Chapter 22), one could reasonably argue that keratinizing basal cell carcinoma represents a distinct, low-grade variant of malignant trichoepithelioma.

MALIGNANT PILOMATRICOMA

(Synonyms: matrical carcinoma, pilomatrix carcinoma)

The first documentation of malignant pilomatricoma in dogs was in 1976 (Sells & Conroy, 1976). The first case report in a human appeared in 1969, and the term 'malignant pilomatrixoma' was coined in 1980 (Prandetsky & Yuzvinkevich, 1969; Lopranski & Mihm, 1980). Although the new World Health Organization veterinary classification defines malignant pilomatricomas as having exclusively matrical differentiation, reports in both dogs (Sells & Conroy, 1976; Johnson et al., 1983; Van Ham et al., 1990; Rodriguez et al., 1995) and humans (Hardisson et al., 2001; De Gálvez-Aranda et al., 2002) also describe limited inner root sheath, outer root sheath and infundibular features. The definition of the term 'matrical carcinoma' is currently controversial, since it is used synonymously with either malignant trichoepithelioma (Goldschmidt et al., 1998) or malignant pilomatricoma. Because benign pilomatricomas often show small areas of inner root sheath differentiation and occasionally have foci resembling outer root sheath, the authors believe it is reasonable to accept scattered areas of nonmatrical epithelium as features of their malignant counterparts as well. Matrical carcinoma may be a more practical nosology that would encompass all high-grade follicular malignancies with a predominance of matrical histologic features.

Clinical features

Malignant neoplasms exhibiting primarily hair matrix differentiation are rare in dogs and have not been reported in cats. They are plaque-like or dome-shaped, alopecic masses that are frequently ulcerated. They are within the same size range as their typical benign counterparts. The tumors reported in the literature occurred on the neck, dorsal trunk, and tail (Sells & Conroy, 1976; Johnson et al., 1983; Van Ham et al., 1990; Rodriguez et al., 1995). There is a wide range of reported ages and breeds; no predilections are known.

The reported cases had multifocal distant metastasis to a variety of organs, including bone and central nervous system, and local recurrence also was sometimes described (Sells & Conroy, 1976; Johnson et al., 1983; Van Ham et al., 1990; Rodriguez et al., 1995). In humans, local recurrences develop in nearly half of the cases, and there is a 16% incidence of metastasis (Hardisson et al., 2001). While some human malignant pilomatricomas arise *de novo*, others are believed to represent malignant transformation of pre-existing pilomatricomas (De Gálvez-Aranda et al., 2002). It is uncertain if this phenomenon occurs in dogs. One canine case report described disseminated metastasis from a primary tumor consistent with benign pilomatricoma (Rodriguez et al., 1995).

Histopathology (Figure 23.53)

Malignant pilomatricomas are poorly-circumscribed dermal neoplasms that often extend into the subcutis. They are composed primarily of basaloid matrical epithe-

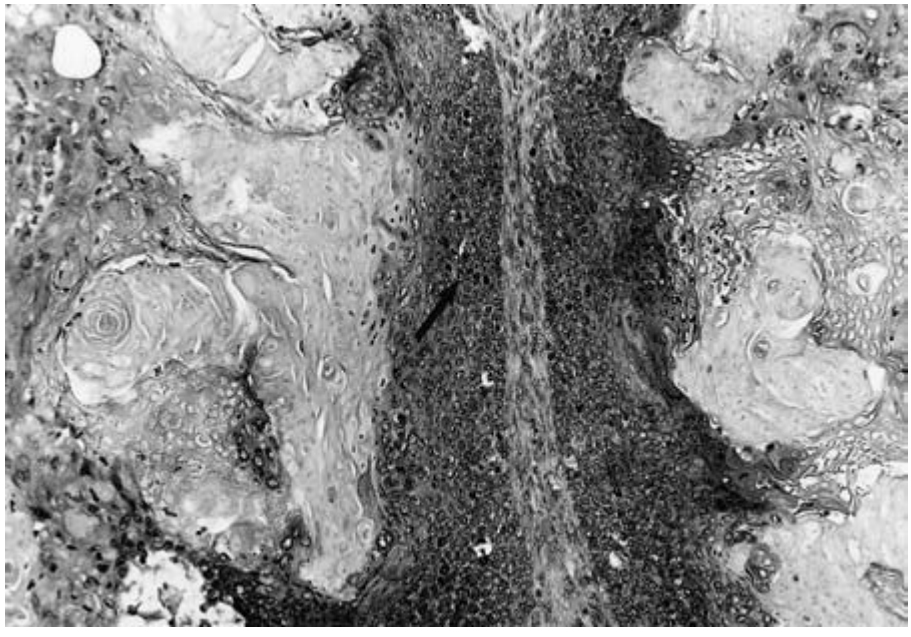


Fig. 23.53 Malignant pilomatricoma in a dog. Large, irregular cystic structures lined predominantly by basaloid matrical epithelial cells are filled with keratinized ghost cells. Note numerous mitotic figures in the matrical cell population (arrow).

lial cells arranged in large, irregular islands and trabeculae. Peripheral palisading is generally absent. Some neoplasms have multifocal contiguity with the epidermis. Ulceration is frequently observed, and there are multiple large zones of necrosis. There is a moderate desmoplastic stroma that often contains clusters and cords of infiltrating tumor cells at the periphery of the lesion. Intralymphatic aggregates of neoplastic cells may be identified. The stroma usually has an inflammatory infiltrate, which may include a granulomatous foreign body-type reaction to the keratinized ghost cells.

The majority of the tumor cells have minimal cytoplasm, hyperchromatic and ovoid nuclei, one or more nucleoli of varying size, and moderate to high mitotic activity. Mitotic atypia is present. There are multiple zones of matrical keratinization manifested by abrupt formation of shadow cells. The shadow cell aggregates are often large, irregular and incompletely surrounded by matrical cells. Calcification or ossification of the shadow cells may be present. The basaloid cells may also show small foci of transition to inner root sheath, outer root sheath, and nonspecific squamous types of epithelium. The inner root sheath keratinocytes are larger than the matrical cells and have clear cytoplasm with brightly eosinophilic trichohyalin granules. The outer root sheath epithelial cells are pale pink and lack a granular layer. The nonmatrical epithelial cells generally do not have cytologic features of malignancy, but foci resembling squamous cell carcinoma may be present.

Malignant pilomatricoma is distinguished from its benign counterpart by an increased ratio of basaloid cells to keratinized ghost cells, poor circumscription with infiltrative borders, increased mitotic activity, and nuclear and mitotic atypia of the basaloid cells. Differentiation between malignant trichoepithelioma and malignant pilomatricoma is problematic and sometimes impossible. Malignant pilomatricomas usually have larger epithelial aggregates, a marked predominance of atypical matrical cells, and larger zones of keratinized ghost cells; foci of inner and outer root sheath differentiation are more prominent in malignant trichoepithelioma, but do not preclude a diagnosis of malignant pilomatricoma. Calcification and ossification are not usually found in malignant trichoepithelioma. The more general term 'matrical carcinoma' may be preferable for borderline lesions. Keratinizing basal cell carcinoma is differentiated from malignant pilomatricoma primarily by its superficial, plaque-like architecture and multifocal connections to the epidermis. Keratinizing basal cell carcinoma can have small clusters of shadow cells; large zones of matrical keratinization are a more typical feature of matrical carcinoma. Stromal–epithelial clefts are typical for basal cell carcinoma, but may not be as consistent a feature as they are in human basal cell carcinoma.

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Chapter 24

Sebaceous tumors

SEBACEOUS DUCT CYST

The misnomer 'sebaceous cyst' is frequently applied to follicular cysts because of the grumous nature of their keratinaceous contents. Sebum, in fact, is a white, milky fluid. Cysts of sebaceous ductal origin in humans are usually multifocal and hereditary. They are still referred to in human dermatopathology by their archaic Latin nomenclature, steatocystoma multiplex, or steatocystoma simplex for the uncommon solitary variant (Murphy & Elder, 1991).

Clinical features

Cysts that involve sebaceous structures are rare in dogs and extremely rare in cats. Sebaceous duct cysts present as solitary, firm dermal nodules that are usually less than 0.5 cm in size. This is much smaller than the analogous lesion in humans. The cysts contain small amounts of keratin and sebum. Lesions occasionally involve the specialized sebaceous glands of the eyelid and are termed meibomian cysts. There is no known age, breed, or site predisposition in animals.

Histopathology (Figure 24.1)

Sebaceous duct cysts are lined by a thin layer of stratified squamous epithelium that has a sparse granular cell layer and a corrugated or undulating inner surface. Essentially, these cysts closely resemble the normal sebaceous duct. A thin, brightly-eosinophilic cuticle may be seen on the inner surface of the cyst. A thin collagenous capsule usually surrounds the epithelium. Projecting outward from the wall of most sebaceous cysts are multiple, atrophic, but architecturally normal, sebaceous gland lobules composed of central lipidized cells and a single layer of peripheral basaloid reserve cells. Occasional cysts are accompanied by moderately hyperplastic sebaceous glands; these lesions may represent cystic dilatation of the ductal component of nodular sebaceous hyperplasia (see below). Most of the cyst contents are lost during tissue processing, but some delicate, lamellar keratin generally adheres to the cyst lining.

Sebaceous duct cysts may need to be differentiated from follicular cysts, particularly the isthmus type (see Chapter 23). Follicular cysts can occasionally have small numbers of sebaceous gland lobules attached to their walls. Numerous sebaceous glands or multiple enlarged sebaceous lobules indicate a diagnosis of sebaceous duct cyst. Further, the inner surface of a follicular cyst does not have a corrugated appearance or an eosinophilic cuticular lining.

NODULAR SEBACEOUS HYPERPLASIA

(Synonym: senile sebaceous hyperplasia)

Clinical features

Nodular sebaceous hyperplasia is a common, focal or multicentric, non-neoplastic lesion of dogs. In one large series, nodular sebaceous hyperplasia comprised 23% of all non-neoplastic canine skin masses (Goldschmidt & Shofer, 1992). Nodular sebaceous hyperplasia is less common in cats, accounting for 11% of non-neoplastic cutaneous tumors (Goldschmidt & Shofer, 1992). Lesions are yellow-white, alopecic, firm, and dome-shaped or papillated nodules that are less that 5 mm in diameter. Some lesions appear as small plaques. A waxy or pearly quality aids in clinical differentiation of nodular sebaceous hyperplasia from papillomas despite their wart-like configuration. Lesions may arise anywhere on the body, but are most common on the dorsal head, ears, face, and legs.

Nodular sebaceous hyperplasia is most common in senior animals. Poodles, Cocker Spaniels, Manchester Terriers, and Wheaten Terriers appear to be predisposed (Goldschmidt & Shofer, 1992), although the lesion can be seen in all breeds of dogs.

Histopathology (Figure 24.2)

Nodular sebaceous hyperplasia is characterized by multiple, enlarged, but otherwise normal sebaceous lobules

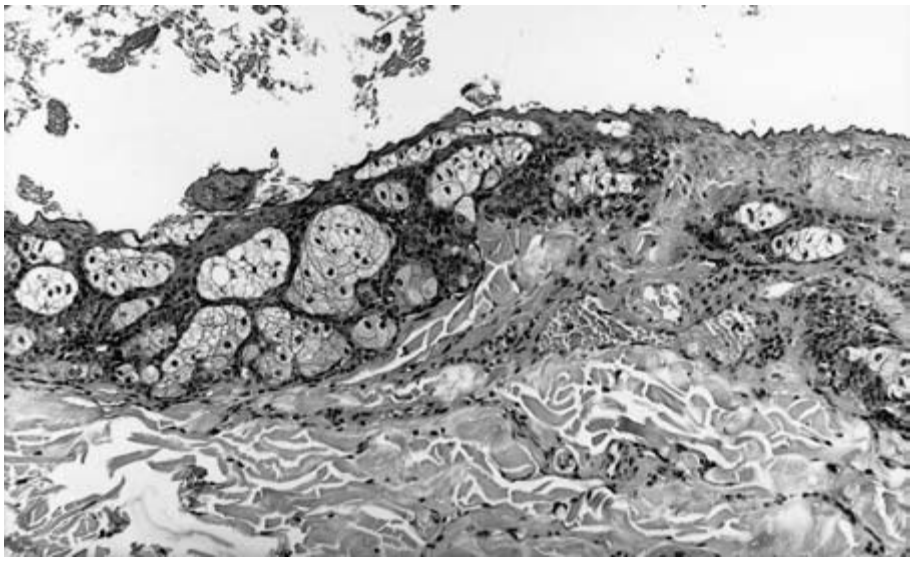


Fig. 24.1 Sebaceous duct cyst in a dog. Note the delicate undulating epithelium lining the cyst lumen.

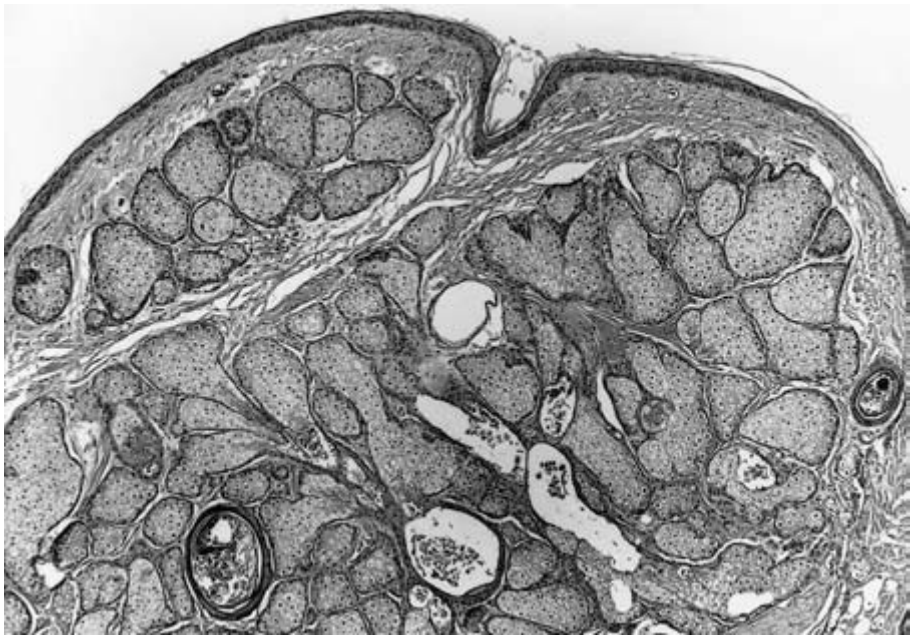


Fig. 24.2 Nodular sebaceous hyperplasia in a dog. Enlarged sebaceous lobules are grouped around duct-like structures lined by keratinizing squamous epithelium.

clustered around one or more dilated sebaceous ducts and hair follicles. The architectural relationships of the folliculosebaceous units are generally well-maintained. Affected folliculosebaceous units may be grouped horizontally, forming a plaque. The sebaceous lobules have central fully-lipidized cells and a single peripheral layer of basaloid reserve cells. The ducts are lined by thickened squamous epithelium that keratinizes through a sparse granular cell layer, and contain loosely-laminated keratin and small amounts of sebum. Hair follicles are also often hyperplastic and dilated. Lesions in which a markedly dilated duct becomes the predominant feature can be classified as sebaceous duct cysts (see p. 641). Foci of nodular sebaceous hyperplasia are occasionally identified at the margins of sebaceous gland adenomas and epitheliomas, suggesting progression from hyperplasia to neoplasia.

Secondary erosion and inflammation are frequent features of larger lesions. The ducts and follicles in traumatized or inflamed lesions may contain colonies of staphylococci. Rupture of ducts or follicles may result in severe, pyogranulomatous inflammation extending into the deep dermis.

Occasionally, primarily in male dogs, some of the sebaceous lobules exhibit a metaplastic transformation to hepatoid gland cells (perianal gland type), characterized by abundant, glassy, eosinophilic cytoplasm. The biochemical or hormonal basis for this change has not been documented. Hepatoid metaplasia may represent a

similar process to the normal development of one type of perianal gland in puppies. Between 20 and 152 days of age in both male and female dogs, some of the perianal sebaceous glands that were present since birth develop groups of hepatoid acini in their deep aspects; these have been designated 'transitional hepatoid glands' and are adjacent to but distinct from the primary hepatoid glands (Isitor & Weinman, 1979).

Nodular sebaceous hyperplasia should be differentiated from sebaceous adenoma and in some cases from sebaceous nevus. Nodular hyperplasia retains the normal orientation of sebaceous glands around ducts or follicular infundibula, in contrast to simple sebaceous adenoma. Degeneration and drop-out of central zones of mature sebocytes are common in sebaceous adenoma, but are not observed in nodular sebaceous hyperplasia. Nodular sebaceous hyperplasia and compound sebaceous adenoma are differentiated by the increased number of basaloid reserve cells and immature sebocytes in the latter. The ductular structures of compound sebaceous adenoma are usually more numerous and more varied in size than those of nodular sebaceous hyperplasia. In addition, both simple and compound sebaceous adenomas are usually larger than sebaceous hyperplasia; however, there is considerable overlap in the size of these lesions. The plaque type of nodular sebaceous hyperplasia can generally be distinguished from sebaceous nevus by the larger size of the sebaceous lobules, lack of multiple follicular infundibula contiguous with epidermis, and absence of consistent hypergranulosis and hyperkeratosis in the former.



Fig. 24.3 Sebaceous hamartoma in a dog demonstrating multiple large sebaceous lobules randomly grouped around tortuous, distended ducts. This example has abundant fat in the stroma.

SEBACEOUS HAMARTOMA

Clinical features

Sebaceous hamartoma is an uncommon variant of fibroadnexal hamartoma (see Chapter 23) and is a malformation of presumed congenital origin. This nomenclature is a new addition to the World Health Organization classification of domestic animal skin tumors (Goldschmidt et al., 1998). Lesions present as alopecic solitary nodules less than 1 cm in diameter, most often on extremities or trunk. There is no known age or breed predisposition.

Histopathology (Figure 24.3)

Sebaceous hamartoma is a circumscribed dermal nodule composed predominantly of large sebaceous lobules with a random distribution. Maturation patterns within the lobules are normal. The sebaceous lobules may be contiguous with and interconnected by tortuous sebaceous ducts and small but malformed hair follicles. The adnexal structures are surrounded by moderate to abundant mature collagen; mature adipose tissue may also be present. As in small fibroadnexal hamartomas, inflammation or ulceration is rarely observed.

Differentiation between sebaceous hamartoma and fibroadnexal hamartoma is based on an obvious predominance of sebaceous lobules in the former. Lesions with a predominance of follicular structures or an approximately equal admixture of follicular and sebaceous elements should be classified as fibroadnexal hamartomas. Sebaceous hamartoma is distinguished from nodular sebaceous hyperplasia and sebaceous adenoma by the abundant connective tissue surrounding individual lobules.

SEBACEOUS NEVUS

(Synonyms: nevus sebaceus, organoid nevus)

Non-neoplastic cutaneous lesions of adnexal (principally sebaceous gland) origin that have histologic features similar to nevus sebaceus of Jadassohn in humans occur

in dogs and cats. Nevus sebaceus of Jadassohn in humans is present at birth, becomes fully developed in adolescence, and can eventuate in a variety of benign and malignant epithelial neoplasms (Elder et al., 1997). The analogous lesions in dogs and cats have been observed too infrequently to determine if they evolve similarly or progress to neoplasia; in addition, lesions are typically excised completely rather than biopsied and then followed clinically. Neoplastic transformation seems unlikely in animals, as the authors have not observed this phenomenon in any sebaceous nevi excised from older patients. The term 'nevus' is generally not preferred by the authors in the designation of growth abnormalities (see Chapter 22 for definitions of hamartoma and nevus); nevertheless, the nomenclature has been retained primarily to distinguish it from sebaceous hamartoma (see p. 643) and secondarily to acknowledge its similarity to the human lesion. Although the term 'organoid' is valid because the lesions include several different cutaneous tissue types, it is not used in the majority of human reference texts. The authors prefer nosology that indicates the predominant tissue found in the fully developed lesions.

Clinical features

Sebaceous nevi are seen uncommonly in dogs and rarely in cats. They generally appear as alopecic, scaly or greasy, circular or linear plaques less than 2 cm in diameter. They have irregular or papillated surfaces and may occasionally be polypoid. A yellow or orange hue may be evident.

Most lesions are detected in middle-aged or older animals, but some have been identified in puppies. Solitary lesions in older dogs are often located on distal limbs or feet. One of the authors (T.L.G.) has seen solitary lesions on the dorsal head of two puppies. One case of multiple and focally extensive sebaceous nevi has been reported in a 10-month-old Standard Schnauzer (Scarampella et al., 2000); this type of clinical presentation is rare in humans and may be associated with mental retardation and other developmental anomalies (Elder et al., 1997). There is no known breed predisposition.

Histopathology (Figures 24.4 and 24.5)

Sebaceous nevus is a plaque-like, fungiform, or polypoid lesion covered by hyperplastic, hyperkeratotic epidermis that has a papillated configuration. Hypergranulosis is also present and may be marked. Hair follicles are present in a normal orientation, but are truncated and incompletely developed; they have thickened, dilated infundibula contiguous with the epidermis, but usually lack obvious bulbs. Dilated hair follicles predominate in nevus sebaceus in children and in the few cases observed in puppies (Scarampella et al., 2000; Scott et al., 2001). The sebaceous glands in fully developed lesions are mildly to moderately enlarged, numerous and randomly distributed through the superficial dermis. Ductal connections may be evident between the sebaceous glands and follicular structures. Sweat glands are generally present and are histologically normal. Some lesions contain increased stromal collagen that is slightly more cellular than that of



Fig. 24.4 Sebaceous nevus in a dog. Numerous, fairly small sebaceous lobules form a plaque below hyperplastic epidermis. Note distinctive papillomatous hyperplasia and hypergranulosis.

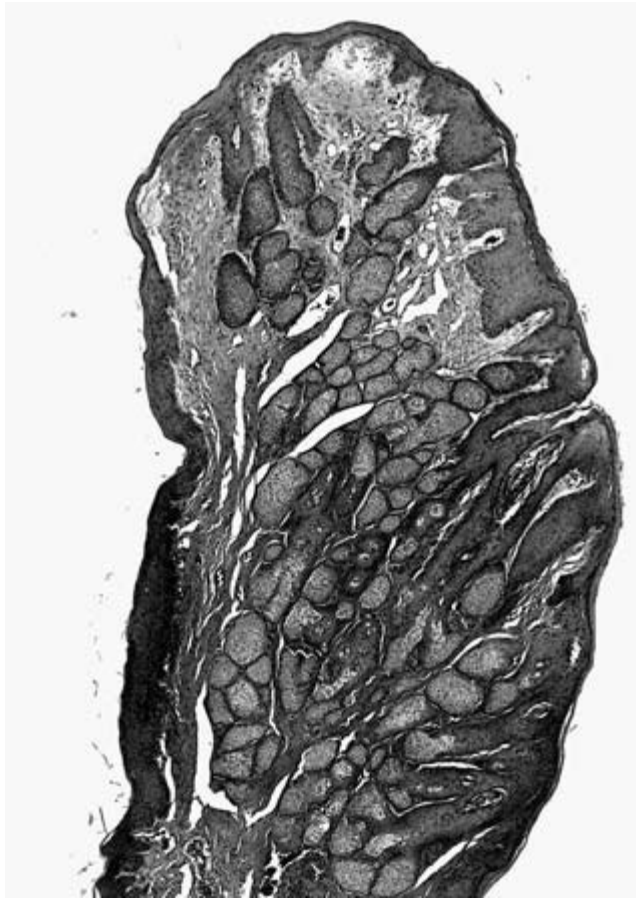


Fig. 24.5 Sebaceous nevus in a dog. This variant has a filiform architecture resembling an acrochordon.

the adjacent dermis. Other lesions, particularly in cats, contain moderate amounts of adipose tissue within the dermis. Mild infiltrates of plasma cells and lymphocytes are common. Ulceration secondary to self-trauma may be observed, particularly in acral lesions.

Sebaceous nevus can usually be distinguished from nodular sebaceous hyperplasia by its involvement of larger numbers of folliculosebaceous units and the smaller size of the sebaceous lobules. Sebaceous nevus does not show the uninodular architecture that is typical for nodular sebaceous hyperplasia; however, plaque-like variants of nodular hyperplasia may be difficult to differentiate from sebaceous nevus (see p. 643). Reactive epidermal hyperplasia with compact hyperkeratosis may occur in nodular hyperplasia if traumatized. However, in sebaceous nevus, irregular acanthosis is a consistent feature and is accompanied by hypergranulosis and laminated hyperkeratosis. Nodular sebaceous hyperplasia generally lacks multiple follicular infundibula contiguous with the epidermis, as seen in sebaceous nevus.

SEBACEOUS ADENOMA

Nomenclature of sebaceous neoplasms in human dermatopathology is currently in a state of flux, and it is thus more difficult to make interspecies comparisons. The newer human classification stresses the concept of a continuum of benign sebaceous neoplasms, collectively termed 'sebaceoma' (Troy & Ackerman, 1984). Classically, human sebaceomas have moderate to large numbers of basaloid reserve cells, and thus incorporate lesions that resemble both compound sebaceous adenoma and sebaceous epithelioma in animals. Some authors recently have recommended an expansion of the original criteria for human sebaceoma to include simple sebaceous adenoma as well; these are identified as 'sebaceoma with advanced sebaceous differentiation' (Misago et al., 2002). Until the dust settles, the authors will continue to employ the more traditional nomenclature for these neoplasms in animals.

Clinical features

Sebaceous adenomas are benign cutaneous neoplasms of glandular or combined ductal and glandular origin; these are designated simple and compound adenomas, respectively. Histologically identical lesions on eyelid margins arise from specialized tarsal sebaceous glands, the meibomian glands, and are thus designated meibomian gland adenomas. Sebaceous adenomas accounted for approximately 6% of all canine skin and subcutaneous tumors in a survey of 1141 neoplasms by one author (E.J.W.). Four percent of 340 feline skin tumors were reported to be sebaceous adenomas in one study (Miller et al., 1991). A larger series of tumors yielded a 7% incidence of sebaceous/meibomian neoplasms in dogs and a 2% incidence in cats (Goldschmidt & Shofer, 1992); however, these data included both sebaceous and meibomian adenomas and epitheliomas. Compound sebaceous adenomas are more common than simple sebaceous adenomas in dogs; compound adenomas are rare in cats. Meibomian gland lesions are rare in cats.

Sebaceous adenomas are solitary or multiple, dome-shaped or papillated tumors which usually measure less than 1 cm in diameter. The overlying skin is usually alopecic and sometimes ulcerated. The tumors may appear yellow or opalescent. They may be melanized, imparting a brown to black color; pigmentation occurs most often in meibomian gland tumors and may lead to clinical confusion with melanocytic neoplasia. Sebaceous adenomas may occur anywhere on the body, but are found most commonly on the head.

The average age of affected animals is 10 years, but lesions occasionally occur in dogs less than 1 year of age. Cocker Spaniels, Siberian Huskies, Miniature Poodles, Coonhounds, Samoyeds, Beagles, Dachshunds, and

Persian cats are reported to have a marked predisposition (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992).

Histopathology

Simple sebaceous/meibomian adenoma (Figure 24.6)

These adenomas typically comprise multiple large lobules of sebaceous cells that show normal maturation from the basaloid peripheral reserve cell layer to large, pale, lipid-laden central cells. Hepatoid metaplasia, characterized by replacement of some of the mature sebocytes by brightly-eosinophilic polygonal cells resembling normal perianal (hepatoid) glands, is observed rarely (also see nodular sebaceous hyperplasia, p. 641). The overlying epidermis is usually intact. Ducts are not a prominent feature. Mature sebocytes have moderate, clear cytoplasm with numerous, delicate, lipid vacuoles and centrally-located nuclei with crenated margins and small nucleoli. Reserve cells have scant, eosinophilic cytoplasm and slightly hyperchromatic, ovoid nuclei with inconspicuous nucleoli. Mitotic activity is low and is confined to the reserve cell layer. Melanization is uncommon.

Cystic degeneration, characterized by zones of acellular, brightly eosinophilic, lacy material, often is present in the centers of the lobules and is analogous to the normal holocrine secretory pattern of sebaceous glands. As would be expected from the high lipid content of the degenerating cells, any accompanying inflammation is predominantly xanthogranulomatous. Occasionally, extensive degenerative changes in a sebaceous adenoma will result in a severe infiltrate composed of distended macrophages containing large lipid vacuoles, in contrast to the delicate lipid droplets of a xanthogranulomatous reaction; this lipogranulomatous reaction occurs most often on the eyelids.

In contradistinction to nodular sebaceous hyperplasia, the lobules in simple adenoma are not oriented around hyperplastic ducts or follicular infundibula. Cystic degeneration and lipogranulomatous inflammation are uncommon in nodular sebaceous hyperplasia.

Compound sebaceous/meibomian adenoma (Figure 24.7)

This variant of sebaceous adenoma contains glandular lobules and ducts in varying proportions. This neoplasm is designated as 'ductal adenoma' in the current World Health Organization histologic classification (Goldschmidt et al., 1998), but this is somewhat inaccurate since both lobular and ductal components are always present.

The sebaceous lobules are grouped in radiating clusters around ductal structures. Basaloid reserve cells and partially-lipidized cells are more frequent than mature sebocytes in some or all of the lobules. Reserve cells have scant, eosinophilic cytoplasm and slightly hyperchromatic, ovoid nuclei with inconspicuous nucleoli. Mature sebocytes have moderate, clear cytoplasm with numerous, delicate, lipid vacuoles and centrally-located nuclei with crenated margins and small nucleoli. Cells with intermediate differentiation have less abundant cytoplasm than mature sebocytes; it is pale eosinophilic, often finely granular, and may contain small numbers of delicate lipid

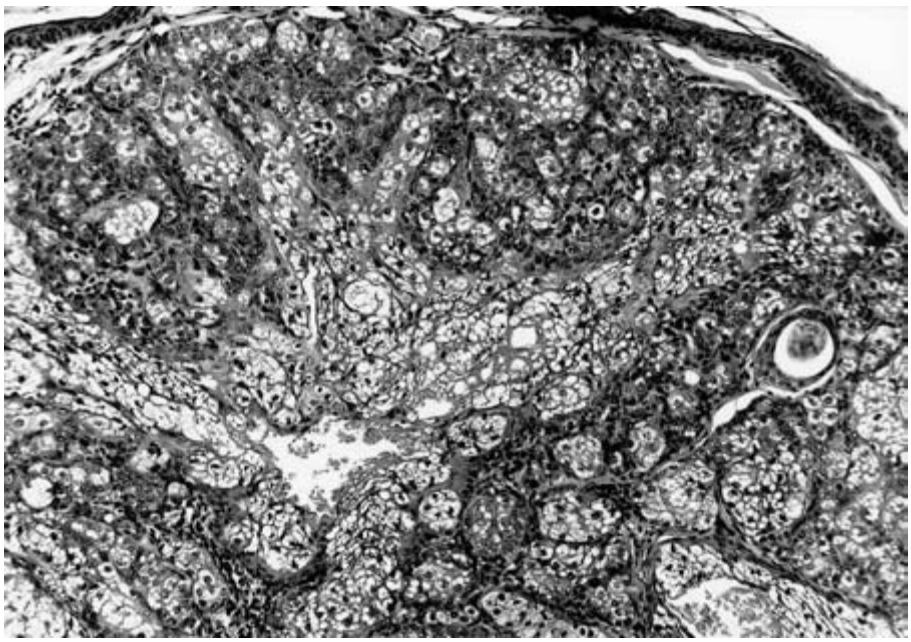


Fig. 24.6 Simple sebaceous gland adenoma in a dog. Tightly grouped lobules of sebocytes demonstrate normal maturation and a predominance of fully-lipidized cells. Note cystic degeneration of mature sebocytes in the center.

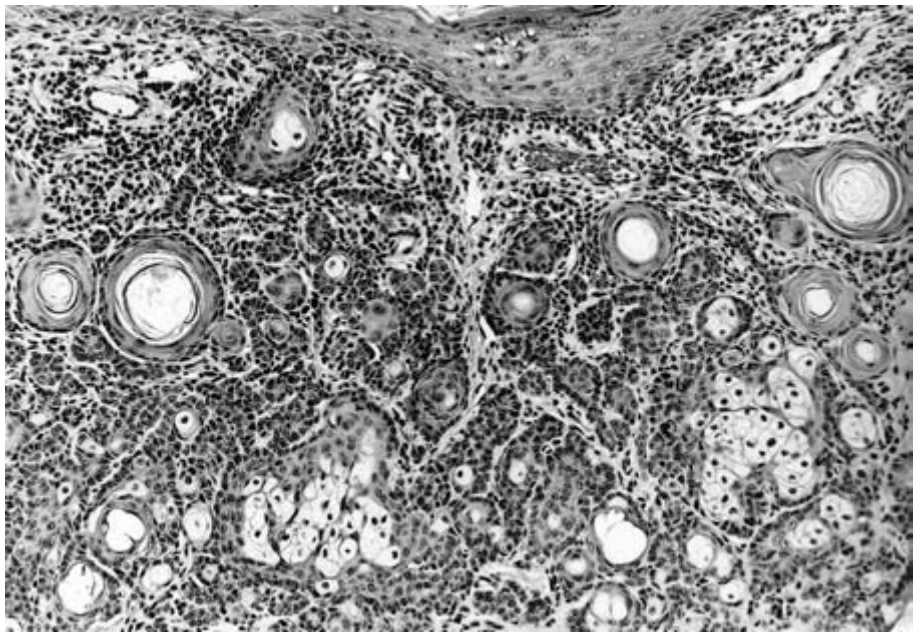


Fig. 24.7 Compound sebaceous gland adenoma in a dog. Small sebaceous lobules radiate from numerous keratinizing ductal structures. Note increased proportion of reserve cells in many of the lobules.

vacuoles. Intermediate cell nuclei are ovoid, slightly larger than those of reserve cells, and are not crenated. Hepatoid metaplasia (see above) is observed rarely. The basaloid reserve cells sometimes form anastomosing cords and trabeculae that may interconnect the ductal structures or merge into overlying epidermis; this pattern is more common in meibomian adenomas. Mitotic activity is low to moderate and is confined to the reserve cells. Atypical nuclei or mitoses are not present. The ductal component is characterized by multiple cysts of varying size that are lined by mature squamous epithelium; a typical corrugated eosinophilic cuticle may be detected on the inner surface of the cysts. Most of the cysts are small. Melanization of the reserve cells is common in eyelid lesions, and uncommon for compound adenomas in other anatomic locations. The stroma is frequently infiltrated by plasma cells, lymphocytes, neutrophils and, particularly in meibomian adenomas, melanophages.

Differential diagnoses for compound sebaceous adenoma include nodular sebaceous hyperplasia for those lesions that have fewer basophilic reserve cells, and sebaceous epithelioma for those lesions with a large reserve cell population. Compound sebaceous adenoma is differentiated from nodular sebaceous hyperplasia by the comparatively higher number of basaloid reserve cells and immature sebocytes in the former. The ductular structures of compound sebaceous adenoma are smaller and more numerous than those of nodular sebaceous hyperplasia. Distinction between compound sebaceous adenoma and sebaceous epithelioma is usually based on smaller size, better circumscription, retention of lobular architecture, fairly large proportion of mature sebocytes, frequent ducts, and low mitotic activity in the former. However, meibomian epitheliomas, in particular, are often small and well-circumscribed, and differentiation from compound adenomas is based primarily on a higher mitotic rate and a larger proportion of basaloid to mature cells. The compound sebaceous adenoma and sebaceous epithelioma are in reality part of a continuum of sebaceous neoplasia, and objective criteria to distinguish between them have not been fully established. Lesions composed predominantly of reserve cells with approximately 10% or fewer mature sebocytes are currently regarded as epitheliomas.

SEBACEOUS EPITHELIOMA

Sebaceous epitheliomas are neoplasms that differentiate primarily toward the basaloid reserve cells of sebaceous glands. Nomenclature for this type of neoplasm in human dermatopathology is currently confusing and controversial. The newer classification stresses the concept of a continuum of benign sebaceous neoplasms, collectively termed 'sebaceoma' (Troy & Ackerman, 1984). Classically, human sebaceomas have moderate to large numbers of basaloid reserve cells and thus incorporate lesions that resemble both compound sebaceous adenoma (see p. 645) and sebaceous epithelioma in animals.

In contrast to the 'sebaceoma' nomenclature, one recent case review in the human literature defines 'low-grade sebaceous carcinoma' by characteristics that are virtually identical to 'sebaceous epithelioma' as defined by veterinary pathologists, and indicates that differentiation between reserve-cell-rich, benign sebaceoma and low-

grade sebaceous carcinoma may not be possible for all lesions. In fact, apparently benign sebaceous tumors in humans may demonstrate overt features of malignancy in recurrent lesions and do occasionally metastasize (Misago et al., 2002). For this reason, some human dermatopathologists prefer to keep sebaceous epithelioma as a separate category from sebaceomas with fewer reserve cells, based on the similarity of its locally invasive biologic behavior to basal cell carcinoma (Dinneen & Mehregan, 1996).

A recent human study using several markers for cellular proliferative activity revealed no significant differences for silver-positive nucleolar organizer regions (AgNOR) counts, proliferating cell nuclear antigen (PCNA) labeling, and Ki67 (another proliferating nuclear antigen expressed during all active phases of the cell cycle) labeling between sebaceoma and basal cell carcinoma, but all three markers were significantly higher in classic sebaceous carcinomas (Ansai et al., 1995). Similar studies comparing compound sebaceous adenomas, epitheliomas, and 'epitheliomatous' carcinomas in dogs (see p. 650) would be very helpful to confirm biologic differences among these entities and to determine if certain morphologic subsets of epithelioma might warrant reclassification. The authors believe that the designation 'epithelioma', in contrast to sebaceoma, is still nosologically useful, at least temporarily, as it specifies a histologic pattern that may possess low malignant potential.

Clinical features

Sebaceous epitheliomas are fairly common neoplasms in dogs. They are rare in cats. Analogous neoplasms develop from the specialized sebaceous glands of the eyelid and are designated meibomian epitheliomas. Reported incidence is difficult to ascertain, as some authors have regarded sebaceous epithelioma as a variant of sebaceous adenoma (Goldschmidt & Shofer, 1992), similar to the human sebaceoma classification system, while others, particularly in older literature, do not clearly separate it from sebaceous carcinoma (Nielsen, 1981; Conroy, 1983). In the authors' experience, the ratio of sebaceous epitheliomas to sebaceous adenomas is approximately 1 : 2. These data correlate well with a study by Scott et al. (2001), who found that 37% of canine sebaceous tumors were epitheliomas.

Sebaceous epitheliomas are firm, nodular, fungiform, or plaque-like masses ranging from several millimeters to several centimeters in diameter. Eyelid lesions rarely exceed 5 mm. The tumors may be multiple, either synchronously or metachronously. Ulceration is frequent. Some tumors, particularly those on the eyelids, are heavily melanized and may be confused clinically with melanocytic neoplasms. Sebaceous epitheliomas occur most often on head, ears, and dorsum.

Affected animals are middle-aged or older. Breeds that are reported to be at increased risk for sebaceous tumors in general, particularly Cocker Spaniels, also have a higher incidence of sebaceous epitheliomas (see sebaceous adenoma, p. 645).

Sebaceous epitheliomas, as defined in dogs in most existing references, can be locally aggressive, may recur deeply after surgical excision, but exhibit lymphatic invasion or regional lymph node metastasis only in rare cases. Meibomian epitheliomas may recur after incomplete excision, but deep recurrence or metastasis has not been observed. The current World Health Organization classification also regards sebaceous epithelioma as a low-grade malignancy (Goldschmidt et al., 1998). Nevertheless, the true malignant potential, if any, of sebaceous epithelioma is still unknown; the possibility that both completely benign tumors (compound sebaceous adenomas) and low-grade malignancies (epitheliomatous sebaceous carcinomas) are being inadvertently included in this category must be considered. Histologic parameters such as large size, irregular tumor margins, and high mitotic rate may be of negative prognostic significance. More careful evaluation for features such as mitotic atypia may reveal a higher incidence of sebaceous carcinoma than previously suspected. Retrospective studies on large case series and application of cell proliferation markers (see above) would aid in determining if compound sebaceous adenoma needs to be assigned a broader morphologic range to include some lesions currently classified as epithelioma, and if stricter criteria for diagnosis of sebaceous carcinoma can be established.

Histopathology (Figures 24.8 and 24.9)

Sebaceous epitheliomas are composed of multiple, large, irregular islands of epithelial reserve cells. Some anastomosing trabeculae and cords of reserve cells may be present. The margins of the neoplasm vary from well-circumscribed in smaller lesions to irregular and infiltrative in larger masses. Similar to basal cell carcinoma (see Chapter 22), multifocal contiguity with the overlying epidermis is present. Ulceration is common, and is often diffuse in larger sebaceous epitheliomas. There is a sparse to moderate stroma of reactive collagenous tissue.

The majority of cells of the neoplasm resemble the basaloid reserve cells at the periphery of normal sebaceous glands. These are fairly small, polyhedral cells with scant, eosinophilic cytoplasm and ovoid, vesicular, fairly uniform nuclei. Nucleoli are small and may be multiple. Peripheral palisading is not present. Mitotic activity varies

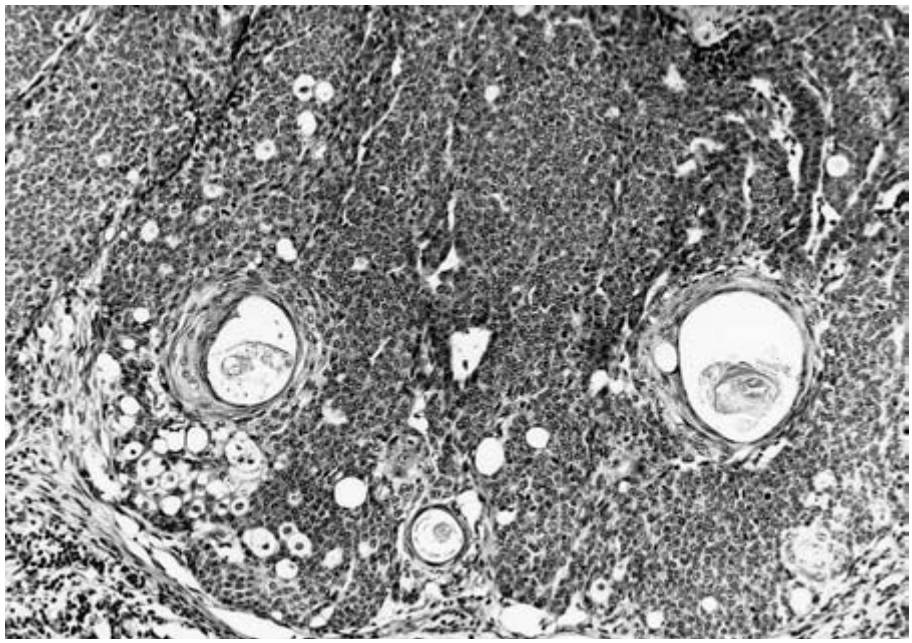


Fig. 24.8 Sebaceous epithelioma in a dog. Lobules and anastomosing trabeculae of reserve cells predominate. Note the individual and clustered mature sebocytes and small keratinizing ducts.

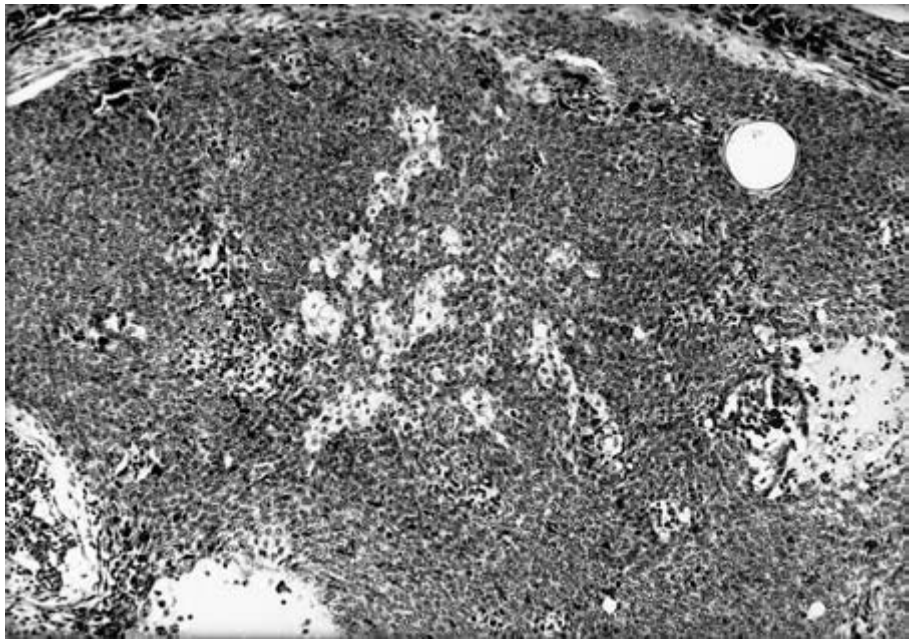


Fig. 24.9 Pigmented meibomian epithelioma in a dog. Clusters of pale mature sebocytes are scattered among sheets and lobules of homogeneous basaloid reserve cells. Note melanization of the epithelial cells and large, dark melanophages in the stroma.

from moderately low to fairly high; the mitotic index is usually higher than expected for a normal reserve cell population. There are multiple small foci of distinct sebaceous differentiation characterized by individual cells or clusters of cells with expanded, lipidized cytoplasm. Nuclei of the mature sebocytes are often crenated. Atypical nuclei are not found, and the mature sebocytes are not mitotically active. Larger foci of mature sebocytes may have necrosis and/or cystic degeneration. Most lesions also have small ducts lined by mature squamous epithelium and containing small amounts of keratin; these resemble normal sebaceous gland ducts. Secondary inflammation, ranging from subacute to granulomatous, is often present.

Meibomian epitheliomas have a much greater tendency to melanize than sebaceous epitheliomas in other locations. Pigmented tumors have variable numbers of melanin granules within the basaloid epithelial cells as

well as many dendritic melanocytes and melanophages in the stroma.

Rare sebaceous epitheliomas contain small numbers of glandular structures with apocrine features, characterized by columnar cells with eosinophilic or glycogenated cytoplasm. This so-called 'sebo-apocrine' pattern has also been observed in human sebaceous epithelioma, as well as in a variety of other adnexal tumor types (Okuda et al., 1995). This divergent differentiation is not surprising considering that both adnexal glands arise embryologically from adjacent foci of partially committed stem cells of hair follicles (see introduction, Chapter 25).

Differentiation of sebaceous or meibomian epithelioma with relatively numerous mature sebocytes from compound sebaceous adenoma is problematic. Smaller size, better circumscription, retention of lobular architecture, larger proportion of mature sebocytes, frequent ducts, and low mitotic activity support a diagnosis of compound sebaceous adenoma. However, meibomian epitheliomas are often small and well-circumscribed, and differentiation is based primarily on higher mitotic rate and increased proportions of basaloid to mature cells in epitheliomas. Compound sebaceous adenomas and sebaceous/meibomian epitheliomas are in reality part of a continuum of sebaceous neoplasia, and objective criteria to distinguish between them have not been fully established. Lesions with approximately 90% or more reserve cells and 10% or fewer mature sebocytes are currently regarded as sebaceous epitheliomas.

Distinction between sebaceous epithelioma and 'epitheliomatous' sebaceous carcinoma (see below) is similarly problematic and currently controversial, as reproducible criteria to differentiate these two closely-related entities are still being evaluated. Both are characterized by a marked predominance of basaloid reserve cells, but carcinomas show increased nuclear size and higher mitotic activity with atypical mitotic figures. The authors believe that the presence of mitoses in intermediate cells and fully-lipidized sebocytes warrants a diagnosis of carcinoma. Epitheliomatous sebaceous carcinomas are often larger and have increased peripheral invasiveness in comparison to the majority of sebaceous epitheliomas.

Solid basal cell carcinoma may need to be differentiated from sebaceous epithelioma. Sebaceous epitheliomas usually contain at least occasional tumor cells with lipidized cytoplasm, whereas true basal cell carcinoma with sebaceous differentiation is not a recognized entity in animals. The predominant reserve cells of epitheliomas are slightly larger and more eosinophilic than those of basal cell carcinoma and do not exhibit peripheral palisading or cytologic atypia. In addition, the architecture of basal cell carcinoma is typically plaque-like, while sebaceous epithelioma tends to be fungiform.

SEBACEOUS CARCINOMA

Clinical features

Sebaceous carcinomas are rare malignant neoplasms in cats and dogs. Histologically identical lesions of the specialized sebaceous glands of the eyelids are designated meibomian gland carcinomas. Sebaceous carcinoma was diagnosed in 0.8% of all canine skin and subcutaneous tumors in a large survey in the older veterinary literature (Strafuss, 1976), although histologic criteria were not specified. More recently, the incidence of sebaceous carcinoma was found to be 0.7% in dogs and 0.9% in cats (Goldschmidt & Shofer, 1992). In the authors' experience the occurrence seems to be considerably less frequent, probably less than 0.1% based on an informal survey of data from one author (E.J.W.); the cause for this discrepancy is unclear. It is possible that a variety of neoplasms comprising large, pale, finely vacuolated cells were assumed to be of sebaceous origin in previous surveys.

Sebaceous carcinomas are usually solitary, firm nodules up to 7.5 cm in diameter (Scott et al., 2001). Alopecia and ulceration are common. The majority of cases in both dogs and cats occur on the head. Interestingly, the eyelid is not reported as a site for sebaceous carcinoma in animals and is observed only rarely by the authors, although this is the most common location in humans.

The average age of affected animals ranges from 9 to 12 years (Strafuss, 1976; Goldschmidt & Shofer, 1992). Cocker Spaniels, Cavalier King Charles Spaniels, Scottish Terriers, and Siberian Huskies appear to be predisposed to develop sebaceous carcinomas (Goldschmidt & Shofer, 1992).

Sebaceous carcinomas can be locally aggressive, but reports of distant metastasis are rare in both dog and cat. Deep local recurrence and regional lymph node metastasis occur occasionally in tumors of this type. In contrast, eyelid sebaceous carcinomas in humans frequently recur and metastasize, and more recent reviews of extraocular sebaceous carcinomas also indicate a higher incidence of metastasis than previously suspected (Jensen, 2000; Moreno et al., 2001).

The authors have elected to separate sebaceous carcinomas that are predominantly sebocytic ('sebocytic' sebaceous carcinoma) from lesions that are composed predominantly of reserve cells, resembling sebaceous epitheliomas ('epitheliomatous' sebaceous carcinoma). This division is somewhat artificial, as the neoplasms show a morphologic spectrum, but may be helpful in refining diagnostic criteria and assessing relative biologic behavior in the future. It is unclear at the present time what proportion of neoplasms usually interpreted as sebaceous/meibomian epitheliomas (see p. 647) might be more appropriately placed in the epitheliomatous carci-

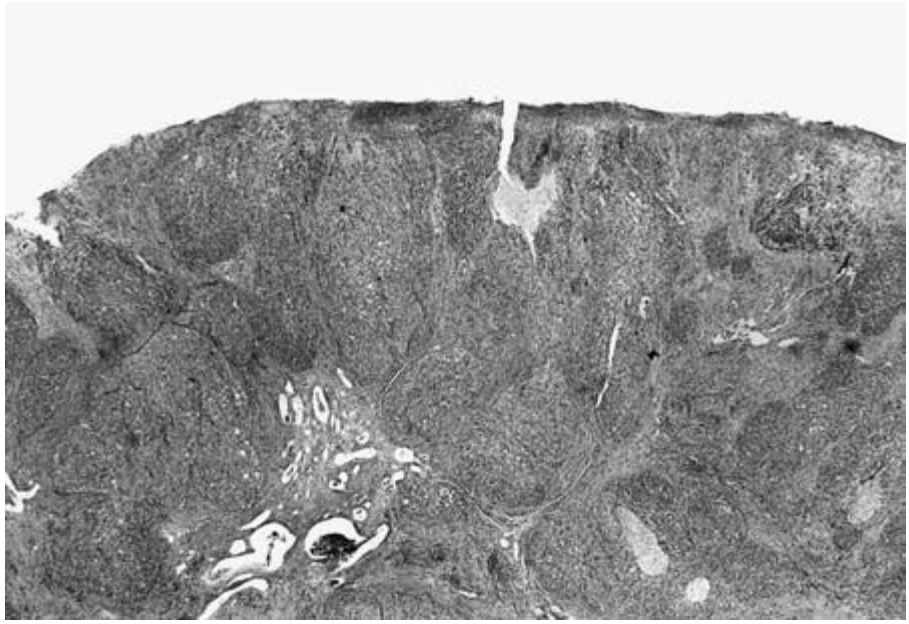


Fig. 24.10 Sebocytic sebaceous carcinoma in a dog. Multiple epithelial lobules form a large, ulcerated, plaque-like mass.

noma category. Application of cell proliferation markers (see sebaceous epithelioma, p. 647) may assist in further differentiation, as will long term clinical studies relating morphology and outcome.

Histopathology

Sebocytic sebaceous carcinoma (Figures 24.10 through 24.13)
Sebocytic sebaceous carcinomas are irregular but circumscribed, multilobular dermal neoplasms composed of islands of epithelial cells that are usually larger than basaloid reserve cells. Ulceration may be present in larger lesions. There may be invasion of the underlying subcutis. The tumor lobules are delineated by a sparse to moderate collagenous stroma without stromal–epithelial cleft formation. Necrosis and cystic degeneration may be present in the centers of the lobules. Orderly centripetal progression from basaloid reserve cells to intermediate cells to obvious sebocytes is markedly distorted or absent. Squamous differentiation, with or without keratin pearl formation, is often present and may be extensive. Small numbers of sebaceous carcinomas contain occasional glandular structures lined by columnar epithelial cells that may show decapitation secretion; this sebo-apocrine pattern is also described in sebaceous carcinomas in humans (Misago & Narisawa, 2001).

Neoplastic cells have eosinophilic cytoplasm with variable vacuolation. Sebocytic sebaceous carcinomas have small to moderate numbers of cells with finely-dispersed lipid droplets resembling normal mature sebocytes. Lipid vacuoles may be larger in size and fewer in number than

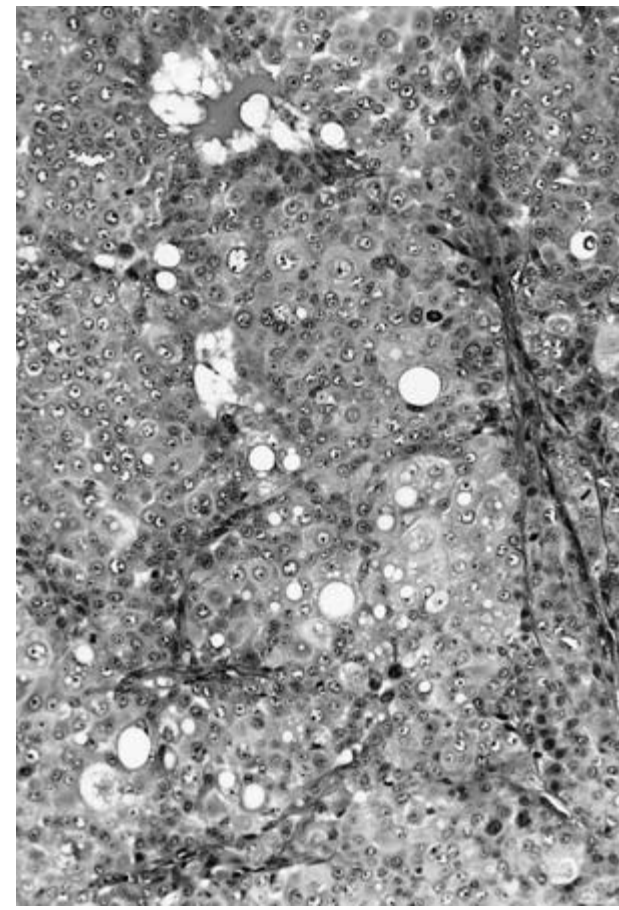


Fig. 24.11 Higher magnification of Fig. 24.10. Some of the large, round to polygonal cells contain one or more lipid vacuoles of varying size; the majority are undifferentiated or squamoid. Note moderately high mitotic activity.

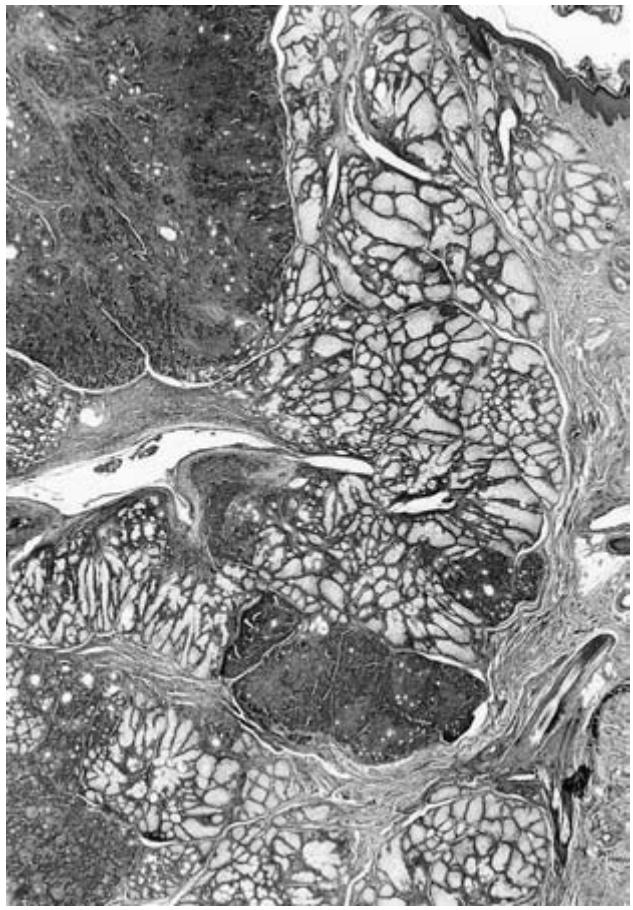


Fig. 24.12 Sebocytic sebaceous carcinoma arising within sebaceous adenoma in a dog. Pale lobules of benign, mature sebocytes contrast with large dark islands of highly cellular carcinoma.

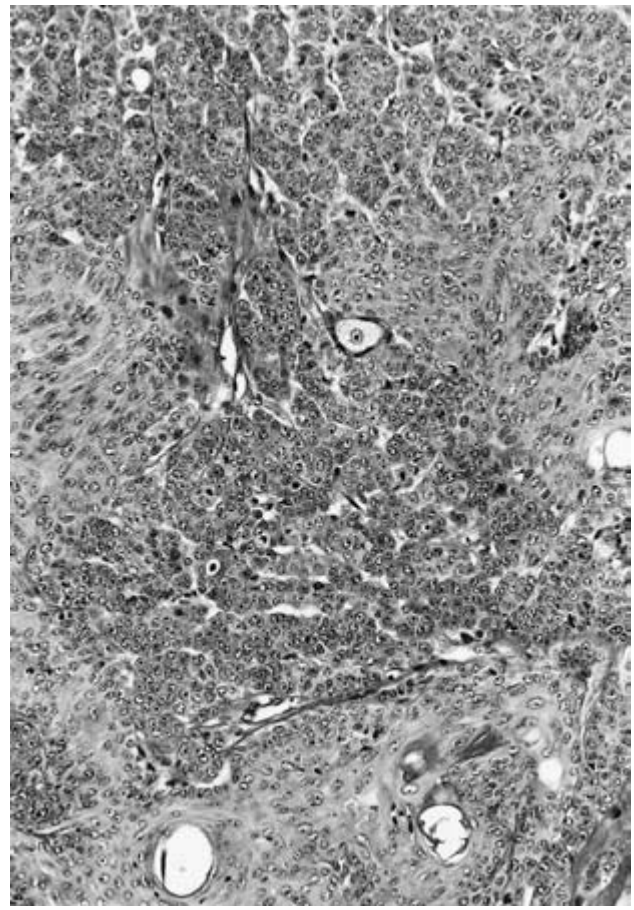


Fig. 24.13 Higher magnification of Fig. 24.12. The sebaceous carcinoma comprises a haphazard admixture of enlarged reserve cells, intermediate cells, and squamous cells. Note the giant fully-lipidized sebocyte in the center.

in normal sebocytes. Bizarre, lipidized giant cells are occasionally present. Poorly-differentiated tumors have sebaceous features limited to small numbers of cells that have clear or finely-granular cytoplasm without obvious lipid content. Other cells in sebocytic sebaceous carcinoma vary from polyhedral to polygonal and have moderate to abundant, pale eosinophilic cytoplasm. In areas of squamous metaplasia, the cells resemble well-differentiated squamous cell carcinoma (see Chapter 22); complete cornification with extracellular deposits of keratin may represent attempts at duct formation. Occasional tumors have zones of hepatoid-type cells (see nodular sebaceous hyperplasia, p. 641). Nuclei are large and have prominent nucleoli and variable chromatin patterns. Crenation of nuclear membranes is often observed in better-differentiated sebocytes. Mitotic activity varies from moderately low to moderately high, and atypical mitotic figures can usually be detected.

Clear cell basal cell carcinoma and squamous cell carcinoma with significant glycogen content are differential diagnoses for sebocytic sebaceous carcinoma, as well as anaplastic carcinomas containing clear or vacuolated cells. Most sebaceous carcinomas contain at least some cells with multiple round vacuoles or foamy cytoplasm indicative of lipid content; these are usually admixed with squamoid cells and large polyhedral cells in varying proportions. Clear cell basal cell carcinomas generally have more uniform cytologic features and diffuse glycogenic vacuolation. Sebaceous carcinoma does not have stromal–epithelial cleft formation as observed in most clear cell basal cell carcinomas. The epithelial aggregates of squamous cell carcinoma show a more orderly transition from basal cells peripherally to fully-keratinized cells and keratin deposits centrally. Differentiation from poorly-differentiated carcinomas may not be possible at the light microscopic level. A positive lipid stain, e.g. oil red O, performed on wet tissue distinguishes sebaceous carcinoma from clear cell basal cell carcinoma and squamous cell carcinoma as well as from anaplastic carcino-

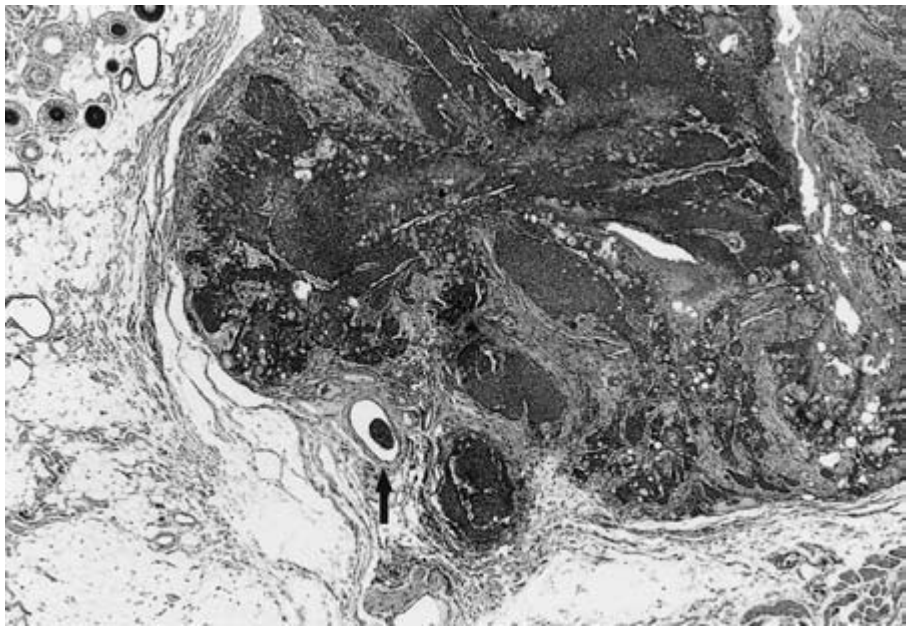


Fig. 24.14 Epitheliomatous sebaceous carcinoma in a dog. The small cell predominance is reminiscent of sebaceous epithelioma, but the aggregates are more pleomorphic. Note that the tumor extends into the panniculus, and there is one focus of vascular invasion (arrow).

mas with clear or vacuolated cells. Sebaceous carcinomas rarely, if ever, show a diffusely-vacuolated large cell population; thus, clear cell apocrine ductular carcinoma and balloon cell melanoma would not need to be considered as differential diagnoses.

Liposarcoma rarely involves dermis but may need to be distinguished from sebaceous carcinoma in these instances. Although both sebaceous carcinomas and liposarcomas have lipid-laden cells, most sebaceous carcinomas have a multilobular architecture, which is absent in liposarcomas. The majority of liposarcomas contains at least some cells with single large lipid vacuoles and peripherally displaced nuclei very similar to mature lipocytes. Immunohistochemistry also may be helpful (see below).

Epitheliomatous sebaceous carcinoma (Figures 24.14 through 24.16)

Epitheliomatous sebaceous carcinoma is an irregular but circumscribed dermal neoplasm composed predominantly of basaloid reserve cells in islands, cords, and trabeculae; the islands generally have angular profiles. Small duct-like structures lined by mature squamous epithelium and containing small amounts of keratin and sebocytic debris are seen in some lesions. The tumors often have a fungiform architecture, and multifocal epidermal contiguity is observed. Ulceration is present and frequently extensive. These neoplasms have infiltrative margins, and there may be invasion of the underlying subcutis. Foci of caseation necrosis and cystic degeneration are common. Rarely, lymphatic invasion is identified. The tumor has a sparse to moderate collagenous stroma without stromal–epithelial cleft formation.

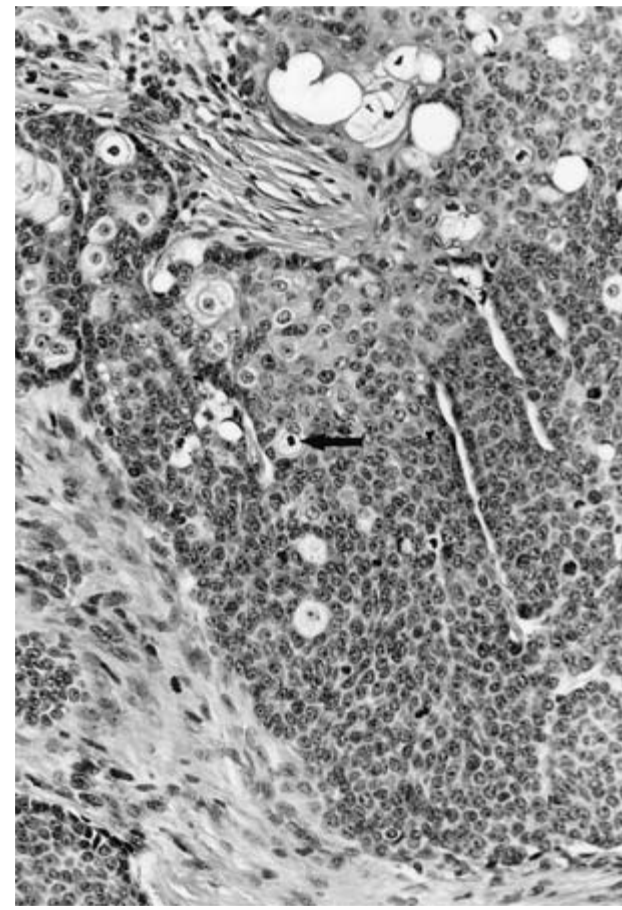


Fig. 24.15 Higher magnification of Fig. 24.14. The predominant reserve cells are fairly homogeneous but show brisk mitotic activity. Several fully-differentiated sebocytes also have mitotic figures (arrow).

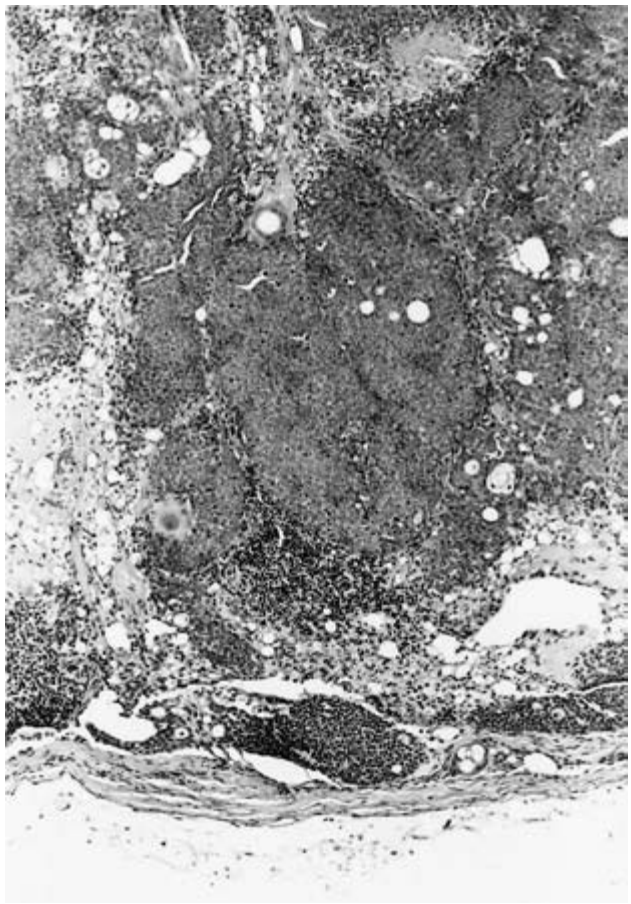


Fig. 24.16 Regional lymph node metastasis of epitheliomatous sebaceous carcinoma of Fig. 24.14.

The basaloid reserve cells are polyhedral and have scant to moderate, pale eosinophilic to amphophilic cytoplasm; they tend to be slightly larger than those in sebaceous epitheliomas. Peripheral palisading and melanization are generally not seen. Nuclei are large, ovoid, and vesicular; nucleoli are small and multiple. As in sebaceous epithelioma, there are scattered small foci of advanced sebaceous differentiation characterized by individual cells or clusters of cells with expanded, lipidized cytoplasm. Nuclei of the mature sebocytes may be small and crenated, or they may be large and vesicular with prominent nucleoli. Aggregates of intermediate cells, which have moderate, pale eosinophilic, finely-granular cytoplasm, may be present between the basaloid cells and differentiated sebocytes. The mitotic activity of the basaloid reserve cells is moderate to high. Atypical mitotic figures are present, and some of the mitotic figures are located in differentiated sebocytes in addition to the reserve cell population. Mature sebocytes in normal glands, hyperplastic glands, and adenomas are terminally differentiated and should not be mitotically active; the finding of mitoses in fully-differentiated sebaceous cells is, therefore, indicative of malignancy.

Distinction between sebaceous epithelioma and epitheliomatous sebaceous carcinoma is problematic and currently controversial. These two entities are probably closely adjacent in the continuum of sebaceous neoplasia. Both are characterized by a marked predominance of basaloid reserve cells, but the carcinomas show increased nuclear size and higher mitotic activity with atypical mitotic figures. The authors believe that the presence of mitoses in intermediate cells and fully-lipidized sebocytes warrants a diagnosis of carcinoma. Epitheliomatous sebaceous carcinomas are often larger, have more pleomorphic cellular aggregates, and have increased peripheral invasiveness in comparison to the majority of sebaceous epitheliomas. Retrospective studies on large case series and application of proliferation markers would be of great benefit in determining if these histologic criteria correlate well with cellular kinetics and biologic behavior (see sebaceous epithelioma, p. 647).

Solid basal cell carcinoma may need to be differentiated from epitheliomatous sebaceous carcinoma. Sebaceous carcinomas usually contain at least occasional sebocyte tumor cells with lipidized cytoplasm, whereas true basal cell carcinoma with sebaceous differentiation is not a recognized entity in animals. The predominant reserve cells of epitheliomatous sebaceous carcinomas are slightly larger and more eosinophilic than those of basal cell carcinoma and do not exhibit peripheral palisading. In addition, the architecture of basal cell carcinoma is typically plaque-like, while sebaceous carcinoma tends to be fungiform. Oil red O or other lipid stain may be required to differentiate a poorly-differentiated, small cell-predominant sebaceous carcinoma from basal cell carcinoma.

Immunohistochemistry

Immunohistochemical staining with multiple individual cytokeratins (CKs) and cytokeratin cocktails can differentiate sebaceous carcinoma from most other epithelial cell types, although the number of stains required seems cumbersome and impractical (Murata et al., 1993; Ansai et al., 1994; Goldschmidt et al., 2002). In humans, the majority of sebaceous carcinomas stain with AE1 (CKs 10, 14, 15, 16, 19), LP34 (CKs 1, 5, 6, 8, 10, 14, 18), CK8, and CK19 but are negative with CK1 and CK13; differences in staining with one or more of these reagents allow distinction from squamous cell carcinoma, basal cell carcinoma, malignant tricholemmoma, and some but not all types of sweat gland carcinomas (Murata et al., 1993; Ansai et al., 1994). In dogs and cats, normal and neoplastic sebocytes (but not reserve cells) were found to stain only with the polyclonal reagent 34βE12 (CKs 1, 5,

10, 11) and were negative with AE1, AE3 (CKs 1–8), CAM5.2 (CK7/8) and CK10; the latter markers, in addition to 34βE12, stained one or more of all of the epidermal, follicular and sweat gland tumors that were evaluated, allowing diagnosis of sebaceous origin by exclusion (Goldschmidt et al., 2002). Positive CK immunostaining of any type will rule out a diagnosis of liposarcoma.

Goldschmidt's group also found that CD79a, the pan-B lymphocyte marker, lightly stained canine sebocytes when used with a modified streptavidin–biotin technique (Goldschmidt et al., 2002). The biochemical basis for this phenomenon is as yet unknown; however, the signaling molecule of B lymphocytes, against which the CD79 antibody was specifically developed, is not expressed in sebocytes. Spurious staining of several tissue types is known to occur with at least one commercially available clone of CD79a, and nonspecific endogenous avidin binding can be a technical problem in sebaceous glands as well as other tissue types when an avidin–biotin methodology is employed. Investigation into the nature of these chemical interactions would be required to determine if there is any diagnostic validity in the use of CD79a staining in sebaceous neoplasms.

It has recently been demonstrated that androgen receptors can be detected immunohistochemically in formalin-fixed paraffin-embedded tissue from a wide range of sebaceous tumor types in humans (Bayer-Garner et al., 1999). Adaptation of this technique for use in veterinary biopsy material may allow definitive diagnosis of equivocal cases with a single marker.

NODULAR PERIANAL GLAND HYPERPLASIA AND PERIANAL GLAND ADENOMA

(Synonyms: nodular hepatoid gland hyperplasia and hepatoid gland adenoma)

Hepatoid glands are modified sebaceous glands in canids located primarily in perianal skin. They can also be found circumferentially around the proximal third of the tail, in the dorsal lumbosacral area, lateral to the prepuce, and along the ventral midline as far cranial as the neck. Although they are present at birth in both males and females, hepatoid glands are larger and more extensive in adult males, suggesting stimulation by androgenic hormones (Isitor & Weinman, 1979). They are not found in cats. The etiology of perianal gland hyperplasia and neoplasia has not been definitively proven, but gonadal hormones appear to play an important role. Androgen binding sites were identified in perianal adenomas in an early report (Wilson & Hayes, 1979). A causal relationship is also implied by the more frequent occurrence in intact male dogs and regression of a large percentage of benign perianal gland tumors following castration alone (Wilson & Hayes, 1979).

Clinical features

Benign perianal (hepatoid) gland proliferations, including hyperplasia and adenoma, are common lesions in dogs and account for 8% to 18% of all canine skin tumors as indicated in several surveys (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992). Perianal gland hyperplasia/adenoma generally has a nodular or polypoid configuration, but hyperplasia may also present as an annular perianal growth. The size of hyperplastic nodules and benign neoplasms varies from several millimeters to 10 cm. Lesions are often multiple, and ulceration is common in larger masses. The nodules have a rubbery consistency and tan coloration.

Because of the widespread normal distribution of hepatoid glands, hyperplastic and neoplastic lesions are not limited to the classical perianal or ventral tailbase location, but can be found anywhere on the tail or trunk. Other aberrant sites, including the head and feet, also have been observed.

Hepatoid gland proliferations of all types occur more frequently in intact males than in females or neutered males. Wilson's data indicate a ratio of males to females of 6:1; the ratio in neutered females to intact females is 3:1 (Wilson & Hayes, 1979). A more recent large-scale survey found only a 3:1 ratio of affected males to females and almost equal proportions of neutered females to intact females (Goldschmidt & Shofer, 1992). This shift may reflect decreased numbers of intact male dogs as well as a trend to neutering at a younger age; both of these factors would contribute to altered proportions of gonadal hormone levels. Most animals with perianal gland tumors are 8 years of age or older. Breed predilections are reported in Cocker Spaniels, Samoyeds, Siberian Huskies, English Bulldogs, Beagles, and mixed breeds (Wilson & Hayes, 1979; Goldschmidt & Shofer, 1992).

Histopathology

Nodular perianal gland hyperplasia (Figure 24.17)
Perianal gland hyperplasia comprises multiple enlarged lobules of well-differentiated hepatoid cells with a single peripheral layer of basaloid reserve cells. The lobules may form a spherical mass or thick plaque. Spherical masses are sometimes pedunculated. Overall glandular architecture is well-maintained; lobules are discernible as discrete units that are frequently centered around small ductal structures. Lobules within an individual lesion are of approximately equal size. Stromal collagen is sparse.

Mature hepatoid cells are characterized by abundant,

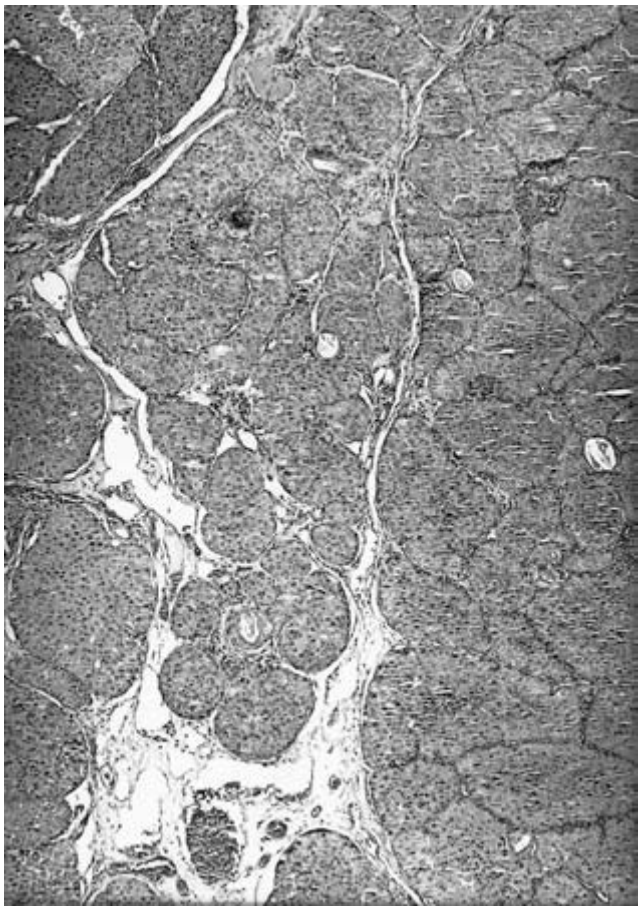


Fig. 24.17 Nodular perianal gland hyperplasia in a dog. Well-demarcated lobules of hepatoid glands and scattered ducts are still discernible.

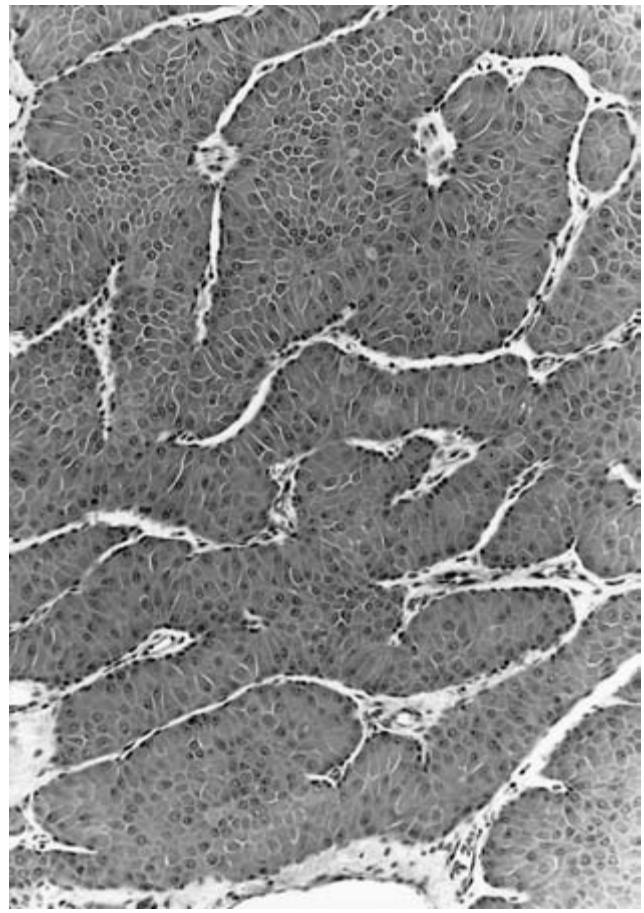


Fig. 24.18 Perianal gland adenoma in a dog. Well-differentiated hepatoid cells are arranged in anastomosing trabeculae.

polygonal, eosinophilic cytoplasm, resembling hepatocytes (thus, 'hepatoid'). Nuclei are centrally located, ovoid, and vesicular, and have small nucleoli. Mitotic activity is low and is confined to the reserve cell layer, which has typical basaloid morphology. The small interlobular ducts are lined by flattened, keratinizing epithelial cells.

Nodular perianal gland hyperplasia is distinguished from perianal gland adenoma by persistence of uniform lobular architecture, in contrast to the trabeculae or islands of hepatoid cells found in adenomas. Necrosis is uncommon in hyperplastic lesions, and sinusoidal vasculature is not present. Several parameters associated with silver-positive nucleolar organizer regions (AgNORs), which are indicators of proliferative activity, show significant differences among perianal gland lesions. Mean AgNOR count and relative AgNOR area are lower in nodular hyperplasia than in adenomas (1.6 versus 1.88 and 4.41% versus 5.18%, respectively). This is associated with a significant decrease in mean nuclear area from 109.3 μm^2 in hyperplasia to 94.1 μm^2 in adenoma (Preziosi et al., 1995).

Perianal gland adenoma (Figures 24.18 through 24.21)

Perianal adenoma is a well-circumscribed nodular or multinodular mass usually comprising broad, anastomosing trabeculae of well-differentiated hepatoid cells and a single peripheral layer of basaloid reserve cells. Small islands of cells may also occur and are occasionally the predominant architecture. The island configuration is more common in females. Discrete glandular lobules are not evident within the mass, and there is frequently compression of adjacent hepatoid glands. A thin fibrous capsule may be present. Most lesions have a delicate fibrovascular stroma. Some perianal adenomas, particularly those with a predominance of small epithelial islands, have a moderate to abundant stroma of mature collagen. Other tumors have mature adipose tissue as the primary stromal component. Perianal gland adenomas may be highly vascular and have dilated sinusoidal blood vessels separating the epithelial trabeculae. When the sinusoidal vessels are markedly dilated and hyperemic, this pattern is referred to as an 'angiomatoid' variant.

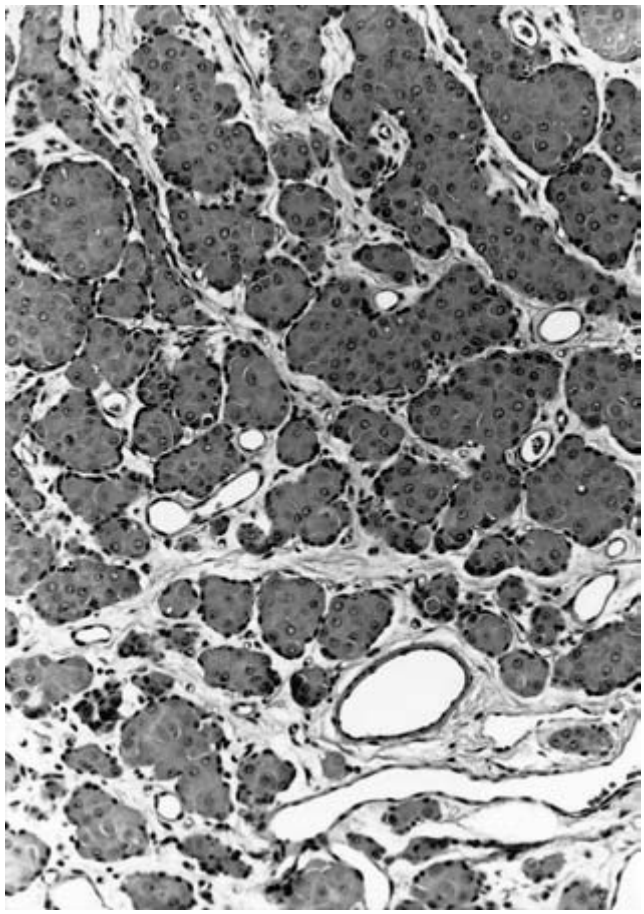


Fig. 24.19 Perianal gland adenoma in a dog. Well-differentiated hepatoid cells are often arranged in small islands and clusters.

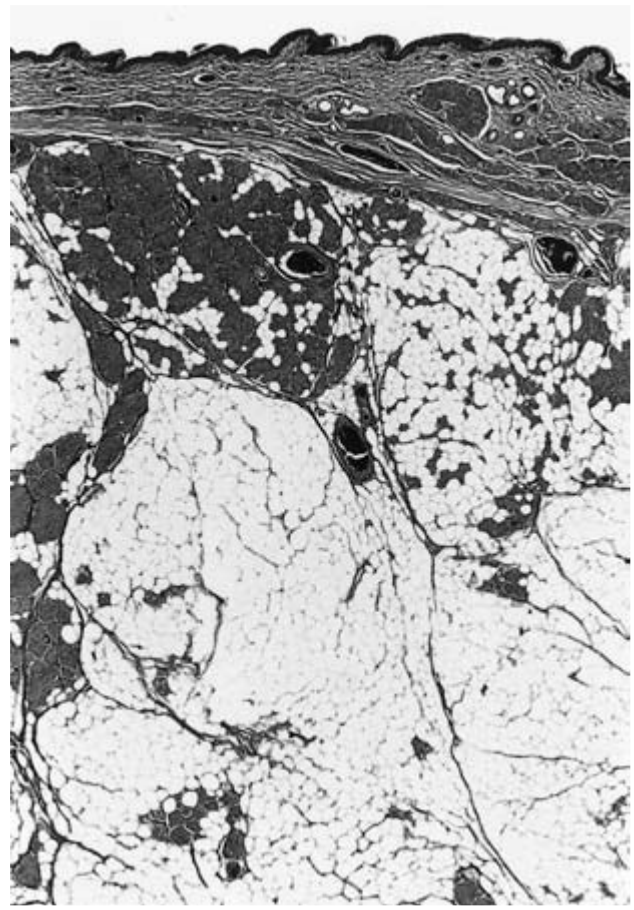


Fig. 24.20 Perianal gland adenoma in a dog. This variant has an abundant stromal component of mature fat.

Ulceration is common in larger perianal gland adenomas, and infarction may also occur. Infarcted perianal gland adenomas have a distinct pattern of inflammation characterized by caseation necrosis, granulomatous inflammation, fibrosis and cholesterol cleft formation. Most or all of the tumor tissue may be obliterated by this degenerative process. Hyperplastic glands are often found adjacent to perianal adenomas.

Cytologic features are identical to those of nodular perianal gland hyperplasia (see above). The hepatoid cells have uniform, eosinophilic cytoplasm, vesicular nuclei, and small nucleoli. Mitotic activity is low and is confined to the reserve cell layer. There are frequently small foci of squamous metaplasia with keratin pearl formation; this is consistent with abortive ductal differentiation. Occasional small zones of sebaceous differentiation, characterized by cells with multiple small lipid vacuoles, may be present.

Distinction between perianal adenoma and nodular hyperplasia is described above. Consistent identification of perianal adenoma, epithelioma, and well-differentiated carcinoma is problematic, in large part due to wide variation in histologic criteria offered by various investigators. The authors believe that neoplasms with more than 90% reserve cells, which have uniform nuclei, small nucleoli, and no mitotic atypia, should be classified as epitheliomas. Neoplasms exhibiting mildly disorganized architecture, irregular margins, scattered foci of sebaceous and/or squamous differentiation, prominent nucleoli, and mitotic activity in large hepatoid cells represent well differentiated carcinomas. Numbers of reserve cells in well differentiated carcinomas vary from mildly decreased to moderately increased, and atypical mitoses may be present. Perianal adenomas, in contrast, show relative uniformity of epithelial aggregates with a narrow rim of reserve cells at the periphery of the aggregates. The differentiated hepatoid cells in adenomas are not mitotically active.

The study of Preziosi et al. (1995) found that mean AgNOR count, mean AgNOR area, and relative AgNOR area are all significantly lower in adenomas than in carcinomas (1.88 versus 2.41, 4.88 versus 6.47 μm^2, and 5.18% versus 8.37%, respectively). This was associated with a significant decrease in mean nuclear area from

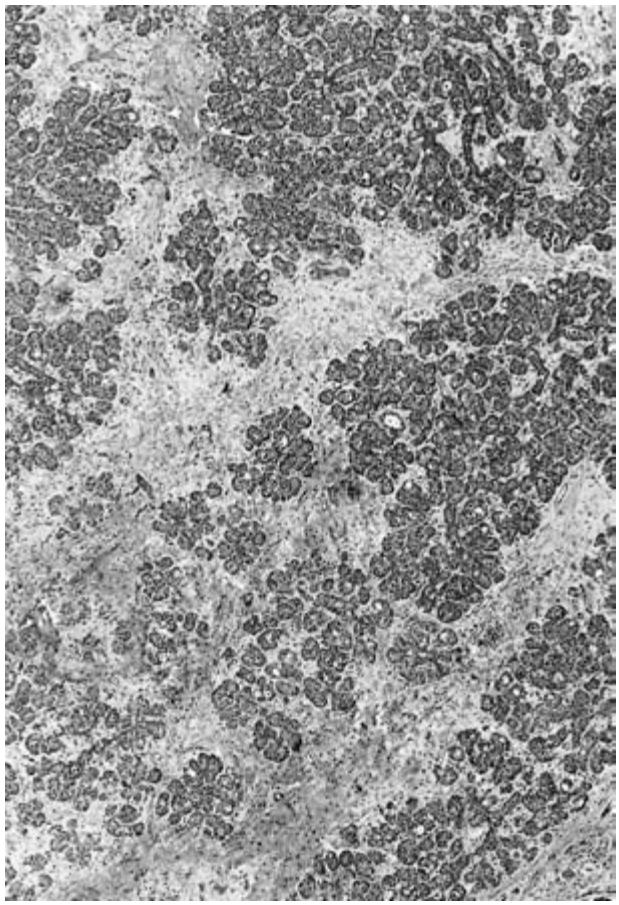


Fig. 24.21 Perianal gland adenoma in a dog featuring abundant fibrous stroma, and small epithelial aggregates as in Fig. 24.19.

94.1 μm^2 in adenoma to 76.6 μm^2 in carcinoma, although perianal gland epithelioma (see below) may have been included in the carcinoma group (Preziosi et al., 1995). Application of other markers of cellular proliferative activity, such as Ki67 (a proliferating nuclear antigen expressed during all active phases of the cell cycle) and proliferating cell nuclear antigen (PCNA), may help to substantiate these differences and refine diagnostic criteria.

PERIANAL GLAND EPITHELIOMA

(Synonym: hepatoid gland epithelioma)

Perianal gland epithelioma is histologically analogous to sebaceous epithelioma, but its biologic behavior may not be identical. Lesions consistent with perianal gland epitheliomas have been combined with perianal gland adenomas by several authors (Conroy, 1983; Pulley & Stannard, 1990; Goldschmidt & Shofer, 1992). Perianal epitheliomas are listed as a separate category in the revised World Health Organization classification (Goldschmidt et al., 1998). Epitheliomas were included with low-grade perianal gland carcinomas in *Veterinary Dermatopathology* (Walder & Gross, 1992), but the authors now believe that they are distinctive enough to warrant separate classification. Additional retrospective studies, and application of cell proliferation markers (see perianal gland adenoma, p. 655) will help to clarify their proper nosologic placement and determine if they possess any metastatic potential.

Clinical features

Perianal epitheliomas are rare neoplasms of dogs that are either benign or of low-grade malignancy. They are clinically similar to adenomas, but are usually ulcerated. Age and breed profiles have not been established for this particular tumor type, but are probably similar to both adenoma and carcinoma.

Recurrence is seen occasionally, but the authors have not observed metastasis. Six of 23 perianal gland tumors described only as 'moderately or poorly differentiated adenomas' recurred but did not metastasize in one study; however, this group probably included epitheliomas as well as well-differentiated carcinomas (Berrocal et al., 1989).

Histopathology (Figure 24.22)

Perianal gland epitheliomas are composed primarily of basaloid reserve cells arranged in sheets, islands, and anastomosing trabeculae. There is a sparse collagenous stroma. The margins of epitheliomas tend to be irregular and mildly infiltrative. The basaloid reserve cells have scant, amphophilic cytoplasm, and ovoid, vesicular nuclei. Nucleoli are small. Mitotic activity varies from moderately low to moderately high. Scattered clusters of cells exhibit typical hepatoid features characterized by abundant, eosinophilic cytoplasm and larger, vesicular nuclei. Mitotic activity is not observed in the mature hepatoid cells. Small foci of ductular differentiation may be present.

Distinction between perianal gland epithelioma and adenoma is straightforward using the above-stated criteria; adenomas contain small numbers of reserve cells that are limited to the periphery of the epithelial aggregates. The differentiated hepatoid cells in adenomas are not mitotically active. The authors believe that neoplasms with more than 90% reserve cells, which have uniform nuclei, small nucleoli, and no mitotic atypia, should be classified as epitheliomas. Perianal gland epithelioma is differentiated from carcinoma by the absence of nuclear atypia, absence of mitotic atypia, and absence of mitotic activity within differentiated hepatoid cells.

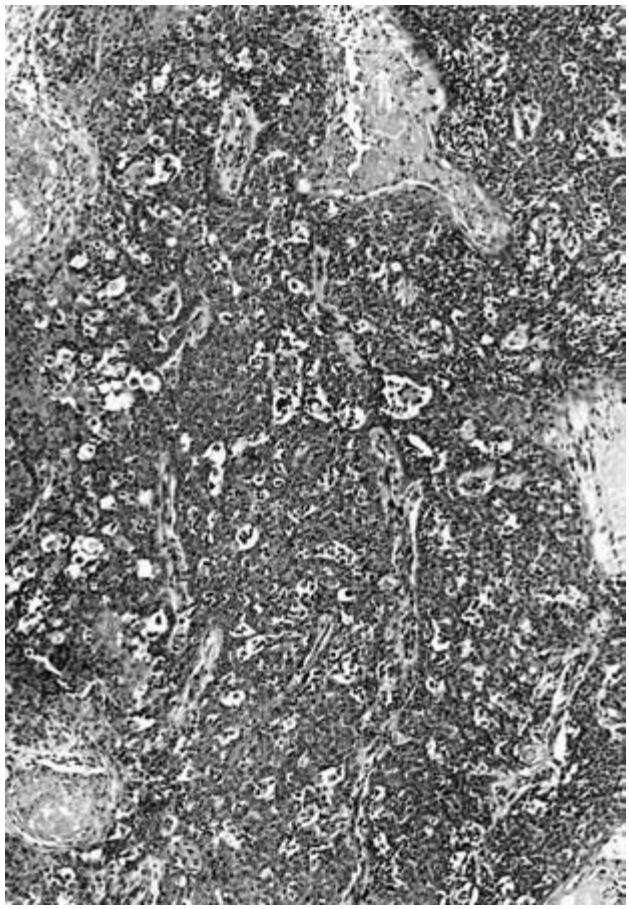


Fig. 24.22 Perianal gland epithelioma in a dog. Anastomosing trabeculae are composed predominantly of homogeneous basaloid reserve cells; mature hepatoid cells are more numerous at the left.

PERIANAL GLAND CARCINOMA

(Synonym: hepatoid gland carcinoma)

Clinical features

Perianal gland carcinomas are uncommon malignant neoplasms of dogs that occur almost exclusively in a perianal location. The authors have seen rare examples on the dorsal tail and prepuce. Perianal gland carcinomas accounted for 2.6% of 1141 canine skin and subcutaneous neoplasms in a survey by one author (E.J.W.). In contrast, these tumors accounted for a mere 0.25% of all skin and soft tissue tumors in a very large series (Goldschmidt & Shofer, 1992). This discrepancy is undoubtedly a reflection of different histologic criteria used to determine malignancy in these neoplasms.

Well-differentiated carcinomas are clinically indistinguishable from adenomas. Most carcinomas are 2 cm or greater in diameter, but smaller nodules also occur. Poorly-differentiated carcinomas are large lesions that are firm, poorly circumscribed, and usually ulcerated.

The majority of perianal gland carcinomas occur in older male dogs. Arctic Circle breeds and German Shepherd Dogs showed a predisposition in one study (Vail et al., 1990).

Recurrence was observed in six of 23 neoplasms designated as 'moderately- or poorly-differentiated perianal gland adenomas'; however, this group probably included epitheliomas as well as low-grade carcinomas based on the histologic description given (Berrocal et al., 1989). Metastasis was not reported, although follow-up on the cases in that report was limited. In the retrospective study of Vail et al. (1990), 14 of 41 dogs had recurrence of their perianal carcinomas and 15% had regional and/or distant metastasis; unfavorable outcomes were closely correlated with an advanced clinical stage of disease at time of presentation. The authors believe that metastasis is common in poorly-differentiated perianal carcinomas, but infrequent in well-differentiated lesions, although this specific variable has not been addressed in the literature.

According to the review of Wilson and Hayes (1979), perianal gland carcinomas are not influenced by gonadal hormones and do not respond to castration; however, no histologic information was provided, and the reported clinical description of deep perirectal location and aggressive biologic behavior suggests that anal sac gland carcinomas may have been included in the study. Although, it seems reasonable that at least well-differentiated perianal carcinomas would retain gonadal hormone receptors, and therefore demonstrate sensitivity to hormonal manipulations, a more recent retrospective using appropriate histologic criteria found that castration indeed had no effect on the outcome of dogs with perianal carcinomas (Vail et al., 1990). Additional studies to quantify plasma gonadal hormone levels and cell surface hormone receptors in perianal gland carcinomas may help determine a biochemical basis for this unexpected phenomenon.

Histopathology (Figures 24.23 through 24.27)

Perianal gland carcinomas vary from well-differentiated to poorly differentiated. The majority are well differentiated. Well-differentiated perianal gland carcinomas have similar architecture and morphology to perianal gland adenomas, but variable infiltrative growth is present at the tumor margins. The tumor cells generally form solid islands and tightly-packed trabeculae. At low magnification, well differentiated carcinomas show partial to total loss of the typical adenoma pattern, characterized by discrete, repetitive trabeculae or islands of hepatoid cells cuffed by single layers of reserve cells; this imparts a 'sloppy' or crowded appearance to the lesion. Stromal collagen is usually sparse. Small foci of squamous

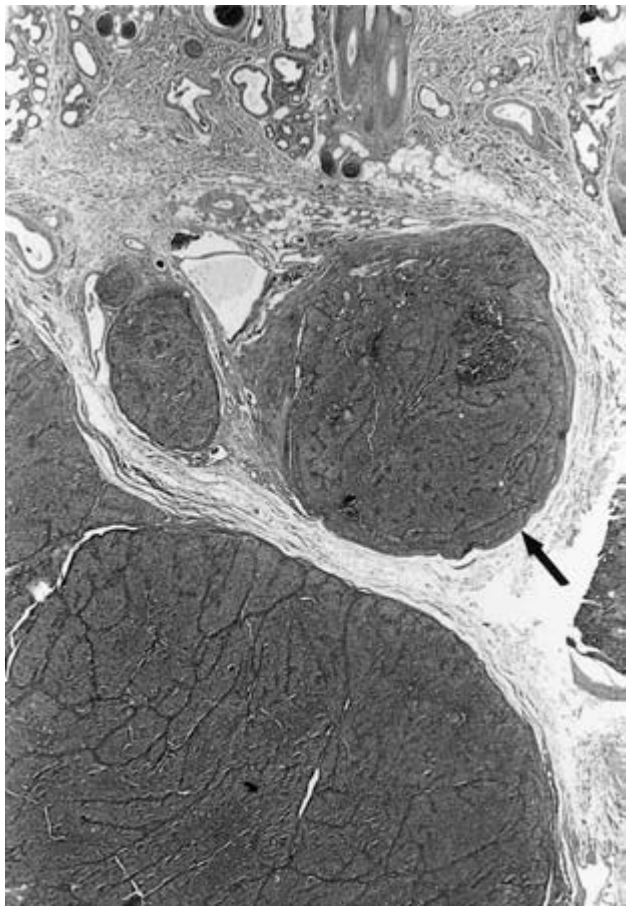


Fig. 24.23 Well-differentiated perianal gland carcinoma in a dog. At scanning magnification this tumor is indistinguishable from a perianal gland adenoma, but the lobule in the center is located within a large blood vessel (note vascular fibromuscular wall; arrow).

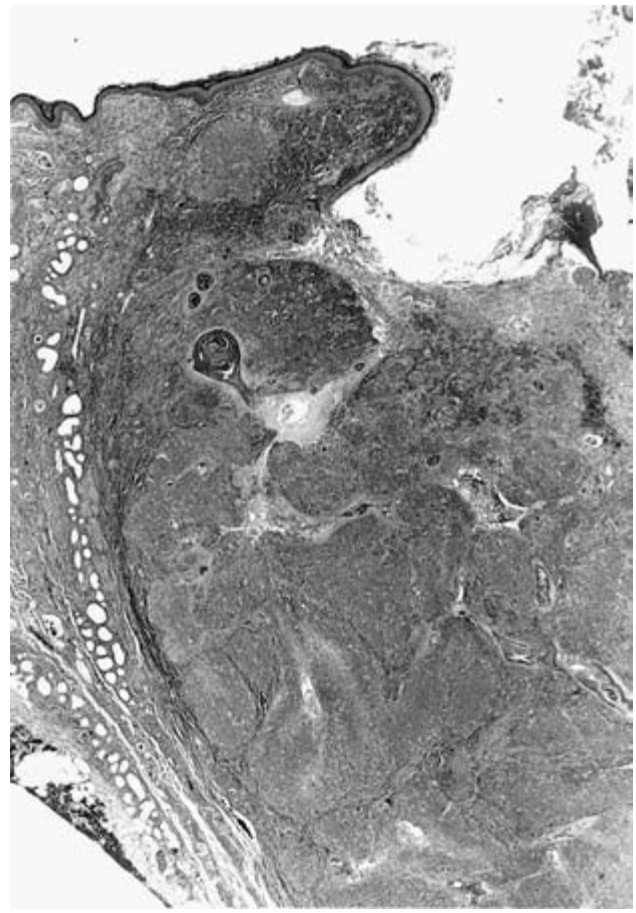


Fig. 24.24 Well-differentiated perianal gland carcinoma in a dog comprising irregular lobules and trabeculae of smaller cells. Note the central crateriform ulcer.

metaplasia with keratin pearl formation may be present. Ulceration, hemorrhage, and necrosis are common secondary features. Small foci of well-differentiated carcinoma may occur within adenomas, particularly large multilobulated lesions; this may represent carcinoma *in situ*.

In well-differentiated carcinomas, maturation patterns from reserve cells to hepatoid cells are somewhat haphazard, although a bimorphic population is still evident. Reserve cells show considerable variation in number between neoplasms and frequently within a given neoplasm. The majority of lesions have a mild to moderate increase in numbers of reserve cells in comparison to adenomas; these are concentrated at the periphery of the hepatoid cell aggregates, but may also occur in more central locations. Occasional tumors show primarily large hepatoid cells and cells of intermediate differentation, with few or no basaloid reserve cells. Scattered groups of hepatoid cells exhibit variable fatty vacuolation reminiscent of their sebaceous gland origin. Nuclei tend to be larger than in benign perianal gland tumors. These are slightly pleomorphic and have multiple or prominent nucleoli. Mitotic activity is low to moderate, and mitotic figures are found in differentiated cells as well as in reserve cells. Atypical mitotic figures are usually discernible in small numbers.

The rare poorly-differentiated variants of perianal gland carcinoma are poorly-circumscribed, invasive masses comprising trabeculae and cords of large, polygonal cells. There is a moderate stroma of reactive collagenous tissue that is often infiltrated by cords and clusters of neoplastic epithelial cells. The origin of the neoplasm may be recognizable only by its location. The cells have eosinophilic or amphophilic cytoplasm with variable vacuolation. Smaller cytoplasmic vacuoles may appear to contain lipid material, while larger vacuoles often have a mucinous appearance. Nuclei are large and

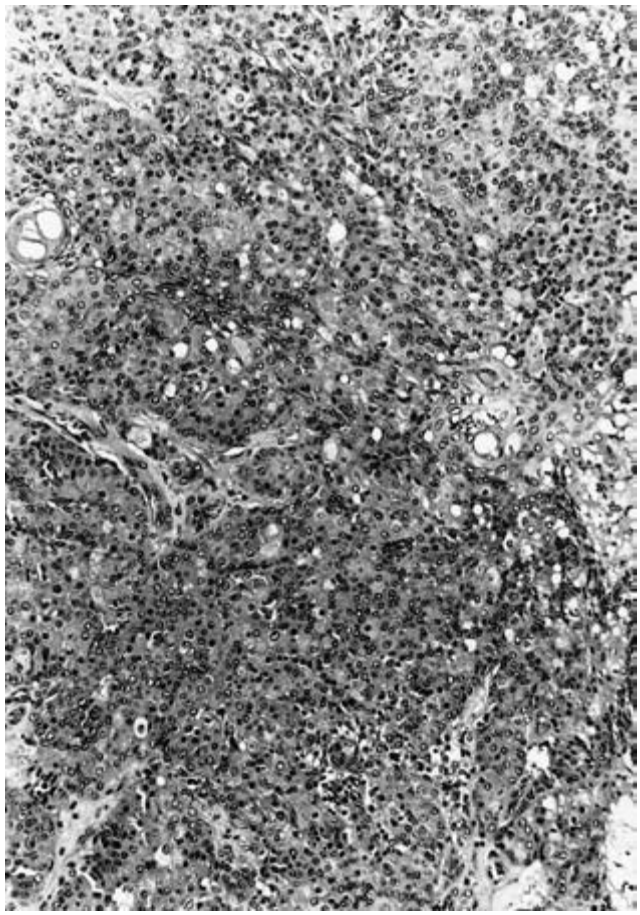


Fig. 24.25 Higher magnification of well-differentiated perianal gland carcinoma in a dog. Reserve cells are increased in number, and maturation patterns are haphazard. Note scattered pale sebaceous cells.

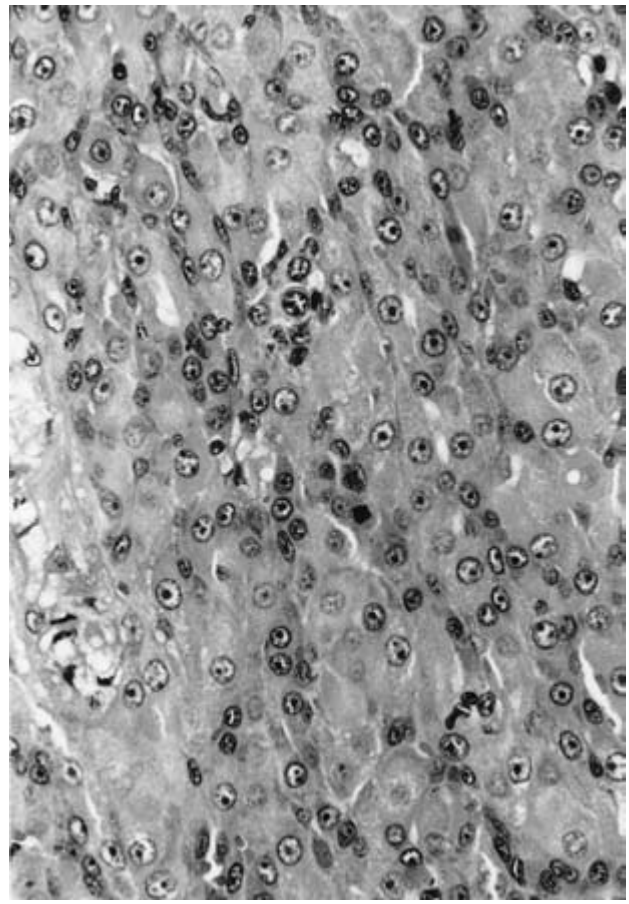


Fig. 24.26 Higher magnification of well-differentiated perianal gland carcinoma in a dog. Relatively mature hepatoid cells predominate in this field. Note mitotic figure in center and zone of sebaceous differentiation at left.

vesicular with prominent nucleoli. Mitotic activity is high, and mitotic atypia is commonly observed. Intermediate variants also exist, which have zones of discernible hepatoid differentiation as well as anaplastic zones.

Differentiation between well-differentiated perianal carcinoma and perianal adenoma may be difficult, in part because specific diagnostic criteria for hepatoid malignancies are not well-documented in the literature. Perianal adenomas are bland, monotonous neoplasms; well-differentiated carcinomas show partial to total loss of discrete, repetitive trabeculae or islands of hepatoid cells, resulting in a 'sloppy' or crowded appearance. Although foci of sebaceous differentiation are occasionally found in otherwise typical perianal gland adenomas, their presence warrants more careful investigation for other features of malignancy. Adenomas have small numbers of reserve cells in a consistent, peripheral distribution; carcinomas have increased or decreased numbers of reserve cells with a haphazard distribution. Mature hepatoid cells in normal glands, hyperplastic glands, and adenomas are terminally differentiated and should not be mitotically active; the finding of mitoses in fully-differentiated hepatoid cells is, therefore, indicative of malignancy. Perianal epitheliomas are distinguished from low-grade carcinomas by their marked predominance of reserve cells, absence of mitotic activity in mature hepatoid cells, and absence of mitotic atypia.

The study of Preziosi et al. (1995) using silver-stained nucleolar organizer regions (AgNORs) found that mean AgNOR count, mean AgNOR area, and relative AgNOR area are all significantly higher in carcinomas than in adenomas (see perianal gland adenoma, p. 655). This was associated with a significant decrease in mean nuclear area from adenoma to carcinoma, although epithelioma may have been included in the carcinoma group (Preziosi et al., 1995). Application of other markers of cellular pro-

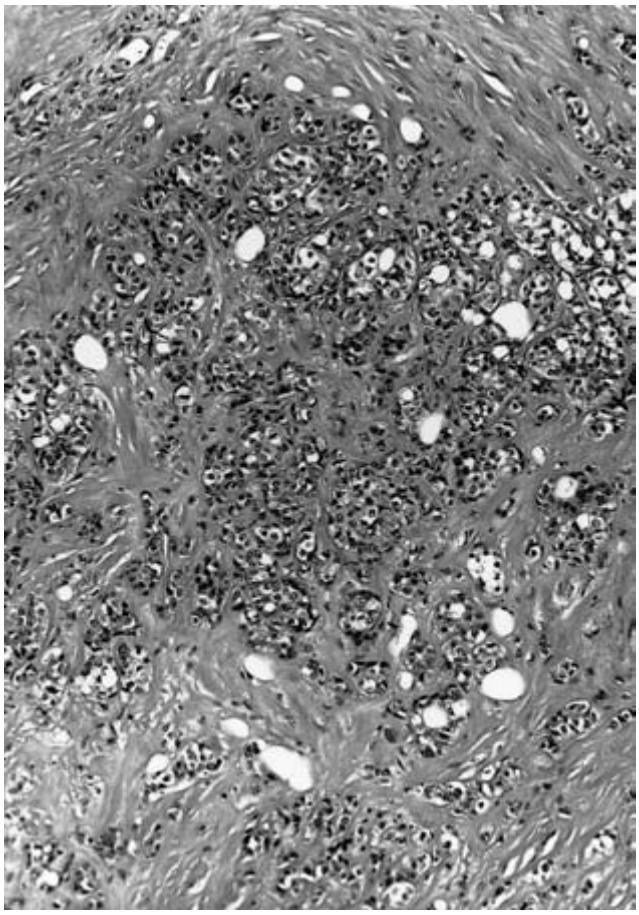


Fig. 24.27 Poorly-differentiated perianal gland carcinoma in a dog. Clusters and cords of vacuolated epithelial cells without obvious hepatoid features are distributed through a hyalinized collagenous stroma.

liferative activity, such as Ki67 (a proliferating nuclear antigen expressed during all active phases of the cell cycle) and proliferating cell nuclear antigen (PCNA), may help to substantiate these differences and refine diagnostic criteria, particularly for well-differentiated perianal gland carcinomas.

Differential diagnoses for the poorly-differentiated perianal gland carcinoma include poorly-differentiated variants of squamous cell carcinoma, sebocytic sebaceous carcinoma, and apocrine sweat gland carcinoma. Absence of contiguity with the overlying epidermis is a useful feature in ruling out squamous cell carcinoma, and may also help to exclude some apocrine ductular carcinomas, such as the solid-cystic variant (see Chapter 25). Tubular, acinar, or cribriform structures would be suggestive of apocrine origin. Differentiation from sebocytic sebaceous carcinoma may not be possible on a histologic basis, in part due to the close embryologic and physiologic relationship of these two cell types.

Immunohistochemistry

Immunohistochemistry may be helpful in the differentiation of poorly-differentiated perianal gland carcinoma from other undifferentiated carcinomas. It has recently been shown that CD79a, the pan-B lymphocyte marker, lightly stains canine sebocytes and hepatoid cells when used with a modified streptavidin–biotin technique (Goldschmidt et al., 2002); however, this may be a spurious staining phenomenon, and its diagnostic validity remains to be proven (see sebaceous carcinoma, p. 654). Negative immunohistochemical staining for specific keratins (CKs), particularly CAM5.2 (CK7/8) or CK13, would probably rule out an apocrine origin. Detailed immunophenotyping of perianal carcinomas has not been reported.

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Chapter 25

Sweat gland tumors

Although an in-depth review of sweat gland anatomy and physiology is beyond the scope of this text, a brief discussion related to terminology is warranted. Sweat glands have traditionally been divided into apocrine or eccrine (or merocrine) based on mode of secretion, morphology, and anatomic distribution. Apocrine glands are characterized by decapitation secretion, in which the apical part of the cell is pinched off and released into the lumen (Scrivener & Cribier, 2002); eccrine glands do not show cytological changes at the light microscopic level during secretion. Some research has suggested that unequivocal apocrine/eccrine distinction is not possible either morphologically or physiologically, and an epitrichial/atrichial classification is more accurate and applies to a wider range of species (Jenkinson, 1989). Epitrichial refers to glands that terminate in the follicular infundibulum; atrichial describes glands with distal ducts that enter directly into the epidermis and lack a follicular connection. The intraepidermal eccrine duct in humans is commonly referred to as the acrosyringium, although this term could probably also be applied to the intrafollicular portion of apocrine ducts.

In general, apocrine glands are microanatomically epitrichial, and eccrine glands are atrichial, but this is not always true (Jenkinson, 1989). Typical epitrichial apocrine glands are present throughout haired skin in dogs and cats; atrichial eccrine glands are limited to the pawpads. However, ceruminous glands, the specialized apocrine sweat glands of the inner pinna and ear canal, have both epitrichial and atrichial units (Goldschmidt & Shofer, 1992). Anal sac apocrine glands, circumanal apocrine glands, and mammary glands, which are modified apocrine structures, are exclusively atrichial (Jenkinson, 1989; Goldschmidt & Shofer, 1992).

It has recently been demonstrated that human eccrine and apocrine sweat glands have very different enzyme sensitivity and localization of anionic sites (Saga, 2002). Additional research has shown that apocrine secretion is not a histologic artifact but rather a specific, alternative extrusion mechanism. The apocrine blebs ('aposomes') are formed by the cytoskeleton, and apocrine-released proteins use serum albumin as a carrier and move through the cell without participation of the endoplasmic reticulum, Golgi apparatus, or secretory granules (Aumuller et al., 1999; Wilhelm et al., 1999). The authors have chosen to continue to use apocrine/eccrine terminology because these two glandular types are histologically distinct in dogs and cats, because the microanatomy of their ductal terminations is not always a differentiating factor, and because these recent studies support physiologic differences between their two secretory modes.

Apocrine glands arise embryologically as a unilateral protrusion from the upper portion of the developing hair peg. Just below this is the sebaceous gland anlage and, at least in some species, the follicular bulge region, in which one group of stem cells is now known to be located in humans and mice (Meyer & Görgen, 1986; Panteleyev et al., 2001). Eccrine glands, in contrast, develop from fetal epidermal buds in a manner very similar to hair follicles (Murphy, 1997).

All sweat glands contain secretory and ductular components. The secretory portion is lined by a single layer of columnar epithelial cells and a peripheral layer of myoepithelial cells; the ductular portion is lined by a double layer of cuboidal epithelial cells over most of its length and by squamous epithelium where it terminates in the follicular infundibulum or epidermis (acrosyringium). These morphologic patterns are often recapitulated in sweat gland neoplasms, creating tumor types that are either predominantly secretory or predominantly ductular in appearance.

Human nomenclature for sweat gland tumors retains many archaic and redundant terms, and it will generally be avoided. In addition, there is continued controversy regarding eccrine versus apocrine origin for some entities in humans, while other lesions have both apocrine and eccrine variants with the same name. Close analogues to human tumors in dogs and cats are infrequent, but will be described when pertinent.

APOCRINE CYST

(Synonyms: sweat gland cyst, epitrichial sweat gland cyst)

Clinical features

Apocrine cysts are non-neoplastic lesions that are fairly common in dogs and uncommon in cats. There is no human analogue for simple apocrine cysts. In a large-scale survey, apocrine cysts comprised 0.9% of all canine skin masses and 1.1% of all feline skin masses (Goldschmidt & Shofer, 1992); however, another reference text describes them as rare in cats (Carpenter et al., 1987). Data from the diagnostic pathology service of one the authors (E.J.W.) yield a canine to feline incidence ratio of approximately 5 : 1. The cause of the discrepancy in these data is undetermined; cystadenomas may have been included in the former statistics.

Ceruminous glands of the inner pinna or ear canal, which have modified apocrine secretory components with atrichial or epitrichial ducts, occasionally give rise to solitary cysts in cats. Apocrine cysts may be a result of obstruction of sweat gland ducts in some cases, but an etiology is usually not apparent. Interestingly, cysts derived from eccrine sweat glands have not been observed in dogs or cats.

Apocrine cysts present as well-defined, tense or fluctuant, bullous nodules ranging from several millimeters to several centimeters in diameter. The cysts are usually solitary, but several lesions may be present in the same patient. The masses often have a blue tint when viewed through the overlying skin, which is frequently atrophic and alopecic. Cyst contents are usually clear and watery, but they are occasionally brown and gelatinous due to inspissation. Sweat gland cysts in dogs occur most frequently on the head, legs, neck, and dorsal trunk. In cats, the majority are on the head. Ceruminous cysts in cats have red-brown contents and appear dark brown to dark blue through overlying skin.

Old English Sheepdogs, Weimaraners, and Persian cats are reported to be predisposed (Goldschmidt & Shofer, 1992). Affected animals are usually 6 years of age or older.

Histopathology (Figure 25.1)

Apocrine cysts are unilocular or multilocular structures lined by a single layer of cuboidal to columnar epithelial cells with small, uniform, basally-located nuclei. The epithelial cells of larger cysts are usually flattened due to pressure atrophy. Apocrine decapitation-type secretory activity, manifested by apical blebbing of the cytoplasm, may be apparent in smaller cysts. Apocrine cyst contents are usually not visible in tissue sections, but occasional cysts will contain inspissated secretory material that stains a deep pink. Inflammation associated with apocrine cysts is uncommon; mild infiltrates of plasma cells and macrophages containing light brown pigment derived from the iron content of apocrine secretion may be present in the surrounding dermis.

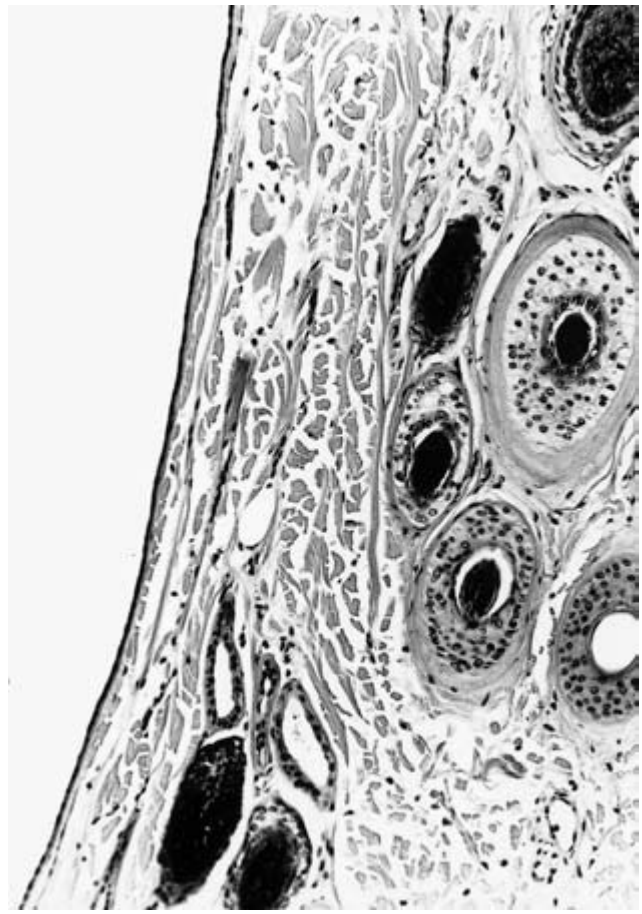


Fig. 25.1 Apocrine cyst in a dog. A single layer of atrophic epithelial cells lines the cyst.

The contents of ceruminous cysts appear light brown to red-brown in tissue sections. Inflammation is more common and may be somewhat more severe than in apocrine cysts in other anatomic locations; pigmented macrophages and some neutrophils may be present within the cyst lumen and in the surrounding dermis.

Differential diagnoses are limited. Large, multilocular sweat gland cysts may need to be distinguished from cystadenomas. Cystadenomas have a predominance of columnar cells, and at least occasional foci of acinar or papillary proliferation can be identified.

CANINE APOCRINE CYSTOMATOSIS

(Synonym: cystic hyperplasia of sweat glands)

Clinical features

Apocrine cystomatosis is a rare, non-neoplastic condition in dogs characterized by multiple clusters of cystically-dilated sweat glands. This condition has also been referred to as cystic hyperplasia in older texts (Pulley & Stannard, 1990). The lesions appear as numerous, solitary or grouped nodules, bullae or vesicles, usually less than 5 mm in diameter, distributed over the head and neck. Rarely, a more generalized distribution is present. The overlying skin is generally atrophic and alopecic. The cysts often have a translucent appearance, and a blue tint may be present.

Affected animals are middle-aged or older. There is no known breed predisposition. The etiology of this condition is unknown; it may be a senile degenerative change.

Histopathology (Figure 25.2)

Apocrine cystomatosis is characterized by clusters of dilated apocrine glands which are grouped among hair follicles in the middle and deep dermis. The cysts within a given lesion are usually of similar size, but single large cysts with smaller satellite cysts may also be observed. The cysts are lined by low cuboidal epithelial cells. Apical blebbing is observed infrequently; this is probably a reflection of pressure atrophy of the lining epithelial cells. Adjacent dermal architecture shows minimal perturbation; mild fibrosis may be present. If cyst rupture occurs, there is moderate inflammation comprising plasma cells, neutrophils, and lymphocytes; some pale siderophages containing pigment derived from the iron content of apocrine secretions may also be present.

Differential diagnoses are very limited. Apocrine cystomatosis may need to be distinguished from a rare case of multicentric cystadenomas. As in their solitary counterparts, cystadenomas are true neoplasms with evidence of cellular proliferation. They have a predominance of columnar cells, and at least occasional acinar or papillary structures can be identified. In contrast, simple cysts are lined by a monolayer of cuboidal or flattened cells.



Fig. 25.2 Apocrine cystomatosis in a dog. Clusters of dilated sweat glands are present around hair follicles. Note that follicular architecture and adnexal interrelationships are normal.

FELINE CERUMINOUS CYSTOMATOSIS

Clinical features

Feline ceruminous cystomatosis is an uncommon non-neoplastic disorder of uncertain etiology. It may be a sequela to otitis externa, which is often reported in the clinical history of affected cats. It may also be a senile degenerative change or, in some cases, a congenital condition. The category 'ceruminous cyst/hyperplasia' accounted for 1.7% of all feline skin tumors in a large survey (Goldschmidt & Shofer, 1992).

The lesions appear as multiple, often numerous, punctate nodules or vesicles, usually less than 2 mm in diameter, in the external ear canal and inner pinna. They are dark blue, brown, or black, and may be mistaken clinically for melanocytic or vascular neoplasms.

The average age is 8 to 9.5 years, although animals as young as 1 year of age may be affected (Carpenter et al., 1987; Goldschmidt & Shofer, 1992). Goldschmidt and Shofer (1992) report a slight male predominance and an over-representation in Abyssinian and Persian cats; domestic shorthaired cats comprise the majority of cases in the diagnostic pathology service of one author (E.J.W.).

Histopathology (Figure 25.3)

Feline ceruminous cystomatosis is characterized by cystic glands that are often grouped into clusters. Most of the cysts contain red-brown, inspissated secretory product that may be admixed with small numbers of pigmented macrophages and neutrophils. The secretory material occasionally undergoes mineralization. The distended ceruminous glands are lined by a single layer of epithelial cells that vary from attenuated to cuboidal to columnar. The cytoplasm may contain light brown iron granules. Nuclei are small and uniform, and no mitotic figures are present. The surrounding dermis often exhibits mild fibrosis with mild infiltrates of mast cells, lymphocytes, neutrophils and pigmented macrophages. Differentiation is not problematic as this entity is diagnostically unique.

APOCRINE CYSTADENOMA

(Synonyms: sweat gland cystadenoma, apocrine hidrocystoma)

'Apocrine hidrocystoma' is the classical human nomenclature for the simple cystic neoplasm arising from the secretory portion of the apocrine sweat gland. This term is confusing, as eccrine hidrocystoma is considered a true retention cyst in humans; thus, the more accurate designation 'apocrine cystadenoma' is preferred by some authors (Murphy & Elder, 1991). The neoplastic nature of the lesion is indicated by the presence of up to five cell layers lining the cyst wall, small tufts or fronds of epithelium projecting into the cyst lumen, and absence of pressure atrophy of epithelial cells. Human apocrine cystadenomas are usually solitary and also may involve the specialized adnexa on the eyelids known as Moll's glands. Multiple lesions are rare in humans and most often affect the face and eyelids (Alessi et al., 1997; de Eusebio et al., 1996; Farina et al., 1995).

Clinical features

Apocrine cystadenoma is uncommon in dogs and rare in cats in the authors' experience. Specific incidence data are not available in the literature, as cystadenoma is not quantified separately from other adenomas. All variants of apocrine secretory adenoma accounted for 1.7% of canine skin tumors and 3% of feline skin tumors in a large survey (Goldschmidt & Shofer, 1992).

Apocrine cystadenomas in dogs are usually solitary and range from 1 to 4 cm in diameter, although some attain sizes of 10 cm or more. The tumors in cats are usually 1 cm or smaller. The overlying skin is generally atrophic and alopecic, and ulceration is uncommon. As in apocrine cysts (see p. 666), a blue or purple hue may be observed through the skin surface. Small cystadenomas contain clear liquid; the secretory product within larger neoplasms is often brown and gelatinous due to inspissation.

The head, neck, and dorsal trunk are the most frequent locations in dogs. The majority of feline apocrine adenomas are on the head (Goldschmidt & Shofer, 1992) and in Persian and Himalayan cats may also affect other anatomic sites, such as the pinna. Lesions may be numerous in Persian and Himalayan cats. Multiple cystadenomas

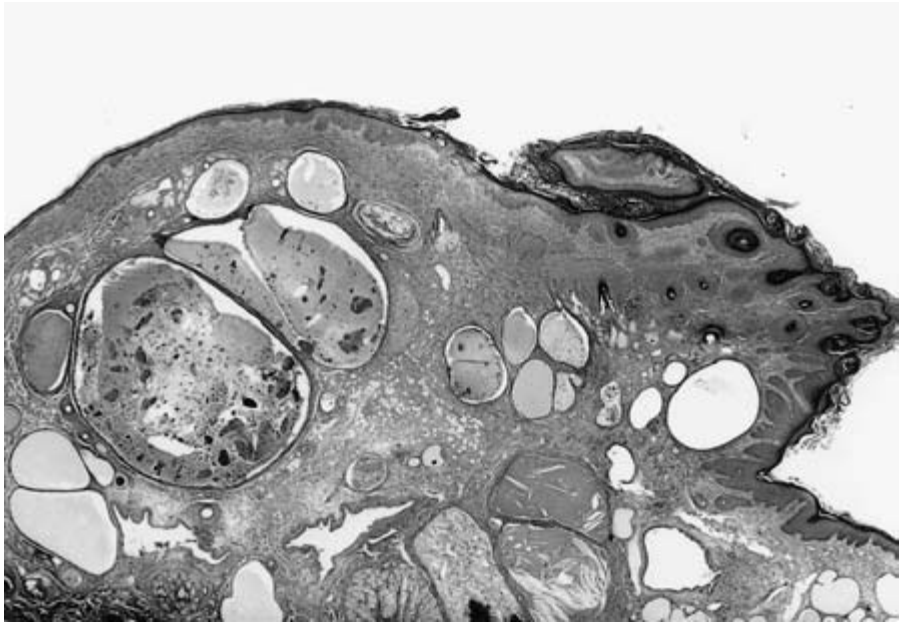


Fig. 25.3 Feline ceruminous cystomatosis featuring multiple clusters of dilated ceruminous glands, often containing inspissated secretory material. Dermal fibrosis and irregular acanthosis reflect chronic otitis externa.

have been described on the eyelid margins and distal ear canals of Persian and Himalayan cats, suggesting a hereditary syndrome; these cases may be designated as apocrine cystadenomatosis (Chaitman et al., 1999; Marignac et al., 2002). A recently described lesion in a young cat had some similarities to apocrine cystadenomatosis, but more closely resembled human syringocystadenoma papilliferum, which is considered to be a type of apocrine hamartoma and typically arises in nevus sebaceus; the lesion presented as an inflamed plaque on the temporal region (Heimann, M., personal communication, 2004). There is one case report of numerous cystadenomas with a generalized distribution in an Old English Sheepdog; these were designated erroneously as apocrine cystomatosis, but were demonstrated to be true neoplasms both by routine histology and epidermal growth factor receptor immunohistochemistry (Vilafranca et al., 1994).

Great Pyrenees, Chow Chows, Malamutes, Old English Sheepdogs, and Persian cats are reported to be predisposed to sweat gland secretory tumors (Goldschmidt & Shofer, 1992). The majority of affected animals are middle-aged. Persian cats may develop eyelid and pinnal lesions as young adults (Marignac et al., 2002).

Histopathology (Figures 25.4 and 25.5)

Apocrine cystadenoma is a circumscribed dermal neoplasm composed of one or more cystic structures of varying size that are generally lined by a single layer of cuboidal to columnar epithelial cells. Multiple layers of lining cells are present in some lesions. Small glandular structures may be present between the cysts or protruding inward from cyst walls. Some cysts contain simple or branching papillary aggregates of columnar epithelial cells. If papillary proliferations are numerous and begin to fill some of the cyst cavities, a diagnosis of papillary cystadenoma is appropriate. The secretory material within cyst lumens frequently stains rose-pink in tissue sections. The sparse collagenous stroma and surrounding dermis are frequently infiltrated by macrophages containing light brown pigment, which likely represents iron from escaped, iron-rich apocrine secretion.



Fig. 25.4 Apocrine cystadenoma in a dog. Note small papillary projections lined by uniform cuboidal cells.



Fig. 25.5 Larger papillary structure from apocrine cystadenoma in a dog. Note apical blebbing of cytoplasm, particularly along top margin.

The epithelial cells have scant to moderate, clear to eosinophilic cytoplasm with variable apical blebbing. Nuclei are generally small and bland. They may be moderately enlarged and contain small nucleoli, but loss of polarity or atypia is not present. Small cells with dark, basaloid nuclei may predominate in some feline lesions. Mitotic activity is absent or minimal. Tumors that have ulceration and/or degeneration of cyst walls exhibit stromal and peripheral fibroplasia with moderate to marked infiltrates of plasma cells, neutrophils, and pigmented macrophages.

Differentiation of apocrine cystadenoma from apocrine cyst requires the identification of cellular proliferation characterized by multiple layers of lining cells and/or acinar or papillary aggregates of cells projecting into cyst lumens. Large, inflamed, or more proliferative lesions may need to be distinguished from cystadenocarcinoma of low-grade malignancy. Cystadenocarcinomas have larger nuclei, nuclear pleomorphism, and loss of nuclear polarity. Mitotic activity is generally low, but atypical mitoses may be detected.

APOCRINE SECRETORY ADENOMA

(Synonyms: sweat gland adenoma, epitrichial sweat gland adenoma)

Simple apocrine secretory adenomas are observed in dogs and cats; simple apocrine adenomas differentiating toward the secretory portion of the gland are rare in humans. The complex adenoma subtype in dogs is very similar to chondroid syringoma in humans, also known as 'mixed tumor of the skin' (Murphy & Elder, 1991; Elder et al., 1997). This was originally classified as an eccrine neoplasm in humans, but may arise from either eccrine or apocrine glands. The proportion of apocrine-origin chondroid syringomas in humans is controversial, and the results of numerous immunohistochemical and ultrastructural studies also leave questions as to whether the stroma and stromal cells are of epithelial or myoepithelial origin (Hassab-El-Naby et al., 1989; Mihara, 1989; Murphy & Elder, 1991; Tsuji, 1996; Elder et al., 1997; Bates & Baithun, 1998; Nakayama et al., 1998). The use of newer markers for smooth muscle, such as calponin, has yielded convincing evidence for a myoepithelial component in mixed salivary gland tumors; application of these markers to cutaneous mixed tumors may allow resolution of this issue in sweat gland tumors as well (Savera et al., 1997).

Clinical features

Apocrine adenomas arising from the secretory component of the gland are benign neoplasms that are uncommon in dogs and cats. Apocrine adenomas, including cystadenomas, accounted for 1.7% of canine skin neoplasms and 3% of feline skin neoplasms in a large-scale survey (Goldschmidt & Shofer, 1992). An additional review of feline neoplasms found a 2.9% incidence of apocrine adenoma (Miller et al., 1991). Complex apocrine adenomas appear to occur exclusively in dogs.

Apocrine adenomas are well-circumscribed, firm or fluctuant dermal nodules that are usually solitary. The lesions in dogs are typically 0.5 to 4 cm in diameter; in cats, they are usually less than 2 cm. The overlying skin is often alopecic, and ulceration is common in larger canine lesions. The head, neck, and dorsal trunk are the most frequent locations in dogs. The most common anatomic location in cats is the head (Carpenter et al., 1987; Goldschmidt & Shofer, 1992).

Great Pyrenees, Chow Chows, Malamutes, and Old English Sheepdogs are reported to be predisposed to sweat gland secretory tumors (Goldschmidt & Shofer, 1992). The average age in dogs is 9 years (Goldschmidt & Shofer, 1992); in cats, the average is 11 to 12 years (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). There is no known breed predilection in cats.

Histopathology

Simple apocrine adenoma (Figure 25.6)
Adenomas that differentiate primarily toward the secretory portion of sweat glands are well-circumscribed but unencapsulated dermal masses exhibiting acinar, tubular, or papillary patterns; combinations of architectural patterns may occur within the same tumor. Large masses may extend into superficial subcutaneous fat. The majority of neoplastic epithelial structures are lined by a single layer of cuboidal to columnar cells with moderate to abundant, eosinophilic cytoplasm. The cytoplasm may also be clear due to glycogen accumulation. Decapitation secretion is discernible in most lesions, and eosinophilic secretory material is often present in glandular lumens. Nuclei are moderately enlarged and vesicular, and have small nucleoli. Mitotic activity is very low or absent. Nuclear or mitotic atypia is not observed. Most neoplasms have a sparse collagenous stroma, and there is variable infiltration by plasma cells and macrophages containing light brown pigment derived from the iron content of apocrine secretion. Secondary ulceration and more intense inflammation may occur in larger tumors.

Complex (mixed) apocrine adenoma (Figure 25.7)
Some apocrine adenomas have multifocal or diffuse, myxoid and/or chondroid differentiation. These lesions are analogous to complex mammary adenomas and

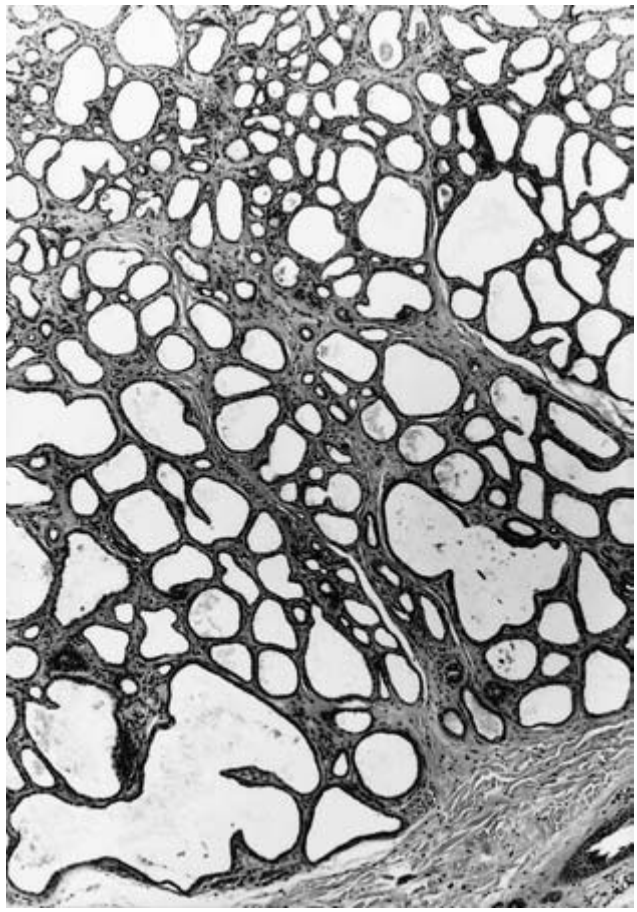


Fig. 25.6 Simple secretory apocrine adenoma in a dog. The glandular structures are lined by a single layer of low cuboidal epithelial cells.

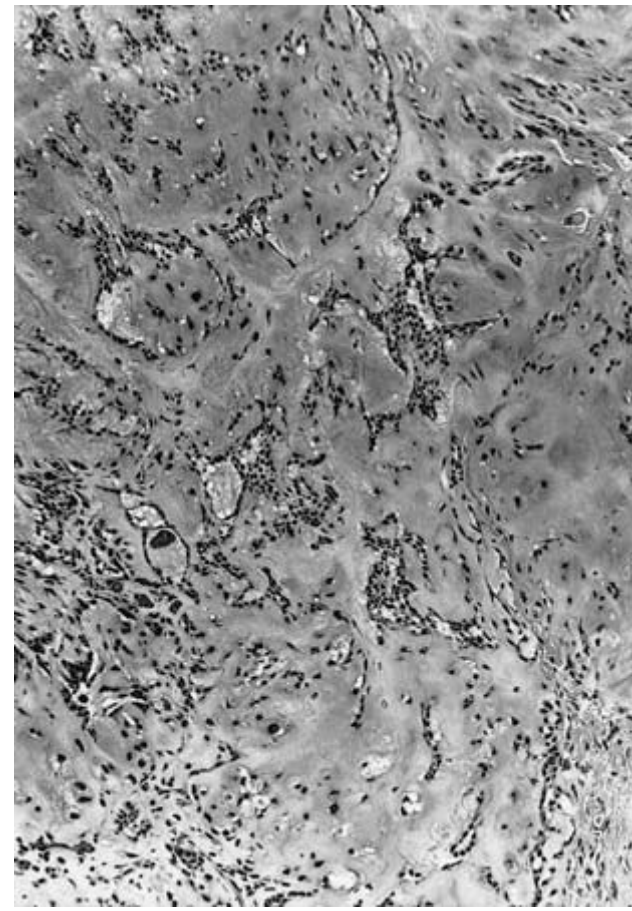


Fig. 25.7 Complex secretory apocrine adenoma in a dog. Small glandular structures are distributed through an abundant, well differentiated chondroid stroma.

benign mixed mammary tumors, and it is presumed that the stroma is a myoepithelial product. The exact nature of the stromal component in these tumors has never been addressed in veterinary pathology.

The epithelial component of complex sweat gland adenoma is usually identical to that of simple adenoma. The stromal component has small spindle and stellate cells with pale cytoplasm and bland, ovoid to fusiform nuclei. The stromal cells are separated by a pale basophilic, mucopolysaccharide ground substance, or are entrapped in lacunar spaces within a more deeply basophilic chondroid matrix. Infrequently, the mesenchymal component has a leiomyomatous appearance characterized by bundles of elongated cells with eosinophilic cytoplasm and no surrounding stroma. Unlike benign mixed mammary tumors, osseous metaplasia in complex sweat gland adenomas is uncommon.

Rarely, neoplasms are composed primarily of pale chondroid matrix with small, scattered acinar structures lined by small cuboidal epithelial cells. Nests and cords of epithelial cells without obvious lumens may also be present. This small cell pattern is typical for eccrine-origin chondroid syringomas in humans; however, the few examples observed in dogs were not located on the pawpads and, thus, are more likely apocrine in origin.

Simple or complex apocrine sweat gland adenomas on the ventrum may need to be differentiated from mammary gland adenomas. Mammary adenomas, with the exception of neoplasms arising in major mammary ducts, are entirely subcutaneous in location and are usually encapsulated. The epithelial cells of mammary adenomas tend to be smaller than those of apocrine sweat gland adenomas and rarely display apical blebbing. Mammary lobules and/or ducts can usually be identified adjacent to mammary neoplasms. Distinction between apocrine adenoma and low-grade adenocarcinoma may be problematic. Asymmetry, infiltrative borders, piling up of cells within lumens, nuclear pleomorphism, prominent nucleoli, increased mitotic activity, or atypical mitoses are indicators of malignancy.

APOCRINE DUCTULAR ADENOMA

(Synonyms: ductular sweat gland adenoma, basaloid sweat gland adenoma, nodular hidradenoma)

When basaloid mammary adenoma was reported in the veterinary literature in 1984, it became apparent that canine apocrine ductular tumors had a distinctive and consistent morphology (Esplin et al., 1984). However, ductular sweat gland adenomas of the skin were not named as specific entities in animals until 1992 (Walder & Gross, 1992; Goldschmidt & Shofer, 1992). Spiradenoma, reported in dogs in the previous version of the World Health Organization histologic classification (Weiss & Frese, 1974) as the analogue of the ductular eccrine neoplasm in humans, appears identical to many canine ductular apocrine adenomas. The 'adenoid' variant of 'basal cell tumor' described by Weiss and Frese (1974) probably also represents an apocrine ductular adenoma.

The authors recognize two types of apocrine ductular adenomas in dogs and cats, classical ductular adenoma, and a recently recognized subtype, the 'solid-cystic' variant. This variant is believed by the authors to represent the veterinary analogue of nodular hidradenoma in humans. This is generally regarded in humans as an eccrine tumor within the larger 'poroma' category, which encompasses several ductular tumor types. Poroma *per se* is an intraepidermal neoplasm differentiating toward the most distal portion of eccrine or apocrine sweat gland duct; its distinctive morphology (see below) is referred to in the human literature as 'poroid'. 'Poroid hidradenoma' is a recently coined term to define human nodular hidradenomas that have these distinct poroid features; it also separates them from the clear cell variant of human nodular hidradenoma (Requeña & Sánchez, 1992; Cho et al., 2001).

Although apocrine versus eccrine origin is virtually impossible to prove by immunohistochemistry, the apocrine origin of some poromas in humans is implied by the presence of sebaceous and, rarely, follicular elements; only apocrine glands have a close embryologic and anatomic association with the folliculosebaceous unit (Harvell et al., 1996; Lee et al., 2000; Kamiya et al., 2001). Variants of nodular hidradenoma with histologic evidence of apocrine differentiation are described (Ackerman et al., 1993; Elder et al., 1997). Multiple immunohistochemical studies have shown nodular hidradenomas to be primitive but complex neoplasms that have features of the acrosyringium, intradermal duct, and secretory coil in varying proportions (Murphy & Elder, 1991; Demirkesen et al., 1995; Ohnishi & Watanabe, 1997).

Solid-cystic apocrine ductular adenomas (nodular hidradenomas) in cats and dogs have previously been lumped into the 'basal cell tumor' category in veterinary pathology, and they are the only remaining entity classified as such in the World Health Organization fascicle (Goldschmidt et al., 1998). The authors had previously regarded them as basal cell carcinomas (Walder & Gross, 1992) based on their contiguity with the epidermis, the overall asymmetrical architecture, variability in size and shape of the epithelial aggregates, moderate mitotic activity, frequent melanization, necrosis and cystic degeneration, and very limited foci of recognizable adnexal differentiation. However, these tumors have convincing indicators of benignity, including a vertical orientation within the dermis, only focal epidermal contiguity, usually sparse stroma, and a lack of stromal–epithelial clefts. Further, small tubular structures suggestive of sudoriferous differentiation have previously been reported as frequent findings in descriptions of feline 'basal cell tumors' (Diters & Walsh, 1984; Carpenter et al., 1987).

Immunostains for low molecular weight cytokeratins (CKs), particularly CAM5.2 (CK7/8) and CK13, are relatively specific markers for glandular epithelia, including sweat glands; they highlight the small tubular structures of solid-cystic ductular adenomas, but are absent in all trichoblastoma variants tested to date (see Chapter 23) (Walder & Haines, 1998; Walder, 2000; Goldschmidt et al., 2002). These immunohistochemical studies, in conjunction with the many histologic similarities to human nodular hidradenoma, strongly support the transfer of the last 'basal cell tumor' into the sweat gland tumor category.

Clinical features

Apocrine ductular adenomas in dogs are uncommon benign neoplasms accounting for only 0.3% of skin tumors in one large survey (Goldschmidt & Shofer, 1992). Solid-cystic ductular adenomas (nodular hidradenomas) occur occasionally in dogs. The incidence of apocrine ductular adenomas in cats is more difficult to estimate, as many have been included in the former basal cell tumor group or with secretory adenomas. They are common neoplasms in cats, comprising 2% of skin tumors in the survey of Goldschmidt and Shofer (1992), which did not include the solid-cystic subtype. 'Basal cell tumors' have traditionally accounted for an average of 20% of feline skin tumors (Carpenter et al., 1987; Diters & Walsh, 1984; Miller et al., 1991; Goldschmidt & Shofer, 1992). Based on observations from one of the authors (E.J.W.), approximately 60% of 'basal cell tumors' in cats represent solid-cystic apocrine ductular adenomas; the other 40% are trichoblastomas. Thus, apocrine ductular adenomas actually appear to account for around 14% of skin tumors in cats.

Apocrine ductular adenomas in dogs are solitary, circumscribed, multinodular, deep dermal and subcutaneous masses that are usually 2 cm in diameter or larger. The solid-cystic adenomas of dogs are intradermal and are typically 0.5 to 1 cm. The epidermis may be alopecic, but ulceration is infrequent. Most tumors are truncal in location, but limbs and head are also commonly affected.

Feline apocrine ductular adenomas of both types are usually solitary, firm nodules 0.2 to 1 cm in size. The neoplasms are often alopecic and have a blue to brown hue. Small foci of ulceration may be present in the solid-cystic variant. They occur most often on the head and neck.

The average age of incidence is the same as for secretory apocrine adenomas (see p. 670). Pit Bull Terriers, Old English Sheepdogs, and English Springer Spaniels are reported to have a marked predisposition (Goldschmidt & Shofer, 1992). There is no known breed predilection in cats.

Histopathology

Canine apocrine ductular adenoma (Figure 25.8)
These circumscribed but unencapsulated, multilobular neoplasms are usually located in the deep dermis and subcutis. Epidermal contiguity is not seen. Each of the lobules is composed of winding trabeculae and tightly-packed tubular structures lined by a double layer of cuboidal cells. There are multiple, patchy foci of squamous metaplasia with formation of irregular keratin lakes but without discrete cystic structures. Infundibular-type keratinization occurs via a granular cell layer. The lobules of tumor tissue are separated by a moderate stroma of mature collagen. There may be a mild stromal infiltrate of plasma cells and histiocytes.

The luminal epithelial cell layer has scant, clear cytoplasm and small, hyperchromatic nuclei. The outer cell layer has moderate, eosinophilic cytoplasm and slightly larger, euchromatic nuclei. Apocrine secretory activity is not observed. Nucleoli are inconspicuous. Mitotic activity is moderate.

The histologic appearance of this neoplasm is virtually identical to basaloid mammary gland adenoma, which is also believed to be of ductal origin. In a ventral location, apocrine ductular adenoma would be distinguishable from basaloid mammary adenoma only by the absence of identifiable mammary glands. Differentiation of ductular apocrine adenoma from ribbon trichoblastoma is based upon numerous tubular structures lined by double rows of cells, and irregular deposits of infundibular-type keratin in the former. Distinction of ductular apocrine adenomas from trichoblastomas with outer root sheath differentiation is more problematic, as both of these tumor types can be large, deep, and have a combination of mitotically active basaloid cells and larger keratinized cells. The small epithelial cells of trichoblastoma form anastomosing cords rather than double-layered tubular structures. The foci of squamous differentiation in ductular adenoma produce keratin deposits via a granular cell layer; neither keratohyalin granules nor keratin lakes are found in trichoblastoma with outer root sheath differentiation. Trichoepithelioma also has a compound basaloid and squamous epithelial population, but tubular structures are absent, and there are true keratin cysts exhibiting a variety of follicular cornification patterns.

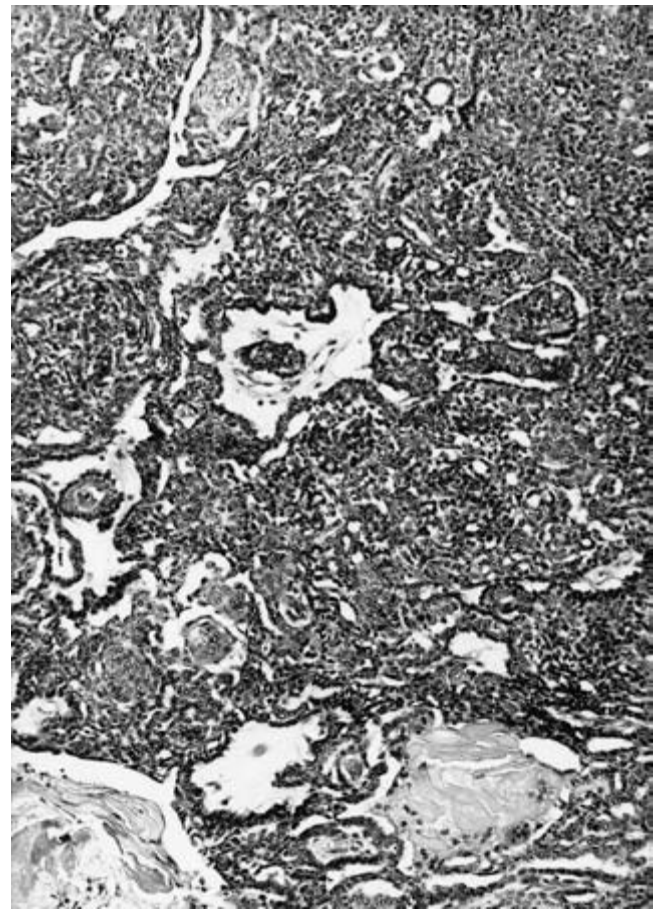


Fig. 25.8 Canine apocrine ductular adenoma demonstrating double layers of small cuboidal epithelial cells lining winding tubular structures. Note keratin lakes at bottom.

Distinction between canine ductular apocrine adenoma and some ductular adenocarcinomas can be problematic, largely because of the relatively high mitotic rate of the benign neoplasm. Adenocarcinomas generally have more irregular, infiltrative borders and larger nuclei with prominent nucleoli. Atypical mitotic figures, larger foci of squamous metaplasia and zones of necrosis may be present in adenocarcinomas.

Feline apocrine ductular adenoma (Figure 25.9)
These tumors are well-circumscribed, small and often multilobular. They are generally situated in the deep dermis. The centers of the lobules have irregular cystic structures that are lined by cuboidal epithelial cells in some areas, but appear to represent cystic degeneration in others. Epidermal contiguity is uncommon, and ulceration is rare. The lobules are separated by a sparse collagenous stroma.

The tumor is composed partially of solid sheets of small, polygonal keratinocytes that have pale eosinophilic cytoplasm and ovoid, euchromatic nuclei. Nucleoli are small, and mitotic activity is low. Distributed through the solid cellular background are multiple, small, often branching, tubular structures lined by a distinct double layer of cuboidal cells indicative of ductal differentiation. The cells lining the tubules have minimal, clear cytoplasm and small, hyperchromatic nuclei. Nucleoli are inconspicuous, and mitotic figures are not observed. Tubular lumens and cyst cavities often contain pale secretory product. Melanization of the epithelial cells is rare. The proportions of cysts, tubules and solid zones are quite variable; at one end of the spectrum are neoplasms that are similar to apocrine cystadenomas (see p. 668), while those with a predominance of solid sheets of cells resemble solid-cystic ductular adenomas (see below).

Feline ductular apocrine adenomas may need to be differentiated from other tumors of small adnexal keratinocytes. Multiple tubular structures are absent in trichoblastomas. If tubular structures are relatively few in comparison to solid zones, the lesion may resemble solid-cystic apocrine ductular adenoma, and, in fact, tumors with overlapping features do occasionally occur. Solid-cystic ductular adenoma typically has few or no tubules, solid lobules with foci of necrosis, racemiform architecture with a vertical orientation, and contiguity with the epidermis. They are distinguished from basal cell carcinomas and apocrine ductular adenocarcinomas by the absence of mitotic atypia, necrosis, melanin pigment, broad epidermal contiguity, and stromal invasion.

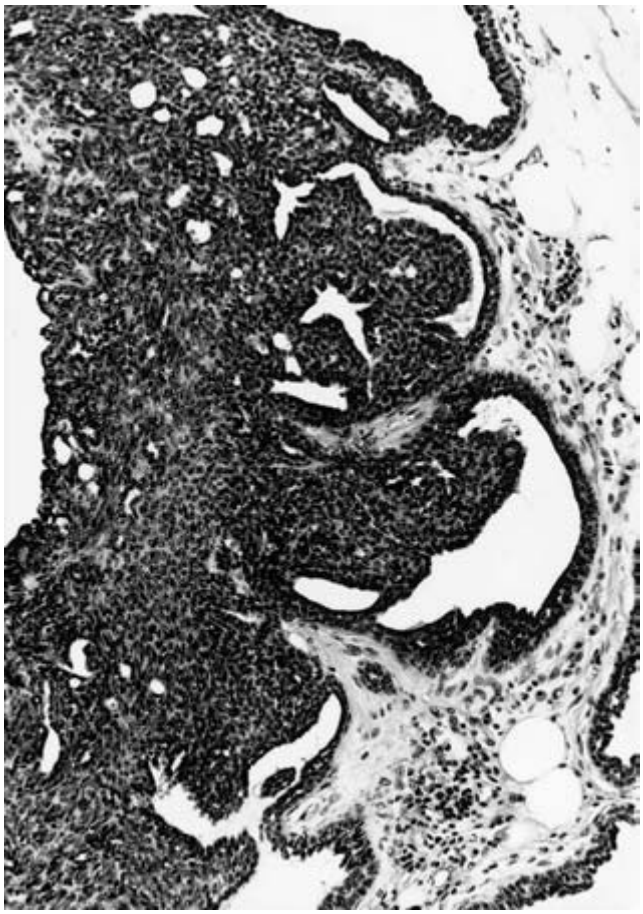


Fig. 25.9 Feline apocrine ductular adenoma. Tubular structures lined by a double cuboidal cell layer are distributed through a more solid background of basaloid epithelial cells. Note margin of central cystic structure at left.

Solid-cystic apocrine ductular adenoma (nodular hidradenoma) (Figures 25.10 through 25.14)
Solid-cystic apocrine ductular adenomas are circumscribed dermal neoplasms with unilobular, multilobular or racemiform (resembling a bunch of grapes) architecture. The multilobular and racemiform lesions are often slightly asymmetric, but are vertically oriented within the dermis. Focal epidermal contiguity is often present and may be associated with ulceration.

Larger epithelial islands may be interspersed with and interconnected by short epithelial trabeculae. The larger islands of cells often exhibit central necrosis and cystic degeneration that varies from punctate to extensive. Dystrophic mineralization of necrotic debris may occur. Unilobular lesions may have only a narrow rim of intact epithelium and were referred to in older literature as 'basal cell cysts' (Stannard & Pulley, 1978).

The stroma of solid-cystic ductular adenoma is typically sparse and of low cellularity. The collagen may be hyalinized and often forms a narrow pseudocapsule around the tumor. Trabeculae of stroma may protrude into the epithelial lobules, creating a deeply-notched or scalloped profile around the periphery; this is referred to as a 'pseudoinvasive' pattern (Murphy & Elder, 1991). Stromal inflammation is uncommon, although melanophages are often present in pigmented lesions.

The keratinocytes of solid-cystic ductular adenoma comprise two distinct but overlapping cell populations in varying proportions, constituting a bimorphic 'poroid' cell population (Requeña & Sánchez, 1992). One cell type (poroid) is small, cuboidal and has a basaloid appearance. The second cell type (cuticular) is somewhat larger and



Fig. 25.10 Solid-cystic apocrine ductular adenoma in a cat. The mass has a circumscribed, vertically-oriented, racemiform silhouette. Note the cystic degeneration in the deeper lobules and focal epidermal contiguity.

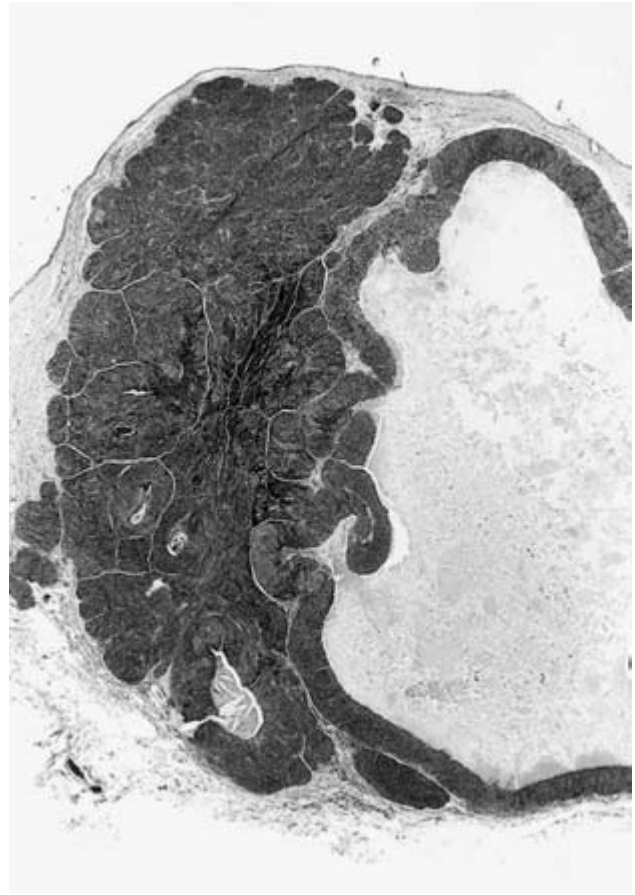


Fig. 25.11 Solid-cystic apocrine ductular adenoma in a cat. The largest lobule has severe cystic change.

polygonal; cytoplasmic outlines tend to be soft and rounded rather than angular. Spindling of either of two epithelial cell types may be present to variable extent. The smaller poroid cells tend to be concentrated around the periphery of the islands, but palisading is not a prominent feature. The smaller cells also comprise the trabecular structures and form scattered, short, double rows with or without discernible lumens. At least occasional ductular structures are present in most lesions, but may be extremely subtle. The larger cuticular cells form solid sheets in the centers of the islands. Occasionally, they line small, round ducts with a delicate, eosinophilic cuticle resembling acrosyringium.

The small basaloid poroid cells have scant, clear cytoplasm and ovoid, euchromatic to hyperchromatic nuclei. The larger cuticular cells have smudgy, pale eosinophilic cytoplasm with round, euchromatic nuclei. Some of the cuticular cells may contain single intracytoplasmic vacuoles with smooth borders consistent with intracellular ductal differentiation (Requeña & Sánchez, 1992; Cho et al., 2001). This morphology closely resembles that of human poroma and 'poroid' hidradenomas (see above).

Melanization is common in solid-cystic ductular adenomas and varies from sparse to moderate, and free melanin granules may be present in necrotic and/or cystic foci. Rarely, small groups of cells with clear cytoplasm are present; tumors composed primarily of clear cells, resembling classic human clear cell hidradenoma, have not been recognized. Small numbers of well-differentiated sebocytes are present in occasional tumors, usually just below the epidermal connection. As indicated above, small foci of divergent adnexal differentiation help to confirm apocrine origin due to the close proximity within the follicular wall of the precursor cells for apocrine and sebaceous glands.

Differentiation of solid-cystic ductular adenoma from trichoblastoma and basal cell carcinoma can be difficult; this is emphasized by the inclusion of all three tumor types in the 'basal cell tumor' category for many years.

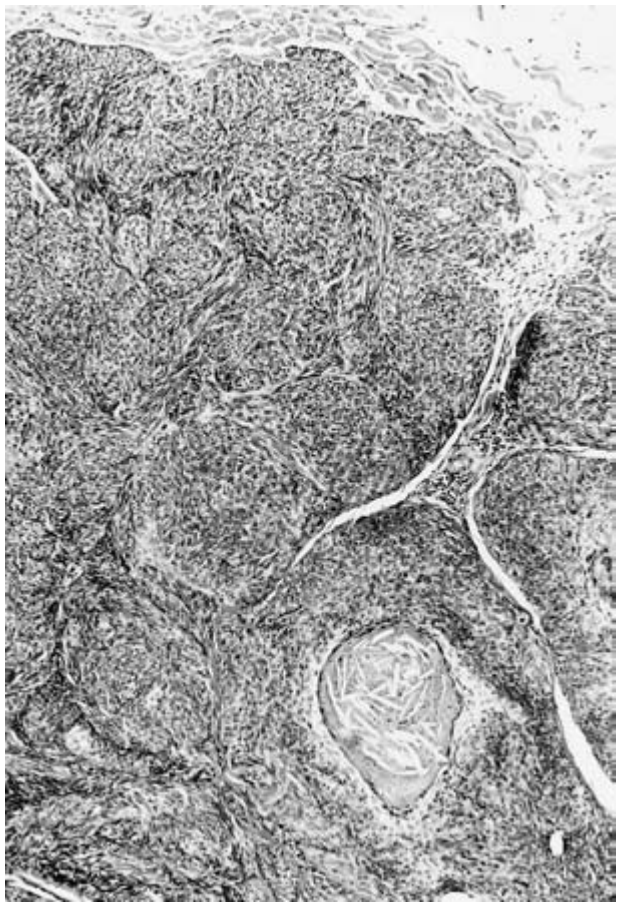


Fig. 25.12 Higher magnification of the solid-cystic apocrine ductular adenoma of Fig. 25.11. Many of the epithelial cells in this example are spindled.



Fig. 25.13 High magnification of solid-cystic apocrine ductular adenoma in a cat. The lobules comprise small to medium-sized, cuboidal to polygonal cells; the larger cells have pale eosinophilic cytoplasm with scattered intracellular ductules (arrows).

Solid-cystic ductular adenomas are distinguished from trichoblastomas by the presence of ductular structures and/or intracellular ductular differentiation, frequent focal epidermal contiguity, extensive necrosis and/or cystic degeneration, and a predominance of large nodular epithelial aggregates. Follicular papillary mesenchymal bodies, as seen in trichoblastomas (see Chapter 23), are not found in ductular adenomas. Solid-cystic ductular adenomas can usually be differentiated from basal cell carcinomas by their localized epidermal connection, vertical orientation, sparse stroma of low cellularity, and absence of stromal–epidermal retraction clefts. Most variants of trichoblastomas and basal cell carcinomas are composed primarily of small, prismatic keratinocytes with frequent nuclear palisading; solid-cystic ductular adenomas show a poroid morphology characterized by a bimorphic population of cells with infrequent palisading. If tubular structures are relatively numerous, solid-cystic ductular adenoma may resemble regular feline apocrine ductular adenoma, and, in fact, tumors with overlapping features do occasionally occur. The later typically has numerous tubules, fluid-filled cysts rather than foci of necrosis, a deeper dermal location, and absence of contiguity with the epidermis.

Immunohistochemistry

Sweat glands in dogs and cats are strongly decorated by markers for simple epithelial CKs, such as CAM5.2 (CK7/8) and CK13. These markers are also positive in all well-differentiated sweat gland tumors and are negative in trichoblastomas studied thus far (Walder & Haines, 1998; Walder, 2000; Goldschmidt et al., 2002). For ductular adenomas, particularly the solid-cystic variant, CAM5.2 or CK13 immunostaining marks the tubular structures that may be subtle or indiscernible, allowing differentiation of these sweat gland tumors from other neoplasms of small adnexal keratinocytes. CAM5.2 also stains follicular inner root sheath and may be positive in

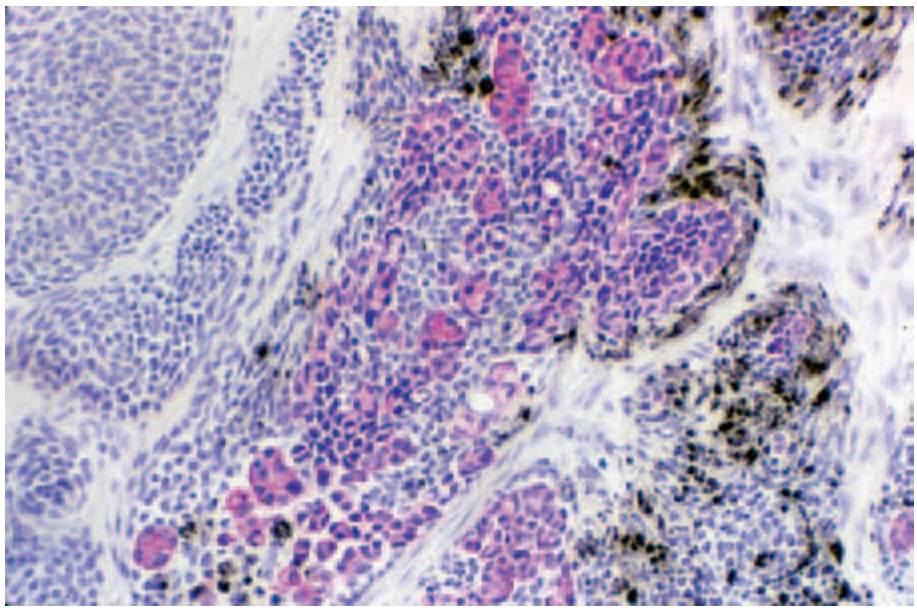


Fig. 25.14 Higher magnification of solid-cystic apocrine ductular adenoma in a cat. Short tubular structures lined by small cuboidal cells are highlighted with an immunostain for CK13 (chromogen new fuchsin).

small areas in follicular tumors that have inner root sheath differentiation (Walder & Haines, 1998; Goldschmidt et al., 2002); however, these foci also have trichohyalin granules, which do not occur in sweat gland neoplasms. CK5/6 diffusely stains all trichoblastoma variants and the small number of solid basal cell carcinomas evaluated to date, but demonstrates only a patchy staining pattern in ductular sweat gland neoplasms (Walder, 2000).

APOCRINE SECRETORY ADENOCARCINOMA

(Synonyms: sweat gland adenocarcinoma, epitrichial adenocarcinoma)

Clinical features

Malignant neoplasms of apocrine sweat glands in general occur uncommonly in dogs and cats. Apocrine adenocarcinomas, which presumably included ductular carcinomas (p. 681) represented 2.2% of canine skin tumors in one survey (Bevier & Goldschmidt, 1981) but only 0.6% in another (Goldschmidt & Shofer, 1992); the basis for this substantial discrepancy is unclear. The incidence in cats ranges from 2.5% to 3.6% (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992).

Apocrine adenocarcinomas are usually solitary, circumscribed masses 0.5 to 10 cm in diameter in dogs and 0.2 to 3 cm in cats (Carpenter et al., 1987). The clinical appearance may vary depending on the histologic subtype. Cystadenocarcinomas may have a fluctuant consistency, and complex tumors may be firmer than simple types due to the presence of cartilage or bone. The overlying skin is frequently alopecic, and ulceration may be present. Poorly-differentiated carcinomas may appear as firm, poorly-circumscribed, diffusely-ulcerated masses.

The majority of apocrine malignancies in general in dogs occur on the legs; the most frequent sites in cats are head, legs, and abdomen (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). The lower lip and chin appear to be preferential sites for apocrine adenocarcinomas on the head in cats.

The average age for most apocrine tumor subtypes is 10 years in dogs and 11 to 13 years in cats (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). Breed predispositions are reported in Coonhounds, Norwegian Elkhounds, and Siamese cats (Goldschmidt & Shofer, 1992).

Numeric data on recurrence and metastasis of apocrine adenocarcinomas are sparse. One small retrospective study found 8% local recurrence and no metastases in dogs, and no recurrence or metastasis in cats, although clinical follow-up was poor or incomplete (Kalaher et al., 1990). In contrast, Goldschmidt and Shofer (1992) report lymph node and pulmonary metastasis in 'many' apocrine adenocarcinomas. It is the authors' opinion that biologic behavior of the common apocrine adenocarcinomas is very similar to that of their mammary counterparts; the metastatic rate probably ranges from low to high and is closely tied to histologic subtype and grade of malignancy. Highly aggressive sweat gland malignancies appear to be infrequent.



Fig. 25.15 Apocrine cystadenocarcinoma in a dog. Delicate papillary structures project into the large cyst lumens, and several more cellular tumor lobules are present at the base of the mass.

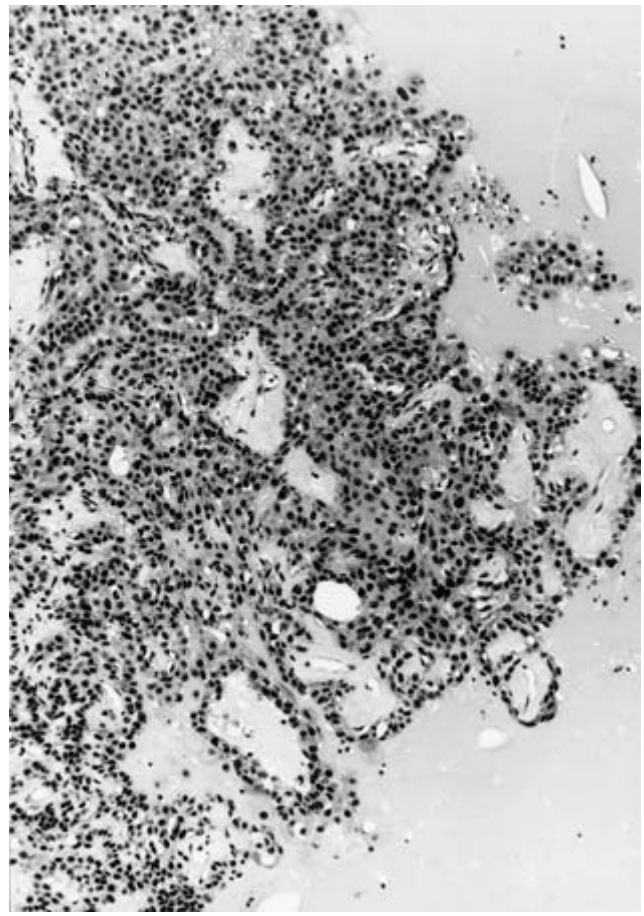


Fig. 25.16 Higher magnification of apocrine cystadenocarcinoma in a dog. The epithelial cells lining this papillary structure have pleomorphic nuclei, prominent nucleoli, and loss of polarity.

Histopathology

Apocrine cystadenocarcinoma (Figures 25.15 and 25.16)
The cystic subtype of apocrine adenocarcinoma is a discrete, multilocular dermal neoplasm resembling cystadenoma (see p. 668), but cytologic features of malignancy are present. There is patchy piling up of cells around cyst lumens with formation of small tufts, cribriform structures, or papillary projections. Nuclei are larger and more pleomorphic than in adenomas, nucleoli may be prominent, and mitotic figures are present in small numbers. There may be loss of nuclear polarity. Secretory activity and apical blebbing may be absent. Invasion beyond the basement membrane is rare.

Differential diagnoses for apocrine cystadenocarcinoma are apocrine cystadenoma and mammary cystadenocarcinoma. In contrast to cystadenomas, cystadenocarcinomas have larger nuclei, nuclear pleomorphism, and loss of nuclear polarity. In a ventral location, apocrine cystadenocarcinoma would be distinguishable from mammary cystadenocarcinoma only by the absence of identifiable mammary glands.

Simple apocrine adenocarcinoma (Figures 25.17 and 25.18)
This is the most frequent variant of sweat gland adenocarcinoma and is architecturally similar to apocrine secretory adenomas with acinar and/or papillary patterns (see p. 670). Most lesions are well-differentiated and comprise neoplastic glandular structures lined by one or more layers of plump, cuboidal to columnar cells that have moderately enlarged, vesicular nuclei, and small nucleoli. Decapitation secretion and luminal accumulation of secretory material are common. Mitotic activity is low to moderate, and atypical mitoses may be identified. There is a sparse to moderate collagenous stroma of low cellularity. Secondary ulceration and inflammation may be present in larger lesions. Lymphatic invasion is rare.

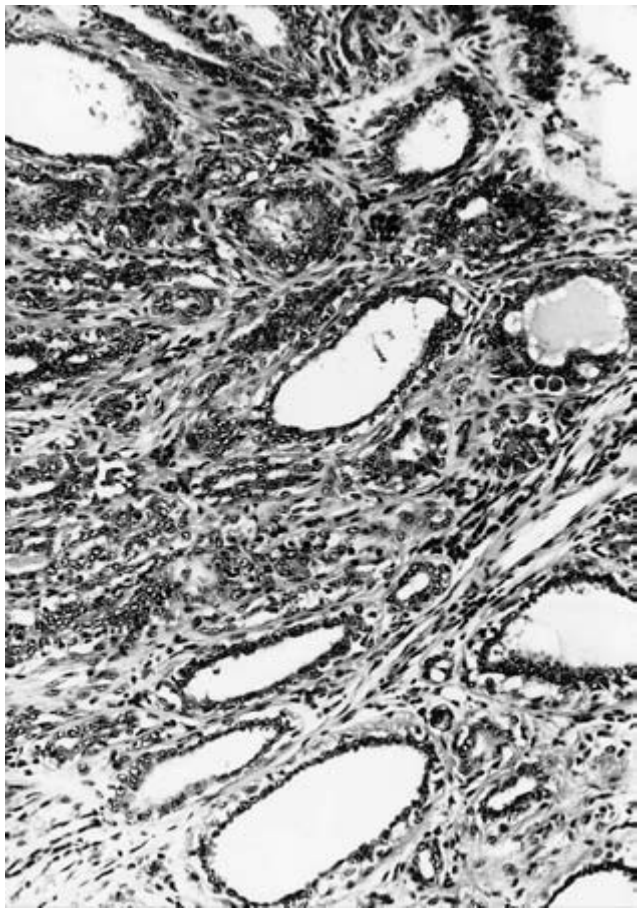


Fig. 25.17 Well-differentiated apocrine adenocarcinoma in a dog. Epithelial cells have enlarged, vesicular nuclei and small nucleoli. Note that apocrine-type secretory activity is still evident.

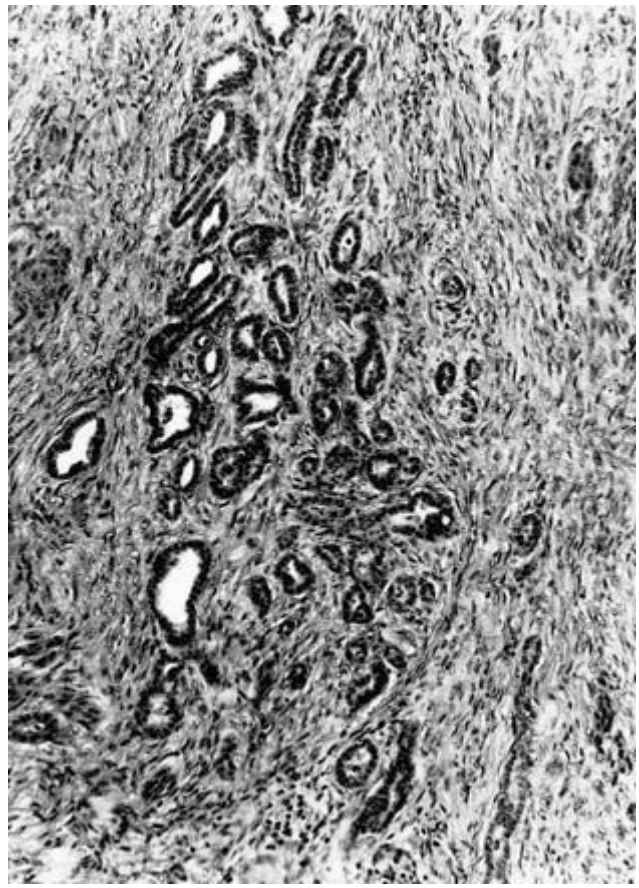


Fig. 25.18 Apocrine adenocarcinoma in a dog. Irregular glandular structures are distributed through an abundant collagenous stroma. Note stromal invasion by clusters of tumor cells.

Poorly-differentiated variants of apocrine adenocarcinoma are infiltrative neoplasms with ill-defined borders. Ulceration is frequent. They are composed of large cuboidal to polygonal cells arranged in glandular and solid aggregates in varying proportions. Small areas of squamous metaplasia may occur. Zones of caseation necrosis are frequently observed. The neoplastic cells generally have amphophilic cytoplasm, large vesicular nuclei, prominent nucleoli, and moderate to high mitotic activity. Mitotic atypia is frequent. Poorly-differentiated apocrine adenocarcinomas have a moderate to abundant stroma of reactive collagenous tissue. Stromal invasion by cords and clusters of neoplastic epithelial cells is common; tumor cells may be detected within lymphatic vessels in stroma and adjacent dermis.

Differential diagnoses for well-differentiated apocrine adenocarcinoma are apocrine adenoma and mammary adenocarcinoma. Mammary lobules and/or ducts can usually be identified adjacent to mammary neoplasms. Distinction between apocrine adenoma and well-differentiated adenocarcinoma may be problematic. Asymmetry, infiltrative borders, piling up of cells within lumens, nuclear pleomorphism, prominent nucleoli, increased mitotic activity, or atypical mitoses are indicators of malignancy.

The differential diagnoses of poorly differentiated apocrine adenocarcinoma include mammary carcinoma as well as other poorly differentiated carcinomas, which may be primary or metastatic in the skin. Histologic distinction is often not possible. Careful search for residual mammary lobules or ducts is required for neoplasms located on the ventrum. Hemorrhage and/or abundant fibroplasia and neovascularization extending peripheral to the mass are suggestive of metastatic disease. Distinction from acantholytic (pseudoglandular) squamous cell carcinoma (see Chapter 22) can be difficult in apocrine adenocarcinomas with squamous metaplasia. Multifocal epidermal contiguity and active acantholysis, characterized by individualized keratinized cells and elongated intercellular bridges within pseudolumens, support a

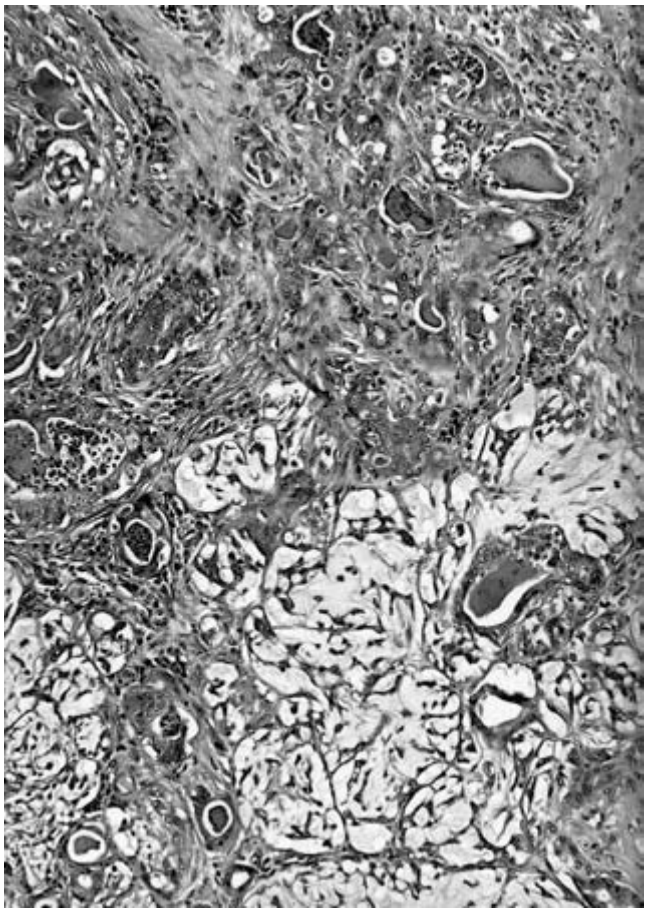


Fig. 25.19 Complex apocrine adenocarcinoma in a dog. Irregular acinar structures containing secretory material and necrotic debris are lined by one or more layers of epithelial cells. Note islands of myxoid myoepithelial tissue at bottom.

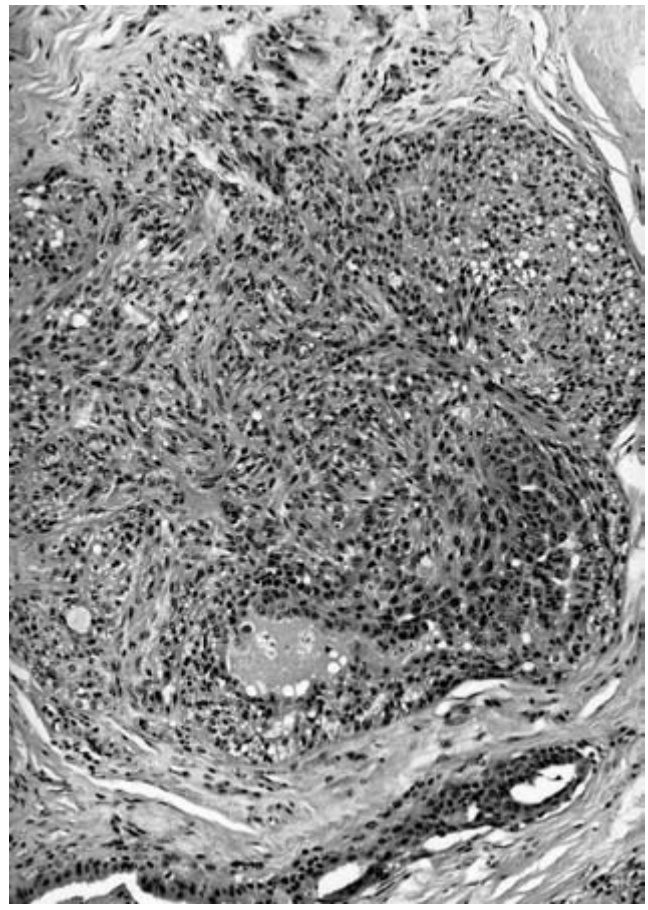


Fig. 25.20 Apocrine carcinosarcoma in a dog. Papillary structures lined by pleomorphic epithelial cells blend into a large island of plump, spindle-shaped myoepithelial cells. Enlarged, hyperchromatic nuclei are present in both glandular and myoepithelial components.

diagnosis of squamous cell carcinoma. Immunohistochemistry can definitively distinguish between adenocarcinoma and squamous cell carcinoma, but distinction of apocrine from other glandular origin may not be feasible with these techniques (see below).

Complex (mixed) apocrine adenocarcinoma

(Figures 25.19 and 25.20)

The majority of complex apocrine adenocarcinomas have an epithelial component resembling well-differentiated simple adenocarcinoma (see above). The myoepithelial portion of the tumor usually has a benign histologic appearance with myxoid or chondroid features, as in complex sweat gland adenomas (see p. 670) and complex and mixed mammary neoplasms. Osseous metaplasia is rare. The mesenchymal component is usually characterized by multiple nodules of small spindle and stellate cells with pale cytoplasm and bland, ovoid to fusiform nuclei. The mesenchymal cells are separated by a lightly-basophilic mucinous stroma or are entrapped in lacunar spaces within a more deeply basophilic chondroid matrix. Occasionally, the myoepithelial component is diffuse and predominates over the epithelial aggregates. In rare instances, when the mesenchymal cells demonstrate nuclear atypia and mitotic activity, a designation of apocrine carcinosarcoma or malignant mixed sweat gland tumor is appropriate. Small numbers of poorly-differentiated apocrine adenocarcinomas show multifocal myoepithelial proliferation with myxoid, chondroid or osseous features.

Differential diagnoses of complex apocrine adenocarcinomas are essentially limited to complex mammary adenocarcinomas and carcinosarcomas. Thus, distinction is based on anatomic location and presence or absence of identifiable residual mammary tissue. Other glands, such as salivary and thyroid, can give rise to neoplasms with mixed epithelial and mesenchymal components, but metastasis to skin has not been reported in dogs or cats.

Immunohistochemistry

For lesions of questionable glandular origin, application of cytokeratins (CKs) that mark simple epithelia (particularly CAM5.2 (CK7/8) and CK13) usually allows differentiation of apocrine carcinomas from purely follicular, sebaceous, or epidermal carcinomas, which are generally negative with these stains. CAM5.2 also stains follicular inner root sheath and may be positive in small areas of neoplasms that have inner root sheath differentiation (Walder & Haines, 1998; Goldschmidt et al., 2002); however, these foci also have trichohyalin granules, which do not occur in sweat gland neoplasms. Carcinoembryonic antigen (CEA), which has long been known to stain human apocrine and eccrine sweat glands and many of their neoplasms, is rarely used in veterinary pathology, but may be an additional useful marker. A pilot study found positive CEA staining in two of three sweat gland adenocarcinomas, while normal glands and two of two benign tumors were negative (Ferrer et al., 1990). The authors have been unsuccessful in utilizing CEA immunostaining. Differentiation between sweat gland and mammary gland origin remains problematic; no markers have been found to be consistently beneficial in making this distinction.

APOCRINE DUCTULAR CARCINOMA

(Synonyms: ductular sweat gland adenocarcinoma, malignant nodular hidradenoma, hidradenocarcinoma)

This section includes two new entities, which parallel the expanded nomenclature in the benign ductular sweat gland tumor category (see p. 672). The first, solid-cystic apocrine ductular carcinoma, is a newly-recognized subtype in cats. This entity was most likely previously included in the basal cell carcinoma category in veterinary pathology. It is similar to human malignant nodular hidradenoma (nodular hidradenocarcinoma) but without classical clear cell morphology (Murphy & Elder, 1991). Clear cell apocrine ductular carcinoma is the second new and controversial entity that is recognized in dogs. The neoplasm has many features in common with human malignant nodular hidradenoma (nodular hidradenocarcinoma, clear cell hidradenocarcinoma) with a predominance of large clear cells (Hernández-Pérez & Cestoni-Parducci, 1985; Murphy & Elder, 1991; Touma et al., 1993). Neoplasms with similar morphology have often been misinterpreted as sebaceous carcinomas in veterinary reference texts, including *Veterinary Dermatopathology* (Walder & Gross, 1992). Four cases of clear cell hidradenocarcinoma in dogs were reported many years ago, although only two of these cases were convincingly of sweat gland origin (Jabara & Finnie, 1978). The entity has recently been rediscovered and has been designated 'follicular stem cell carcinoma' (Mikaelian & Wong, 2003). Although the neoplasm may show some divergent adnexal differentiation, a phenomenon that occurs in a wide variety of tumors of the folliculosebaceous-apocrine unit, the authors believe that the morphologic and immunohistochemical appearance confirm a predominance of sweat gland features (see below).

Clinical features

Malignant neoplasms of apocrine sweat glands in general occur uncommonly in dogs and cats. Apocrine carcinomas of ductular origin were not named as specific entities in animals until 1992 (Walder & Gross, 1992), making application of numeric data somewhat difficult. Apocrine adenocarcinomas, which presumably included ductular carcinomas, represented 2.2% of canine skin tumors in one survey (Bevier & Goldschmidt, 1981) but only 0.6% in another (Goldschmidt & Shofer, 1992); the basis for this substantial discrepancy is unclear. The incidence in cats ranges from 2.5% to 3.6% (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). Solid-cystic apocrine ductular carcinoma appears to occur exclusively in cats, and is rare; true incidence is obscured by its likely previous inclusion with basal cell carcinomas. Clear cell apocrine ductular carcinoma in dogs is rare.

Apocrine ductular carcinomas are usually solitary masses 2 to 10 cm in diameter in dogs and 0.5 to 3 cm in cats. The clinical appearance may vary depending on the histologic subtype. The overlying skin is frequently alopecic, and ulceration may be present. Poorly-differentiated carcinomas may appear as firm, poorly-circumscribed, diffusely-ulcerated masses.

The majority of apocrine malignancies in general are reported to occur on the legs in dogs and on the head, legs, and abdomen in cats (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). However, separate data for ductular carcinomas are not provided. Solid-cystic ductular carcinomas in cats occur most often on the extremities. No site predilections were apparent for clear cell apocrine ductular carcinoma in dogs (Mikaelian & Wong, 2003).

The average age for most apocrine tumor subtypes is 10 years in dogs and 11 to 13 years in cats (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). Breed predispositions are reported in Coonhounds, Norwegian Elkhounds, and Siamese cats (Goldschmidt & Shofer, 1992). Dogs with clear cell apocrine ductular carcinoma had a mean age of 7 years; there was no breed predilection (Mikaelian & Wong, 2003).

Numeric data on recurrence and metastasis of apocrine malignancies in general are sparse. It is the authors' opinion that highly aggressive sweat gland malignancies are infrequent. Ductular carcinomas in dogs and solid-

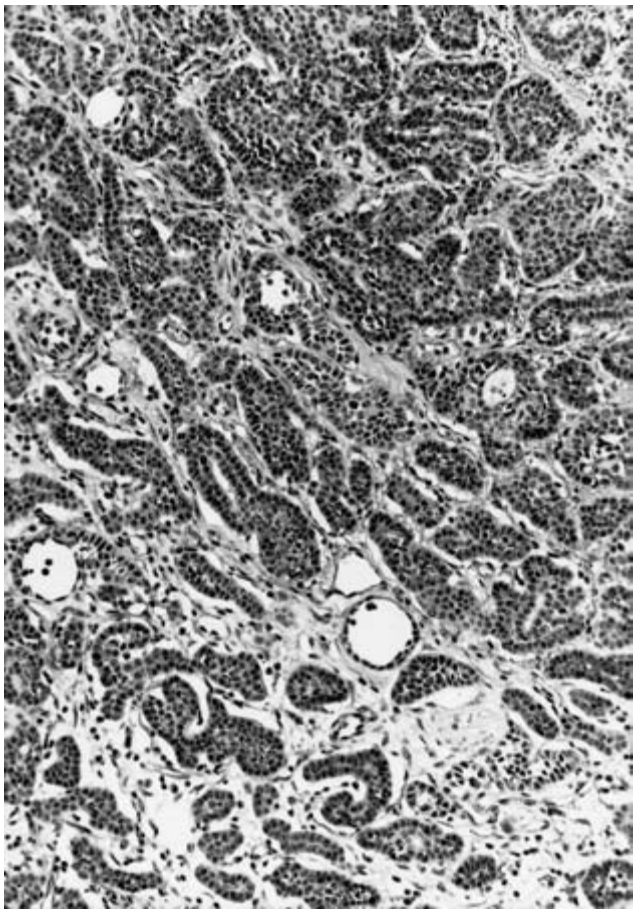


Fig. 25.21 Apocrine ductular carcinoma in a dog. The irregular tubular structures are frequently lined by a distinct double layer of plump cuboidal cells.

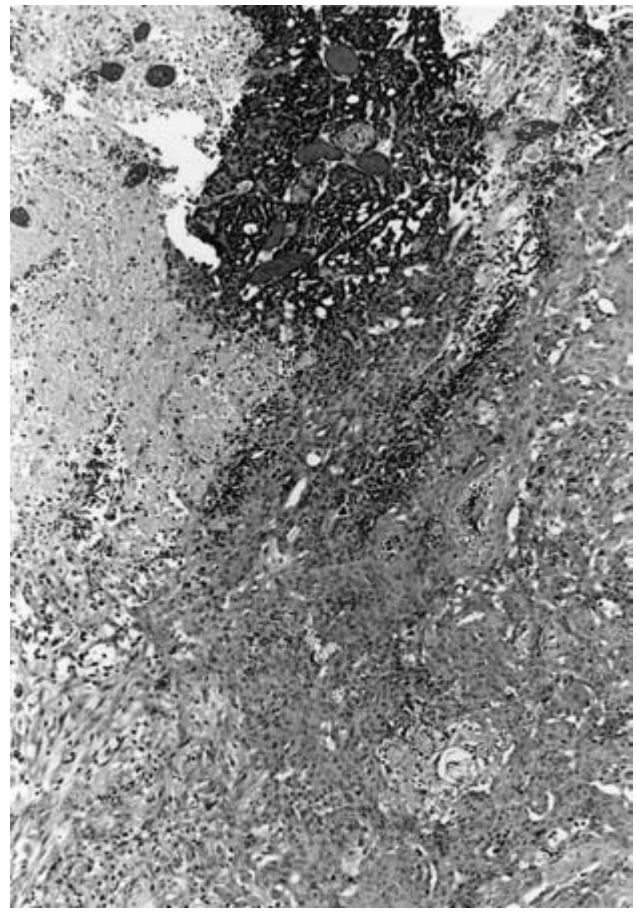


Fig. 25.22 Apocrine ductular carcinoma in a dog. An area resembling ductular adenoma at the top merges into a poorly-differentiated neoplasm with extensive squamous metaplasia.

cystic ductular carcinomas in cats are the most likely to have lymphatic invasion or regional lymph node involvement at time of initial biopsy. The recent retrospective study of clear cell apocrine ductular carcinomas had a 13% rate of metastasis (Mikaelian & Wong, 2003).

Histopathology

Apocrine ductular carcinoma (Figures 25.21 through 25.25)

This subtype resembles a ductular adenoma (see p. 672) but is usually larger and less circumscribed than its benign counterpart. Ulceration and necrosis are frequent features, and tumor margins are infiltrative. There is a sparse to moderate collagenous stroma that is often highly cellular. The neoplastic tubules of apocrine ductular carcinoma are generally lined by a double layer of cuboidal epithelial cells, as in ductular adenoma. However, the epithelial cells are larger and more pleomorphic. Papillary hyperplasia, characterized by small tufts of polygonal cells, may be present within tubular lumens. Nuclear to cytoplasmic ratios are increased. Chromatin patterns and nucleolar features are variable. Cells with large cytoplasmic mucin vacuoles are sometimes present. Mitotic activity is moderate to high, and atypical mitoses can usually be detected. Tumor cells within stromal lymphatic vessels may be seen.

Multiple foci of squamous epithelium, sometimes with complete keratinization via a granular layer, occur in some canine apocrine ductular carcinomas and probably represent differentiation toward acrosyringium (terminal sweat gland duct). The squamous foci may be randomly scattered through the tumor in a pattern resembling canine apocrine ductular adenoma. The squamous epithelium may have atypical nuclei, mitotic figures, and disordered cornification, resembling well differentiated squamous cell carcinoma.

Other lesions, particularly on the elbow in dogs, show prominent squamous metaplasia limited to the superficial

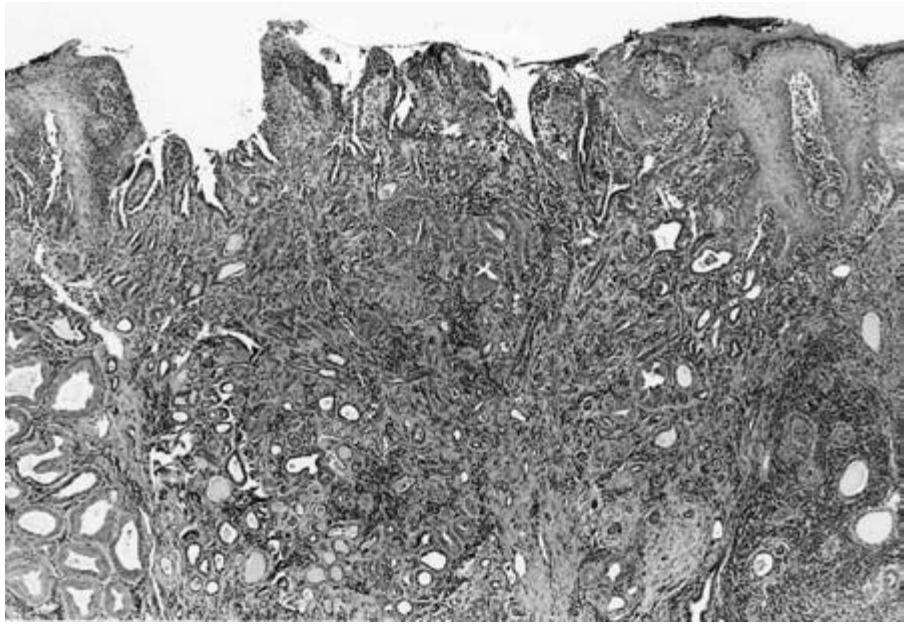


Fig. 25.23 Apocrine ductular carcinoma on the elbow of a dog. Low magnification reveals a poorly-circumscribed mass with a fissured surface caused by neoplastic ducts merging into and disrupting follicular infundibula.

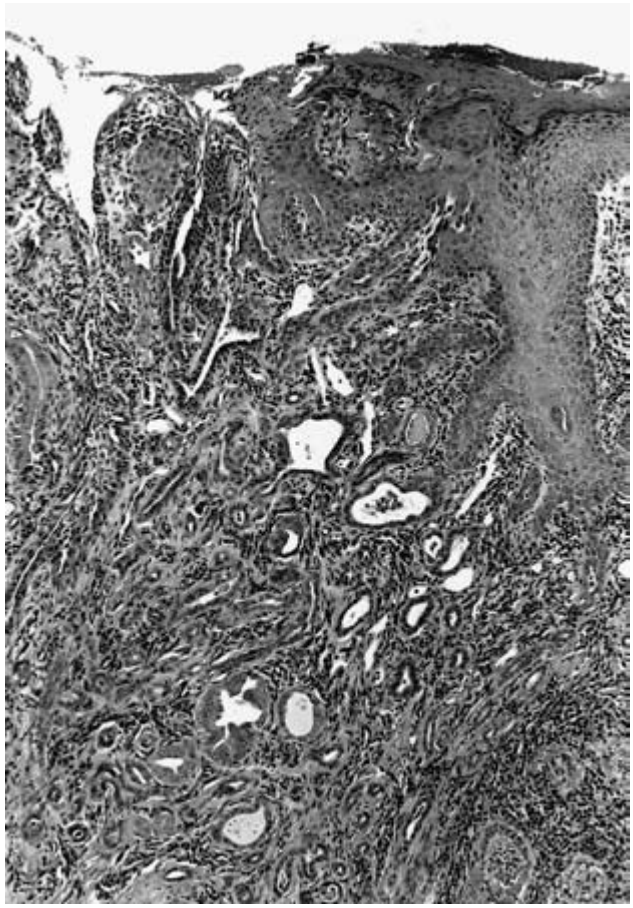


Fig. 25.24 Higher magnification of Fig. 25.23. Small tubuloacinar structures are undergoing squamous metaplasia superficially where they are contiguous with hair follicles. Note inflamed desmoplastic stroma.

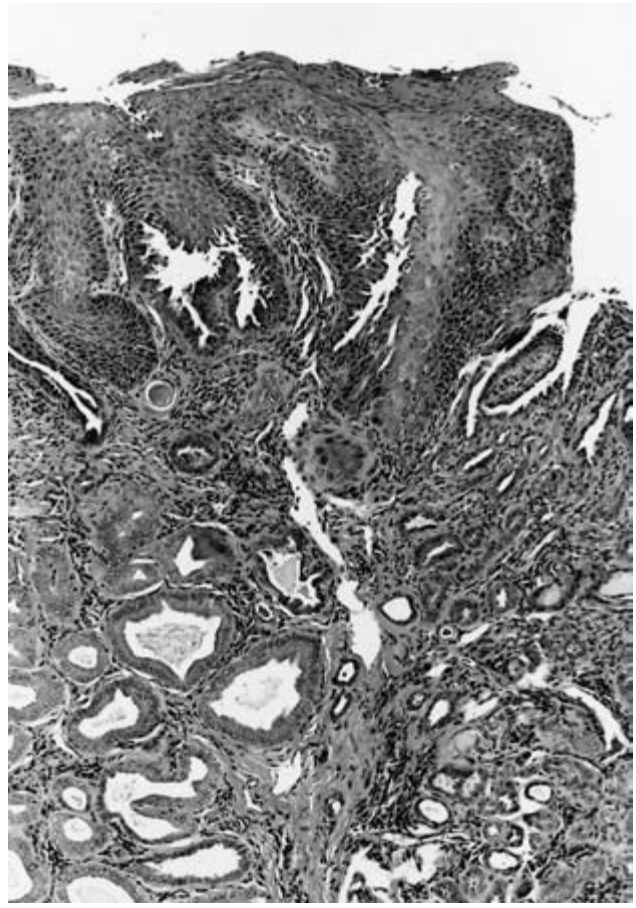


Fig. 25.25 Higher magnification of Fig. 25.23. Superficial neoplastic ducts often have ragged lumens due to mild papillary hyperplasia. Small neoplastic tubuloacinar structures at bottom right blend with hyperplastic sweat glands at bottom left.

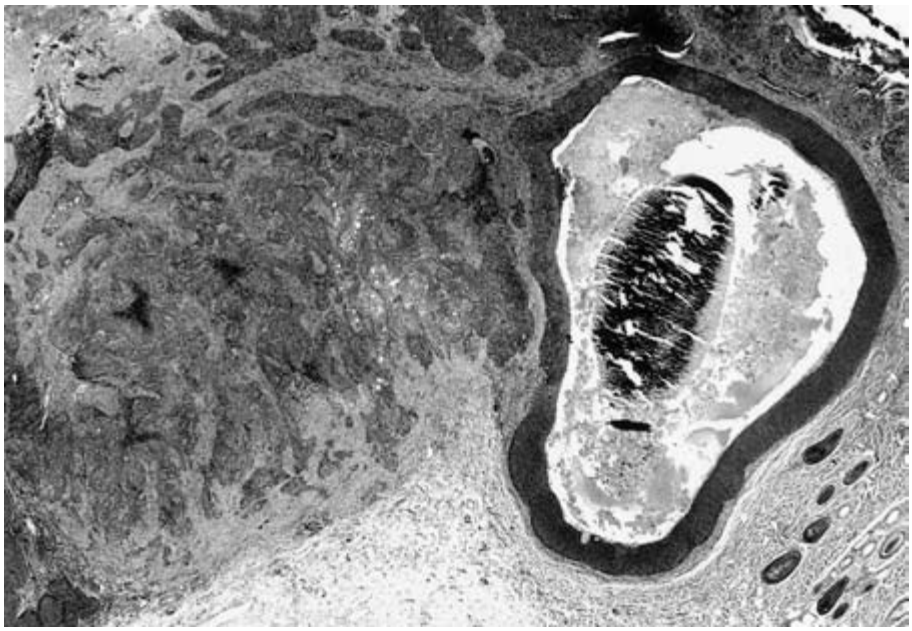


Fig. 25.26 Solid-cystic apocrine ductular carcinoma in a cat. A large cystic lobule resembling solid-cystic ductular adenoma on the right is contiguous with an invasive neoplasm resembling basal cell carcinoma.

aspects of the tumor in association with multifocal follicular infundibular contiguity. Papillary hyperplasia of the ductular epithelium in conjunction with squamous metaplasia may produce a ragged appearance, resembling acantholysis, to the lining of the duct lumen. It is often difficult to distinguish these neoplastic apocrine ducts from surrounding hyperplastic follicular infundibula and epidermis. Rarely, small clusters of undifferentiated cells are found within follicular infundibular epithelium, resembling extramammary Paget's disease in humans (Kirkham, 1997); this phenomenon is also described in ceruminous gland neoplasms (Goldschmidt & Shofer, 1992). The deeper aspects of the elbow carcinomas comprise tubuloacinar structures lined by one or more layers of cuboidal epithelium; these suggest that this particular tumor type may represent both ductular and secretory portions of the sweat gland apparatus.

Differential diagnoses include benign apocrine ductular adenoma, basaloid mammary adenocarcinomas (for ventral neoplasms), and acantholytic (pseudoglandular) squamous cell carcinoma. The double layer of cells lining most of the neoplastic structures is the salient feature of apocrine ductular origin. In contrast with adenomas, ductular adenocarcinomas generally have more irregular, infiltrative borders and larger nuclei with prominent nucleoli. Atypical mitotic figures, larger foci of squamous metaplasia with cytologic atypia, and zones of necrosis are not expected in benign ductular adenomas. The epidermal contiguity of squamous cell carcinoma can be difficult to distinguish from acrosyringial differentiation and/or follicular contiguity in apocrine ductular carcinoma; active acantholysis, characterized by individualized

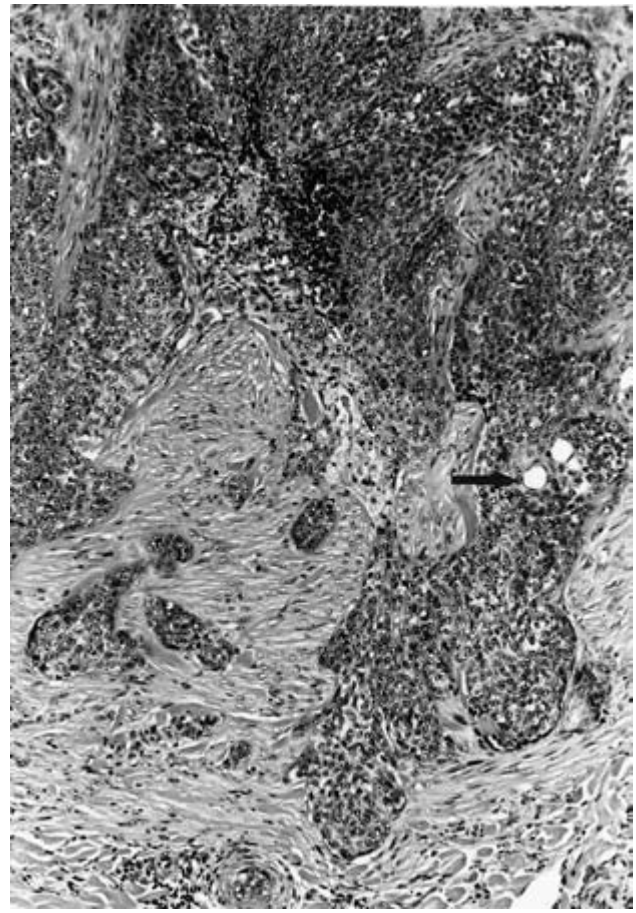


Fig. 25.27 Higher magnification of Fig. 25.26. The bimorphic cell population of solid-cystic ductular adenoma is still discernible, and several intracellular ductules are present (arrow).

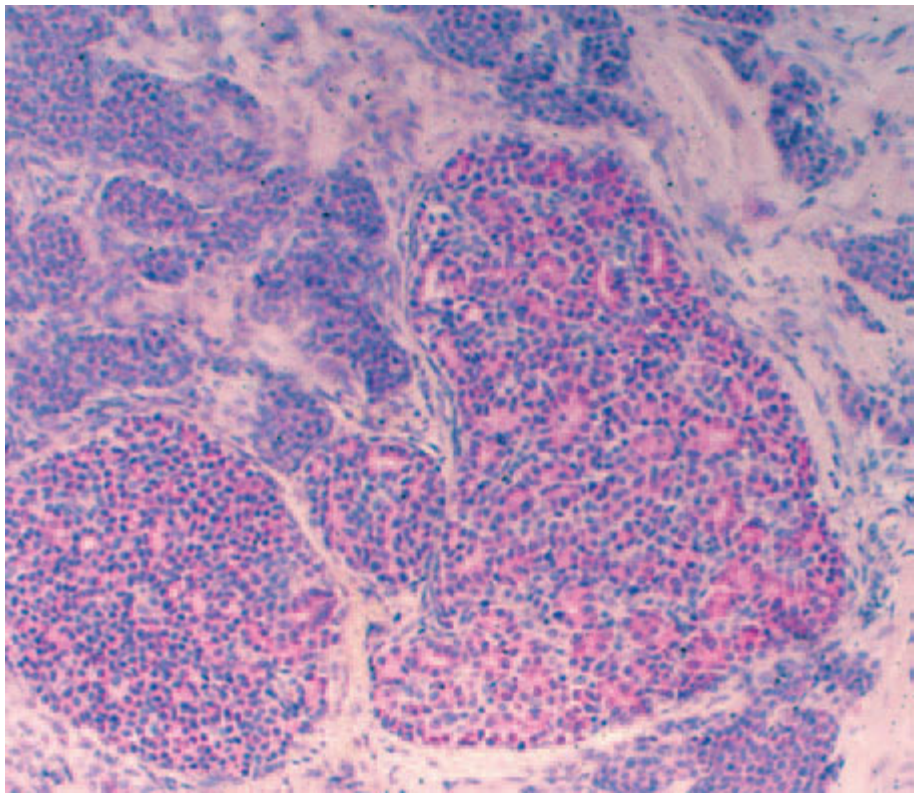


Fig. 25.28 Solid-cystic apocrine ductular carcinoma in a cat. CK13 immunostain reveals ductular differentiation in a neoplasm with solid architecture (chromogen new fuchsin).

keratinized cells and elongated intercellular bridges within pseudolumens, and necrosis and drop-out of keratinized cells from the centers of epithelial aggregates, support a diagnosis of squamous cell carcinoma. Immunostaining may be required for definitive diagnosis (see below).

Solid-cystic apocrine ductular carcinoma

(Figures 25.26 through 25.30)

This variant usually appears as an ulcerated, endophytic, asymmetric dermal mass that tends to be horizontally-oriented. Larger lesions may extend into the subcutis. Solid-cystic carcinoma comprises multiple lobules of large, basaloid cells that may be focally or multifocally contiguous with the epidermis. The lobules are often large and have angular or jagged profiles. Caseation necrosis may be extensive, but large cystic spaces are uncommon. Well-defined tubular structures are usually absent, but scattered acinar or cribriform patterns may occur. Rarely, one may see areas of typical solid-cystic ductular adenoma adjacent to a carcinoma, suggesting malignant transformation. Squamous metaplasia is a common feature in the human analogue (malignant nodular hidradenoma) and may be extensive (Park et al., 2000); too few cases have been identified to determine if this also occurs in the feline neoplasms.

The neoplastic cells have scant to moderate, pale cytoplasm; a diffuse bimorphic poroid cell population or clusters of large clear cells, as seen in solid-cystic apocrine ductular adenoma (see p. 672), are not observed. Small numbers of cells have single round vacuoles consistent with intracytoplasmic lumens. Nuclei are large, ovoid and variably hyperchromatic. Nucleoli are generally small, and mitotic activity is moderate to high. The stroma usually shows moderate cellularity, and clusters of tumor cells are frequently present within dilated lymphatic vessels at the margins of the mass.

Solid-cystic apocrine ductular carcinoma is distinguished from its benign counterpart by its obvious asymmetry, horizontal orientation, and angular rather than rounded profiles in the majority of epithelial aggregates. A typical bimorphic poroid cell population is absent, and mitotic activity is higher in carcinomas. Solid-cystic apocrine ductular carcinoma must also be differentiated from basal cell carcinoma, which is a less aggressive malignancy. This is problematic not only because of their cytologic similarities, but also because the histologic criteria of the former have not yet been well defined. Features that appear to be more supportive of basal cell carcinoma are peripheral palisading and stromal–epithelial retraction clefts. If the lesion is deeply invasive and has lymphatic infiltration, solid-cystic apocrine ductular carcinoma should be more strongly considered, and careful search for extra- or intracellular luminal structures is warranted.

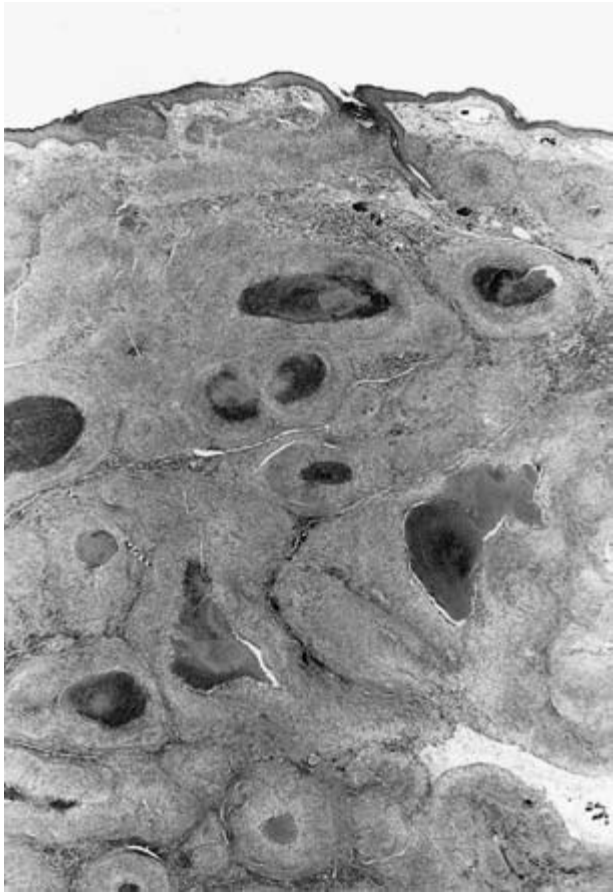


Fig. 25.29 Solid-cystic apocrine ductular carcinoma in a dog. A large, multilobular mass of pale cells has architecture resembling solid-cystic apocrine ductular adenoma. Note necrosis and cystic degeneration in the centers of many lobules and several foci of epidermal/follicular contiguity.



Fig. 25.30 Higher magnification of solid-cystic apocrine ductular carcinoma of Fig. 25.29. Tumor tissue pushes into and partially replaces follicular infundibular epithelium at the level of insertion of normal apocrine duct.

Immunohistochemical staining is required for definitive diagnosis (see below).

Clear cell apocrine ductular carcinoma (clear cell nodular hidradenocarcinoma) (Figures 25.31 through 25.34)

This is usually a sessile, expansile dermal mass that may extend into the subcutis. The lesions are often ulcerated and occasionally pedunculated. Focal contiguity with epidermis or follicular infundibulum is often present; rarely, multifocal contiguity is observed. Clear cell apocrine ductular carcinomas comprise large, polygonal cells in lobules and nests. Zones of cystic degeneration may be present within large lobules. Sparse to moderate melanin pigment with a patchy distribution is present in approximately half of the cases of clear cell apocrine ductular carcinoma. Spindling of the epithelial cells and peripheral palisading may be present in limited areas. Subtle tubules lined by one to three layers of cells can be identified in the majority of cases. Occasional apical blebbing along tubular lumens is reported (Mikaelian & Wong, 2003).

The neoplastic cells have moderate to abundant, pale eosinophilic or clear cytoplasm. The cytoplasm frequently appears feathery, reticulated, or finely-vacuolated. Periodic acid–Schiff (PAS) staining is positive in variable numbers of the cells. Diastase-sensitive material predominates; this is indicative of glycogen. Small amounts of diastase-resistant PAS positive material are also described; this is consistent with mucin (Jabara & Finnie, 1978; Mikaelian & Wong, 2003). Nuclei are moderately to markedly enlarged and vesicular with single, central nucleoli. Most tumors contain multinucleated cells with up to ten nuclei (Mikaelian & Wong, 2003). Some cases have marked nuclear pleomorphism with intranuclear cytoplasmic invaginations. Mitotic activity ranges from

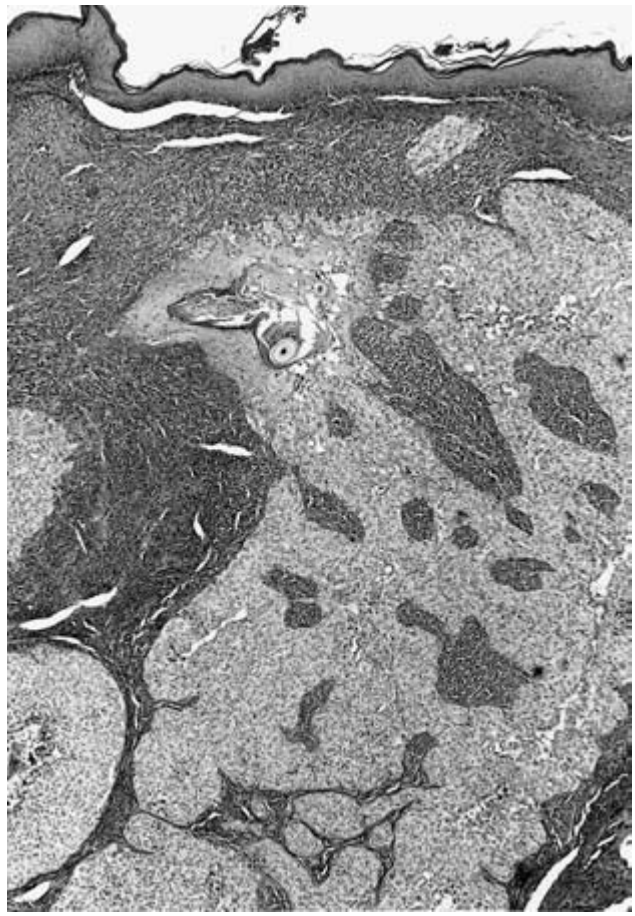


Fig. 25.31 Clear cell apocrine ductular carcinoma in a dog. The tumor comprises large lobules and broad anastomosing trabeculae of large cells with clear cytoplasm. Note small areas of cystic change in the centers of some of the aggregates (lower left). The darker stroma is infiltrated by numerous lymphocytes and plasma cells.

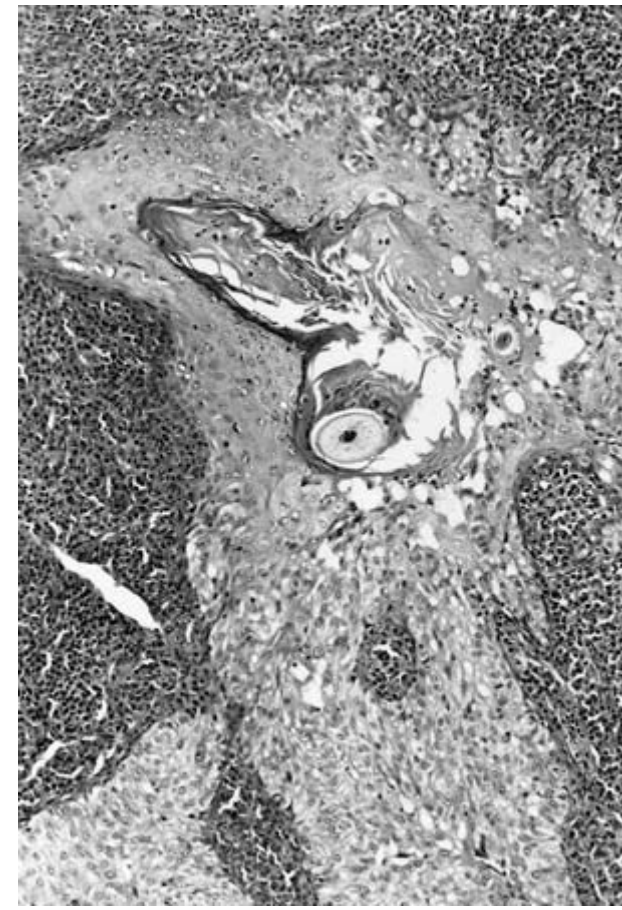


Fig. 25.32 Higher magnification of Fig. 25.31. As in Fig. 25.30, tumor tissue pushes into follicular infundibular epithelium.

absent to moderately high (Jabara & Finnie, 1978; Mikaelian & Wong, 2003).

The tumors have a sparse to moderate fibrous stroma that occasionally contains nests of diminutive mesenchymal cells consistent with follicular papillary bodies (see trichoblastoma, Chapter 23); it is undetermined if these indicate neoplastic follicular differentiation or represent pre-existing papillae of follicles that have been diffusely infiltrated by tumor cells. Large tubular structures interpreted as remnants of hair follicles progressively replaced by apocrine ductular epithelium have been reported in human clear cell hidradenomas (Gianotti & Alessi, 1997). Chondroid metaplasia of the stroma, possibly indicating a myoepithelial component, is also reported (Mikaelian & Wong, 2003).

Correct diagnosis of clear cell apocrine ductular carcinoma is often problematic due to its rarity and unusual morphology. The primary differential diagnosis is balloon cell melanoma. Melanin pigment and spindle cells can be present or absent in both of these tumor types, and are therefore not useful distinguishing properties. Balloon cell melanomas also have a positive PAS reaction (Nowak et al., 1998). Clear cell apocrine ductular carcinoma often has architectural features that are similar to benign solid-cystic ductular adenoma, namely, focal epidermal or follicular infundibular contiguity and subtle tubular structures; these characteristics aid in confirming sweat gland origin and are not seen in balloon cell melanoma. The detection of follicular papillary mesenchymal bodies may be helpful in ruling out a diagnosis of balloon cell melanoma. Immunohistochemistry is ultimately required for definitive diagnosis (see below).

Clear cell basal cell carcinoma can be differentiated from clear cell apocrine ductular carcinoma by its multifocal epidermal contiguity, horizontal orientation, infiltrative margins, stromal–epithelial retraction clefts, and smaller cell size. Although a malignant variant of bulb-type tricholemmoma has not been reported, theoretically

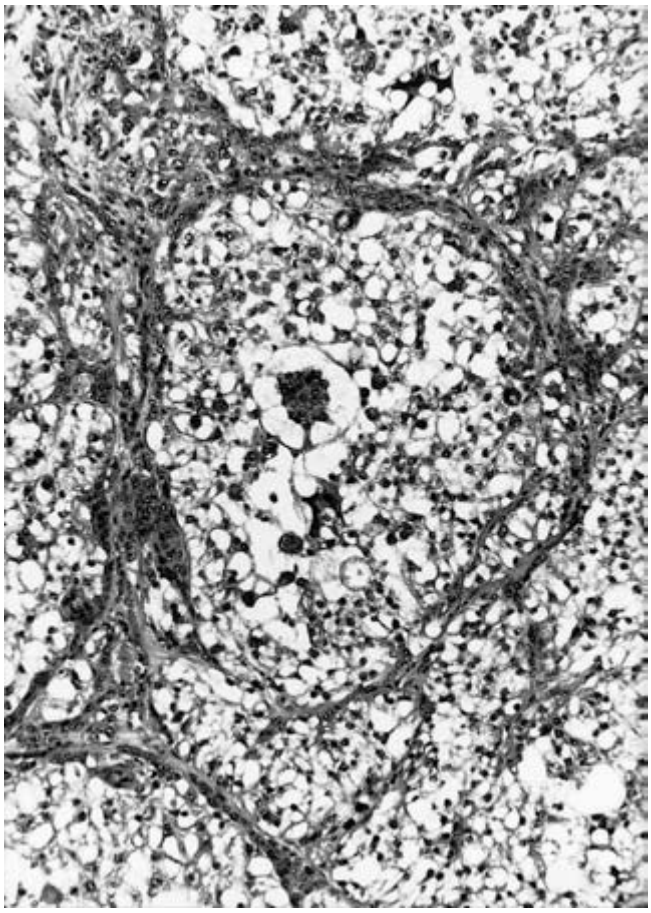


Fig. 25.33 Higher magnification of clear cell apocrine ductular carcinoma in a dog. Many tumor cells have abundant, markedly vacuolated, foamy cytoplasm and pleomorphic, eccentric nuclei.

this is another glycogen-rich tumor type that could be a differential diagnosis for clear cell apocrine ductular carcinoma. Distinguishing features of tricholemmal carcinoma potentially would be nests and cords of cells bordered by exaggerated vitreous membranes, more abundant stroma, and absence of tubular structures. Sebaceous carcinoma, contrary to previous perceptions, does not have a pure large cell variant and, therefore, should not be confused with clear cell apocrine ductular carcinoma.

Immunohistochemistry

For lesions of questionable glandular origin, application of specific cytokeratins (CKs) that mark simple epithelia (CAM5.2 (CK7/8), CK13) usually allows differentiation from purely follicular, sebaceous, or epidermal carcinomas, which are generally negative with these stains. CAM5.2 also stains follicular inner root sheath and may be positive in small areas in malignant trichoepitheliomas and malignant pilomatricomas that have inner root sheath differentiation (Walder & Haines, 1998; Goldschmidt et al., 2002); however, these foci also have trichohyalin granules, which do not occur in sweat gland neoplasms. All clear cell apocrine ductular carcinomas stained by the authors with CAM5.2 exhibited strong diffuse or multifocal positivity (6/6); this provides strong support for sweat gland origin. Although pan-cytokeratin immunostaining was positive, monoclonal cytokeratin panels were not performed in the previous report on 'follicular stem cell carcinomas' (Mikaelian & Wong, 2003). Until reliable markers specific for hair follicle epithelium

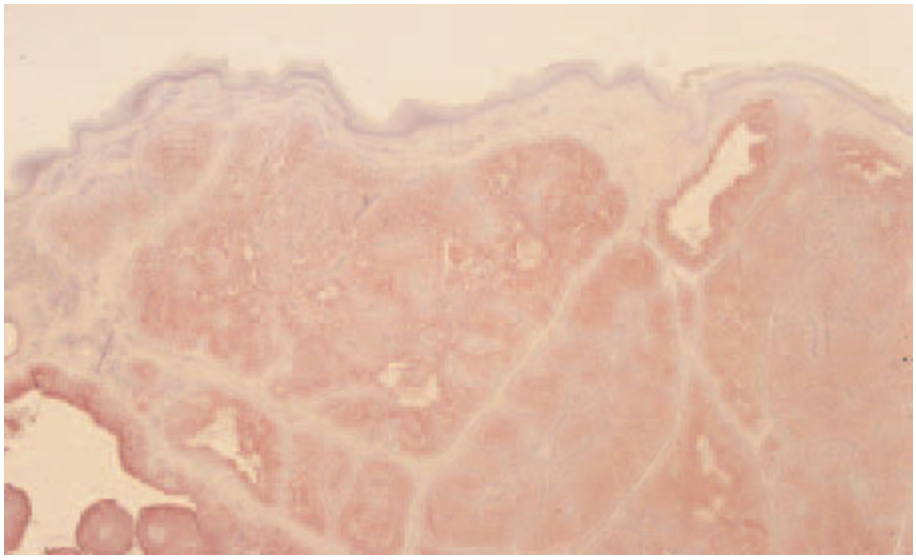


Fig. 25.34 Clear cell apocrine ductular carcinoma in a dog. CAM5.2 immunostain decorates the majority of cells in these tumors, as seen in this example (chromogen aminoethylcarbazole [AEC]).

become available in veterinary pathology, a follicular component in clear cell apocrine ductular carcinoma cannot be verified or excluded. Trichoblastomas in humans have recently been demonstrated to be tumors of follicular stem cells based on immunohistochemical staining with CKs 15, 17, and 19; they are negative for CK8 and CK13. This CK profile is shared by most human basal cell carcinomas, suggesting that they also have the immunophenotype of follicular stem cell carcinomas (see Chapters 22 and 23), unlike apocrine ductular tumors. Complete monoclonal keratin profiles have not been established for canine or feline basal cell carcinoma, but cases evaluated to date are negative for CK13 (Walder, 2000).

The mesenchymal intermediate filament vimentin, the melanoma-associated antigen (Melan-A), and the melanoma antigen recognized by T lymphocytes (MART-1) can be identified immunohistochemically in significant quantities in some sweat gland tumors, particularly clear cell apocrine ductular carcinoma (Mikaelian & Wong, 2003), and therefore cannot be employed as single markers for ruling out balloon cell melanoma. However, S100a was reported to decorate only scattered dendritic cells in clear cell apocrine ductular carcinoma (Mikaelian & Wong, 2003), in contrast to its staining of tumor cells in balloon cell melanomas as well as common types of melanoma. This discrepancy suggests that the Melan-A positivity in clear cell apocrine ductular carcinomas may represent staining of subcellular melanocyte structures phagocytized by epithelial cells. This possibility is supported by recent evidence that the Melan-A/MART-1 antigen is concentrated in the Golgi region, melanosomes, premelanosomes, and cytoplasmic vesicles in melanocytes (De Maziere et al., 2002).

ECCRINE CARCINOMA

(Synonym: atrichial sweat gland carcinoma)

There are more than fifteen categories of non-neoplastic, benign, and malignant eccrine tumors in humans. Despite the fact that their anatomic distribution in dogs and cats is limited to the pawpads, it is still surprising that non-neoplastic and benign tumors of eccrine sweat glands are virtually nonexistent in these species. Eccrine adenomas are described but not illustrated in the current World Health Organization fascicle (Goldschmidt et al., 1998). A single case of eccrine adenoma in a dog is illustrated but not described in a previous edition of *Small Animal Dermatology* (Muller et al., 1989). There are no other known reports. The authors have not observed examples of eccrine adenoma.

Clinical features

Malignant neoplasms of eccrine sweat glands are extremely rare in dogs and cats. Eccrine carcinomas have been observed occasionally by the authors in the pawpads of cats and dogs, and they are described in the current World Health Organization fascicle (Goldschmidt et al., 1998). One case is reported in a dog (Kusters et al., 1999) and another is described in a cat (Carpenter et al., 1987). There are no other convincing reports of neoplasms originating from the pawpad.

Eccrine carcinoma presents as a solitary, poorly-defined swelling of pawpad and may also involve the digit or distal leg. Ulceration is present, and lysis of adjacent phalangeal or metatarsal bone may be observed radiographically. Breed and age predilections have not been determined.

Eccrine carcinomas are aggressive neoplasms that recur locally or exhibit rapid metastasis to regional lymph nodes and subcutaneous tissues of the affected leg. The single reported canine case also had metastasis to the ipsilateral internal iliac lymph node (Kusters et al., 1999).

Histopathology (Figures 25.35 through 25.37)

Eccrine carcinoma is a poorly-circumscribed, infiltrative neoplasm involving the pawpad fat, overlying dermis and, in some cases, associated bone. Bone invasion by tumor tissue is accompanied by marked desmoplasia (proliferative fibroblastic reaction) and secondary lysis. Ulceration with secondary inflammation is usually found. Most lesions are adenocarcinomas characterized by irregular tubular, acinar, cribriform, or papillary structures in variable combinations, lined by one or more layers of cuboidal to polygonal epithelial cells. Small foci of squamous metaplasia may be present, but orderly keratinization with keratin pearl formation is not seen. The glandular lumens often contain small numbers of necrotic cells; secretory product is occasionally observed. Stromal collagen is moderate to abundant and variably cellular.

The neoplastic cells have pale amphophilic or eosinophilic cytoplasm and large, hyperchromatic nuclei. Nucleoli are usually prominent, and mitotic activity is high. Atypical mitotic figures are often present. Aggregates of tumor cells may be visible within lymphatic vessels in the stroma, adjacent pawpad fat, or dermis. The canine case was unique in that myoepithelial proliferation with chondroid and osseous metaplasia was present (Kusters et al., 1999); it would thus be classified as a complex eccrine carcinoma. Rarely, a neoplasm composed of solid lobules of polygonal cells with pale cytoplasm

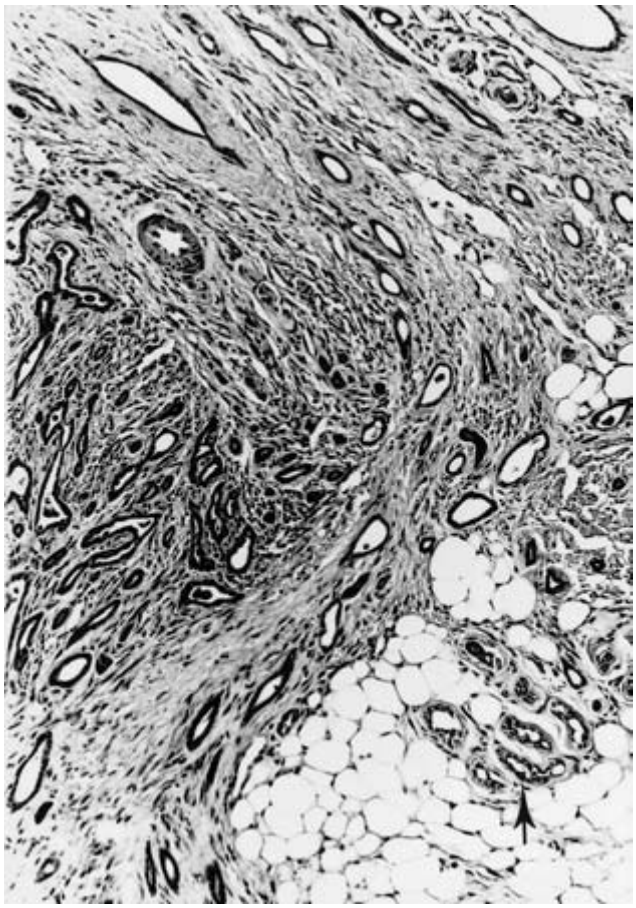


Fig. 25.35 Eccrine adenocarcinoma in the pawpad of a dog. Irregular glandular structures infiltrate the fat of the pawpad. Note residual eccrine glands at lower right (arrow).



Fig. 25.36 Eccrine carcinoma in the pawpad of a dog. This unusual solid, clear cell variant has very similar architecture to clear cell apocrine ductular carcinoma (Fig. 25.31).

and minimal tubular differentiation is observed; this is similar to solid-cystic apocrine ductular carcinoma (see p. 681).

Differential diagnoses for eccrine carcinoma are apocrine adenocarcinoma, the acantholytic variant of nailbed squamous cell carcinoma (digital lesions only), acantholytic squamous cell carcinoma arising from pawpad epidermis, and metastatic pulmonary adenocarcinoma (cats only). For the rare solid eccrine carcinoma, the only differential diagnosis would be solid-cystic apocrine ductular carcinoma. Distinction between eccrine and apocrine tumors is often not possible either by light microscopy or immunohistochemistry. If decapitation-type secretion can be identified in tubular structures, this supports an apocrine origin. If foci of divergent differentiation with sebaceous or follicular features are found, this is also an indicator of an apocrine neoplasm, based on the close anatomic and embryologic relationships among the three components of the folliculosebaceous-apocrine unit. Adequate tissue sectioning is critical for establishing contiguity with eccrine sweat glands and excluding connection to nailbed epithelium or apocrine glands in haired skin at the pawpad margins. If bone involvement is absent or minimal, primary nailbed neoplasia and metastatic pulmonary neoplasia are unlikely. Thoracic radiographs in addition to pedal radiographs should always be recommended for cats. Careful search for ciliated epithelium is also warranted if metastatic pulmonary adenocarcinoma is being considered. It is not known if periodic acid–Schiff (PAS) reaction or other stains for mucin, which are positive in pulmonary adenocarcinoma, would be negative in eccrine carcinoma in animals; one human study found mucin in two-thirds of a variety of benign eccrine and apocrine neoplasms (Fitzgibbon & Googe, 1996). Active acantholysis, characterized by individualized, fully-keratinized cells and elongated intercellular bridges within pseudotubules, supports a diagnosis of squamous cell carcinoma. However, distinction from squamous metaplasia occurring in poorly-differentiated adenocarci-

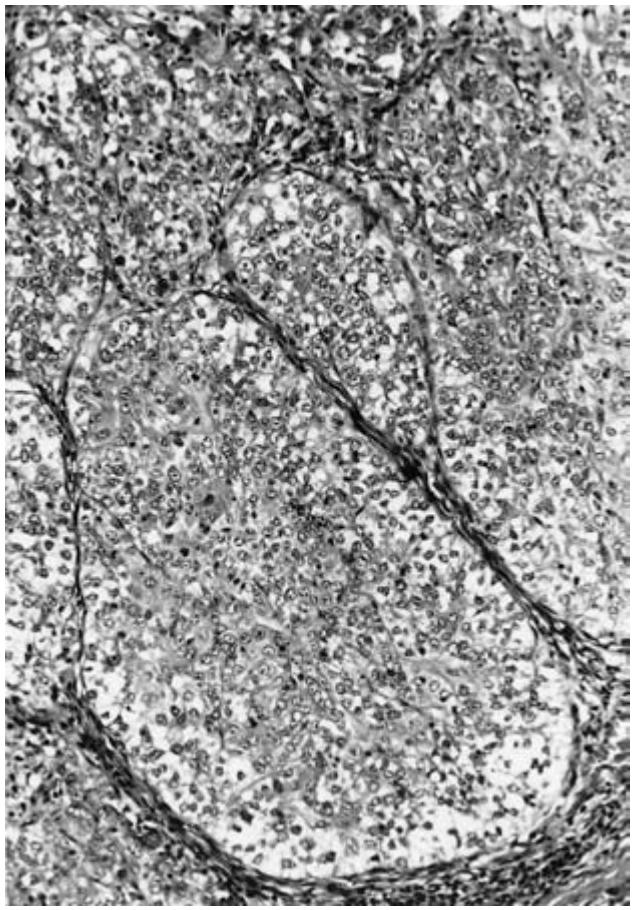


Fig. 25.37 Higher magnification of eccrine carcinoma of Fig. 25.36. The tumor cells have abundant glycogenated cytoplasm and are arranged in solid lobules.

nomas may be difficult; immunohistochemistry may be beneficial.

Immunohistochemistry

As with adenocarcinomas of apocrine origin, positive staining with specific simple epithelial cytokeratins (CKs), such as CAM5.2 (CK7/8) or CK13, can distinguish eccrine carcinoma from squamous cell carcinoma. Unfortunately, there is no reliable immunohistochemical technique for separating eccrine carcinoma from apocrine adenocarcinoma at present. Immunohistochemical differentiation of metastatic pulmonary adenocarcinoma from eccrine carcinoma has not been investigated in animals. In humans, the majority of pulmonary adenocarcinomas are reported to be negative for CKs 5/6, 14 and 18 (Moch et al., 1993; Lyda & Weiss, 2000; Carella et al., 2001; Chu & Weiss, 2002), while these markers are positive in many other epithelial neoplasms, including most sweat gland tumors.

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Chapter 26

Nailbed epithelial tumors

The Latin word *unguis* is defined in all versions of Webster's dictionaries as a 'nail, claw, talon, or hoof of a finger, toe, or other appendage'. Additionally, the first definition of the word claw is 'the sharp hooked nail of a mammal, bird or other animal. The third definition in Collins English Dictionary for the word nail is 'the horny plate covering part of the dorsal surface of the fingers or toes'; the fourth is 'the claw of a mammal, bird, or reptile'. Roget's Thesaurus includes claws, talons, ungues, nails, fingernails, chelae, and pincers as synonyms in the category of prehensile organs. Based on the foregoing, the authors have chosen to regard nail and claw as synonymous. The authors prefer the nomenclature 'nailbed' over the human term 'subungual' because, due to species differences in anatomy, lesions in dogs and cats typically start proximal or caudal to the relatively cylindrical, horizontally-oriented nail, rather than beneath a flat nailplate.

Primary nailbed (subungual) tumors of all types are uncommon in dogs and rare in cats. Relative incidence of the different tumor types is difficult to estimate, as epithelial lesions other than squamous cell carcinoma are not usually described in this anatomic location in the veterinary literature. Non-neoplastic lesions, benign tumors, and malignant tumors of the nailbed have many clinical features in common because of the restrictive nature of the anatomy of distal digits and nails. Any expansile mass at this site can result in lameness, digital enlargement, replacement or lysis of the third phalanx, and in many cases, disruption of normal nail growth.

Because of the similarity in clinical appearance of benign and malignant tumors, as well as the difficulty in obtaining adequate biopsy material by soft tissue surgical techniques, amputational biopsy of one or more phalanges is the most accurate diagnostic technique for nailbed masses. This procedure is also curative in many cases. Parasagittal soft tissue sections and midsagittal, decalcified sections are required in almost all cases for complete evaluation of the gross architecture and histomorphology of the lesions.

NAILBED EPITHELIAL INCLUSION CYST

Nailbed cysts are most likely a result of trauma leading to embedment of portions of cuticular epidermis or germinative nailbed epithelium in subjacent connective tissue. Thus, the term 'epithelial inclusion cyst' is appropriate. A congenital malformation of ungual or periungual epithelium is also a possible pathogenesis. Subungual epidermoid cysts are reported rarely in the human literature, although this may not reflect their actual incidence. Many but not all cases are associated with previous trauma (Yung & Estes, 1980; Fanti & Tosti, 1989; Saez de Ocariz et al., 2001).

Clinical features

Epithelial cysts occur infrequently in the nailbed of dogs and cats. The primary presenting sign is a single swollen digit. The nail may be cracked or irregular. Previous onychectomy sites and dewclaws are affected most often. Radiographically, there is a circumscribed zone of partial to total bone loss in the third phalanx with little periosteal response.

The cysts are generally less than 0.5 cm but can be as large as 2 cm in diameter. Size is difficult to assess accurately until midsagittal section of the digit is made in preparation for histologic processing. The cysts contain semifluid, caseous or dry, granular material that is often pigmented. There is no known age or breed predilection.

Although epithelial inclusion cysts are non-neoplastic lesions, neoplastic transformation may occur in rare instances. The authors have observed a single case of squamous cell carcinoma arising from a nailbed epithelial inclusion cyst in a dog. A similar phenomenon occurs rarely in follicular cysts in humans and dogs (see Chapter 23).

Histopathology (Figure 26.1)

Nailbed inclusion cysts have a similar histologic appearance to follicular cysts of infundibular origin (see Chapter

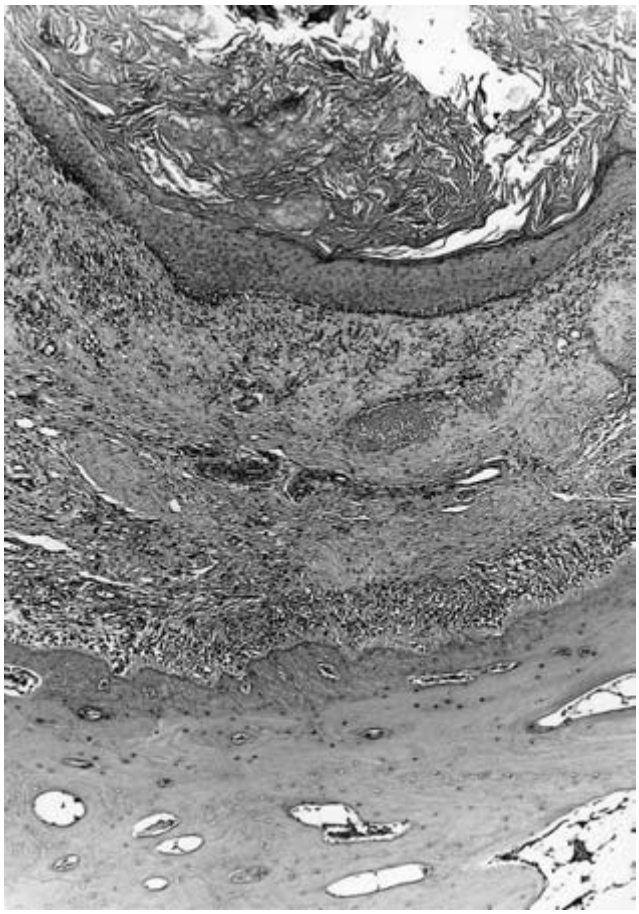


Fig. 26.1 Nailbed epithelial inclusion cyst in a dog. Squamous epithelial-lined cyst filled with lamellar keratin is at top, phalangeal bone is at bottom.

23). The cyst is lined by a thick wall of architecturally normal squamous epithelium that keratinizes through a sparse granular cell layer. The cyst lumen contains laminated keratin; occasionally, the keratin is densely-packed and translucent, resembling normal ungual keratin. The epithelium and cyst contents are often melanized in animals with dark haircoats and nails. The surrounding connective tissue often has mild infiltration by lymphocytes and plasma cells. There may be degeneration of the cyst wall accompanied by a granulomatous or pyogranulomatous inflammatory response to released keratin. There is pressure-induced lysis and replacement of the third phalanx by the expanding cyst in proportion to its size. Periosteal fibrosis and periosteal bone proliferation may be observed in association with more severe inflammation.

Diagnosis of nailbed inclusion cyst is straightforward. There are no known differential diagnoses for a mature squamous epithelial cyst in this anatomic location.

NAILBED INVERTED SQUAMOUS PAPILLOMA

(Synonym: subungual inverted squamous papilloma)

Nailbed inverted squamous papilloma is a benign neoplasm of dogs arising from the germinative epithelium of the nail. This lesion appears to be analogous to inverted papilloma arising in haired skin (see Chapter 22). The etiology of the nailbed variant of papilloma is unknown, but it is likely that it also is virally-induced. Special preparation techniques required for nail biopsies, i.e. decalcification or dekeratinization, seriously limit the efficacy of immunohistochemical staining for papillomavirus antigens. Ultrastructural studies or testing by polymerase chain reaction (PCR) for canine papillomavirus antigen may provide further evidence for a viral cause.

Clinical features

Nailbed inverted papilloma may be rare. Incidence data are not published. It is possible that this lesion was previously presumed to be a low-grade variant of nailbed squamous cell carcinoma. The frequency ratio of inverted papillomas to nailbed squamous cell carcinomas is approximately 1:4 based on incidence data from one of the authors (E.J.W.).

Nailbed inverted squamous papilloma presents as a single swollen digit, usually with a thickened, abnormally soft nail. The increase in diameter of the nail may be dramatic, and longitudinal ridges are often visible. The nail may be broken or absent. Secondary ulceration sometimes is present. Radiographs usually show moderate to marked destruction of the third phalanx; periosteal proliferation of the second phalanx also may be observed.

Midsagittal section of the toe reveals a well-delineated, cup-shaped mass filled with dense keratin, which usually measures less than 1 cm in diameter. In some cases, the entire nailbed is diffusely expanded and replaced by the papilloma. There is no known age or breed predisposition. Distal digital amputation is curative.

Histopathology (Figures 26.2 and 26.3)

The nailbed inverted squamous papilloma is a well-circumscribed, cup-shaped mass filled with compact keratin. Much of the keratin retains the translucent appearance of normal ungual keratin. The wall of the cup is a thick layer of squamous epithelial cells that form delicate conical or papillary projections extending centripetally into the keratin core. The epithelial papillae are frequently sectioned tangentially and appear as ovoid or circular structures entrapped in compact keratin. The papillae have narrow cores of bland connective tissue. In



Fig. 26.2 Nailbed inverted squamous papilloma in a dog. Conical structures project into the central compact keratin core. Note well-circumscribed margin of tumor at lower right.

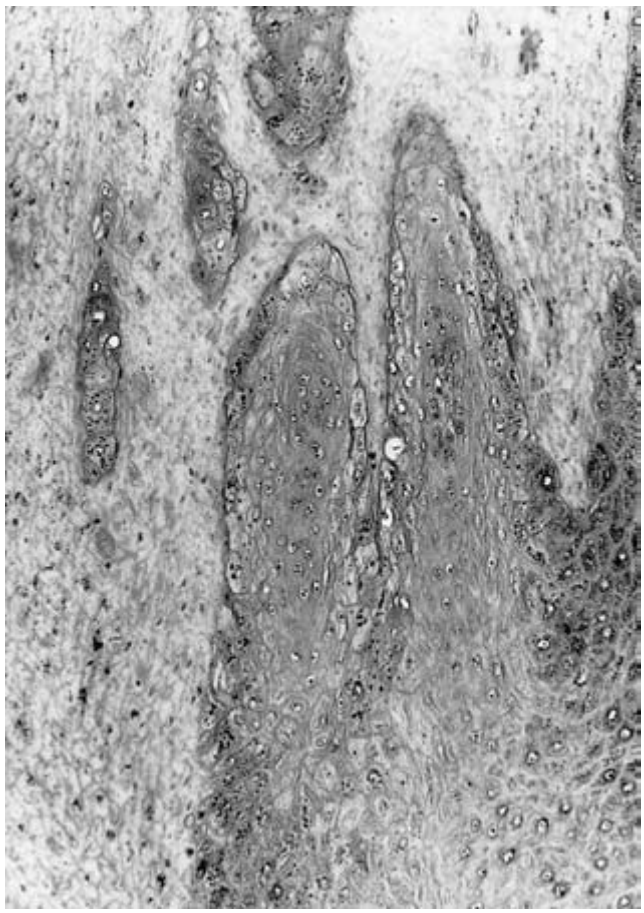


Fig. 26.3 Higher magnification of nailbed inverted squamous papilloma of Fig. 26.2. Note glassy cytoplasm, sparse granular cell layer, and slight cytoplasmic vacuolation.

lesions in which the nailbed is diffusely replaced by proliferative epithelium, the conical papillae have a more parallel orientation to one another, and the columns of soft keratin produced by the tumor papillae project into and partially replace the hard keratin of the nail.

The majority of epithelial cells have moderate, pale pink, glassy cytoplasm. Keratinization proceeds in an orderly pattern through a sparse granular cell layer. Nuclei are small and vesicular with inconspicuous nucleoli. Occasional epithelial cells may exhibit cytoplasmic vacuolation resembling koilocytosis, which is a marker for viral induction in other papillomas (see Chapter 22). Nuclear inclusions observed in cutaneous viral papillomas are not found (see Chapter 22). Mitotic activity is low, and mitotic figures are limited to the basal cell layer at the periphery of the mass.

The third phalanx exhibits pressure-induced lysis and replacement in proportion to the size of the neoplasm. Periosteal fibrosis, periosteal bone proliferation, and secondary inflammation may be observed.

Distinction between nailbed inverted squamous papilloma and nailbed keratoacanthoma may be required. Keratoacanthoma does not possess the central conical epithelial projections of the inverted papilloma. Keratoacanthoma has islands, sheets, and peripheral trabeculae of epithelial cells, in contrast to the uniform wall of cells characterizing the inverted squamous papilloma. Prominent apoptosis can be seen in keratoacanthoma but not in nailbed papilloma. Differentiation between inverted squamous papilloma and squamous cell carcinoma of the nailbed may be required, but diagnosis is usually straightforward. Inverted squamous papilloma has smooth

margins with no invasive tendencies. Nuclei are uniform, and mitotic figures are infrequent. There is no nuclear or mitotic atypia, as observed in squamous cell carcinoma.

NAILBED KERATOACANTHOMA

(Synonym: subungual keratoacanthoma)

Nailbed keratoacanthoma (KA) is a benign neoplasm of dogs that arises from the nailbed epithelium. This neoplasm appears to be identical to human subungual KA. It is not analogous to canine infundibular keratinizing acanthoma (see Chapter 23), which has previously been referred to as keratoacanthoma in the veterinary literature. Human cutaneous KA is a fairly common, rapidly-evolving crateriform nodule with a central keratin plug that usually occurs in sun-exposed skin (Murphy & Elder, 1991). The development and spontaneous regression of the lesion take place in weeks to months (Murphy & Elder, 1991). In contrast to common cutaneous KA in humans, the rare subungual variant in humans does not undergo spontaneous involution (Macaulay, 1976; Stoll & Ackerman, 1980; Keeney et al., 1988; Lovett et al., 1995).

It is currently highly controversial whether human cutaneous KA is a benign entity that may undergo malignant transformation, or a biologically distinct variant of low-grade squamous cell carcinoma; many cytologic, immunophenotypic and molecular parameters have been investigated in this regard (Binder et al., 1998; Cribier et al., 1999; Sánchez Yus et al., 2000; Melendez et al., 2003). Despite the fact that the dilemma remains unresolved, none of the studies has dealt with subungual KA, nor has any suggestion been made that the subungual lesions have malignant potential.

Clinical features

Nailbed KAs are rare in dogs. Incidence data are not published. Nailbed KA in dogs may be misdiagnosed as well-differentiated squamous cell carcinoma, resulting in underestimation of occurrence. The frequency ratio of nailbed KA to nailbed squamous cell carcinoma is approximately 1:4 based on incidence data from one author (E.J.W.).

Nailbed KA presents as a single, often severely swollen digit. Focal ulceration may be present. Affected digits may have deformed or broken nails. Almost all cases have radiographic evidence of lysis of the third phalanx. Lysis of the second phalanx and periosteal bone proliferation are observed less commonly.

Midsagittal section of the toe reveals a circumscribed, but unencapsulated mass with an irregular central zone of caseous keratin. Lesions are generally less than 1.5 cm in diameter. There is no apparent breed or sex predilection. Affected animals are adults. Digital amputation is curative.

Histopathology (Figures 26.4 through 26.6)

Nailbed KAs are symmetrical, circumscribed, but unencapsulated masses with a cup-shaped, tubular, or inverted funnel-shaped configuration. The tumor borders are irregular or scalloped. The mass has a central core of keratin that may open onto the skin surface directly ventral or adjacent to the nail. The epithelial wall of the neoplasm is contiguous with the nailbed epithelium. The wall is composed of large squamous epithelial cells arranged in sheets, islands, and broad trabeculae. There is orderly keratinization that proceeds centripetally and without a granular cell layer, resulting in a central core of amorphous keratin. Many tumors also have large lakes of parakeratotic cells without nuclear atypia admixed with the amorphous keratin in the central zone.



Fig. 26.4 Nailbed keratoacanthoma in a dog featuring broad sheets and trabeculae of pale, glassy keratinocytes. Note circumscribed but irregular margin of the tumor at bottom.



Fig. 26.5 Nailbed keratoacanthoma in a dog showing two cores of parakeratotic cells within irregular epithelial islands.

The majority of neoplastic epithelial cells have abundant, pink cytoplasm with a ground glass appearance. This is a manifestation of high glycogen content, which can be confirmed with positive periodic acid–Schiff (PAS) staining. There are small to moderate numbers of apoptotic keratinocytes characterized by rounded, brightly eosinophilic cytoplasm, and pyknotic nuclei. Occasional KAs are composed predominantly of these apoptotic cells; the significance of this degenerative alteration is unknown. Most nuclei are moderately enlarged and vesicular with small nucleoli. Small numbers of atypical epithelial cells with amphophilic cytoplasm, enlarged nuclei, and prominent nuclei are present at the periphery of most tumors. Mitotic activity is low and is also confined to this proliferating peripheral zone.

The third phalanx exhibits pressure lysis in proportion to the size of the expansile neoplastic mass. Tumor tissue does not invade into the interstitium of the bone. Large KAs may cause complete pressure destruction of the third phalanx, but tumor tissue does not cross the interphalangeal joint space. Periosteal fibrosis and bone proliferation are often present. Secondary osteomyelitis may be observed. The connective tissue surrounding the mass has a moderate to marked infiltrate of plasma cells and neutrophils. Chronic proliferative and inflammatory changes may be present in the synovial tissue of the interphalangeal joint, particularly in larger tumors.

Differentiation between nailbed KA and well-differentiated squamous cell carcinoma is often problematic. This is especially true if specimens are too small or tangential to allow adequate visualization of tumor

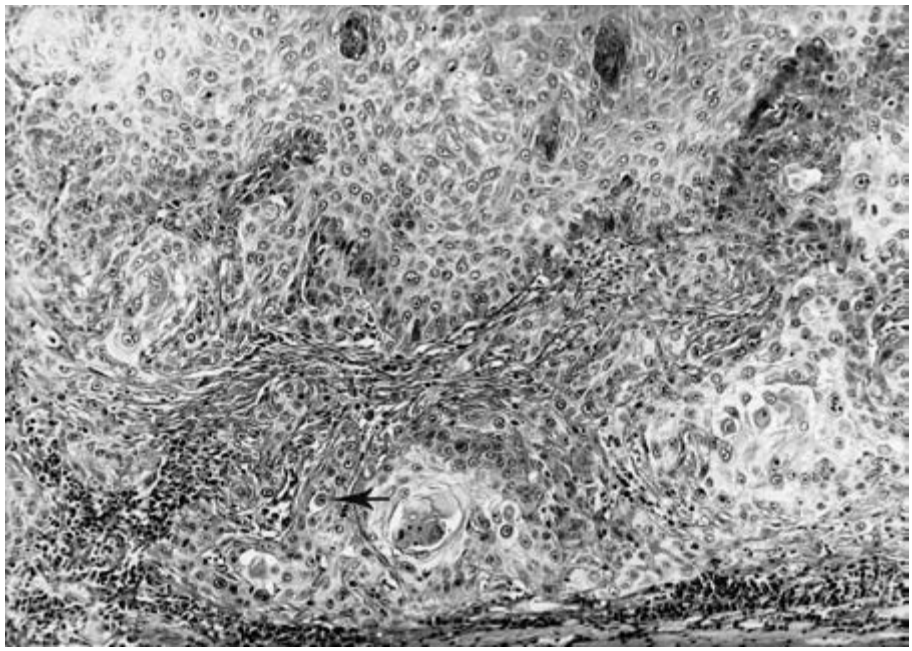


Fig. 26.6 Higher magnification of nailbed keratoacanthoma showing glassy cytoplasm and scattered apoptotic keratinocytes (arrow). Note mild cytologic atypia and infiltrative growth at the tumor margin at bottom.

architecture. Low-power features of a symmetrical but complex cellular wall and central keratin core are critical diagnostic features of KA. Soft tissue sections from the margin of a KA will often contain short trabeculae with atypical cells and mitotic figures, leading to an erroneous diagnosis of malignancy. Bone invasion is not observed in KA, but is a classic feature of squamous cell carcinoma. Positive PAS staining has been proposed as an aid in distinguishing between cutaneous KA and squamous cell carcinoma in humans based on the high glycogen content of the former (King & Barr, 1980). Unfortunately, many well-differentiated nailbed squamous cell carcinomas also show strong PAS positivity, although the staining pattern may be irregular. If histologic distinction is not possible, it is preferable to err on the side of caution and render a diagnosis of well-differentiated squamous cell carcinoma. Differentiation of nailbed KA from nailbed inverted squamous papilloma is based on the greater complexity and irregularity of the epithelial wall, apoptosis, and absence of uniform, central papillary projections in KA.

NAILBED SQUAMOUS CELL CARCINOMA

(Synonym: subungual squamous cell carcinoma)

Clinical features

Nailbed squamous cell carcinoma (SCC) is uncommon in dogs and very rare in cats. One report on canine nailbed SCC indicated an incidence of 0.2% of all canine neoplasms (Madewell et al., 1982). However, they are also reported to be the most frequent canine digital tumor, comprising 38% of cases in one study (Marino et al., 1995). Nailbed SCC is not as common overall as cutaneous SCC in this species, but the frequency ratio may be higher in geographic locations that have a low overall incidence of solar-induced skin disease. A large survey from the University of Pennsylvania found 328 nailbed SCCs in a total of 592 non-visceral SCCs (Goldschmidt & Shofer, 1992). In contrast, only one of 52 SCCs in a large survey on feline cutaneous tumors was found in a periungual location (Miller et al., 1991). In a study of bone tumors in cats, only one of 25 SCCs involved phalangeal bone (Quigley & Leedale, 1983).

Nailbed SCC is usually solitary, but may affect multiple digits either synchronously or metachronously in dogs, or two adjacent digits in cats (Madewell et al., 1982; van der Linde-Sipman & van den Ingh, 2000). The presenting signs are similar to benign nailbed tumors and include lameness, digital swelling, and deformity or loss of the nail. Ulceration is more common and generally more extensive than is observed with benign tumors. There is radiographic evidence of phalangeal lysis. Periosteal bone proliferation is common and may extend to the proximal phalanges.

The appearance on midsagittal section of the digit varies considerably, depending on the size and degree of histologic differentiation. Tumor diameter varies from 0.3 cm to more than 3 cm. Some lesions are well-circumscribed, while others are diffusely infiltrative. Small, early lesions may be confined to the nail pulp and distal third phalanx. Keratin production, manifested grossly by deposits of caseous yellow-white material, may be focal and centrally located in small, well-differentiated tumors. Larger tumors often have numerous small zones of keratinization. Poorly-differentiated SCCs may have no gross evidence of keratin production.

The majority of affected animals are 7 years of age or older, although dogs as young as 4 years of age are reported (O'Brien et al., 1992; Marino et al., 1995). There is a marked predilection for large breed dogs with black coats, particularly Labrador Retrievers, Standard Poodles, Rottweilers, Giant Schnauzers, Gordon Setters, and Kerry Blue Terriers. This curious relationship of body size and coat color to the incidence of nailbed SCC is still enigmatic.

The reported metastatic incidence of these neoplasms varies widely. Marino et al. (1995) found a 29% occurrence of pulmonary metastasis, but both nailbed and primary epidermal SCCs were included in this figure. The study of O'Brien et al. (1992) had a less than 5% incidence of pulmonary metastasis; 20 of 21 dogs had no metastasis to the regional lymph nodes or the lungs. Ten dogs in a small survey by one of the authors (E.J.W.) were followed for 9 months to 2 years; only one developed regional lymph node metastasis following digital amputation. Reports of primary feline nailbed SCC are too few to provide meaningful data. In the largest series, one of eight cats developed regional lymph node metastasis (van der Linde-Sipman & van den Ingh, 2000).

Histopathology (Figures 26.7 through 26.9)

Nailbed SCCs are unencapsulated, asymmetrical neoplasms with focal or multifocal connection to nailbed epithelium. Tumor margins are irregular and infiltrative. The architecture and morphology of the neoplastic epithelial cell aggregates are usually similar to well-differentiated or poorly-differentiated variants of SCC in other anatomic locations (see Chapter 22). Acantholytic features, characterized by dyscohesion, rounding up, and drop-out of cells in the centers of the aggregates, may be present in some lesions; if these features are extensive, a diagnosis of acantholytic SCC is appropriate (see Chapter 22). The majority of nailbed SCC is of the well-differentiated type and has multiple large foci of keratinization. The cytoplasm is often more pale and glassy

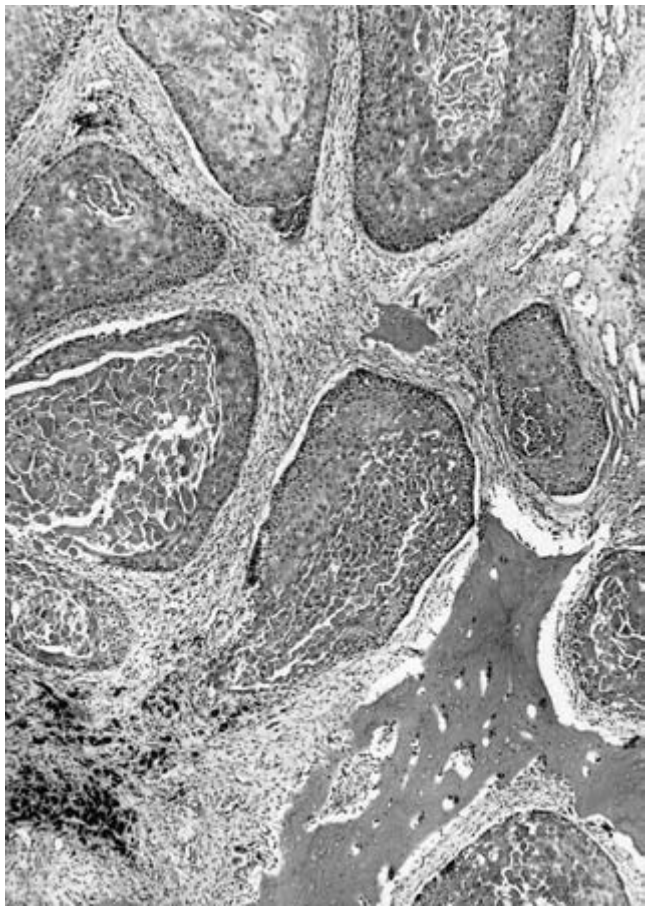


Fig. 26.7 Nailbed squamous cell carcinoma in a dog. Islands of well-differentiated squamous epithelial cells invade phalangeal bone. Note early acantholysis in the centers of the tumor islands.

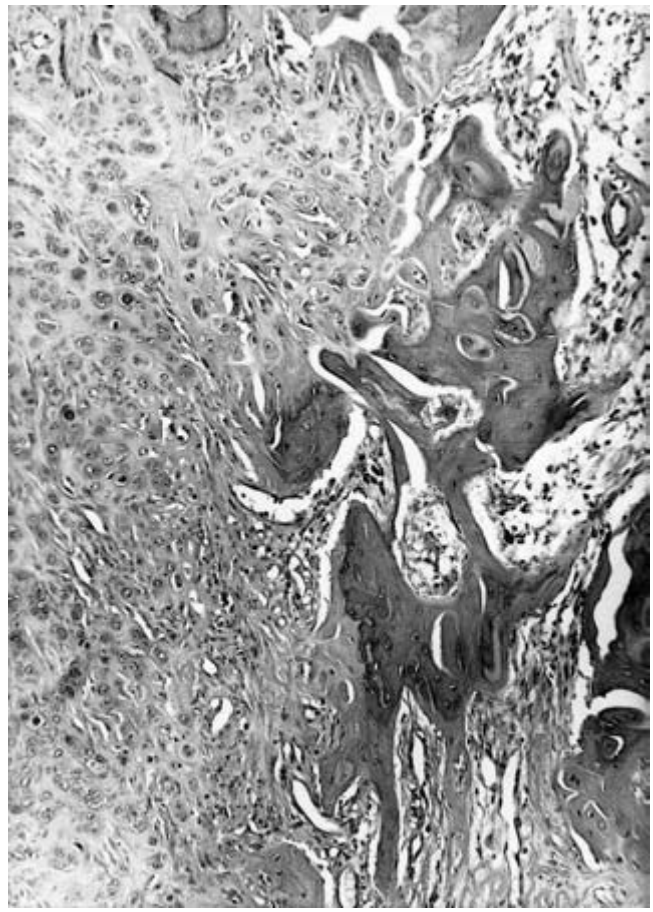


Fig. 26.8 Poorly-differentiated nailbed squamous cell carcinoma in a dog. Epithelial cells arranged individually and in clusters diffusely infiltrate phalangeal bone.

than in cells of the cutaneous counterpart, and a granular cell layer may be sparse or absent. Rarely, the verrucous variant of SCC (see Chapter 22) arises in nailbed epithelium. This is a low-grade malignancy characterized by broad, blunt-ended, anastomosing trabeculae of polyhedral keratinocytes. The trabeculae have central tunnels filled with keratin and cellular debris. All tumor types are accompanied by a desmoplastic stromal response. Infiltrates of plasma cells and neutrophils are present and may be severe in extensively ulcerated lesions.

The third phalanx shows some degree of lysis and periosteal bone proliferation, and the medullary spaces are infiltrated by aggregates of neoplastic squamous epithelial cells. Early lesions may be confined to the distal tip of the bone. Osteomyelitis may be present. The interphalangeal joint may show tumor invasion in addition to chronic synovitis. More commonly, neoplastic tissue does not violate the joint space but extends along the periosteum and infiltrates periarticular connective tissue. The distal second phalanx may also show lysis and periosteal proliferation due to inflammation and/or infiltration by neoplastic epithelial cells from adjacent connective tissue or joint. More proximal portions of the second phalanx are rarely involved.

The primary differential diagnosis for well-differentiated nailbed SCC in dogs is nailbed keratoacanthoma. Keratoacanthomas are recognizable in most cases by their symmetry, central keratin cores, and absence of bone invasion. The epithelial cells of keratoacanthomas usually contain more abundant, uniformly-distributed glycogen than those of SCC. Mitotic activity is usually higher in SCC, and prominent nucleoli are more prevalent.

The rare acantholytic variant of nailbed SCC may need to be differentiated from eccrine carcinoma arising from the pawpad (see Chapter 25); foci of keratinocyte dyscohesion and drop-out (pseudoglandular change) can mimic true glandular lumens. However, acantholysis usually occurs only in limited areas of the tumor, and the pseudolumens may contain some residual individualized cells. Serial sections to establish connection to ungual epithe-

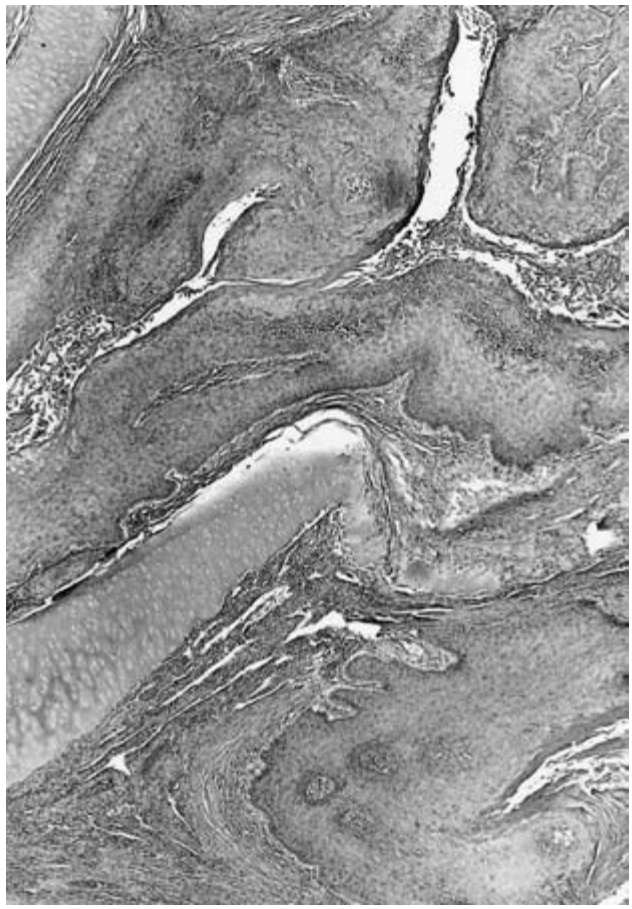


Fig. 26.9 Verrucous nailbed squamous cell carcinoma in a dog. Broad, blunt-ended trabeculae of well-differentiated keratinocytes have central tunnels containing keratin and cellular debris. The neoplasm has effaced the entire third phalanx except for the articular cartilage.

lium may be required in rare instances. Immunohistochemical stains are often helpful (see below). Adequate soft tissue and decalcified sections are required to distinguish primary nailbed carcinoma from digital SCC arising from epidermis of haired skin or pawpad that has secondarily infiltrated phalangeal bone.

In cases of multicentric digital SCC, primarily in cats, a differential diagnosis of metastatic carcinoma must be considered, particularly the mucoepidermoid (adenosquamous) and SCC (epidermoid) variants of pulmonary carcinomas. Metastatic pulmonary carcinomas are much more common than primary carcinomas in the distal phalanges in cats (see p. 703); thoracic radiography should be recommended in all cases of feline digital carcinomas. Metastatic lesions should not exhibit contiguity with epidermis or ungual epithelium, and bone lysis is often not accompanied by a periosteal proliferative response (Pollack et al., 1984). Vascular invasion is often discernible in metastatic carcinomas, although its presence does not exclude a very aggressive primary carcinoma. Periodic acid–Schiff (PAS) stain may highlight small foci of luminal mucin secretion (van der Linde-Sipman & van den Ingh, 2000) that are often present even in predominantly squamoid pulmonary carcinoma.

Immunohistochemistry

Immunohistochemical stains for specific cytokeratins (CKs), particularly CAM5.2 (CK7/8) and CK13, are limited in their distribution in canine and feline tissue to simple epithelia and thus are useful markers for glandular neoplasms. CAM5.2 or CK13 will be positive in a pawpad eccrine carcinoma and negative in an acantholytic SCC. Similarly, CAM5.2 immunostaining aids in detecting subtle features of glandular differentiation (van der Linde-Sipman & van den Ingh, 2000) in metastatic pulmonary carcinoma.

NAILBED BASAL CELL CARCINOMA

(Synonym: subungual basal cell carcinoma)

Basal cell carcinoma (BCC) in a subungual location is rare in humans; only about a dozen cases have been reported (Bhagchandani et al., 1995; Mikhail, 1985; Rudolph, 1987). Melanonychia (streaks of dark pigmentation in one or multiple nails) was a feature of one of these cases (Rudolph, 1987). The prognosis for subungual BCC in humans is favorable, as it is for BCC in other locations.

Clinical features

Nailbed BCC is an extremely rare entity; only a single example has been seen by the authors. It occurred in an 11-year-old domestic shorthaired cat that had apparent chronic paronychia and a thickened nail affecting a single digit. The nail had focal, asymmetric, dark brown discoloration. Midsaggital section through the amputated distal digit revealed a neoplasm less than 3 mm in diameter that was contiguous with the nailbed epithelium and extended proximally.

To the best of the authors' knowledge, nailbed BCC has not been previously described in the veterinary literature. The prognosis in animals remains to be determined. The sentinel case developed recurrence around and within the second phalanx 2 years following distal digital amputation.

Histopathology (Figures 26.10 and 26.11)

The single nailbed BCC observed was composed of polyhedral, basaloid cells arranged in small islands,

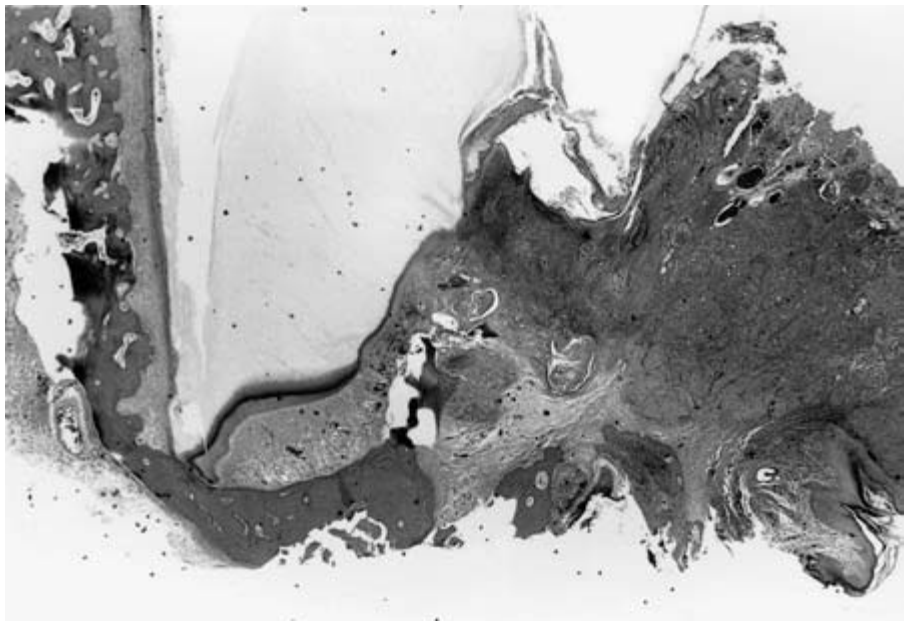


Fig. 26.10 Nailbed basal cell carcinoma in a cat. This plaque-like mass is focally contiguous with nailbed epithelium at the left.

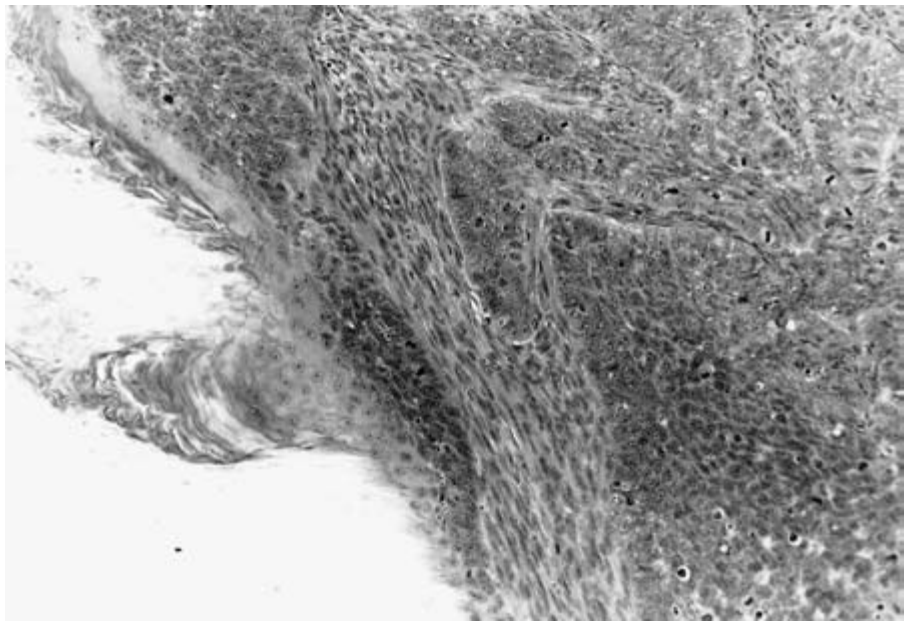


Fig. 26.11 Higher magnification of nailbed basal cell carcinoma of Fig. 26.10. Trabeculae of small, polyhedral tumor cells show peripheral palisading and numerous mitoses. Ungual keratin is at the left.

nests, and trabeculae. The cells had scant, pale cytoplasm and large, ovoid nuclei with small nucleoli and moderate mitotic activity. There was prominent peripheral palisading. Several foci of squamous metaplasia with formation of keratin microcysts were present. Some of the epithelial cells were moderately pigmented, and melanophages were present in the moderate collagenous stroma. There was slight invasion and lysis of the third phalanx.

The appearance of this neoplasm is virtually identical to BCC occurring in the skin (see Chapter 22). Any difficulty in diagnosis would be largely due to the rarity of the lesion.

METASTATIC PULMONARY CARCINOMA IN CATS

Distant metastases from internal malignant neoplasms rarely present predominantly as cutaneous disease in dogs and cats. In humans, 5–10% of patients with visceral carcinoma have cutaneous metastases (Johnson, 1997). Metastases to distal digits are very rare in humans; only

about 120 cases are reported in the literature (Baran & Tosti, 1994). Subungual metastases in one retrospective survey in humans occurred most often from the lung, and the frequency was greater than the next three most common primary sites combined (Cohen, 2001). One or multiple digits may be affected. The lesions present with pain, swelling, and erythema, and are often misdiagnosed as infection. In 44% of the human patients in that survey, visceral neoplasia was not suspected until the digital metastasis was identified (Cohen, 2001). The cause for the predilection of pulmonary carcinomas for phalangeal bone or digital soft tissue is unknown.

The syndrome of digital metastasis of pulmonary carcinomas in cats is well documented in case reports, retrospective surveys, and reference texts (Pollack et al., 1984; Carpenter et al., 1987; Gottfried et al., 2000; van der Linde-Sipman & van den Ingh, 2000). Recognized subtypes of metastatic pulmonary carcinoma in cats include adenosquamous (mucoepidermoid) carcinomas, squamous cell carcinomas (SCCs), and adenocarcinomas. Phalangeal metastasis has not been reported in dogs with pulmonary carcinoma.

Clinical features

The overall metastatic rate of pulmonary carcinoma in cats is 75% (Hahn & McEntee, 1997). In one survey covering a period of 5 years, 56 of 64 cats with digital carcinomas had primary pulmonary carcinoma (van der Linde-Sipman & van den Ingh, 2000). Another review found 116 pulmonary carcinomas in cats, 36 cases of digital metastatic carcinoma, and nine cases of primary digital SCC in a 6 year period (Gottfried et al., 2000).

Affected cats present with lameness and one or more swollen, painful digits. The toes are often erythematous and ulcerated, and there may be loss of nails. Respiratory signs are usually absent, despite the fact that lung masses are identified radiographically or ultrasonographically.

Gross sectioning of the digit reveals diffuse soft tissue swelling and osteomalacia. Because of the poorly circumscribed and nonkeratinizing nature of these lesions, no discrete mass or keratin deposits are visible.

There is no breed or sex predilection. The average age is 12 years, although cats as young as 4 years have been reported. The prognosis for these patients is grave; the average survival time is 1 to 2 months, and many have disseminated metastases at the time of presentation (Gottfried et al., 2000; van der Linde-Sipman & van den Ingh, 2000).

Histopathology

Metastatic pulmonary carcinoma of the digit is characterized by a poorly-circumscribed neoplasm associated with bone lysis. Epithelial aggregates infiltrate bone and soft tissue; one or more phalanges may be involved, and the tumor may cross interphalangeal joint spaces. Continuity with epidermis, ungual epithelium, or sweat glands should not be present; however, this may be impossible to verify if there is ulceration, loss of nail or extensive infiltration into pawpad. Aggregates of tumor cells can usually be detected within vascular lumens, including arterioles. There is a moderate to marked desmoplastic reaction in soft tissue, but periosteal bone proliferation is usually mild or absent.

The tumor morphology corresponds to the subtype of the primary lung tumor; the majority arise from the more aggressive adenosquamous (mucoepidermoid) and SCC variants of bronchial carcinoma. Pure adenocarcinomas are more unusual, but present less of a diagnostic challenge.

Adenosquamous (mucoepidermoid) carcinoma

(Figure 26.12)

In this subtype the epithelial cells form small islands, nests, and cords, and create variable tubular and cribriform patterns. Glandular lumens may contain mucin, and goblet cells may be present. Larger islands often exhibit necrosis and drop-out of cells. The epithelial cells are columnar to polygonal and have moderate, pale eosinophilic or amphophilic cytoplasm. There may be prominent glycogenic vacuolation of the cytoplasm. Cilia can sometimes be detected on the surface of some of the luminal cells. There are scattered foci of squamous differentiation characterized by glassy, brightly eosinophilic cytoplasm and faint intercellular bridges. Complete cornification is infrequent. Nuclei are large and pleomorphic with prominent nucleoli. Mitotic activity is highly variable, and nuclear polarity is poorly preserved.

Periodic acid–Schiff (PAS) staining accentuates the intracellular and extracellular mucin in these neoplasms. In the glandular lumens, the mucin is condensed along the surface of the lining epithelium, forming a thin band referred to as a luminal cuticle; this stains a deep magenta with PAS (van der Linde-Sipman & van den Ingh, 2000).

Differentiation from poorly-differentiated digital epidermal or nailbed SCC can be problematic, and this distinction is of utmost importance for the patient's prognosis. Poorly-differentiated SCCs can have few or no keratin pearls, and pseudoglandular change due to acantholysis (acantholytic SCC) can be present, thus mimicking the appearance of a metastatic adenosquamous pulmonary carcinoma. If ciliated cells or obvious mucin-producing glandular structures are identified, the diagnosis of metastatic pulmonary adenosquamous carcinoma is straightforward. If nailbed or epidermal contiguity can be demonstrated, the neoplasm is most likely primary in the digit. Intra-arterial tumor emboli will also confirm a

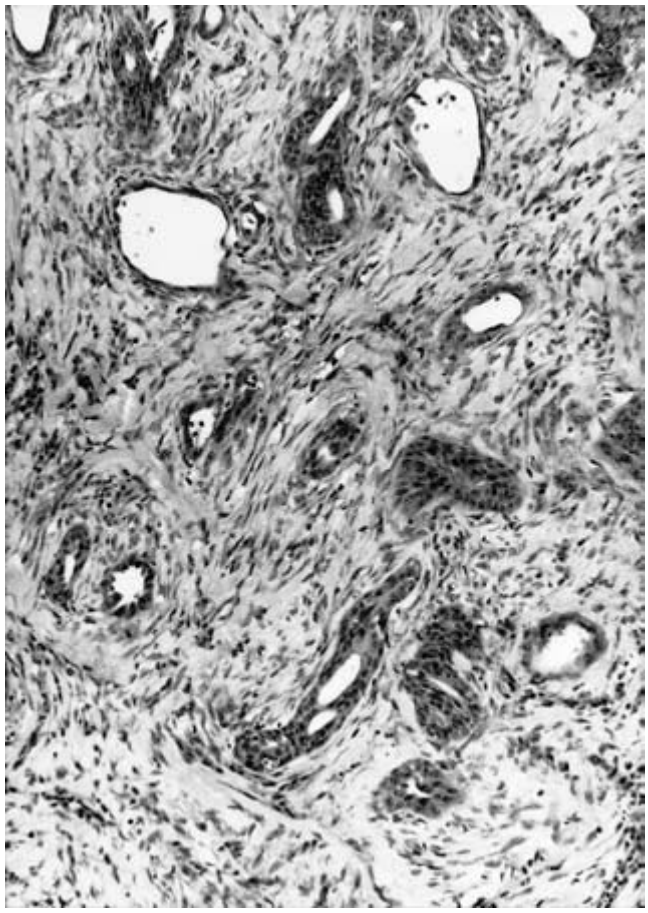


Fig. 26.12 Digital metastasis of pulmonary adenosquamous carcinoma in a cat. Some of the infiltrating epithelial structures have obvious glandular differentiation, while others have solid or cribriform patterns.



Fig. 26.13 Digital metastasis of pulmonary squamous cell carcinoma in a cat. Irregular aggregates of squamous epithelial cells diffusely infiltrate phalangeal bone and soft tissue; many aggregates have small cystic spaces containing necrotic debris. Note absence of reactive periosteal bone proliferation.

metastatic lesion. Step sections may be required to search for these features. Periodic acid–Schiff staining may be helpful, but must be interpreted with caution as glycogenated squamous cell carcinomas will also yield positive cytoplasmic staining. Alcian blue stain would be an alternative histologic technique to confirm the presence of mucin. Thoracic radiographs should be requested for all cases in which histologic findings are equivocal. Involvement of multiple digits is strongly suggestive of metastatic disease.

Squamous cell carcinoma (Figure 26.13)

The histologic appearance of this subtype of metastatic pulmonary carcinoma (previously termed 'epidermoid' carcinoma) is similar to cutaneous SCC, although very well differentiated variants, as seen in skin, are uncommon. Intercellular bridges and keratin pearls or lakes are usually present. Mitotic activity is usually high, and caseation necrosis is often extensive. Necrosis and drop-out of central cells may result in pseudoglandular foci. There may be areas of marked glycogenic vacuolation of the cytoplasm. Because squamous differentiation in these neoplasms represents a metaplastic change, it is often possible to identify small areas of residual glandular features. Poorly differentiated tumors may lack extracellular keratin deposits and glandular structures.

Differentiation of metastatic pulmonary SCC from primary epidermal or nailbed SCC can be extremely difficult and is of great prognostic significance. Residual glandular structures indicate a diagnosis of metastatic pulmonary carcinoma. Intra-arterial tumor tissue will also confirm a metastatic lesion. If unequivocal nailbed or epidermal contiguity can be demonstrated, the neoplasm is most likely primary in the digit. Step sections may be required to search for these features. Periodic acid–Schiff staining may aid in the detection of subtle secretory material, but must be interpreted with caution; glycogenated squamous cell carcinomas will also yield positive

cytoplasmic staining. Alcian blue stain would be an alternative histologic technique to confirm the presence of secretory mucin.

One retrospective study states that many of the previously reported cases of feline digital SCC were probably metastases from pulmonary SCC, based on their biologic behavior (Gottfried et al., 2000). Involvement of multiple digits is strongly suggestive of metastatic disease. Thoracic radiographs are probably warranted for all cases of digital SCC in cats.

Adenocarcinoma

In this subtype of pulmonary carcinoma, columnar to polyhedral epithelial cells form acinar, tubular, papillary, and cribriform structures in varying proportions. Ciliated cells, goblet cells, or luminal mucin deposits can usually be detected. Lumens may contain necrotic cellular debris. Small foci of incomplete squamous differentiation may be present. The cells typically have pale, eosinophilic cytoplasm and large nuclei with one or more nucleoli. Mitotic activity is variable.

Differential diagnoses for this variant are limited; digital metastasis of other types of adenocarcinomas is exceedingly rare in cats (Walters et al., 1998). Primary cutaneous apocrine or eccrine carcinoma should be a consideration if ciliated epithelium is not present and if contiguity with sweat glands cannot be ruled out. Eccrine carcinomas are very rare, so this diagnosis should be made with caution. Some of the cases previously interpreted as feline eccrine carcinomas in *Veterinary Dermatopathology* (Walder & Gross, 1992) are likely, in retrospect, to have been metastatic pulmonary neoplasms. Bone invasion by an apocrine adenocarcinoma is highly unlikely. Involvement of multiple digits will support a diagnosis of metastatic disease.

Immunohistochemistry

Immunohistochemical stains for specific cytokeratins (CKs), particularly CAM5.2 (CK7/8) and CK13, are limited in their distribution in canine and feline tissue to simple epithelia, and thus are useful markers for glandular neoplasms. CAM5.2 immunostain should be positive in metastatic pulmonary adenosquamous carcinoma and negative in primary digital squamous cell carcinoma (van der Linde-Sipman & van den Ingh, 2000). It is unknown if immunostaining with markers for simple epithelium (CAM5.2, CK13) is of benefit for SCC of pulmonary origin; the case series in which immunohistochemistry was utilized included only adenocarcinomas and adenosquamous carcinomas (van der Linde-Sipman & van den Ingh, 2000).

Immunohistochemical differentiation of metastatic pulmonary adenocarcinoma from other adenocarcinomas has not been investigated in animals. In humans, the majority of pulmonary adenocarcinomas are reported to be negative for CKs 5/6, 14 and 18 (Moch et al., 1993; Lyda & Weiss, 2000; Carella et al., 2001; Chu & Weiss, 2002), while these markers are positive in many other epithelial neoplasms, including most sweat gland tumors.

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Part II

Mesenchymal Neoplasms and other Tumors

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Chapter 27

Fibrous tumors

Similar to fibrous tumors in humans, canine and feline fibrous tumors are diverse and include reactive lesions and hamartomas, as well as benign and malignant neoplasms (Weiss & Goldblum, 2001a–c). Fibrous connective tissue is composed of fibroblasts and extracellular matrix. The latter comprises fibrillar components, including collagen and elastin, and nonfibrillar components, also referred to as ground substance. Immature fibroblasts and mature fibrocytes consistently express the intermediate filament vimentin (Folpe & Gown, 2001). Some fibroblastic proliferations have numerous admixed histiocytes (Weiss & Goldblum, 2001d–f). Many of the recognized fibrous proliferations may be reactive rather than neoplastic in origin (Weiss & Goldblum, 2001a,d).

In some instances the proliferating fibroblasts undergo differentiation to myofibroblasts. These have morphologic features of both fibroblasts and smooth muscle cells (Weiss & Goldblum, 2001a). Similar to muscle cells, myofibroblasts exhibit a partial basement membrane and bundles of parallel-arranged microfilaments (Weiss & Goldblum, 2001a,b). They express α-smooth-muscle actin and occasionally also desmin. Myofibroblasts were first recognized in granulation tissue, and their presence has been associated with injury and local trauma (Gabbiani et al., 1972).

COLLAGENOUS HAMARTOMA

(Synonym: collagenous nevus)

The concepts of 'nevus' and 'hamartoma' tend to be elusive and confusing in most pathology texts. Throughout the veterinary literature both are used essentially interchangeably, and are often selected more by convention or preference rather than by strict adherence to definition. The current World Health Organization nomenclature avoids the use of nevus entirely, a principal reason being that nevus has connotations of melanocytic origin in human nomenclature (also see linear epidermal hamartoma, Chapter 22). Thus, whenever possible, the authors prefer to use the more inclusive term 'hamartoma' for most lesions that are believed to be malformations, both congenital and acquired.

Canine collagenous hamartomas were first described by Scott et al. (1984) and previously were most likely identified as fibromas. These intradermal collagenous nodules resemble 'connective tissue nevi' or 'collagenomas' in humans (Weiss & Goldblum, 2001). The late onset of clinically evident collagenous hamartomas in dogs may be explained by the fact that thick pelage makes early small or nonelevated lesions difficult to detect. However, the pathogenesis of collagenous hamartoma has not been proven, and lesions occurring in adult animals may be acquired rather than congenital.

Clinical features

Collagenous hamartomas are relatively common lesions in dogs. Incidence data have not been reported. They usually present as a solitary, dome-shaped or gumdrop-shaped, firm nodule measuring less than 1 cm in diameter. Collagenous hamartomas are frequently hyperpigmented and may be alopecic. The overlying skin is usually intact, except for lesions located in areas of constant friction. Lesions occur most commonly on the head, neck, and proximal legs.

Affected animals are middle-aged or older. There are no breed or sex predilections. Surgical excision is curative.

Histopathology (Figure 27.1)

Collagenous hamartomas are noncircumscribed nodules of the dermis that are composed of redundant dermal collagen. The fiber pattern is similar to the arrangement of normal dermal collagen bundles. Lesional collagen bundles may be slightly thicker, more eosinophilic, or more compact than in the adjacent normal dermis. Adnexa within the lesion are decreased in number or absent. As the collagenous hamartomas expand, the adnexal structures become variably distorted as they are pushed marginally; folliculosebaceous enlargement at the base is not uncommon. Fibroblasts are not obviously

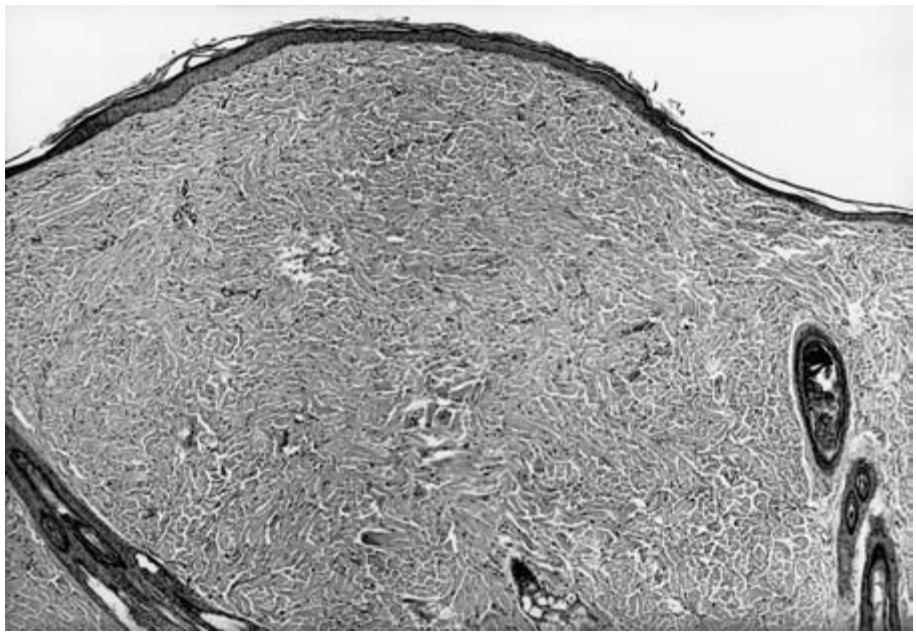


Fig. 27.1 Collagenous hamartoma in a dog characterized by a nodule of redundant collagen within the dermis.

increased in size or number. The overlying epidermis is usually intact and may be hyperpigmented. Inflammation is not observed, except for traumatized and secondarily infected nodules.

Differential diagnoses for collagenous hamartoma include fibroma, nodular dermatofibrosis, and nodular scar. Fibromas in the dermis are usually larger than collagenous hamartomas and often encroach on the subcutis. Fibromas generally are more cellular and have a repetitive, swirled or interlacing pattern of collagen fibers. Although the appearance of the collagen is similar to collagenous hamartoma, nodular dermatofibrosis is a multicentric condition, while collagenous hamartoma is almost always solitary. The lesions of nodular dermatofibrosis are often larger than collagenous hamartomas; the bulk of those lesions is in the deep dermis and may encroach on the subcutis. Hair follicles are usually not displaced by the collagen of nodular dermatofibrosis and are hyperplastic and elongated. Nodular dermatofibrosis lesions are often secondarily inflamed. In contrast to collagenous hamartomas, nodular scars are characterized by marked acanthosis, and the lesional collagen bundles are markedly thickened and often hyalinized.

CANINE NODULAR DERMATOFIBROSIS

Several familial syndromes of multiple cutaneous tumors associated with specific internal malignancies exist in man (McLean & Haynes, 2003). Nodular dermatofibrosis is the first such entity to be documented in animals and is associated with renal epithelial and, less commonly, uterine muscular tumors. It was first reported in German Shepherd Dogs, but has since been described in other breeds (Suter et al., 1983; Lium & Moe, 1985; Atlee et al., 1991; Marks et al., 1993; White et al., 1998).

The predominance of lesions in German Shepherd Dogs supports a hereditary predisposition; pedigree analysis revealed that nodular dermatofibrosis is an inherited disease with an autosomal recessive pattern in this breed (Moe & Lium, 1997). The Birt–Hogg–Dube human syndrome, which is characterized by a variety of organ defects and neoplasms, shares the development of renal neoplasia and benign skin tumors (trichofolliculomas) with canine nodular dermatofibrosis (Vincent et al., 2003). Recently, gene mapping localized the suspected gene of canine nodular dermatofibrosis to a small region of canine chromosome 5 that overlaps the human Birt–Hogg–Dube locus, suggesting that the same gene may be responsible for both conditions; subsequently a disease-associated mutation in exon 7 was identified (Lingaas et al., 2003). Overexpression of transforming growth factor β1 (TGF-β1) has been observed in human patients with several cancers, including renal carcinomas (Ananth et al., 1999). In a recent small study, TGF-β1, a potent stimulator of fibrosis, showed increased expression in the skin and kidney (hair follicles and renal tubules) of a German Shepherd Dog with nodular dermatofibrosis and renal cystadenocarcinoma, when compared to two normal German Shepherd Dogs (Vercelli et al., 2003). Serum levels were similar among all three dogs of that study, suggesting a role for local production of this cytokine. The cutaneous, renal, and uterine lesions may develop independently from each other but may be

induced by a common genetic defect that is partially mediated by abnormalities in production and/or expression of fibrosis-stimulating cytokines.

Clinical features

The incidence of cutaneous nodular dermatofibrosis has not been documented; it is probably rare. Firm, dermal and subcutaneous, well-circumscribed nodules develop that vary in size from several millimeters to 4 cm in diameter. The overlying skin may show irregular thickening and hyperpigmentation. In areas of friction, the nodules are often ulcerated. Larger lesions are often alopecic. Lesions are found primarily on legs, head, and ears.

Nodular dermatofibrosis mostly occurs in middle-aged and older dogs, but animals as young as 2 years of age may be affected. The lesions have been reported in German Shepherd Dogs (Suter et al., 1983; Lium & Moe, 1985; Atlee et al., 1991; Vilafranca, 1994), a Golden Retriever, a Boxer, and mixed-breed dogs (Marks et al., 1993; White et al., 1998); one author (T.L.G.) has seen a case in a German Shorthaired Pointer. Sex predilection has not been reported.

Renal lesions associated with nodular dermatofibrosis include renal cysts, cystadenomas and cystadenocarcinomas. A chromophilic-eosinophilic oncocytoma-like renal cell carcinoma has been documented (Vilafranca et al., 1994). Renal lesions are often multicentric and bilateral. The metastatic rate of the renal tumors is approximately 20%. Uterine leiomyomas are less common, which may be due to the ovariohysterectomized state of most of the affected bitches reported in the literature.

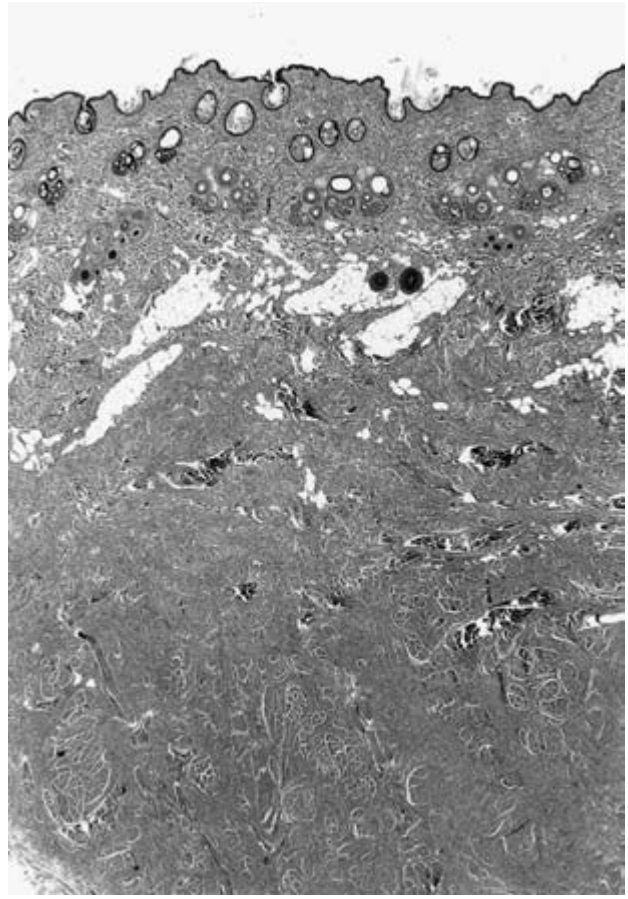


Fig. 27.2 Subcutaneous nodular dermatofibrosis in a German Shepherd Dog characterized by replacement of subcutaneous adipose tissue by dense mature collagen.

Histopathology (Figures 27.2 through 27.4)

The cutaneous lesions of nodular dermatofibrosis are characterized by focal dermal thickening due to increased numbers of slightly thickened collagen bundles. Cellularity is not increased and the collagen is ultrastructurally normal (Suter et al., 1983; Lium & Moe, 1985). There is no obvious demarcation of the lesions from the adjacent normal dermis. However, the deep margins of the dermal lesions often encroach upon and are well demarcated from the subjacent subcutaneous fat. The subcutaneous lesions are well-circumscribed nodules and plaques of mature collagen that are usually contiguous with the deep dermal collagen.

The collagen bundles surround and isolate adnexal structures. The adnexal structures may appear essentially normal, or hair follicles may be hyperkeratotic, and hyperplastic and elongated. The overlying epidermis has mild to moderate acanthosis. Smaller lesions are usually not inflamed. Larger lesions often ulcerate, and secondary folliculitis and furunculosis may develop.

The histologic appearance of nodular dermatofibrosis may be subtle, and differentiation from collagenous hamartomas, fibromas, and nodular scars may be difficult in incisional or punch biopsy specimens unless an appropriate clinical history increases the index of suspicion. Multiple excisional biopsies provide the most useful diagnostic material. Fibromas and collagenous hamartomas are usually solitary lesions. Collagenous hamartomas affect primarily the superficial dermis and have peripheralized adnexa. Fibromas are somewhat more cellular than nodular dermatofibrosis and have a more complex pattern of collagen bundles; adnexa are rarely incorporated. In nodular scars the collagen bundles are hypertrophic and hyalinized, while collagen bundles in nodular dermatofibrosis are increased in number but morphologically normal. Moreover, the presence of epidermal hyperplasia in nodular scars separates them from nodular dermatofibrosis.

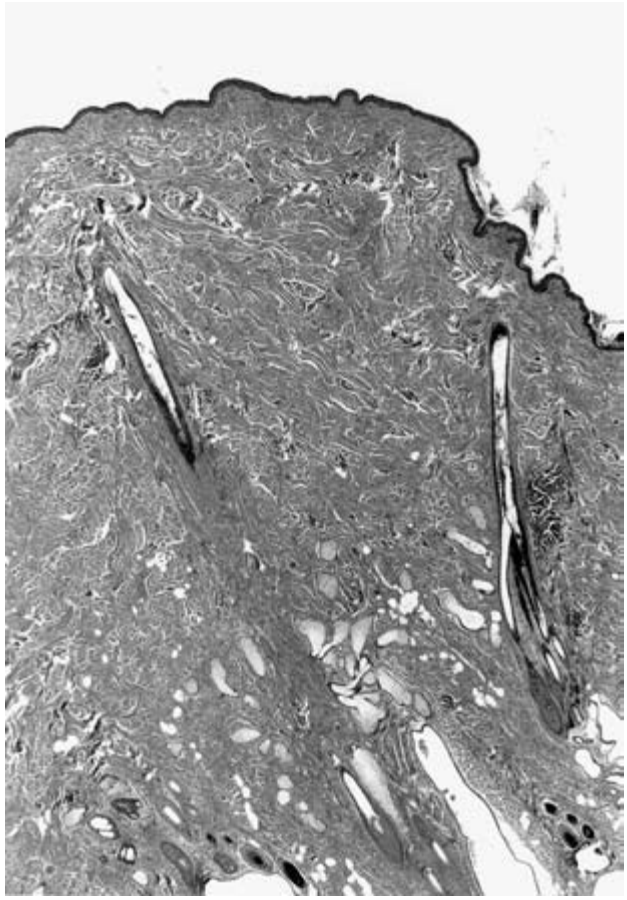


Fig. 27.3 Dermal nodular dermatofibrosis in a German Shepherd Dog. A poorly demarcated zone of dermal expansion by mature collagen separates, but does not disturb, adnexa.

ACROCHORDON AND ACROCHORDONOUS PLAQUE

(Synonyms: skin tag, fibroepithelial polyp, fibromatous polyp, fibromatous plaque)

Acrochordons are common hyperplastic lesions of the dermis and overlying epidermis in humans (Heenan, 1997; Mehregan et al., 1995). The etiology of acrochordons or fibroepithelial polyps is not clear. Some may be a proliferative response to trauma or resolving focal furunculosis.

Acrochordons, often referred to as skin tags, have been recognized in dogs and cats. Numerous closely associated small acrochordons, creating a plaque, have been seen in dogs and are referred to as acrochordonous plaques (Bidaut et al., 2003).

Clinical features

Acrochordons

These lesions, also referred to as skin tags, are fairly common in dogs and uncommon in cats. Solitary or multiple, polypoid or filiform masses are usually several millimeters in diameter and less than 1 cm in length. The overlying epidermis is thickened, alopecic and often hyperpigmented. Larger lesions may be focally eroded or ulcerated due to self-trauma or frictional damage. Lesions are usually truncal, but may also occur at pressure points on the legs or sternum. Sternal and leg lesions may be up to 3 cm in length and 1 cm in diameter.

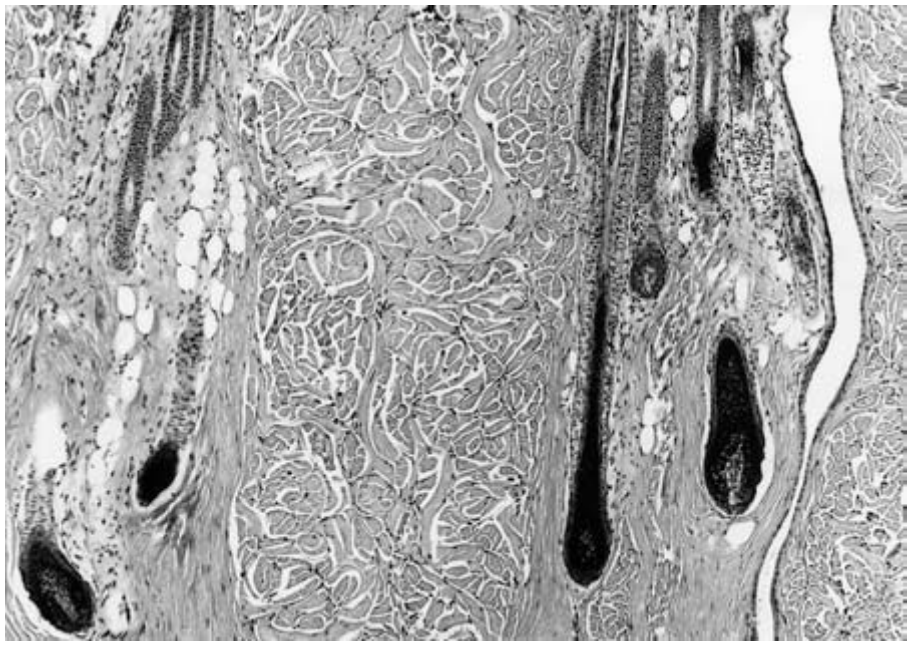


Fig. 27.4 Higher magnification of nodular dermatofibrosis showing thickened collagen bundles and low cellularity.

Affected animals are middle-aged or older. There are no known breed predilections. Acrochordons are benign lesions and excision is curative.

Acrochordonous plaques

These lesions, also referred to as fibromatous plaques, are nonpruritic and nonpainful (Bidaut et al., 2003). They are composed of small filiform polyps, resembling villi, which are clustered closely together to form a plaque. Each polyp resembles a small acrochordon. The entire plaque may have a linear configuration and may measure up to 5 cm. Acrochordonous plaques occur on the dorsal neck or on the head.

The plaques have been reported in English Bulldogs and a Pug (Bidaut et al., 2003) and have been observed in a Pit Bull Terrier as well. This suggests that these lesions may preferentially develop in bulldog type breeds with heavy necks and redundant skin. Most lesions are seen in young dogs, but have been reported in dogs up to 6 years of age (Bidaut et al., 2003). Based on the few cases observed, acrochordonous plaques are benign and surgical excision is curative.

Histopathology

Acrochordons (Figures 27.5 and 27.6)

These filiform or polypoid lesions generally are composed of mature collagen arranged as in normal dermis, but often with slightly increased vascularity. In some cases the dermal component is markedly vascular. Collagen



Fig. 27.5 Acrochordon in a dog. A small polypoid mass is composed of mature collagen.

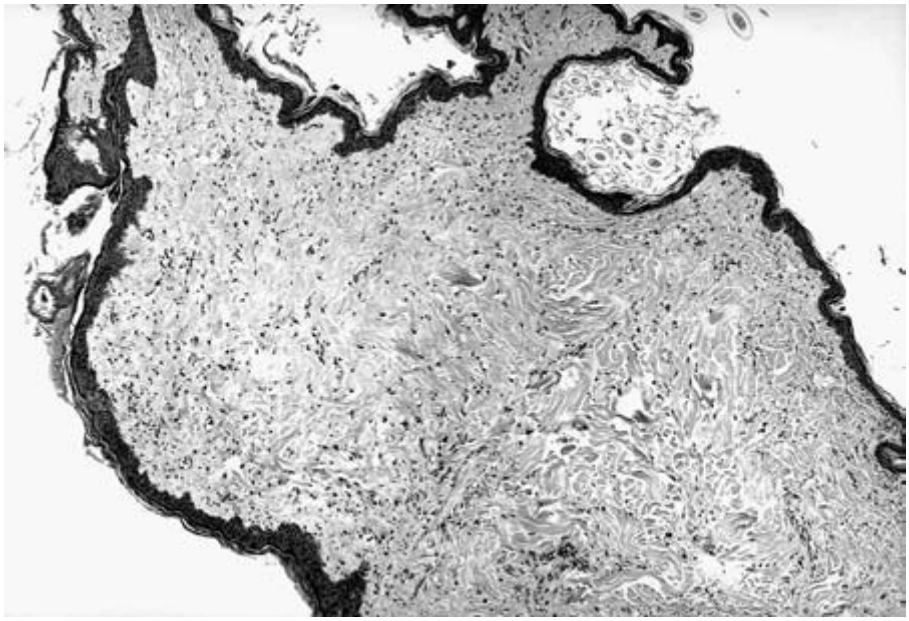


Fig. 27.6 Acrochordon in a dog. There is a sprinkling of inflammatory cells between the mature collagen bundles; note digitated configuration of overlying epidermis.

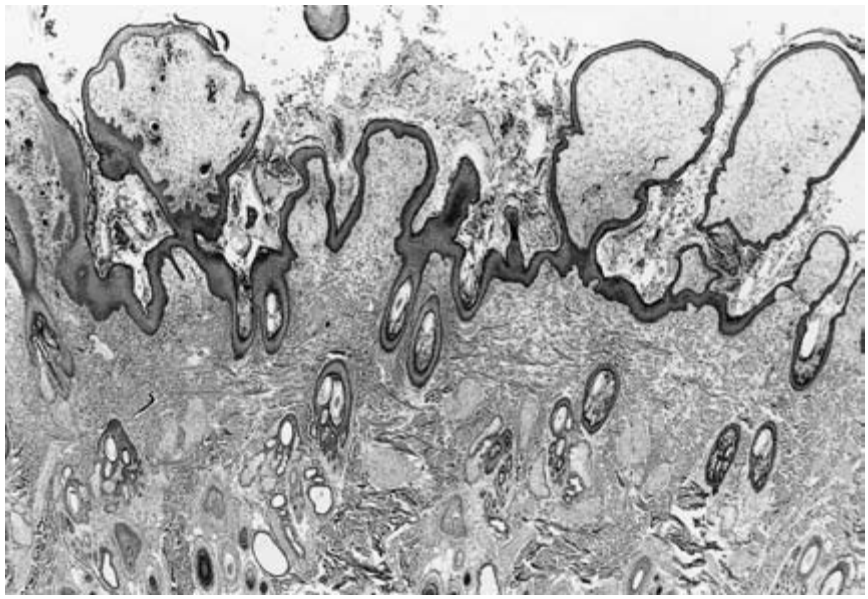


Fig. 27.7 Acrochordonous plaque in a dog. Multiple small acrochordons form villous structures; note prominent pale edema.

bundles in the larger polyps may be thicker and more tightly packed than those of the normal dermis. The overlying epidermis is acanthotic, hyperkeratotic, and often has a digitated configuration. Epidermal hyperpigmentation is frequently observed. Larger lesions often have a sprinkling of mononuclear inflammatory cells below the epidermis. Focal erosions or ulcers are common, and are accompanied by serocellular crusting and infiltration of neutrophils and plasma cells. Hair follicles and adnexal glands are not present within the polyp, but may be hyperplastic and/or dysplastic at its base. Hair follicles may exhibit hyperplasia of the follicular epithelium, hyperkeratosis, and/or degeneration accompanied by trichogranuloma formation.

Differential diagnosis of acrochordons is limited due to the distinctive filiform or cylindrical conformation of the lesion. Larger polypoid acrochordons may need to be differentiated from polypoid fibromas. Acrochordons are more filiform, tend to have increased vascularity, and lack the repetitive swirled or bundled collagen fibers of fibromas. Markedly vascular acrochordons may resemble polypoid hemangiomas, granulation tissue-type hemangiomas, or small lymphangiomas; however, vessels are not as numerous or uniform as in these vascular neoplasms (see Chapter 28).

Acrochordonous plaques (Figures 27.7 and 27.8)

These are characterized by a discrete area of numerous small acrochordonous lesions with little intervening normal skin. Each individual villus-like structure is composed of normal appearing collagen. The collagen bundles may be separated by marked edema or focal mucin limited to the superficial aspect. The dermal vessels in the enlarged papillae are dilated, and microhemorrhage may



Fig. 27.8 Higher magnification of acrochordonous plaque in a dog. Secondary changes include focal erosion, severe congestion with hemorrhage, and diffuse inflammation due to surface perturbation.

be observed. The overlying epidermis may be normal or moderately hyperplastic with formation of rete ridges, basketweave hyperkeratosis, and focal plaques of parakeratosis or compact keratin. The tips of some papillae are eroded or ulcerated, and there is subjacent neutrophilic inflammation. Intralesional follicles at the base of larger papillae are dilated and have an increased amount of keratin. There is a pleocellular, perivascular to interstitial dermatitis predominantly around these adnexa. The surrounding dermis may be fibrotic. Differential diagnosis of acrochordonous plaque is not problematical as these lesions have a unique morphologic appearance.

DERMATOFIBROMA

In humans, dermatofibromas are listed under the group of fibrohistiocytic processes (Rosai, 1996; Weiss & Goldblum, 2001). Controversy exists as to whether these lesions are reactive or neoplastic. Human dermatofibromas do not undergo involution, which supports a neoplastic etiology (Heenan, 1997; Weiss & Goldblum, 2001). Alternatively, some dermatofibromas have been interpreted as a form of fibrosing dermatitis with slow regression; a reactive process in response to trauma or arthropod bites has been suggested (Ackerman et al., 1982). Analyzing lesions in female patients for clonality by assessing the methylation of the androgen receptor gene on the X chromosome (HUMARA) reveals conflicting results; both clonal and polyclonal proliferations have been observed (Chen et al., 2000; Hui et al., 2002).

Dermatofibromas have been recognized in dogs and cats. The natural progression of dermatofibroma in animals has not been studied as biopsies of these lesions are invariably excisional rather than incisional. Hence, no conclusive data are available to indicate whether canine and feline dermatofibromas should be considered reactive lesions or benign neoplasms.

Clinical features

Dermatofibroma occurs uncommonly in cats, and is seen rarely in dogs. Dermatofibromas present as solitary, firm, circumscribed dermal nodules that are generally less than 2 cm in diameter. There is alopecia and the overlying epidermis is thickened. Lesions occur most often on the head, but other sites may be affected.

Affected animals are usually less than 5 years of age. There are no known breed or sex predispositions. Dermatofibromas are benign lesions and surgical excision is curative.

Histopathology (Figures 27.9 through 27.11)

Dermatofibroma is a circumscribed but unencapsulated dermal mass comprising spindle and stellate cells arranged in haphazard bundles and small whorls. The lesion extends to the dermal–epidermal junction and often has a base-narrow architecture. The spindle cells are interspersed with a moderate stroma composed of collagen fibers and bundles of varying thickness, some of which may represent pre-existing dermal collagen. Whorls of spindle cells are frequently oriented around thick collagen bundles seen in cross-section. Mineralization of collagen bundles is occasionally observed. The central portion of the nodule may have decreased cellularity as compared to the periphery, suggesting centrifugal maturation or possibly regression. The margins of dermatofibroma often have a ragged appearance due to dissection of collagen bundles of the adjacent dermis by the spindle cells.

The spindle and stellate cells have scant, pale cytoplasm and fusiform, hyperchromatic nuclei. Nucleoli are inconspicuous, and mitotic figures are rare. The overlying epidermis is acanthotic. In some cases there is variable reactive inflammation, predominantly along the margins.



Fig. 27.9 Dermatofibroma in a cat. Fibrocytic cells and collagen fibers are arranged in haphazard bundles and small whorls; note moderate cellularity.

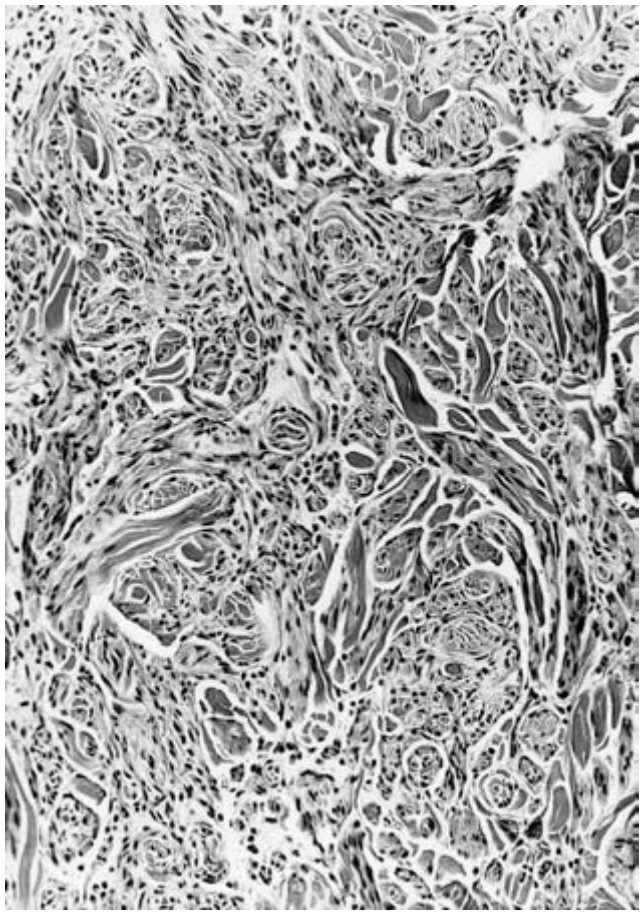


Fig. 27.10 Higher magnification of dermatofibroma of Fig. 27.9, showing thick collagen bundles entrapped by whorls of proliferating fibrocytes and delicate collagen fibers.

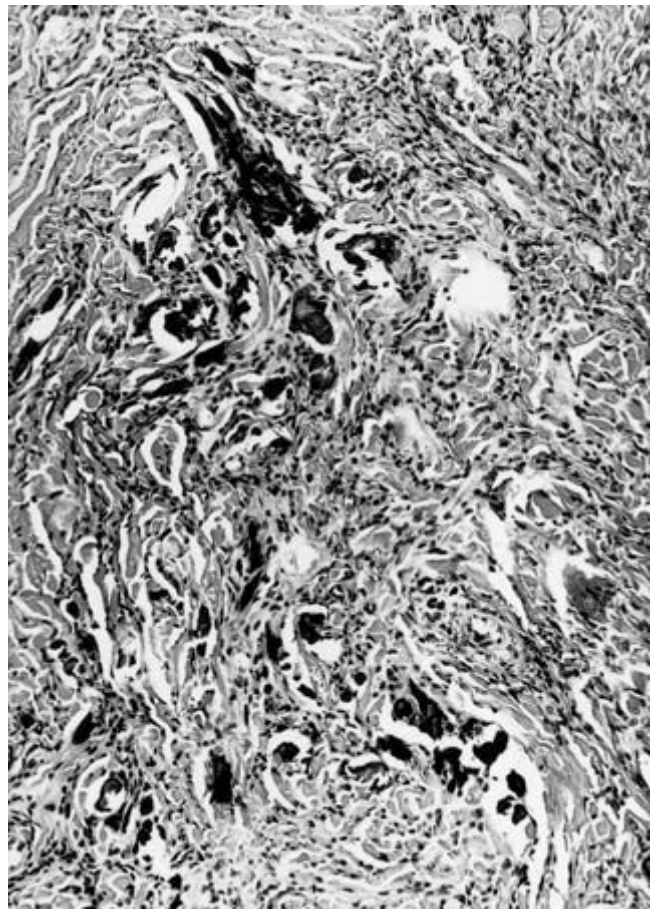


Fig. 27.11 Dermatofibroma in a cat. Note patchy darkly staining mineralization of collagen fibers.

Lymphocytes, mast cells, histiocytes, and occasional eosinophils and neutrophils are observed. In contrast to human dermatofibromas, xanthomatous macrophages are rarely seen.

Differential diagnoses for dermatofibroma include fibroma, keloidal fibroma, well-differentiated fibrosarcoma, and superficial benign peripheral nerve sheath tumor. Fibroma has lower cellularity, uniform collagen fiber diameter, and a more repetitive bundled or swirled patterning of the fibrocytic cells when compared to dermatofibroma. Keloidal fibroma has characteristic markedly enlarged hyalinized collagen bundles and usually lacks the reactive inflammatory component seen in dermatofibroma. The cellularity of dermatofibroma may be similar to that of well-differentiated fibrosarcoma and peripheral nerve sheath tumor, but the haphazard fibrocytic arrangement, minimal mitotic activity, entrapment of thickened collagen bundles, and secondary inflammation are differentiating features of dermatofibroma.

Immunohistochemistry

Dermatofibromas are positive for vimentin, but lack expression of additional markers that would assist in confirming the diagnosis and differentiating it from fibroma or well-differentiated fibrosarcoma. Canine dermatofibromas also are characterized by admixed spindle shaped and/or round histiocytes that express CD45 and CD18. Negative staining for S100 and neuron-specific enolase (NSE) may help to exclude a nerve sheath neoplasm.

NODULAR FASCIITIS

Nodular fasciitis in humans has often been referred to as a 'pseudosarcomatous' proliferation (Weiss & Goldblum, 2001), as some lesional cells exhibit anisocytosis and anisokaryosis. Nodular fasciitis is considered a benign reactive lesion, as it is composed of a mixture of fibroblasts, myofibroblasts, and inflammatory cells (Coffin et al., 1998), and displays benign clinical behavior.

The etiology of nodular fasciitis has not been confirmed, but underlying trauma has been suggested in humans (Heenan, 1997; Weiss & Goldblum, 2001). Involvement of myofibroblasts in tissue repair and wound healing has been well established (Gabbiani et al., 1972); the presence of myofibroblasts may support the hypothesis of a traumatic etiology.

Nodular fasciitis has been recognized in dogs, but unfortunately the term has been used to designate diverse proliferative processes in veterinary medicine. The authors will limit the use of the term 'nodular fasciitis' to a lesion characterized by a poorly demarcated mass attached to subcutaneous fascia (Hendrick et al., 1998), or, occasionally, involving deep dermis. This lesion is most consistent with nodular fasciitis described in humans (Heenan, 1997; Weiss & Goldblum, 2001). Other lesions previously documented as nodular fasciitis include granulomatous episcleritis and conjunctivitis, and retrobulbar infiltrating tumor masses in dogs (Bellhorn & Henkind, 1967; Gwin et al., 1977). The clinical behavior, response to immunosuppressive therapy, morphologic features, and phenotypic characteristics of granulomatous episcleritis and conjunctivitis are consistent with the systemic form of reactive histiocytosis (Affolter & Moore, 2000) (see Chapter 13). The reported retrobulbar masses were markedly infiltrative and exhibited aggressive behavior, which suggests a fibrosarcoma or myofibroblastic fibrosarcoma rather than a reactive process.

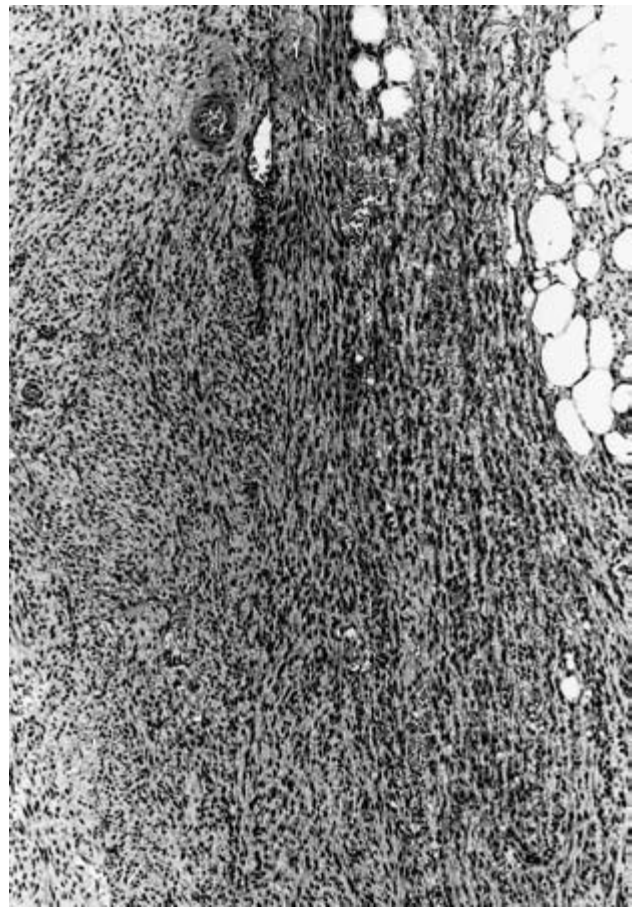


Fig. 27.12 Nodular fasciitis in a dog. This poorly demarcated mass is composed of irregularly arranged spindle cells. Note the prominent interstitial hemorrhage and congestion in the right half and incorporation of adipose tissue at upper right.

Clinical features

Nodular fasciitis is fairly uncommon in dogs; the exact incidence, however, is unknown. Some animals have a history of previous trauma to the area. However, marked tenderness or pain in the affected area, as seen often in humans with nodular fasciitis, is not a consistent finding. Canine nodular fasciitis usually presents as a solitary, subcutaneous, poorly demarcated mass that is less than 2 cm but may measure up to 5 cm in diameter. The location may be anywhere in the subcutis. Rarely, lesions involve the deep dermis and are less than 1 cm in diameter.

Nodular fasciitis is often observed in young dogs. Breed predilections have not been reported, although large breed dogs with rambunctious temperaments seem to be most often affected, which supports a role for trauma. The lesions are benign and complete surgical excision is curative.

Histopathology (Figures 27.12 and 27.13)

Nodular fasciitis is characterized by a subcutaneous, poorly demarcated mass attached to fascia. Rarely, lesions involve the deep dermis and are significantly smaller. The mass is composed of irregularly arranged spindle cells resembling a mixture of fibrocytes and immature fibroblasts. The margins of the lesion are typically jagged or spiked, and may incorporate adjacent skeletal muscle fibers. The proliferative tissue is highly vascularized and in some areas resembles an organizing hematoma. Only scant amounts of collagen are present, and the extracellular matrix may be rich in mucopolysaccharides.

The spindle cells have a moderate amount of cytoplasm and oval, elongated, and pointed nuclei. Moderate anisocytosis and anisokaryosis may be present and, occasionally, mitotic figures are numerous. Admixed are small numbers of lymphocytes, macrophages, and plasma cells. Extravasated erythrocytes are often present.

Nodular fasciitis should be differentiated from fibrosarcoma, myofibroblastic fibrosarcoma, spindle cell lipoma, granulation tissue, and a reactive nodular process that also has been referred to as 'inflammatory pseudotumor' in humans (Weiss & Goldblum, 2001). With

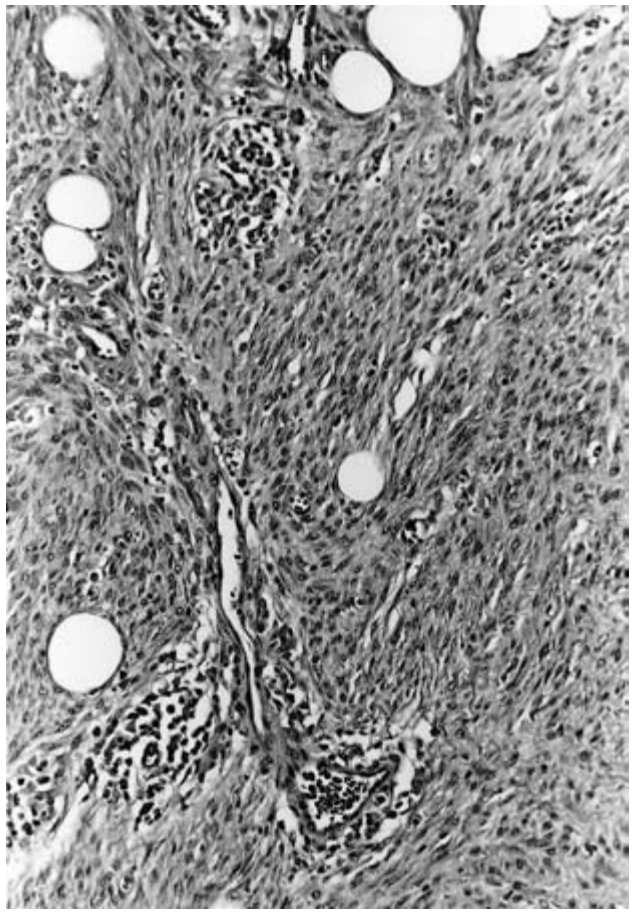


Fig. 27.13 Higher magnification of nodular fasciitis of Fig. 27.12. Note the prominent vascularization and multifocal inflammation.

fibrosarcomas and myofibroblastic fibrosarcomas, the cells are less haphazardly arranged, and repetitive interlacing bundles and whorls are often present. Moreover, reactive inflammation, neovascularization, and hemorrhage are either absent or less pronounced in the sarcomas. In some cases, clinical differentiation is required. Lesions of nodular fasciitis are usually smaller than soft tissue sarcomas. Nodular fasciitis is benign and self-limiting, while fibrosarcoma and myofibroblastic fibrosarcoma are characterized by local infiltration, marked tendency for recurrence, and a potential for metastasis. In spindle cell lipomas, the fusiform cells are more regularly arranged and are admixed with mature lipocytes; the borders of the mass are well circumscribed. Regular granulation tissue shows a transition from large, pleomorphic cells centrally to more mature fibrocytes peripherally, and a central hematoma cavity is often present. Nodular fasciitis has a more irregular admixture of the spindle cells. The process referred to as 'inflammatory pseudotumor' in humans, which is seen by the authors in dogs, is a discrete mass composed of reactive mesenchymal cells with numerous aggregates of lymphocytes and plasma cells, and fewer granulocytes. In contrast to nodular fasciitis, which is characterized by jagged edges, 'inflammatory pseudotumors' are well circumscribed.

Immunohistochemistry

Evaluation of nodular fasciitis in humans indicates that the majority of the proliferating spindle cells express vimentin, consistent with fibroblasts. In humans some cells coexpress α-smooth-muscle actin, indicating that they are of myofibroblastic origin (Zuber & Finley, 1994; Coffin et al., 1998; Weiss & Goldblum, 2001). Similar observations have been made in dogs. Thus, immunohistochemistry is of limited assistance in the separation of nodular fasciitis from fibrosarcoma, myofibroblastic fibrosarcoma, and spindle cell lipoma. The differential diagnosis of these lesions relies upon histomorphologic features (see above).

FIBROMA

Fibromas are benign fibrocytic neoplasms that may arise in the dermis or subcutis (Mehregan et al., 1995; Weiss & Goldblum, 2001). Fibromas include moderately cellular masses with scant collagen as well as masses with few fibroblasts embedded in abundant collagen. Similar to humans, the etiology of canine and feline fibromas is not known.

Clinical features

Dermal or subcutaneous fibromas are relatively uncommon in dogs and cats, accounting for fewer than 2% of all canine skin tumors in one large survey (Goldschmidt & Shofer, 1992) and for 1% to 3% of feline skin tumors in two retrospective studies (Carpenter et al., 1987; Miller et al., 1991). Fibromas present as solitary, firm or rubbery, circumscribed masses with an ovoid, dome-shaped, or polypoid conformation. Fibromas usually range from 1 to 5 cm in diameter, but are occasionally much larger. The overlying epidermis is often alopecic and atrophic. Ulceration may be present in larger lesions. Common sites in the dog are the head and legs (Goldschmidt & Shofer, 1992). Although reported feline cases are few, legs and head are also typical sites (Carpenter et al., 1987; Miller et al., 1991).

Affected animals are middle-aged or older. There is no sex predilection (Goldschmidt & Shofer, 1992). Although breed incidence may be obfuscated by inclusion of multiple fibrous proliferations in the data, Doberman Pinschers, Boxers, and Golden Retrievers are likely predisposed (Goldschmidt & Shofer, 1992).

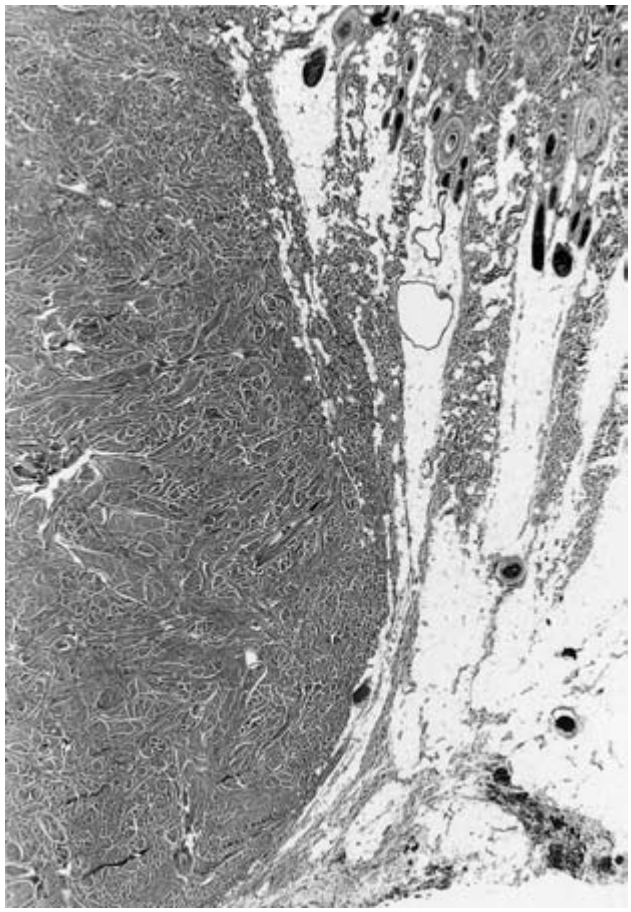


Fig. 27.14 Fibroma in a dog. The predominantly subcutaneous, well-demarcated nodule is composed of dense mature collagen.

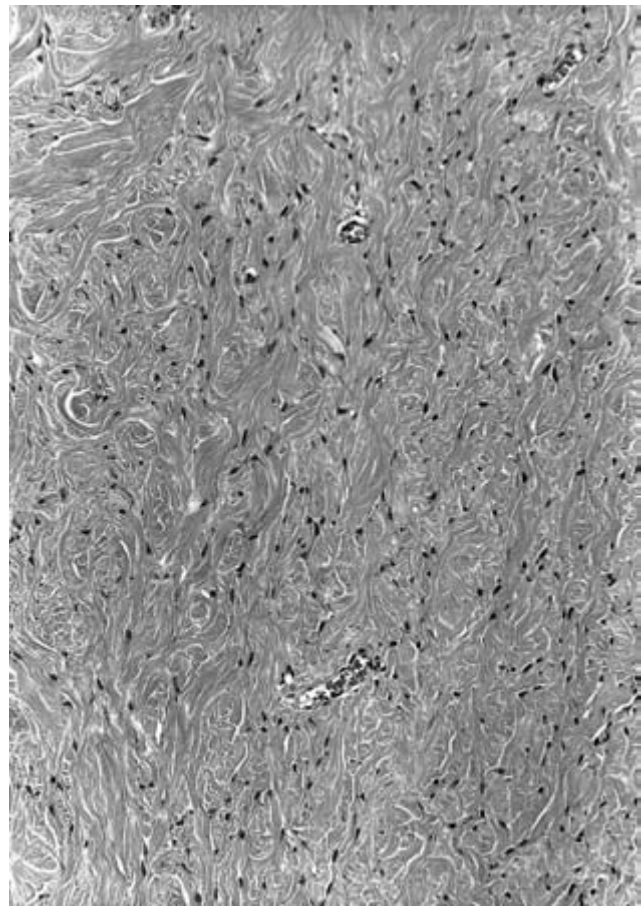


Fig. 27.15 Higher magnification of fibroma in a dog. Collagen fibers and fibrocytes are arranged in a repetitive pattern of interlacing bundles and swirls. Note low cellularity.

Histopathology (Figures 27.14 and 27.15)

Dermal fibromas are small and circumscribed but unencapsulated masses that often blend gradually into adjacent dermal collagen. Subcutaneous fibromas are very well circumscribed and usually larger than their dermal counterparts. Fibromas are composed of bundles of collagen that are generally thicker and have more repetitive patterns than those of the normal dermis. The collagen of a fibroma is often arranged in interlacing bundles with a slightly undulating configuration. Broad swirls or waves of collagen may also be observed. The stroma may contain small amounts of mucin. The overlying epidermis is generally normal or atrophic. Adnexal structures are usually completely displaced by the collagen of dermal fibromas, but adnexal entrapment is occasionally noted.

Cellularity is usually low and uniform throughout the mass; occasional tumors show moderate cellularity diffusely. Small, well-differentiated fibrocytes are distributed between the collagen bundles. The fibrocyte nuclei may be slightly enlarged and are fusiform and euchromatic. Nucleoli are inconspicuous, and mitotic figures are rarely observed.

Differential diagnoses for fibroma include collagenous hamartoma, nodular dermatofibrosis, nodular scar, keloidal fibroma, dermatofibroma, large acrochordons, and benign peripheral nerve sheath tumor (for cellular fibromas). Differentiation of dermal fibroma from collagenous hamartoma and nodular dermatofibrosis can be problematic, particularly when adnexal entrapment is present in the fibroma. However, fibromas are more discrete, tend to be more cellular, and have a repetitive, swirled or interlacing pattern of collagen fibers. Nodular dermatofibrosis is a multicentric syndrome, while fibroma is almost always solitary. The collagen bundles of hypertrophic scars are thicker and denser than those in fibroma, and there is usually residual evidence of an inflammatory etiology. Keloidal fibromas are characterized by large and markedly hyalinized collagen fibers and numerous admixed spindle-shaped or round histiocytic cells. Dermatofibromas are more cellular, have irregular

borders and collagen fiber arrangement, and may have mineralization of collagen bundles. The presence of inflammatory cells is common in dermatofibromas and rare in fibromas. Large acrochordons are differentiated from polypoid fibromas by the presence of increased vascularity and absence of a repetitive swirled or bundled collagen fiber pattern in the former. In comparison to benign peripheral nerve sheath tumors, fibromas are less cellular and lack palisading and whorling of cells. The stromal collagen is coarser and often abundant in fibroma, while peripheral nerve sheath tumors have a delicate collagenous matrix.

Immunohistochemistry

Fibromas are composed of vimentin+ fibroblasts. In contrast to fibromas, canine dermatofibromas are characterized by admixed spindle-shaped and/or round histiocytes that express CD45 and CD18. Some benign peripheral nerve sheath tumors are positive for S100 and glial fibrillary acidic protein (GFAP), which assists in differentiating them from more cellular cutaneous fibromas.

CANINE KELOIDAL FIBROMA

The term 'keloid' refers to marked overgrowth of scar tissue in the skin associated with deposition of large hyalinized collagen bundles (Weiss & Goldblum, 2001). Keloidal fibromas resemble regular fibromas, but they are characterized by the presence of large keloid-like collagen bundles (Weiss & Goldblum, 2001). Keloidal fibromas have been recognized in dogs (Goldschmidt & Shofer, 1992; Mikaelian & Gross, 2002), but have not been documented in cats.

The exact etiology of keloidal fibromas is not known, but they are considered to emerge from an inflammatory process. The lesions consistently contain various numbers of reactive histiocytes, which supports this hypothesis. Occasionally, foci of resolving hemorrhage resembling organizing hematomas are also seen, suggesting a traumatic etiology.

Clinical features

Keloidal fibromas in dogs are rare (Goldschmidt & Shofer, 1992; Mikaelian & Gross, 2002). They present usually as poorly demarcated nodules or plaques, which measure 6 to 18 mm in diameter. Most lesions have an intact surface, but occasionally ulcerate. Keloidal fibromas may develop at any site and have been reported to occur on the thorax, thighs, shoulder, flank, and perineal regions (Mikaelian & Gross, 2002).

Keloidal fibromas may develop at any age. The study of Mikaelian & Gross (2002) reported keloidal fibromas in dogs 2 to 12 years of age, with a higher incidence in male dogs. Shorthaired breeds (Rhodesian Ridgeback, Pit Bull Terrier, American Staffordshire Terrier, Boston Terrier, and Boxer) were over-represented in this study of 16 dogs; however, the small number of reported cases does not permit an accurate assessment of breed predisposition.

The vast majority of keloidal fibromas are benign and surgical excision is curative. Rare transformation into keloidal fibrosarcomas has been recognized (Mikaelian & Gross, 2002).

Histopathology (Figures 27.16 and 27.17)

Keloidal fibromas may be limited to the dermis or extend into the subcutis. They usually protrude above the skin surface. Alternatively, keloidal fibromas may arise from the subcutaneous tissue. Most keloidal fibromas are poorly demarcated and gradually blend into the surrounding tissue. Occasionally, well demarcated, discrete nodules are observed. The nodules comprise streams of markedly thickened, hyalinized collagen fibers

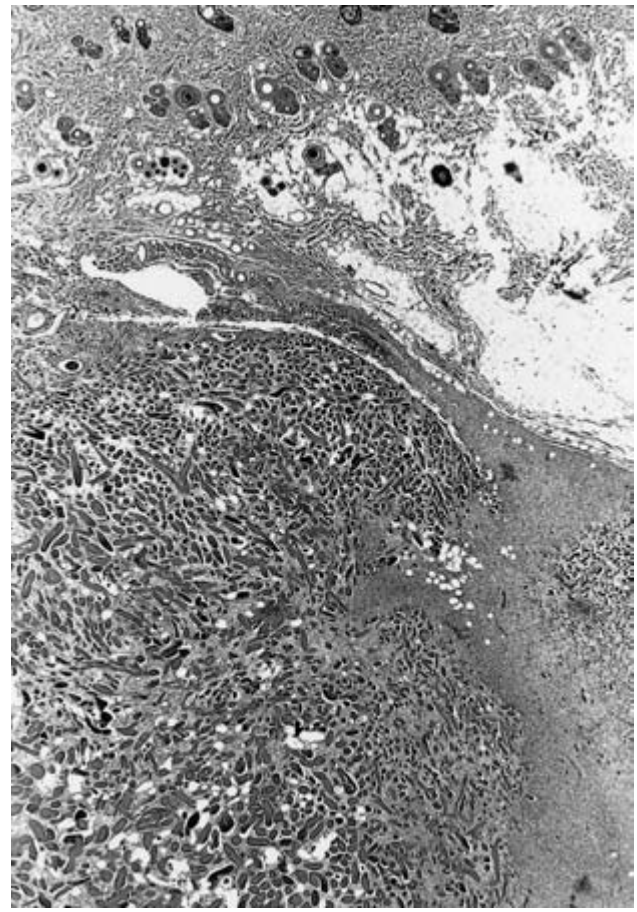


Fig. 27.16 Keloidal fibroma in a dog. The subcutaneous nodule is composed of streams of markedly thickened collagen.

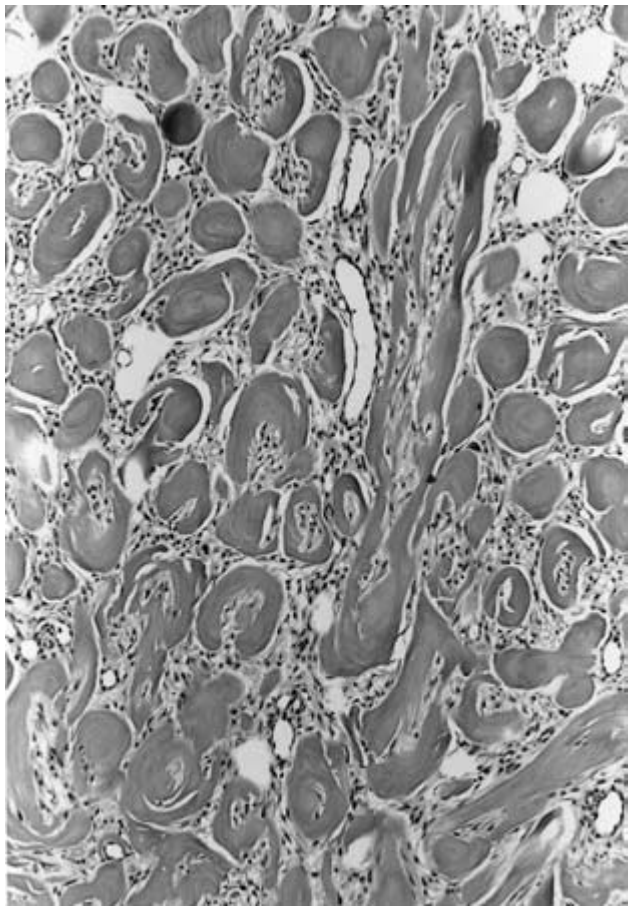


Fig. 27.17 Higher magnification of keloidal fibroma in a dog. The markedly thickened and irregular, hyalinized collagen bundles are surrounded by proliferating fibrocytes.

surrounded by spindled fibroblastic cells arranged in fascicles and packets. Fibers are often irregular in shape; some appear to be undergoing replacement by the spindle cell population. The center generally is less cellular than the periphery of the nodule, and variable numbers of thinner collagen fibers are intermingled with the large, hyalinized collagen fibers.

The spindle cells are characterized by pale cytoplasm, indistinct cell borders, and centrally located, elongated, pointed, normochromic nuclei with small basophilic nucleoli. Mitotic figures are rare. Admixed there are large, round to oval cells with vacuolated cytoplasm, and oval, slightly elongated or occasionally indented nuclei. These cells are consistent with histiocytes. Numerous microhemorrhages are dispersed throughout the nodules.

Rarely, transformation into keloidal fibrosarcomas occurs (see below); the reported case showed gradual transition beginning in the deep subcutaneous portion of the fibroma (Mikaelian & Gross, 2002). The presence of cellular atypia, increased mitotic rate, and infiltrative growth separate keloidal fibrosarcomas from their benign counterparts.

Keloidal fibromas may need to be distinguished from dermatofibromas, fibromas, nodular hyperplastic scars, and keloidal change of collagen within mast cell tumors. With the exception of mast cell tumors with keloidal change of the lesional collagen, the other proliferative diseases lack the presence of the distinctive, large hyalinized collagen bundles. The absence of proliferating mast cells separates keloidal fibromas from mast cell tumors.

Immunohistochemistry

Similar to regular fibromas, keloidal fibromas are composed of vimentin-positive fibroblasts. The admixed reactive fusiform or rounded histiocytes express the common leukocyte antigens CD45 and CD18.

FIBROSARCOMA

Fibrosarcoma, a malignant neoplasm arising from fibroblasts, can mimic various other spindle cell tumors in humans, and hence has become a diagnosis of exclusion (Weiss & Goldblum, 2001). As mesenchymal cells, the neoplastic fibroblasts retain their expression of vimentin. Fibrosarcomas occur in dogs and cats. Variants recognized include fibrosarcoma of follicular papillary origin, keloidal fibrosarcoma, and myofibroblastic sarcoma.

Fibroblasts in culture tend to form adherent sheets of long, stellate, haphazardly arranged cells, while dermal papillary cells in culture form structures very similar to the hair follicle papillae (Bratka-Robia et al., 2002). These findings support the hypothesis that the cells of the unique fibrosarcoma of alleged follicular papillary origin do arise from the dermal papilla. This neoplasm has no known human analogue.

In some spindle cell tumors the proliferating cells express α-smooth-muscle actin, which indicates differentiation to myofibroblasts, a cell type most commonly associated with granulation tissue secondary to trauma in humans (Gabbiani et al., 1972). Tumors of myofibroblasts have been referred to as myofibroblastic sarcoma, myofibrosarcoma, and myofibroblastic fibrosarcoma. A direct association with previous trauma has not been proven in most cases of canine and feline myofibroblastic fibrosarcoma.

The causal relationship between feline sarcoma virus (FeSV) and multicentric fibrosarcoma in young cats is well established (Hardy, 1981). Vaccine-induced fibrosarcoma, a subtype of vaccine-induced sarcoma in cats, is a complication of rabies and feline leukemia virus (FeLV) vaccines primarily (Macy & Hendrick, 1996). Vaccine-induced sarcomas display multiple morphologies, often

within a single tumor, and may originate from different cell types other than fibroblasts. This complex neoplasm will be discussed separately (see Chapter 33).

Clinical features

Fibrosarcoma has been considered the most common malignant mesenchymal neoplasm in cats and represents 15% to 17% of all feline skin and subcutaneous tumors in several surveys (Carpenter et al., 1987; Miller et al., 1991; Goldschmidt & Shofer, 1992). Fibrosarcomas are uncommon in dogs and represent about 1.5% of all skin and subcutaneous tumors in one large survey (Goldschmidt & Shofer, 1992). Fibrosarcomas of follicular papillary origin are rare in the authors' experience.

Fibrosarcomas are firm, poorly circumscribed, often multilobular masses that measure from less than 1 cm to more than 15 cm in diameter. Alopecia and ulceration commonly are observed.

Most fibrosarcomas arise in the subcutis and may occur at any anatomical site. Intradermal fibrosarcomas are uncommon in cats and rare in dogs. The majority of both canine and feline subcutaneous fibrosarcomas are located on the trunk and legs. Pinnae and digits appear to be preferential sites for dermal fibrosarcoma in cats. The authors have observed keloidal fibrosarcoma arising within a vaccine-induced sarcoma (see Chapter 33).

The average age of animals with fibrosarcoma is approximately 9 years in cats and 8.5 years in dogs; there is no sex predilection in either species (Goldschmidt & Shofer, 1992). Feline sarcoma virus-induced multicentric fibrosarcomas occur in cats as young as a few months of age (Goldschmidt & Hendrick, 2002). Fibrosarcoma also is occasionally observed in dogs less than 1 year of age. Gordon Setters, Irish Wolfhounds, Brittany Spaniels, Golden Retrievers, and Doberman Pinschers appear to be at higher risk (Goldschmidt & Shofer, 1992).

Fibrosarcomas are generally of low to moderate malignancy. They are locally invasive, which is manifested by frequent postexcisional local recurrence. The incidence of distant metastasis is low and tends to occur late in the course of the disease. A recurrence rate of 34% and an incidence of pulmonary metastasis of 9% have been reported for canine fibrosarcomas (Bostock & Dye, 1980); tumors with a high mitotic rate (>9 per 10 high power fields) had a significantly higher rate of metastasis. The study of Kuntz et al. (1997) described local recurrence of 15% for canine soft tissue spindle cell sarcomas, including fibrosarcomas; the lower recurrence rate in this study may reflect more sophisticated or aggressive surgical techniques. The combined rate of metastasis for all sarcomas in this retrospective study was 17% and occurred primarily in high-grade tumors (mitotic index 20 or greater) (Kuntz et al., 1997).

The overall recurrence rate of feline fibrosarcomas is more than 70% for most anatomic locations, and multiple recurrences are common (Brown et al., 1978; Bostock & Dye, 1979). Metastatic rates of 11% to 14% have been reported; the lung is the most common site (Brown et al., 1978; Bostock & Dye, 1979). According to Bostock and Dye (1979), fibrosarcomas on the pinna and flank of cats had no recurrence or metastasis compared with those on the head, thorax, or legs; this may be a reflection of relative ease of wide surgical excision at those sites. A mitotic index of less than 5 per 10 high power fields (40×) was also associated with significantly longer survival times, but was unrelated to the rate of recurrence (Bostock & Dye, 1979).

Currently, there is no documentation specifically regarding the behavior of canine and feline myofibroblastic fibrosarcoma; these were probably grouped with other fibrosarcomas previously. The biologic behavior of fibrosarcoma of follicular papillary origin is also unknown; local recurrence developed in one case observed by the authors.

Histopathology

Fibrosarcoma (Figures 27.18 to 27.20)

Fibrosarcomas are irregular, often multilobular neoplasms involving the subcutis, occasionally the dermis, or both. Occasionally, tumors are circumscribed and may be partially encapsulated, but most tumors have ill-defined, infiltrative margins. Fibrosarcomas are composed of large spindle cells arranged predominantly in interlacing bundles of varying size. The individual bundles are usually fairly broad, and the angles of intersection are highly variable. Some undulating or swirled cell arrangements may occur. The classically described chevron or herringbone pattern of small bundles intersecting at consistent angles is uncommon. Cellularity varies considerably among individual tumors and often from field to field within a given tumor. The major component of the stroma is mature collagen. In highly cellular variants with scant stroma, the presence of intercellular collagen may be confirmed by Masson's trichrome stain. Small amounts of mucin may be admixed with the collagen. Chondroid or osseous metaplasia is occasionally observed.

The tumor cells have pale, poorly defined, scant cytoplasm. Nuclei are oval to fusiform and vesicular, and have one or more prominent nucleoli. Some neoplasms have a mixture of vesicular and hyperchromatic nuclei. Variable numbers of dispersed multinucleated giant cells may be present; poorly differentiated fibrosarcomas with abundant giant cells may present as anaplastic sarcoma with giant cells (see Chapter 33). Nuclear hyperchromatism and multinucleation are more commonly observed in feline fibrosarcomas. The mitotic rate of fibrosarcomas is

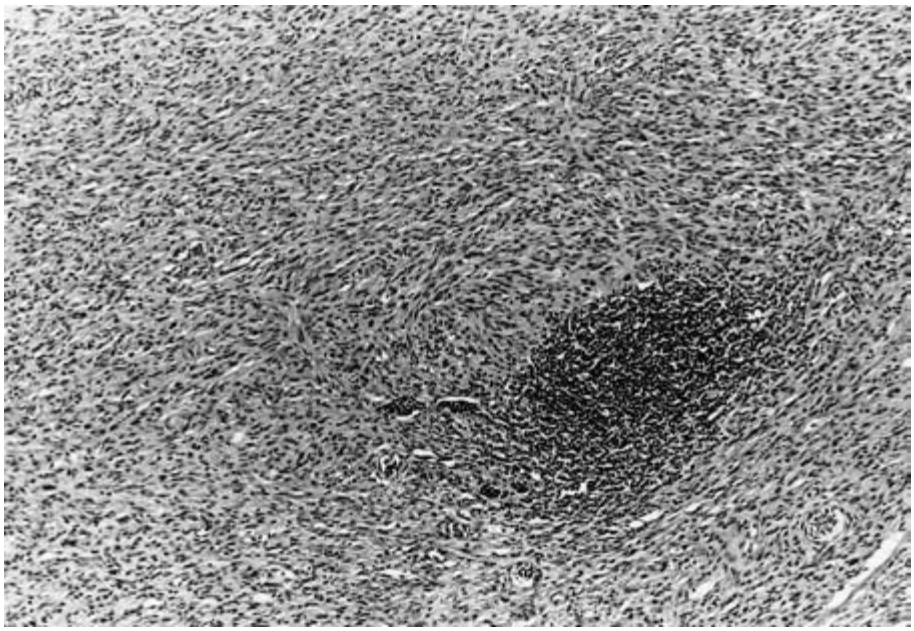


Fig. 27.18 Fibrosarcoma in a cat. Spindle cells are arranged in tight interweaving bundles; note a focal aggregate of small lymphocytes.

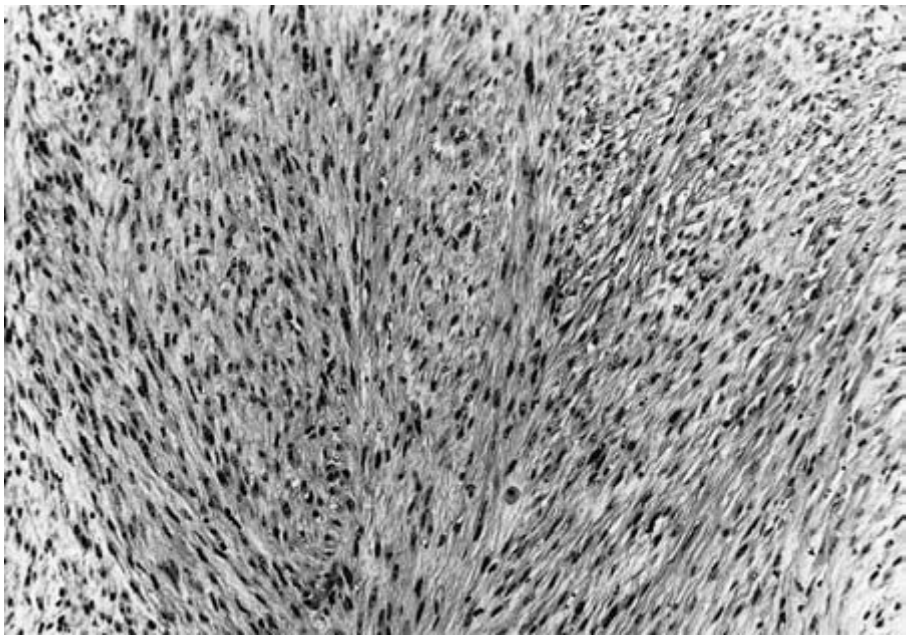


Fig. 27.19 High magnification of fibrosarcoma in a cat. Spindle cells are arranged in broad interlacing bundles in moderate collagenous stroma.

highly variable. A median of 14 mitotic figures per 10 high power fields (40×) has been reported (Kuntz et al., 1997). Atypical, bizarre mitotic figures may be present. Nuclear morphology and mitotic index do not correlate well with degree of stromal collagen production. Fibrosarcomas with abundant, sclerotic stroma can have highly malignant cytologic features, while very cellular neoplasms can be composed of relatively mature fibroblasts.

Ulceration, necrosis and hemorrhage are common secondary features. Neutrophils may predominate in necrotic foci. The presence of a dispersed reactive inflammatory infiltrate varies; it may be more prominent in FeSV-induced fibrosarcomas of young cats. However, feline fibrosarcomas often have mild to moderate peripheral lymphoplasmacytic inflammation, even in those with no known vaccine association. Occasionally, there are admixed large round and spindle-shaped histiocytes and intralesional reactive multinucleated giant cells of histiocytic origin, as seen in anaplastic sarcoma with giant cells (see Chapter 33). Identification of these reactive histiocytic cells requires immunohistochemistry (see below).

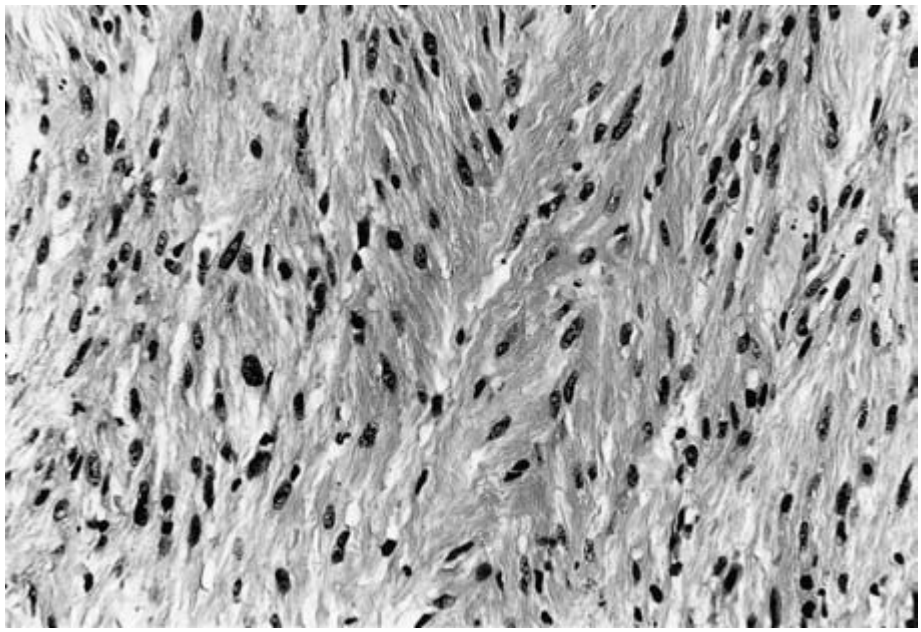


Fig. 27.20 Higher magnification of feline fibrosarcoma of Fig. 27.19, showing pleomorphic oval-to-fusiform nuclei, variable chromatin patterns, and prominent nucleoli.

Differential diagnoses for fibrosarcoma include spindle cell predominant histiocytic sarcoma, malignant peripheral nerve sheath tumor, leiomyosarcoma, nodular fasciitis, anaplastic sarcoma with giant cells of other mesenchymal cell origin, and, for intradermal lesions only, dermatofibroma and spindle-cell squamous cell carcinoma. Histiocytic sarcomas composed largely of spindle cells may be indistinguishable from fibrosarcomas featuring giant cells; immunohistochemistry is required for differentiation (see below). Peripheral nerve sheath tumors may have a more complex architecture characterized by palisades, whorls, and neuroid structures. Long, serpentine or twisted nuclei are more suggestive of neural origin. In contrast to fibrosarcomas, the tumor cells in peripheral nerve sheath tumors have a basement membrane, which can be demonstrated by electron microscopy. Leiomyosarcoma is distinguished from fibrosarcoma by minimal or absent collagenous stroma, abundant cytoplasm with perinuclear vacuoles, and frequent nuclear chromatin crossbars. Although leiomyosarcomas are composed of spindle cells with oval blunt-ended nuclei, and fibrosarcomas typically feature spindle cells with pointed nuclei, clear differentiation using nuclear morphology is often problematic. Leiomyosarcomas usually lack intercellular collagen, while the tumor cells of fibrosarcomas produce variable amounts of collagen. Masson's trichrome stain may allow detection of small amounts of collagen in questionable cases, but immunohistochemistry is preferable for definitive diagnosis. Nodular fasciitis may mimic a well-differentiated fibrosarcoma associated with fascia. However, it tends to be highly vascularized and in some areas resembles an organizing hematoma. Extravasation of red blood cells may be seen. The cellularity of dermatofibroma may be similar to that of a low-grade dermal fibrosarcoma, but the nonrepetitive meshwork arrangement of fibrocytes, minimal mitotic activity, and entrapment of thickened collagen bundles are indicative of dermatofibroma. Differentiation from spindle-cell squamous cell carcinoma is particularly important for dermal fibrosarcomas in cats. Spindle-cell squamous cell carcinoma usually shows contiguity with the epidermis and may have foci of keratinization. Immunohistochemistry may be required (see below). Anaplastic sarcoma with or without giant cells may originate from various mesenchymal cells, not only fibroblasts. Thus, immunohistochemistry is required to separate anaplastic sarcomas of fibroblastic origin from other anaplastic sarcomas (see Chapter 33).

Fibrosarcoma of follicular papillary origin

(Figures 27.21 and 27.22)

These tumors are characterized by poorly-circumscribed dermal masses that often entrap multiple dysplastic hair follicles and may extend into the subcutis. Embedded within a dense proliferation of long spindle cells arranged in broad bundles, as seen in regular fibrosarcoma (see above), there are small islands and nests of tightly-packed ovoid or short spindle cells with minimal, poorly-defined cytoplasm and slightly elongated, small nuclei with condensed chromatin. These nests of cells resemble dermal papillae of hair follicles. The small cell aggregates tend to be located below residual hair follicles, and transitional zones between the large and small cell populations are occasionally observed. Fibrosarcoma of follicular papil-

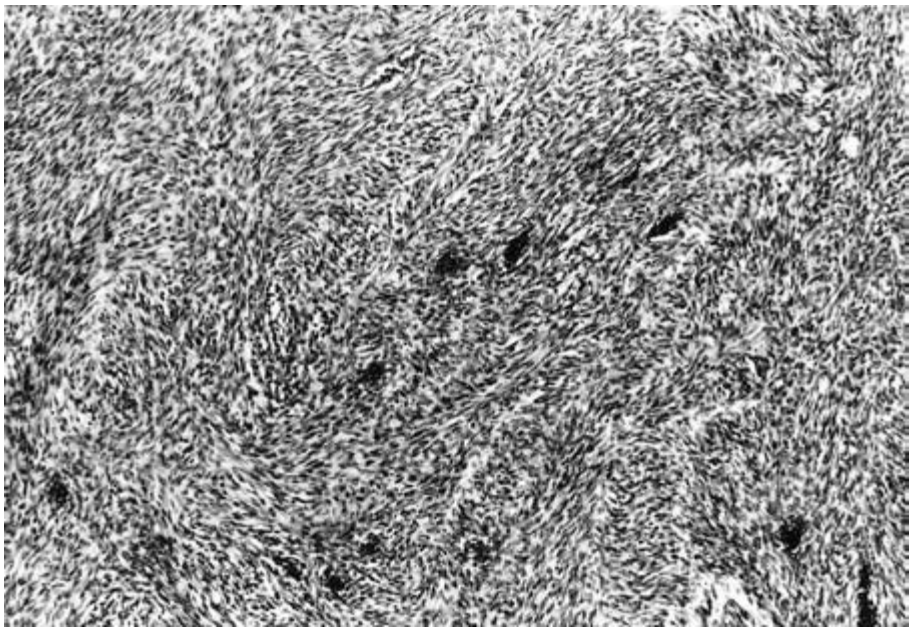


Fig. 27.21 Fibrosarcoma of follicular papillary origin in a dog. Numerous small nests of tightly packed cells are embedded in bundles of larger spindle cells.

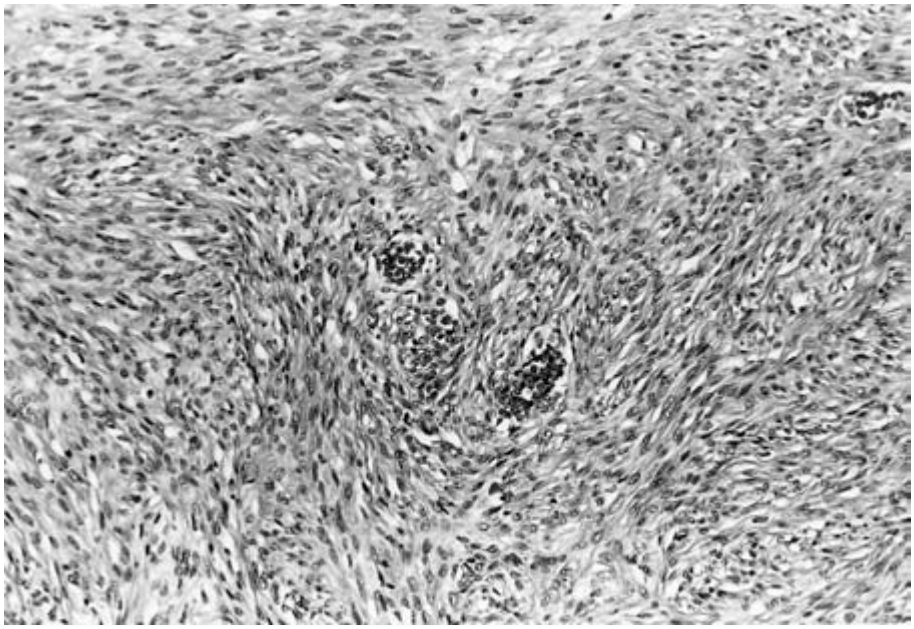


Fig. 27.22 Higher magnification of fibrosarcoma of follicular papillary origin of Fig. 27.21, demonstrating dermal papilla-like nests of small round cells embedded in interlacing fascicles of fibroblasts.

lary origin is distinct; differential diagnosis is uncomplicated if papillary structures are recognized.

Keloidal fibrosarcoma

Rarely, keloidal fibromas progress to keloidal fibrosarcomas. While the dermal portion often resembles keloidal fibroma (see p. 721), the subcutaneous portion of the tumor may develop invasive growth. These deeper nodules are characterized by closely packed, interlacing bundles of spindle cells accompanied by a fibrovascular stroma with entrapped large hyalinized collagen fibers. There is mild anisokaryosis and a mitotic index of 1 to 2. Admixed are moderate numbers of CD18+ histiocytic cells, which may represent dendritic cells or macrophages (Mikaelian & Gross, 2002). Keloidal fibrosarcomas are differentiated from other fibrosarcomas by the presence of keloidal change.

Myofibroblastic fibrosarcoma

In general, myofibroblastic fibrosarcomas have morphologic features similar to fibrosarcomas (see above) and share their differential diagnoses. In myofibroblastic fibrosarcoma, tumor cells may be more haphazardly arranged, larger, more pleomorphic and variably stellate.

The mitotic rate varies markedly. Occasionally, myofibroblastic fibrosarcomas may tightly encircle small vessels and hence, may mimic hemangiopericytomas. The latter lacks the haphazardly arranged spindle cell pattern often seen in myofibroblastic fibrosarcoma. However, immunohistochemistry is often required to confirm myofibroblastic origin (see below).

Immunohistochemistry

All fibrosarcomas consistently express vimentin only, and thus immunohistochemical diagnosis is by exclusion of other neoplasms. The intralesional reactive multinucleated giant cells, seen within some fibrosarcomas, express the common leukocyte markers CD45 and CD18, while multinucleated tumor giant cells of fibroblastic origin express vimentin but lack leukocyte markers. Myofibroblastic fibrosarcomas express α-smooth-muscle actin and, on rare occasions, also desmin.

In contrast to fibrosarcomas, histiocytic sarcomas diffusely express the common leukocyte markers CD45 and CD18 together with CD1, CD11c, and MHC II. Leiomyosarcomas are consistently positive for α-smooth-muscle actin as well as desmin. Differentiation of leiomyosarcomas from desmin-positive myofibroblastic fibrosarcoma may, therefore, not be possible based on immunophenotyping. Some peripheral nerve sheath tumors express S100 and glial fibrillary acidic protein (GFAP), which will allow differentiation from fibrosarcomas. In contrast to fibrosarcomas, peripheral nerve sheath tumors are surrounded by a laminin+ and collagen IV+ basement membrane. Immunohistochemistry for intermediate filaments will differentiate between cytokeratin+ spindle-cell squamous cell carcinoma and vimentin+ fibrosarcoma. In contrast to myofibroblastic fibrosarcomas, hemangiopericytomas consistently lack expression of α-smooth-muscle actin and desmin.

MYXOMA

(Synonym: myxofibroma)

Myxomas arise from fibrocytes or other primitive mesenchymal cells that produce an abundant amount of extracellular matrix composed of mucin rather than collagen (Graadt van Roggen et al., 1999). Mucin is composed of acid mucopolysaccharide rich in hyaluronic acid, and stains blue with Alcian blue (pH 2.5). Positive staining disappears after pretreatment with hyaluronidase.

Clinical features

Myxomas are rare in dogs and cats (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992). A survey by one of the authors (E.J.W.) revealed six myxomas out of 1143 total cutaneous and subcutaneous tumors in dogs. Most myxomas are subcutaneous but may involve the dermis secondarily. Occasionally, purely intradermal myxomas are observed. Myxomas are soft, ill-defined masses of variable size; dermal myxomas can be smaller than 1 cm, while subcutaneous tumors often attain large proportions. There may be partial alopecia. The cut surface of a myxoma oozes clear, viscous fluid. The majority of myxomas arise on the trunk or legs.

Affected dogs and cats are middle-aged or older. The mean age in dogs is 9 years (Goldschmidt & Shofer, 1992). There is no known breed predilection. In dogs myxomas are more common in females than in males (Goldschmidt & Shofer, 1992). Myxomas may recur locally due to difficulty in surgical assessment of tumor margins.

Histopathology (Figures 27.23 and 27.24)

Myxomas are unencapsulated tumors that arise in the subcutis and, occasionally, the dermis. Overall cellularity is low. Myxomas are composed of small stellate and spindle

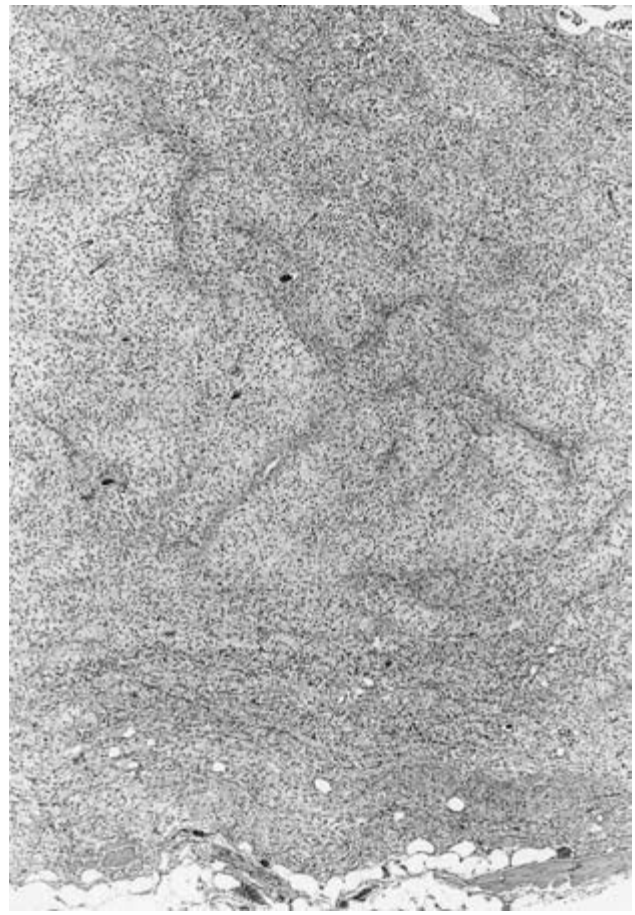


Fig. 27.23 Myxoma in a dog. Bundles and whorls of spindle cells are arranged in a pale mucinous stroma.

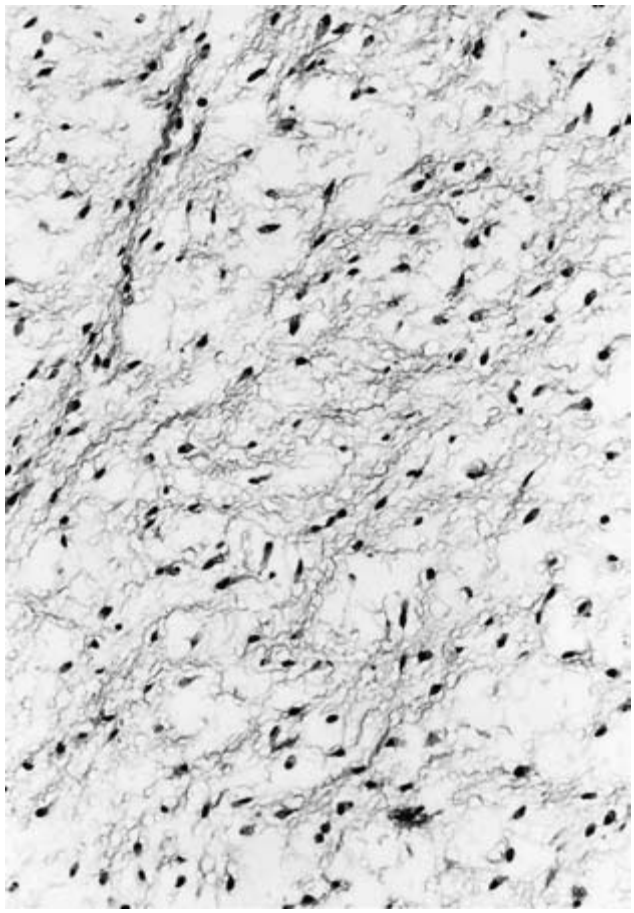


Fig. 27.24 Higher magnification of myxoma in a dog. Large amounts of mucin separate the narrow spindle and stellate cells.

cells embedded in an abundant stroma of acid mucopolysaccharide rich in hyaluronic acid. Distribution may be diffuse, or cells may be arranged in bundles. The mucinous matrix generally has a slightly basophilic tint with hematoxylin and eosin (HE) stain and appears blue with Alcian blue (pH 2.5). The stroma may also contain scant, wavy collagen fibers. The tumor cells have discrete, eosinophilic cytoplasm and small, ovoid to fusiform nuclei. Nucleoli are inconspicuous and mitotic figures are rare.

Differential diagnosis for myxoma is limited due to its distinctive stromal characteristics. Myxomas may need to be differentiated from myxoid peripheral nerve sheath tumors and myxosarcomas. In contrast to myxomas, myxoid peripheral nerve sheath tumors have a multilobular configuration, and the tumor cells are arranged in concentric whorls or form palisades. Peripheral nerve sheath tumor cells have a basement membrane that can be demonstrated by electron microscopy. Differentiation between myxoma and myxosarcoma can be problematic, as both the benign and malignant variants may have abundant stroma, low cellularity, and poor circumscription. Cytologic features of malignancy in myxosarcomas are increased nuclear to cytoplasmic ratio, nuclear pleomorphism and hyperchromatism, and the presence of atypical mitotic figures.

Immunohistochemistry

Similar to fibromas, myxomas express vimentin, but have no known specific protein markers that phenotypically separate them from other mesenchymal tumors. Some peripheral nerve sheath tumors are positive for S100 and glial fibrillary acidic protein (GFAP).

MYXOSARCOMA

(Synonym: myxofibrosarcoma)

Similar to their benign counterparts, myxosarcomas arise from fibrocytes or other primitive mesenchymal cells that produce an abundant amount of extracellular matrix, composed of mucin rather than collagen (Graadt van Roggen et al., 1999). Mucin, composed of acid mucopolysaccharide rich in hyaluronic acid, stains blue with Alcian blue (pH 2.5); this positive staining disappears after pretreatment with hyaluronidase.

Clinical features

Myxosarcomas are rare in dogs and cats (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992). A survey by one of the authors (E.J.W.) revealed two myxosarcomas out of 1143 total cutaneous and subcutaneous tumors in dogs. The clinical features are essentially the same as for myxoma. Myxosarcomas are soft, ill-defined masses of variable size. Subcutaneous masses are usually larger than dermal tumors. There may be partial alopecia, and secondary ulceration may be present in larger lesions. The cut surface of myxosarcomas oozes clear, viscous fluid. The majority of myxosarcomas arise on the trunk or legs.

Mean age in dogs and cats is approximately 9 years (Goldschmidt & Shofer, 1992). Basset Hounds and Doberman Pinschers are reported to be predisposed (Goldschmidt & Shofer, 1992). There is no known sex predilection.

Myxosarcoma is a low-grade malignancy characterized by frequent local recurrence and invasion, but rare distant metastasis. The lung has been reported as the most common metastatic site (Pulley & Stannard, 1990).

Histopathology (Figures 27.25 and 27.26)

Myxosarcomas are unencapsulated, poorly circumscribed neoplasms involving the subcutis and/or dermis. Myxo-

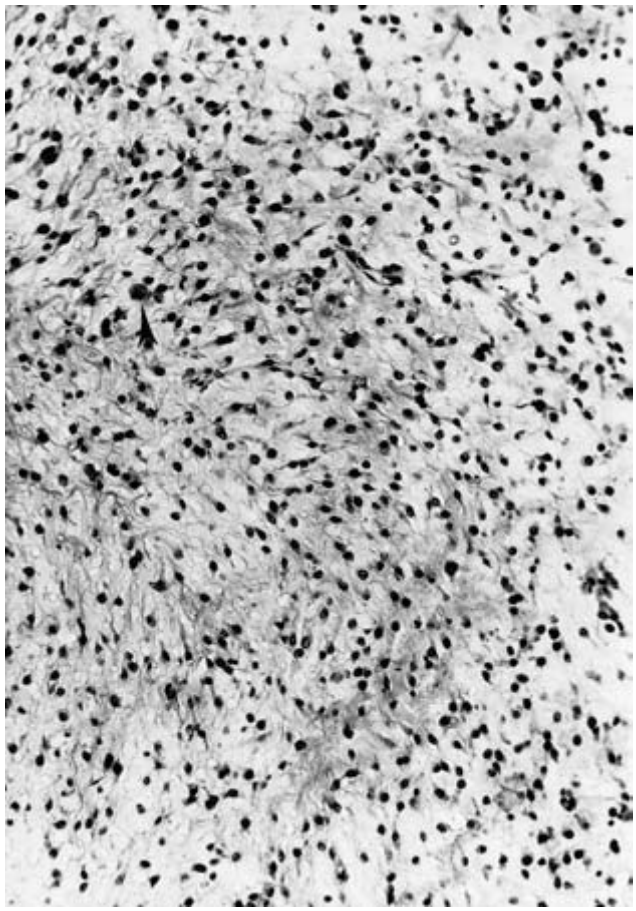


Fig. 27.25 Myxosarcoma in a dog. Stellate and spindle cells are distributed through an abundant stroma of mucin and collagen fibers. Note that cellularity is similar to myxoma, but there are hyperchromatic nuclei, scattered binucleated cells, and mitotic figures (arrow).

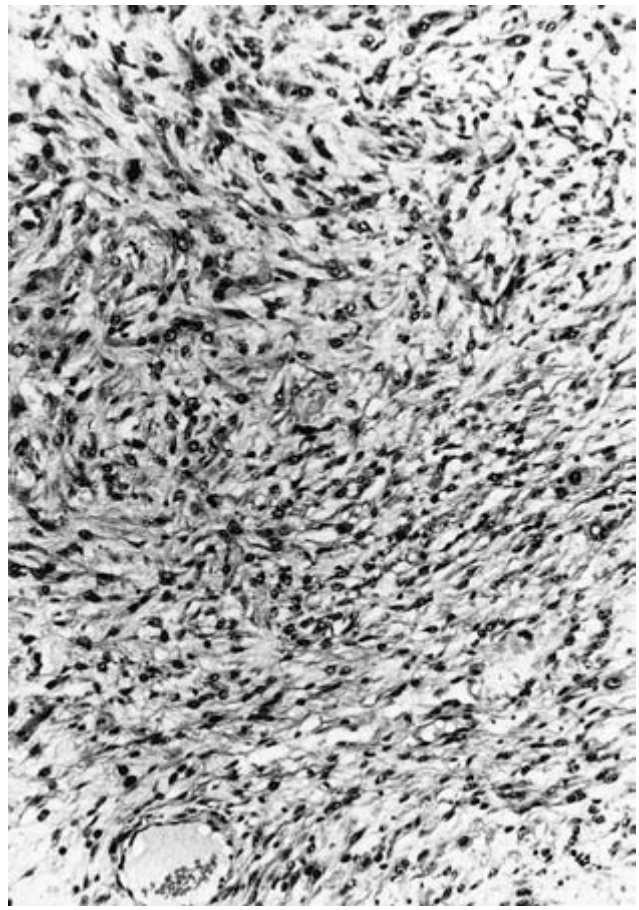


Fig. 27.26 Myxosarcoma in a cat. Spindle cells are arranged in broad fascicles in a moderate stroma of mucin and collagen. Note nuclear pleomorphism, prominent nucleoli, and mitotic figures.

sarcomas are composed of pleomorphic stellate and spindle cells distributed haphazardly through an abundant stroma of acid mucopolysaccharide rich in hyaluronic acid. The mucinous stroma is lightly basophilic with hematoxylin and eosin and is Alcian blue-positive (pH 2.5); positive staining disappears after pretreatment with hyaluronidase. The matrix also contains small amounts of collagen. Overall cellularity is moderately low, as in myxomas, but many tumors contain areas of increased cellularity, resembling poorly differentiated fibrosarcomas.

The neoplastic fibroblasts have scant, eosinophilic cytoplasm and pleomorphic nuclei, which are slightly larger than those of myxomas. Nuclei are often hyperchromatic and may contain cytoplasmic invaginations. Nucleoli are inconspicuous, and mitotic activity is low. Occasional atypical mitotic figures can usually be detected. Larger neoplasms may have areas of hemorrhage, necrosis and fibrosis. Ulceration and secondary inflammation may be present.

Differentiation between myxoma and myxosarcoma can be difficult as most benign and malignant variants have abundant stroma, low cellularity, and poor circumscription. Cytologic features of malignancy in myxosarcomas are increased nuclear to cytoplasmic ratio, nuclear pleomorphism and hyperchromatism, and the presence of atypical mitotic figures. Myxosarcoma may need to be distinguished from myxoid liposarcoma and myxoid peripheral nerve sheath tumors. In contrast to myxosarcomas, most myxoid liposarcomas have lipoblasts and well-differentiated lipocytes admixed with the spindle cell population. Lipid stain, such as oil red O, on nonparaffinized tissue is useful in confirming adipocyte origin. In contrast to myxosarcoma, myxoid peripheral nerve sheath tumors are composed of spindle cells arranged in concentric whorls or palisades; the tumor cells have a basement membrane demonstrable by electron microscopy.

Immunohistochemistry

Myxosarcomas express vimentin, but no additional specific proteins that allow separation from other mesenchymal tumors. Some peripheral nerve sheath tumors are positive for S100 and glial fibrillary acidic protein (GFAP). This phenotype separates them from myxosarcomas. Occasionally, myxoid liposarcomas may express S100, but in general immunohistochemistry is not useful in the differentiation of these tumors from myxosarcoma.

FELINE SARCOID

(Synonym: fibropapilloma)

Papillomavirus-induced fibroblastic proliferations, referred to as 'sarcoids', have been well documented in horses (Lory et al., 1993; Marti et al., 1993; Goodrich et al., 1998; Carr et al., 2001). The lesions are induced by bovine papillomavirus-1 and -2 (BPV1 and BPV2) located within the proliferating fibroblasts. This is in contrast to species-specific papillomaviral infections, which are characterized by intraepithelial papillomavirus.

Yager described lesions similar to equine sarcoid in cats in rural areas (Gross & Affolter, 1998). These lesions also have been referred to as fibropapillomas (Gumbrell, 1998). The involvement of papillomavirus in these feline lesions has been confirmed by Schulman et al. (2001). In that report, testing of affected tissues by polymerase chain reaction (PCR) and DNA analysis revealed sequences consistent with papillomavirus (Schulman et al., 2001). The sequence of the papillomavirus has relatively high identity with bovine and ovine papillomavirus (82%) as well as papillomavirus from deer and European elk (Teifke et al., 2002; Teifke et al., 2003). Similar to equine sarcoid, *in situ* hybridization or testing by PCR is required to demonstrate intralesional papillomavirus; Yager reported that immunohistochemical identification of the virus is not possible (Gross & Affolter, 1998).

Clinical features

The incidence of feline sarcoid is not known. It has been mostly seen in cats in rural areas, and 'barn' cats are predisposed. Feline sarcoids occur as solitary or multiple nodules that may measure up to 2 cm in diameter. The nodules are firm and often have an ulcerated surface. Yager described lesions that tended to develop on the philtrum, nares, upper lip, digits, the tip of the tail, and ears (Gross & Affolter, 1998) and it was suggested that feline marking behavior may be involved in the induction of these neoplasms. Occasionally, lesions also may occur in the oral cavity.

Feline sarcoids are predominantly seen in domestic shorthaired or domestic longhaired cats. As reported by Yager, lesions mainly affect young cats; the median age is about 12 months and male cats are predisposed (Gross & Affolter, 1998).

The lesions have virtually identical behavior to equine sarcoids. The nodules are slowly growing and may show infiltrative growth. Recurrence after surgery is common and is usually characterized by a markedly increased growth rate. As reported by Yager, better therapeutic results are seen with cryosurgery, radiation therapy, or amputation of lesions located on the tail or ears (Gross & Affolter, 1998). Metastasis has not been observed.

Histopathology (Figures 27.27 and 27.28)

Feline sarcoids are characterized by nonencapsulated, poorly demarcated dermal nodules that may extend into the underlying subcutis. The nodules are composed of densely packed spindle cells and stellate cells that are haphazardly arranged or whorled to form variably dense fascicles. The tumor cells tend to abut the epidermis and may be perpendicularly arranged along the dermal–epidermal junction. The overlying epidermis is hyperplastic and forms long spikes resembling rete pegs. A small amount of collagen is deposited between the tumor cells.

The tumor cells have indistinct borders, a small to moderate amount of eosinophilic cytoplasm, and oval to elongated nuclei. There is finely stippled chromatin and usually one small nucleolus. The mitotic rate varies from 1 to 5 per 10 high power fields (40×) (Schulmann et al., 2001). Small numbers of inflammatory cells may be dispersed throughout the mass and occasionally include a moderate number of mast cells.

Feline sarcoid should be differentiated from other spindle cell tumors, including fibrosarcomas, spindle cell predominant histiocytic sarcomas, peripheral nerve sheath tumors, and amelanotic melanomas. Fibrosarcomas, histiocytic sarcomas, and peripheral nerve sheath tumors mostly arise in the subcutis or deep dermis. They are characterized by a prominent tumor-free space, or 'Grenz zone', between the tumor tissue and the overlying epidermis, while feline sarcoid cells closely interact with the hyperplastic epidermis. Fibrosarcomas and histiocytic sarcomas may have a variable number of multinucleated tumor cells; stellate cells are not a primary feature. Moreover, histiocytic sarcomas are often composed of mixed spindle cell and round cell populations. Amelanotic dermal melanomas extend to the epidermis, and hence may mimic feline sarcoid; however, dermal melanomas tend to have a mixed spindle and epithelioid morphology.

Immunohistochemistry

Immunohistochemistry does not allow differentiation between fibrosarcoma and feline sarcoid as both tumors

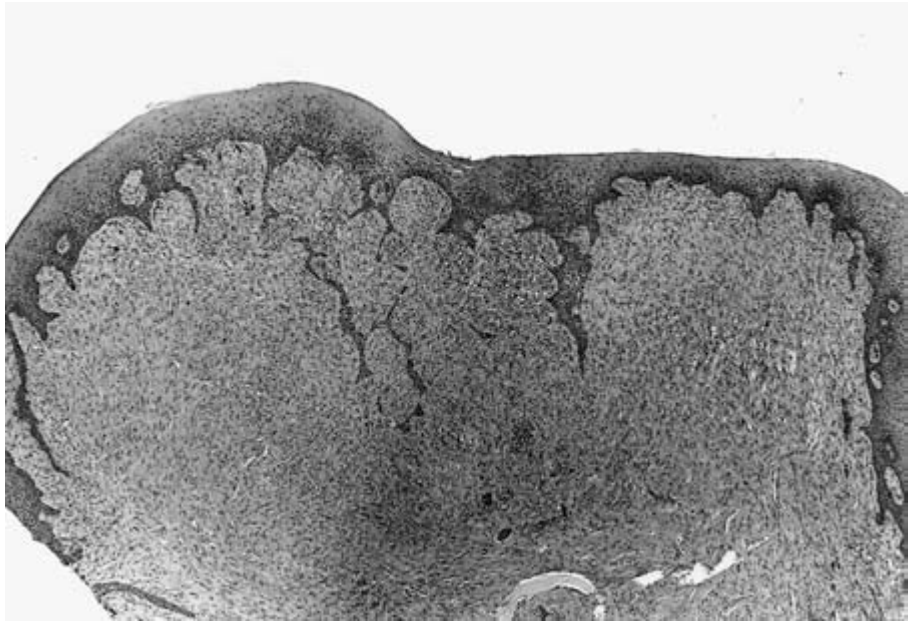


Fig. 27.27 Feline sarcoid. A dense proliferation of spindle cells throughout the dermis abuts the epidermis, which is hyperplastic and forms long rete peg-like spikes.



Fig. 27.28 Higher magnification of Fig. 27.27 showing haphazardly arranged spindle and stellate cells, which occasionally form bundles. Note intimate association with overlying epidermis.

express vimentin only. In contrast to feline sarcoids, peripheral nerve sheath tumors are characterized by a laminin+, and collagen IV+ basement membrane surrounding the tumor cells. Peripheral nerve sheath tumors may also express S100 and glial fibrillary acidic protein (GFAP). Histiocytic sarcomas consistently express the leukocyte markers CD45 and CD18, and expression of CD1, CD11c, and MHC II confirms their dendritic cell origin. Immunohistochemistry for S100, melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), tyrosinase, HMB45/gp100, tyrosinase-related protein-2 (TRP-2), or melanoma isoform of microphthalmia transcription factor (MITF-M) may assist in separating amelanotic melanomas from feline sarcoids.

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Chapter 28

Vascular tumors

Vascular tumors in humans are composed of vascular endothelial cells, endothelial cells lining lymphatics, or a mixture of the two (Breiteneder-Geleff et al., 1999; Weiss & Goldblum, 2001a–d). Endothelial cell proliferations include vascular hamartoma, angiomatosis, hemangioma, lymphangioma, hemangiosarcoma, and lymphangiosarcoma. Hemangiosarcomas and lymphangiosarcomas are often collectively referred to as angiosarcomas in the human literature (Weiss & Goldblum, 2001a,b). The proliferating endothelial cells may be accompanied by fibroblasts, pericytes, and smooth muscle cells, as seen in some forms of angiomatosis. Vascular proliferations in dogs and cats range from benign hamartomatous lesions to sarcomas with very aggressive behavior.

Vascular and lymphatic endothelial cells are indistinguishable based on hematoxylin and eosin evaluation. Electron microscopy reveals a continuous basement membrane associated with vascular endothelial cells, while lymphatic endothelial cells have a discontinuous or absent basement membrane (Swayne et al., 1989; Weiss & Goldblum, 2001a–d). Moreover, lymphatic endothelial cells contain numerous pinocytotic vesicles (Weiss & Goldblum, 2001a).

CD31, the clotting factor VIII, and several lectins (*Ulex europaeus*, soybean, and hairy vetch) are helpful markers for endothelial cells of both vascular and lymphatic origin (Folpe & Gown, 2001). Moreover, CD34, a protein expressed by embryonic cells of the hematopoietic system, is also expressed by both lymphatic and vascular endothelial cells (Cerilli & Wick, 2002). The expression of lymphatic vessel endothelial receptor-1 (LYVE-1), vascular endothelial growth factor receptor-3 (VEGFR-3), and podoplanin is a feature of lymphatic endothelial cells only (Banerji et al., 1999; Weiss & Goldblum, 2001a). LYVE-1, a receptor for the extracellular matrix glycosaminoglycan hyaluron, is the equivalent of CD44 on vascular endothelia. Instead of podoplanin, vascular endothelial cells express podocalyxin (Weiss & Goldblum, 2001b).

ANGIOMATOSIS

Angiomatosis is the term used to encompass a heterogeneous group of vascular proliferations in humans, and includes both vascular malformations and hyperplasia (Requeña & Sangueza, 1997; Breugem et al., 2001). The human lesions comprise infantile hemangiomas, angioma serpiginosum, acral arteriovenous hemangioma, cherry angioma, nevus flammeus, diffuse hemangioma, bacillary angiomatosis, hereditary hemorrhagic telangiectasia, Sturge–Weber syndrome, and Klippel–Trenaunay syndrome (Harwood & Mortimer, 1995; Ramirez et al., 1995; Requeña & Sangueza, 1997; Breugem et al., 2001; Weiss & Goldblum, 2001). Some of these processes have a tendency to regress; others have progressive behavior.

A variety of factors appear to affect vascular proliferation in humans. The importance of vascular endothelial growth factors (VEGF) and endothelial cell expression of receptors for VEGF has been documented (Breugem et al., 2001). In addition, the influence of adhesion molecules and their receptors, as well as fibroblast growth factor (FGF) and coagulation factors have been reported in these processes, and are still under investigation (Breugem et al., 2001). The Klippel–Trenaunay syndrome in humans is considered a vascular proliferation secondary to tissue lymphedema resulting from hypoplastic lymphatics and lymph nodes (Harwood & Mortimer, 1995). Some lesions of angiomatosis are associated with an infectious etiology; bacillary angiomatosis has been observed with *Bartonella bacilliformis* infections (Ramirez et al., 1995). Some angiomatoses in humans are considered reactive as they appear to develop after vascular occlusion of various causes (Rongioletti & Rebora, 2003).

Cutaneous angiomatosis occurs in dogs and cats. In contrast to the lesions in humans, spontaneous regression of canine and feline angiomatosis has not been documented. Some of these lesions develop in young animals; this supports a hamartomatous derivation rather than a true neoplastic origin. However, the proliferative process often mimics reactive neovascularization, which supports

a secondary proliferation that is driven by angiogenic growth factors, perhaps in response to trauma. As a general rule, progressive angiomatosis is a lesion that cannot be removed by simple soft tissue excision. Some of the canine and feline lesions are progressive and tend to expand into surrounding tissues, mimicking the behavior of low-grade malignancies, and are hence best referred to as 'progressive angiomatosis'. Based on morphologic variations, location of the lesions, and clinical behavior, feline and canine angiomatoses can be categorized as progressive angiomatosis and scrotal-type vascular hamartoma. Angiomatosis secondary to lymphedema (also referred to as Klippel–Trenaunay-like syndrome) also has been observed (DeCock, H.E.V., personal communication, 2003). Most of the canine and feline angiomatoses are newly recognized or newly documented syndromes, and nomenclature and classification may need to be modified as more cases are gathered.

Clinical features

Angiomatosis is rare in dogs and cats. In general, canine and feline lesions are characterized by dark red macules and patches, similar to the 'port-wine stains' described in humans, or may present as multiple plaques and nodules. The lesions have irregular margins, and partial blanching with diascopy (pressure over the lesion using a glass slide) is common. Nodules and plaques are prone to periodic hemorrhaging due to irritation. Hemorrhages are less common with macular lesions and patches. Macular lesions may remain unnoticed in a dense, long haircoat. Some lesions may appear as a poorly defined thickening of the skin with a normal skin surface.

Progressive angiomatosis

This type of angiomatosis occurs in dogs and cats. It most often affects the digits and feet (digital progressive angiomatosis), but has been seen in other areas, such as the face, tongue, neck, and axillary region. It may present as macules, patches, plaques or small nodules. The reported cases of feline angiomatosis were located on the face and on the front leg; the canine case was located on the face (Peavy et al., 2001). Generalized cutaneous angiomatosis has been observed in two dogs (Roccabianca, P., personal communication, 2004). Both dogs developed widespread, predominantly truncal lesions with subsequent traumatically induced cutaneous and subcutaneous hematomas and seromas.

Progressive angiomatosis usually develops in young to middle-aged animals; however, it has been documented in older animals as well (Peavy et al., 2001). No breed or sex predilections have been established in cats or dogs. The reported case of canine angiomatosis was observed in a 7-year-old mixed breed terrier dog (Peavy et al., 2001), and the authors have observed lesions of angiomatosis in Labrador Retrievers, Shar Peis, and mixed breed dogs. The dogs with generalized cutaneous angiomatosis were a Boxer and a Doberman Pinscher (Roccabianca, P., personal communication, 2004). The two reported cases of feline angiomatosis were observed in male neutered domestic shorthaired cats, 6 years and 10 years of age (Peavy et al., 2001); most cases observed by the authors also have been in domestic shorthaired cats.

Digital angiomatosis exhibits progressive and destructive behavior. Phalangeal bone lysis may be observed, and rapid progression to the proximal extremity may occur. In one canine case of pedal angiomatosis observed by the authors, there was relentless and rapid progression of lesions from the distal extremity to the shoulder. An extensive monomelic distribution is also a typical presentation for some types of human angiomatosis, particularly the entity referred to as diffuse hemangioma (Requeña & Sangueza, 1997). Angiomatosis of other locations, although progressive, appears less destructive. The two dogs with generalized cutaneous angiomatosis developed progressive lesions over several years (Roccabianca, P., personal communication, 2004). Metastasis has not been observed or reported with progressive angiomatosis.

Scrotal-type vascular hamartoma

Scrotal-type vascular hamartoma is uncommon in dogs and has not been described in cats. The lesion begins as single or multiple, hyperpigmented macules that progress to firm plaques. Most lesions are 1 to 2 cm in diameter. The overlying epidermis becomes thickened and is frequently ulcerated due to chronic licking. Periodic hemorrhage may occur. Occasionally, similar vascular hamartomas may occur in other nonscrotal, caudal locations including the caudal trunk and tail base; one author (E.J.W.) has observed a lesion on the medial carpus.

In contrast to other types of angiomatosis, scrotal-type vascular hamartoma is mainly seen in middle-aged or older dogs. Early reports indicated prevalence in breeds with pigmented scrotal skin; however, the pathogenetic basis for this finding is unclear and unsubstantiated to date.

Angiomatosis secondary to lymphedema (Klippel–Trenaunay-like syndrome)

This syndrome was observed in a Border Collie puppy that presented with a lesion on the proximal foreleg (DeCock, H.E.V., personal communication, 2003). Similar to the condition in humans (Hardwood & Mortimer, 1995), the cutaneous macular lesions were associated with marked progressive swelling of the leg, and formation of skin nodules. Similar cases of angiomatosis secondary to lymphedema have been observed by

the authors in a 6-year-old female Siberian Husky involving one hock, and a 5-year-old female Maine Coon cat. In contrast to Klippel–Trenaunay syndrome in humans and the canine cases, the cat presented with bilateral lesions of the hocks.

Histopathology

In general, angiomatosis is characterized by numerous dermal and/or subcutaneous, variably circumscribed, unencapsulated nodules composed of blood-filled vascular structures; the vessels are separated by normal mesenchymal tissue components. Some nodules have irregular margins, and small vessels extend peripherally among surrounding collagen bundles or adipocytes. Adjacent nodules are often connected by blood-filled channels, forming an anastomosing network of vascular spaces. In other areas there may be a diffuse, seemingly unconnected pattern of vascular structures, characterized by dilated vessels distributed loosely within the dermis and subcutis. The vascular channels may have large lumens or, alternatively, may resemble capillaries. Thrombosis may be present. There may be intraluminal, partially occlusive, papillary endothelial hyperplasia, characterized by endothelial cells proliferating as delicate fimbria along compact fibrous or organizing fibrinous trabeculae. The endothelial lining is either composed of normal, mature endothelial cells or slightly enlarged endothelial cells with hyperchromatic nuclei. Mitotic figures are absent or very rare. Myxomatous extracellular matrix may be deposited in the surrounding tissue. The overlying skin may be ulcerated.

The walls of the branching vascular structures vary in their composition and thickness. Many resemble capillary walls, and hence have no admixed fibrocytes or smooth muscle cells, as in humans (Weiss & Goldblum, 2001). However, the proliferating endothelial cells may be accompanied by variable amounts of smooth muscle and fibrous tissue, creating vascular structures that resemble small arterioles and veins. These latter lesions have also been referred to as 'arteriovenous angiomatosis' in humans (Weiss & Goldblum, 2001). Occasionally, a transition from an arteriolar to a venous-type vascular channel can be seen, suggesting that arteriovenous shunting may be occurring.

Progressive angiomatosis (Figures 28.1 through 28.5) Typically, these lesions are characterized by variably sized vascular channels that may contain luminal thrombi. Often there are central cavernous vessels surrounded by small, capillary-type vascular structures. The expansive and progressive growth pattern of the vascular structures may result in destruction of bone in digital locations. The vascular channels are lined by well differentiated and, occasionally, slightly plump endothelial cells. Most of the vessels are fully enclosed, but occasional clusters of anastomosing, sinusoidal spaces may be present. There is papillary endothelial hyperplasia. Some of the vascular structures may have admixed smooth muscle and fibrous tissue in their walls.

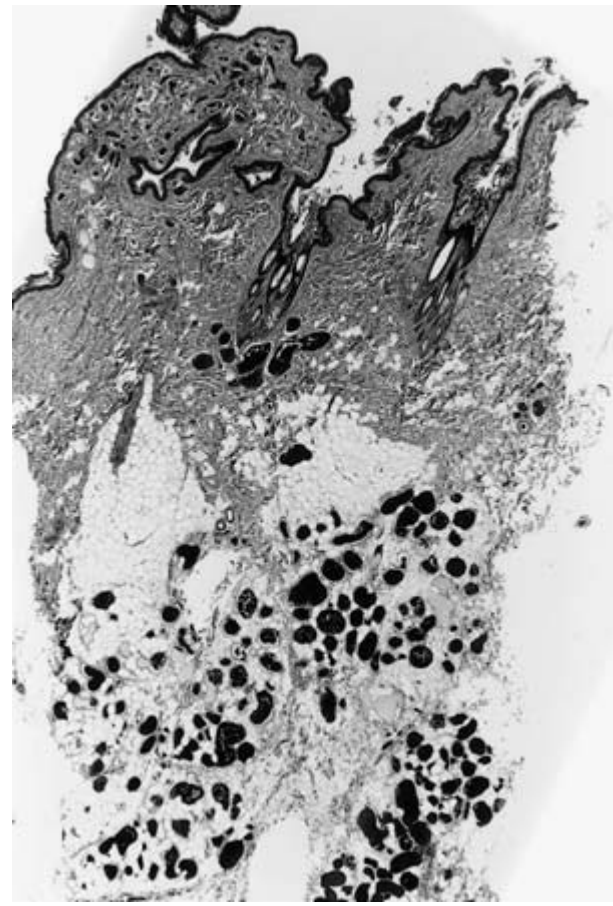


Fig. 28.1 Progressive angiomatosis in a dog demonstrating diffuse proliferation of thin-walled vessels throughout the dermis and subcutis.

The authors have seen rare cases of angiomatosis that do not entirely conform to the above description; these have been in nondigital locations. These lesions are characterized by diffuse proliferations of regular, large or medium-sized vascular channels that are diffusely distributed in normal dermal and subcutaneous tissue. Occasionally, these vascular channels are arranged in groups, which may or may not be interconnected. The vascular channels are lined by flat, well-differentiated endothelial cells. Papillary endothelial hyperplasia and thrombi have not been observed.

The generalized form of cutaneous angiomatosis, as observed in two dogs (Roccabianca, P., personal communication, 2004), was characterized by a proliferation of

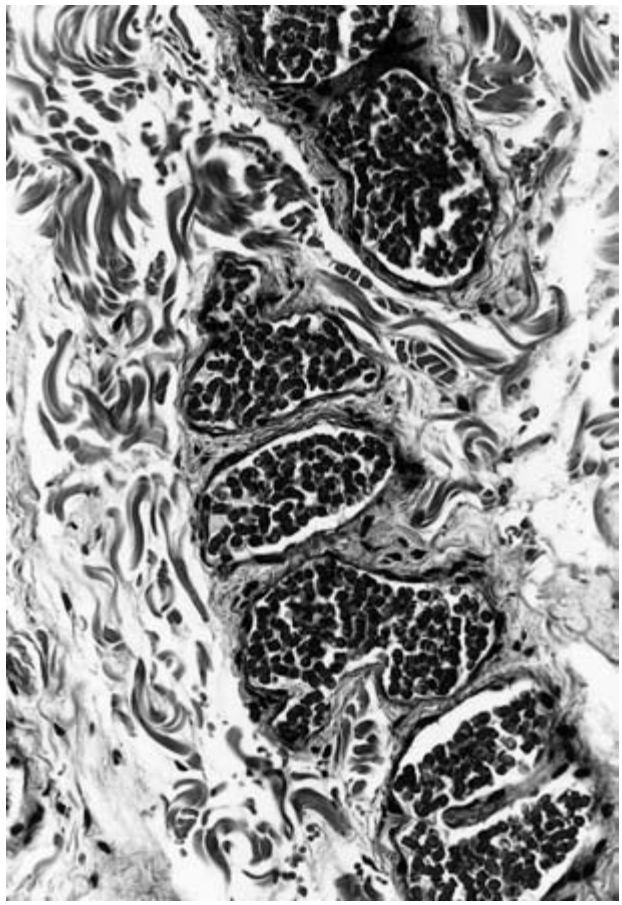


Fig. 28.2 Higher magnification of progressive angiomatosis in a dog. The vascular structures are lined by flat, well-differentiated endothelial cells.

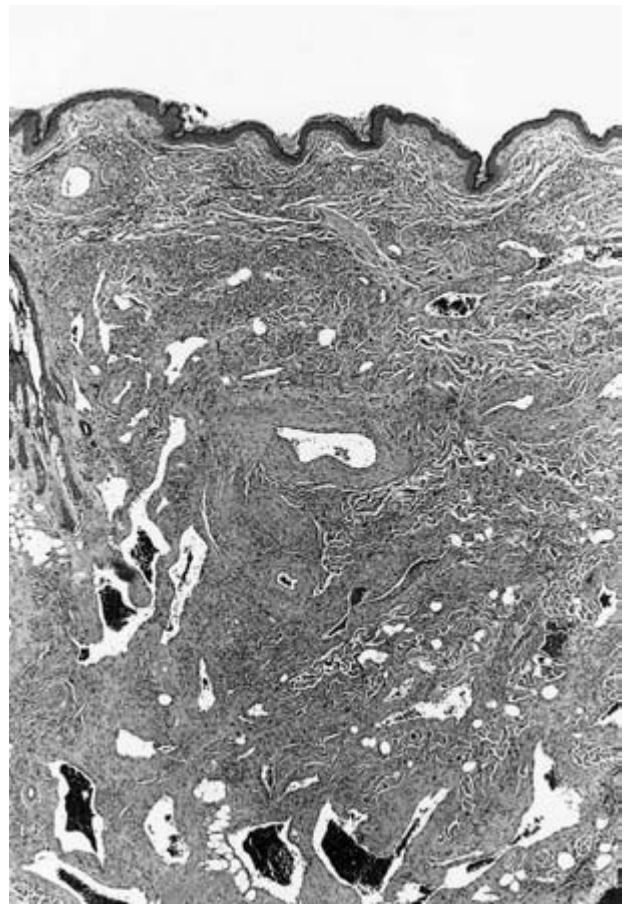


Fig. 28.3 Progressive angiomatosis in a digit of a dog predominated by arteriolar structures.

arterioles and venules in one dog and included arteriovenular shunts. The second dog developed lesions composed of primarily small, capillary type vascular structures.

The principal differential diagnosis for typical progressive angiomatosis is low-grade hemangiosarcoma, and in some cases, angiolipoma, infiltrative angiolipoma, or infiltrative hemangioma. The loose infiltration of blood vessels and the presence of papillary endothelial hyperplasia support angiomatosis. The lack of cellular atypia and mitotic figures also separates progressive angiomatosis from hemangiosarcoma. Angiolipomas are characterized by a proliferation of thin-walled vascular channels within a lipoma. In contrast, while progressive angiomatosis may affect the subcutis, the fatty tissue is otherwise normal. The second pattern of angiomatosis, seen less commonly, is distinctive in that invading vessels are more regular and uniform throughout the lesion. Such a lesion may be extremely difficult to differentiate from angiolipoma or infiltrative hemangioma in a single biopsy specimen; clinicopathologic correlation is required to confirm the extensive distribution of angiomatosis. Angiomatosis in sparsely haired, nonpigmented areas of the skin should be differentiated from solar-induced telangiectasia (see Chapter 10), particularly for superficial biopsy samples. The latter, however, is associated with additional solar-induced lesions such as actinic keratosis, actinic comedones, solar vasculopathy, or solar fibrosis and elastosis (see Chapters 7, 8, 10, 15).

Scrotal-type vascular hamartoma (Figures 28.6 through 28.8)

Scrotal vascular hamartomas are characterized by poorly circumscribed dermal plaques containing multiple clusters or lobules of redundant vascular structures that surround pre-existing dermal blood vessels. In most lesions, hyperplastic vessels in the center are larger and dilated. The vessels at the periphery comprise capillary buds with barely discernible lumens. The vascular structures are lined by a single layer of endothelial cells with plump, dark, uniform nuclei. Mitotic figures are very rare, and

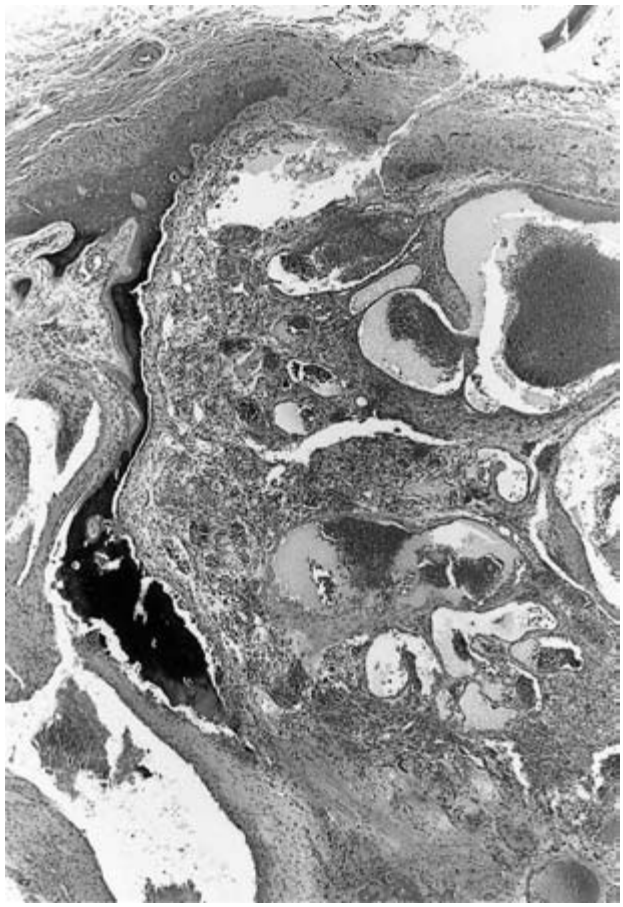


Fig. 28.4 Progressive angiomatosis in a digit of a dog. Extensive infiltrative and expansile growth of the vascular structures is resulting in resorption of P3 at left.

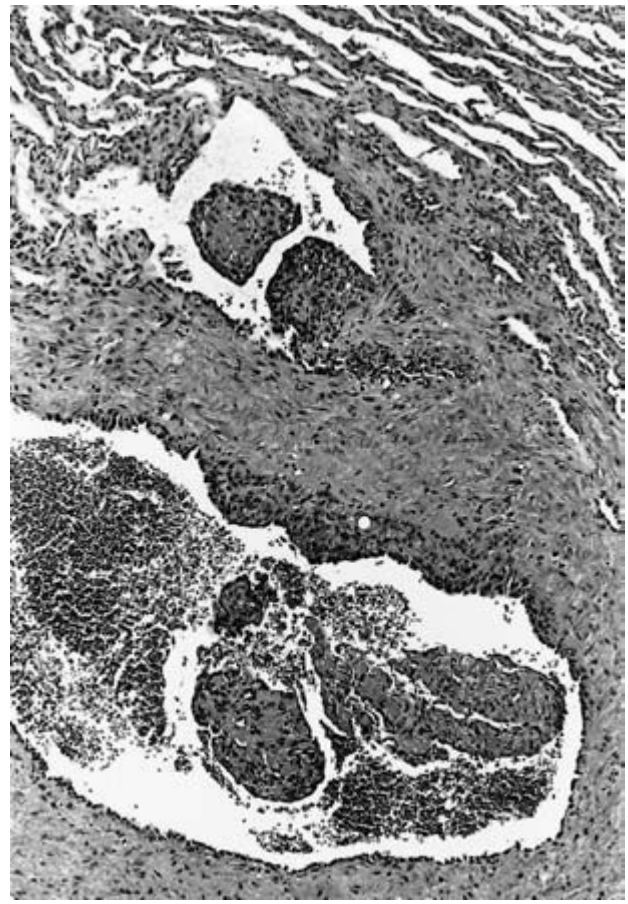


Fig. 28.5 High magnification of progressive angiomatosis in a dog. Nodular papillary endothelial hyperplasia protrudes into the vascular lumens.

mitotic atypia is not present. Proliferation of spindle cells with narrow elongated nuclei may accompany the blood vessels. These spindle cells may be fibroblasts or pericytes. Dermal fibrosis may be observed. The overlying epidermis is characterized by acanthosis and hyperpigmentation. Traumatic ulceration, hemorrhage, and secondary inflammation are frequently present.

Scrotal-type vascular hamartomas have a fairly characteristic morphology. However, they may be confused with well-differentiated hemangiosarcomas, spindle cell hemangiomas, or capillary hemangiomas. Scrotal type vascular hamartomas and well-differentiated hemangiosarcomas are both poorly circumscribed and characterized by nuclear immaturity of the peripherally developing capillaries. However, lack of mitotic figures and the maintenance of normal architectural relationships between the redundant vascular structures and the admixed proliferating fibroblasts and pericytes support the benign nature of vascular hamartoma. While scrotal-type vascular hamartomas are characterized by clusters and lobules of vascular structures, spindle cell hemangiomas are solitary tumor nodules with rather haphazardly arranged spindle cells and vascular channels. The small vessels of scrotal-type hamartoma may resemble capillary hemangioma, but the latter does not show orientation of the small vascular structures around larger, distended blood vessels. In addition, the capillaries of scrotal-type hamartoma are interspersed with other spindle cell elements.

Angiomatosis secondary to lymphedema (Klippel–Trenaunay-like syndrome)

(Figures 28.9 and 28.10)

This is a mixed vascular anomaly. The two cases of canine angiomatosis secondary to lymphedema were characterized by marked hypoplasia of the deep lymphatic vessels, as demonstrated by immunohistochemistry (see below), while the remaining superficial lymphatics were markedly dilated. There was a marked increase in extracellular matrix and inflammation was noted. Prominent vascular

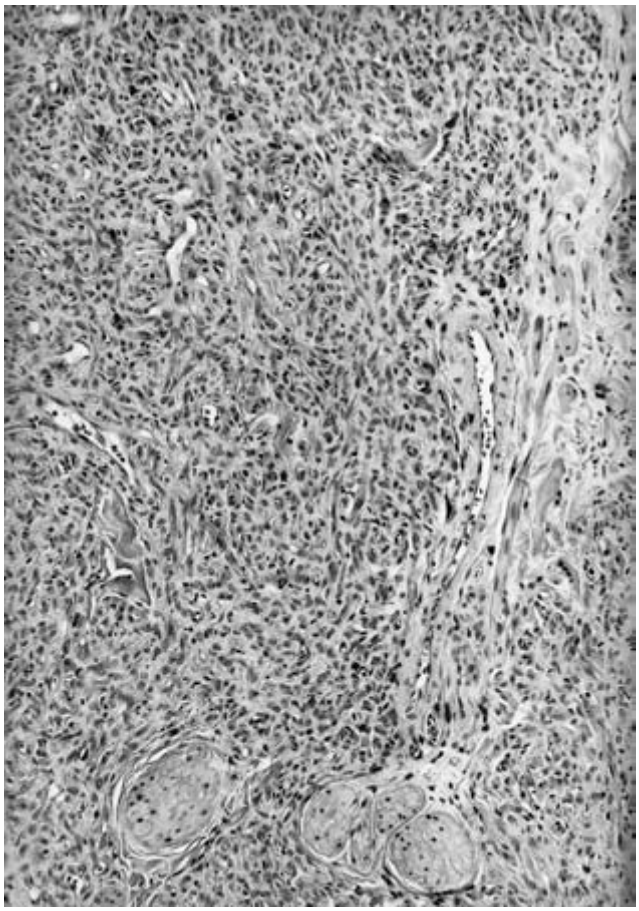


Fig. 28.6 Scrotal-type vascular hamartoma in a dog. Proliferating capillaries lined by plump endothelial cells are admixed with cellular connective tissue containing pericytes and fibrocytes. Note scrotal smooth muscle bundles at bottom.

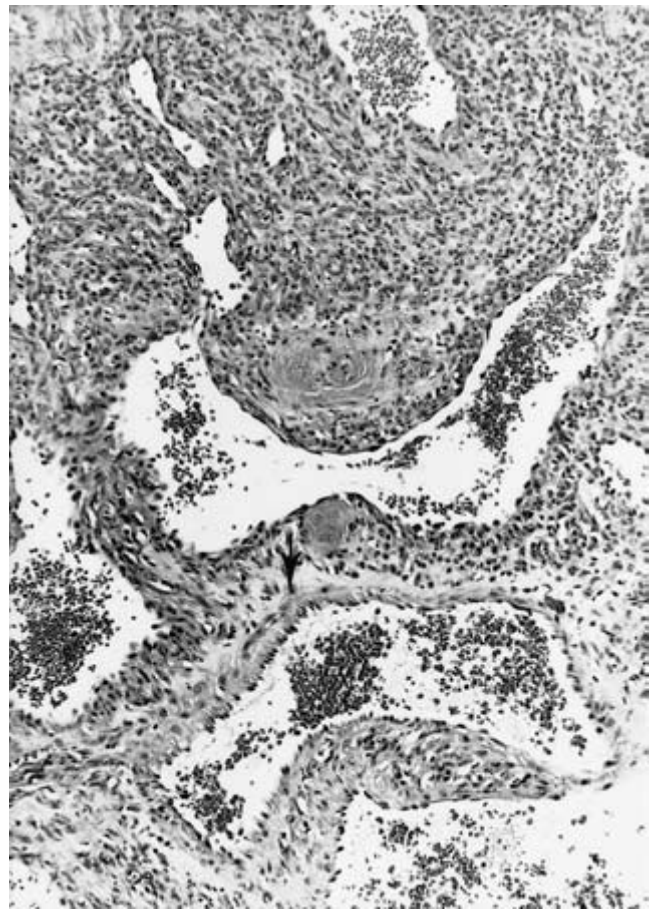


Fig. 28.7 Scrotal-type vascular hamartoma in a dog. Irregular cavernous vascular structures are present in the center of the lesion. Residual scrotal blood vessels, such as the one at bottom, are recognizable by the presence of a muscularis (arrow).

proliferation resembling neovascularization was present, often in clusters or aggregates. Electron microscopic evaluation of the lesions in one dog revealed that the proliferating vascular structures had a continuous basement membrane; this finding is consistent with blood vessels rather than lymphatics (DeCock, H.E.V., personal communication, 2003). Over time the edematous tissue surrounding the vascular structures was infiltrated by fibroblasts resulting in marked fibrosis. The deeper tissues of the affected extremity were characterized by lack of lymphatic vessels.

The feline case observed by the authors was characterized by multiple, irregular thick-walled vascular structures of varying size in the dermis and subcutis. These were admixed with numerous clusters of hyperemic capillaries and venules. Also present were dilated superficial lymphatics surrounded by edema, hemorrhage, variable inflammation, and reactive fibroplasia. Unfortunately, the deeper tissues were not available for evaluation of potential hypoplasia of deep lymphatics.

The hypoplasia of deep lymphatics and the presence of dilated superficial lymphatics separate angiomatosis secondary to lymphedema from other vascular proliferations, particularly granulation tissue-type hemangioma (see p. 741). Granulation tissue-type hemangiomas are typically small, polypoid lesions, and the inflammatory component may be more pronounced when compared to angiomatosis secondary to lymphedema. In contrast to Klippel–Trenaunay-like syndrome, lymphangiomatosis lacks proliferation of vascular structures.

Immunohistochemistry

Immunophenotyping is usually not an important tool in the diagnosis of angiomatosis. In humans, differentiation of vascular from lymphatic proliferations can be achieved by evaluating the lesions for expression of CD44 and podocalyxin versus lymphatic vessel endothelial receptor-1 (LYVE-1), podoplanin, and vascular endothelial growth factor receptor-3 (VEGFR-3) (see introduction, p. 735).

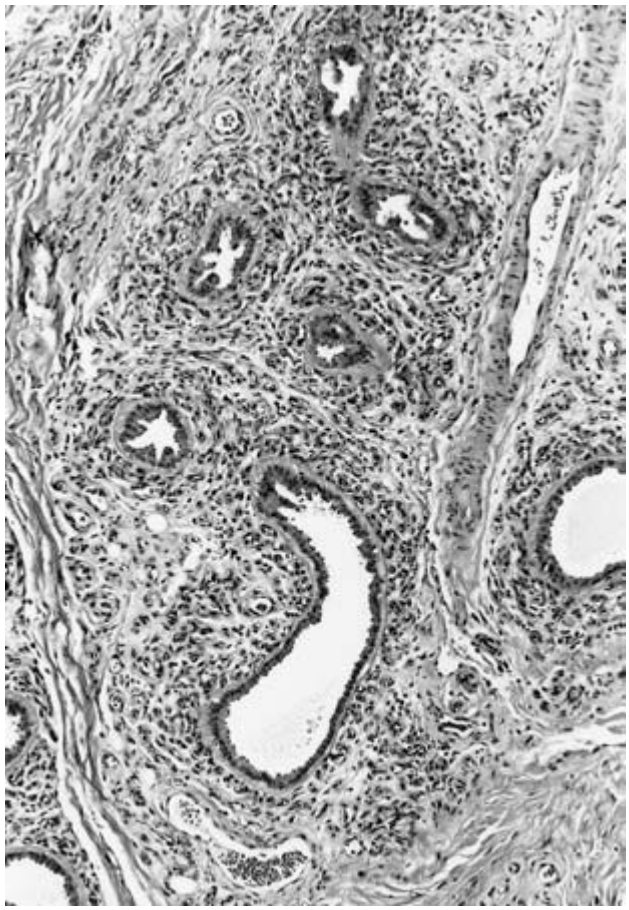


Fig. 28.8 Scrotal-type vascular hamartoma in the tail of a dog. Proliferating capillaries surround sweat glands; note similarity to Fig. 28.6.

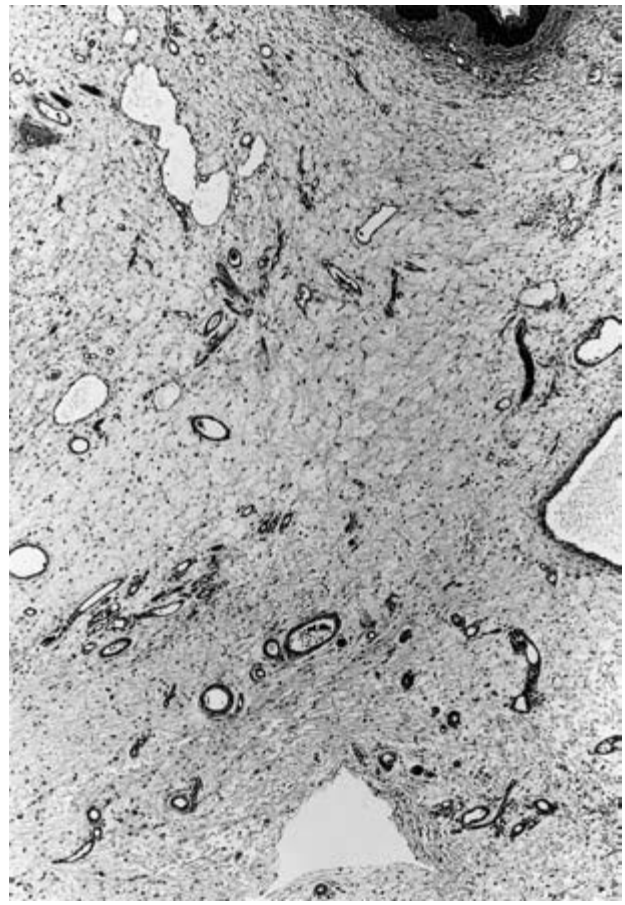


Fig. 28.9 Angiomatosis secondary to lymphedema (Klippel–Trenaunay-like syndrome) in a cat. The dermal tissue is markedly edematous. Prominently dilated lymphatics are accompanied by aggregates of proliferating vascular structures.

The latter are expressed only by lymphatic endothelial cells, and not by vascular endothelial cells. LYVE-1 expression in neoplastic lymphatics but not in blood vessels also has been documented in cats (Galeotti et al., 2004).

HEMANGIOMA

In humans, hemangioma is the most frequent tumor of infancy and childhood (Calonje & Wilson-Jones, 1997; Weiss & Goldblum, 2001). There are numerous subtypes, many of which (cherry, glomeruloid, targetoid, microvenular, or verrucous) are not recognized in dogs and cats.

Hemangiomas are considered benign neoplasms; but distinction between a true neoplasm, vascular hyperplasia, and vascular malformation may not be possible in some cases. An infectious etiology or previous penetrating injuries have been suggested as causes of granulation tissue-type hemangioma (pyogenic granuloma, lobular capillary hemangioma) in people; the neoplastic nature of this lesion is still controversial (Requeña & Sangueza, 1997; Breugem et al., 2001; Weiss & Goldblum, 2001). Based on the indolent course of spindle cell hemangiomas in humans (originally termed spindle cell hemangioendothelioma and considered a low-grade malignancy), it has been suggested that they may represent a reactive condition in response to repeated episodes of intravascular thrombosis and recanalization (Requeña & Sangueza, 1997).

Hemangiomas occur in both dogs and cats. Subtypes include cavernous, infiltrative, capillary, arteriovenous, granulation tissue type, spindle cell, and solar-induced hemangioma, as well as angiokeratoma. As in humans, some of these may be more consistent with vascular malformations than true neoplasms. In contrast to humans, chronic solar damage has been identified as an important etiologic factor for canine dermal hemangiomas (solar induced hemangioma) of light-skinned breeds with thin haircoats (Hargis et al., 1992). The etiology of feline hemangiomas and canine hemangiomas of nonsolar origin is unknown. C-type virus particles have

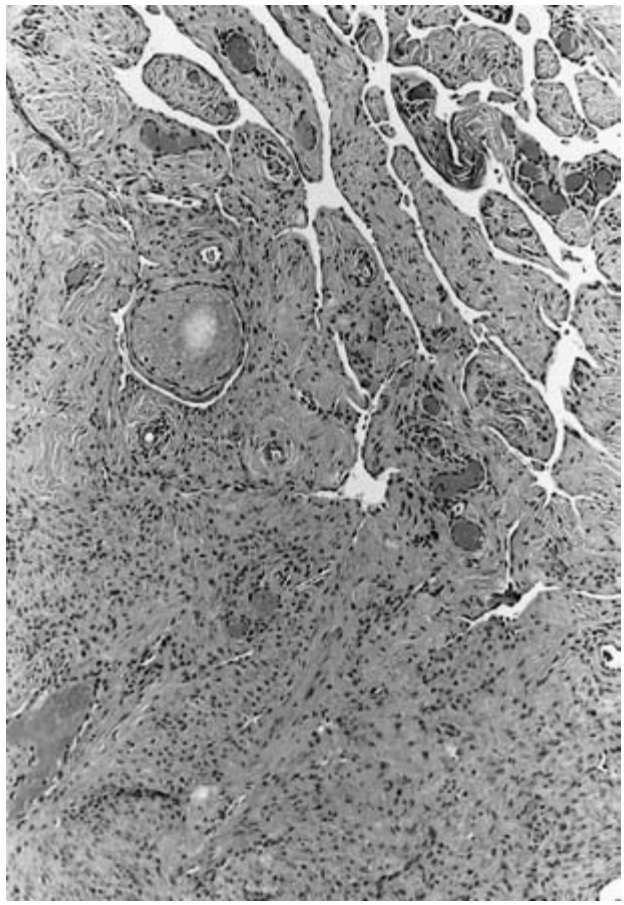


Fig. 28.10 Angiomatosis secondary to lymphedema (Klippel–Trenaunay-like syndrome) in a dog. Clusters of thin walled dermal vascular structures are associated with markedly dilated, interconnected superficial lymphatics.

been found in a subcutaneous hemangioma in a cat (Scott, 1980).

Clinical features

Canine hemangiomas in dogs account for 4.5% of all skin neoplasms; in cats the incidence is approximately 1.5% to 2% (Carpenter et al., 1987; Goldschmidt & Shofer, 1992). Hemangiomas may arise in the dermis or subcutis.

Hemangiomas of the subcutis are usually solitary, well-circumscribed, meaty, ovoid, or discoid masses that range from 0.5 to 4 cm in diameter. Deep subcutaneous lesions are generally larger than those confined to the superficial subcutis or panniculus (above the panniculus carnosus). The overlying skin is elevated and often partially alopecic, and the lesions have a blue or purple tint through intact skin. Secondary ulceration is uncommon.

Infiltrative hemangioma is usually found in areas of subcutaneous fat on the trunk or proximal extremities. Grossly it may present as a nodule or locally extensive mass with poorly defined boundaries. The lesions are dark red to purple, and hemorrhage may occur.

Spindle cell hemangioma in dogs are usually solitary nodules and may originate within a blood vessel. Large lesions may be grouped with smaller satellite lesions in the same location.

Dermally-located hemangiomas, which include angiokeratomas and solar-induced hemangiomas, present as well-circumscribed, dome-shaped, or polypoid masses with red or red-black coloration. Granulation tissue-type hemangiomas are small, dome-shaped or polypoid dermal masses, as described in humans (Weiss & Goldblum, 2001). Solar-induced hemangiomas may be multiple. Very early solar-induced hemangiomas may be flat and mimic telangiectasia. Dermal hemangiomas are smaller than those of the subcutis, and range from several millimeters to 1 cm in size. With larger solar-induced hemangiomas, the overlying epidermis is usually alopecic; ulceration and hemorrhage are frequent findings.

Solar-induced dermal hemangiomas have a predilection for glabrous skin (ventral abdomen, inguinal region, medial thighs, and axillae) in dogs with nonpigmented skin and short haircoats (Hargis et al., 1992). Nonsun-induced dermal hemangiomas can occur at any anatomic site. Canine nonsun-induced hemangiomas of the subcutis often favor the caudal dorsum or tailhead region. Feline cutaneous hemangiomas may occur at any site, but the head, legs, and abdomen have been listed as preferential locations (Goldschmidt & Shofer, 1992). Interestingly, cutaneous hemangiomas in the feline study of Miller et al. (1992) tended to occur in sites with pigmented hair, in contrast to hemangiosarcomas (see p. 749).

In one study, Whippets, Bloodhounds, Salukis, and English Pointers had significantly increased prevalence of cutaneous vascular neoplasia in general (Hargis et al., 1992). Another survey (Goldschmidt and Shofer, 1992) found Airedale Terriers, Gordon Setters, Boxers, Soft-coated Wheaten and Wirehaired Fox Terriers, Golden Retrievers, Old English Sheepdogs, English Springer Spaniels, and German Shepherd Dogs to be at increased risk for all hemangiomas. Short-haired dogs with lightly pigmented skin, notably Whippets, Beagles, Dalmatians, American Bull Terriers, and Basset Hounds are likely predisposed to the development of solar-induced vascular neoplasms; this was supported by the tendency of these breeds to develop superficial (dermal) rather than subcutaneous vascular tumors, as well as a tendency to develop these tumors in sun-exposed regions (Hargis et al., 1992). A marked male predominance in cats was found in one study (Miller et al., 1992), but this was not confirmed in the larger retrospective of Goldschmidt and Shofer (1992). There are no feline breed predispositions.

The average age of incidence for all cutaneous hemangiomas in dogs is approximately 9 years (Goldschmidt &

Shofer, 1992). Infiltrative hemangiomas occur in middle-aged to older dogs; no breed predilections are known. The average age for hemangioma in cats is 9 to 11 years (Goldschmidt & Shofer, 1992; Miller et al., 1992). Hemangiomas have been observed in dogs and cats as young as 1 year (Goldschmidt & Shofer, 1992). Hemangiomas in young animals may represent vascular malformations rather than true neoplasms.

Histopathology

Cavernous hemangioma (Figure 28.11)

Cutaneous hemangiomas, as typified by the so-called 'cavernous' hemangioma, are well circumscribed but nonencapsulated tumors involving the dermis or subcutis. They are composed of vascular spaces filled with erythrocytes. Each vascular structure is enclosed and lined by a single layer of normal-appearing endothelial cells. The endothelial cells are aligned on collagenous septa, which are usually thin. The septal collagen frequently shows mild infiltration by mast cells, lymphocytes, and hemosiderophages. The proliferating endothelial cells have scant cytoplasm and flattened, dark, uniform nuclei. Nucleoli and mitotic figures are not evident.

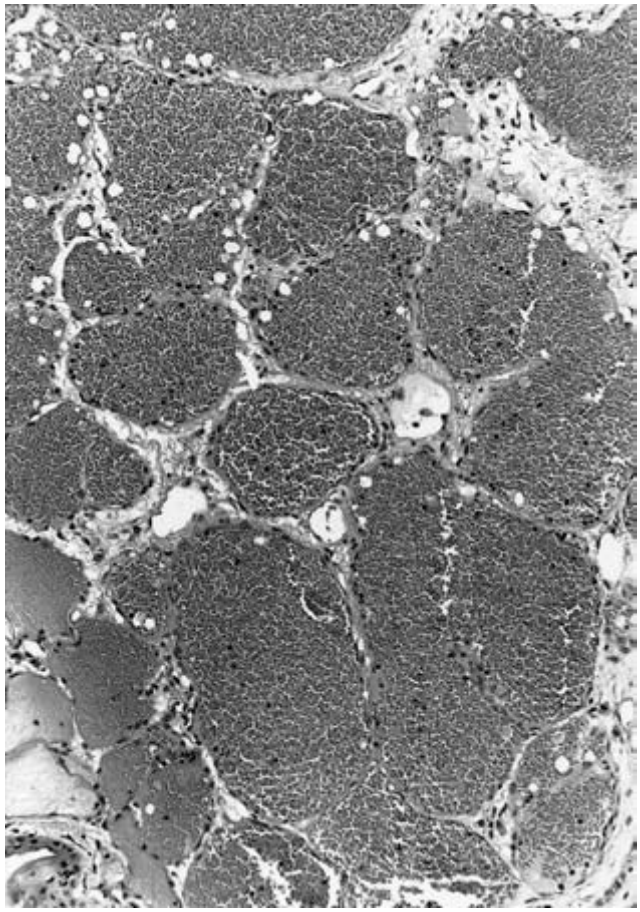


Fig. 28.11 Cavernous hemangioma in a dog. Tightly packed, large vascular structures form a well-circumscribed nodule. Note that all vascular spaces are completely enclosed.

The vascular spaces may be occluded by organized thrombi. Thrombosis is accompanied by fibroplasia and deposition of hemosiderin. The overlying epidermis of both dermal and subcutaneous hemangiomas often is mildly to moderately acanthotic. Secondary ulceration and hemorrhagic crusting are observed more often in dermal hemangiomas.

Major differential diagnoses for cavernous hemangioma include lymphangioma or lymphangiomatosis, and angiolipoma. The vascular spaces of lymphangioma contain no or only sparse erythrocytes, while hemangiomas usually have numerous red blood cells. Moreover, the stroma of lymphangioma exhibits edema and lymphoplasmacytic infiltrates. Subcutaneous angiolipomas are characterized by proliferating vascular structures within an otherwise typical lipoma, while subcutaneous hemangiomas are generally well-demarcated nodules within normal subcutaneous fat.

Infiltrative hemangioma (Figure 28.12)

These tumors are primarily located in the subcutaneous adipose tissue. At the center there is a relatively discrete mass composed of large vascular channels, resembling cavernous hemangioma. Thrombosis and occasional infarction may be observed. Surrounding this central lesion there are numerous medium to small-sized vascular channels, sometimes branching, and of fairly regular appearance. These are lined by well differentiated endothelium and are loosely distributed throughout adipose tissue, often to specimen margins.

Infiltrative hemangiomas should be differentiated from angiolipomas. The latter contain clusters of small vascular structures that are enclosed and dispersed within an otherwise typical lipoma. In contrast, infiltrative hemangioma usually has a central more mass-like proliferation of vessels, surrounded by vascular structures infiltrating normal fat. Some lesions of angiomatosis may be extremely difficult to differentiate from infiltrative hemangioma in a single biopsy specimen if adipose tissue is predominantly sampled; clinical differentiation may be required.

Capillary hemangioma (Figure 28.13)

This is an uncommon histopathologic pattern of hemangioma. Pure capillary hemangiomas occur only in the dermis. The vascular spaces are small and are lined by a single layer of slightly plump endothelial cells that may protrude into vessel lumens. These vascular channels resemble capillaries with a reactive endothelium. As in cavernous hemangioma, the vascular structures are

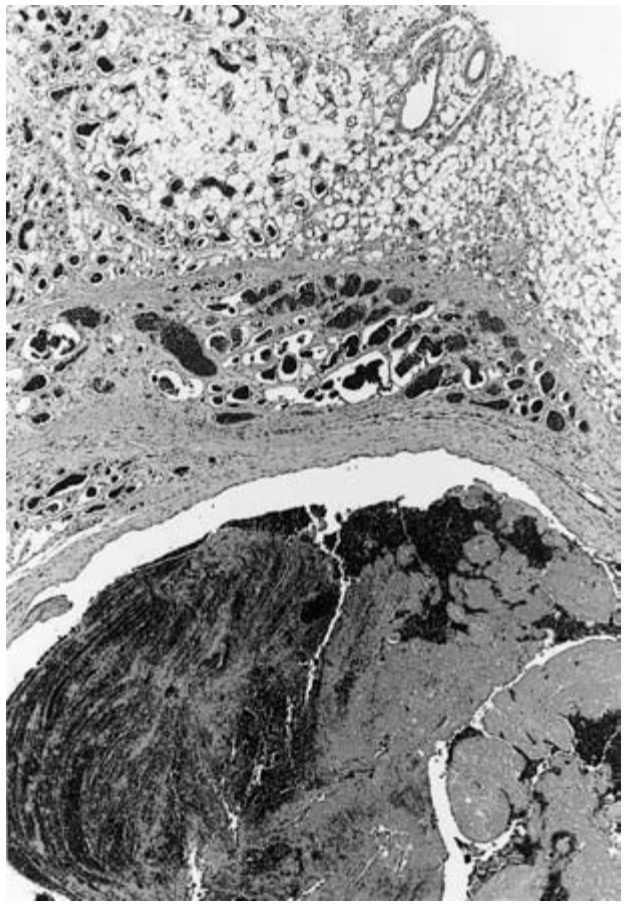


Fig. 28.12 Infiltrative hemangioma in a dog. There is thrombosis of the central large vessel at the bottom; small vessels infiltrate the surrounding connective and fatty tissue.



Fig. 28.13 Capillary hemangioma in a dog. The dermal nodule is composed of small, thin-walled vascular structures lined by well-differentiated endothelial cells.

completely enclosed by their endothelial lining. A distinct collagenous supporting network is not present. Nucleoli are not evident, but mitotic figures can be observed. Subcutaneous hemangiomas may have a combination of capillary and cavernous vascular structures.

The major differential diagnosis for capillary hemangioma is well-differentiated hemangiosarcoma. Circumscription of tumor margins, complete enclosure of vascular spaces, nuclear uniformity, and absence of atypical mitotic figures are important features for differentiation of capillary hemangioma from hemangiosarcoma. The small vessels of scrotal-type hamartoma may resemble capillary hemangioma, but the latter does not show orientation of the small vascular structures around larger, distended blood vessels. In addition, the capillaries of the hamartoma are interspersed with other spindle cell elements.

Arteriovenous hemangioma (Figure 28.14)

This rare variant is composed of proliferating vascular structures resembling small arterioles and venules. As in humans, the branching blood-filled channels of arteriovenous hemangiomas are lined by endothelial cells accompanied by variable amounts of fibrous tissue and smooth muscle cells (Weiss & Goldblum, 2001). Occasionally, a transition from an arteriolar wall to a venous wall can be observed, representing probable arteriovenous shunting. In contrast to angiomatosis with a prominent arteriovenous component, which is a poorly demarcated process that exhibits progressive and infiltrative behavior, arteriovenous hemangiomas are well demarcated masses.

Angiokeratoma (Figure 28.15)

This is an uncommon variant of dermal hemangioma that involves the superficial dermis (Vala & Esteves, 2001). Angiokeratoma is characterized by a small, well-circumscribed, elevated dermal mass. The vascular component is essentially the same as in dermal (cavernous) hemangioma. The epidermis exhibits irregular hyperplasia without dysplasia, and epithelial trabeculae (rete peg-like) extend downward to separate and partially surround some of the vascular structures. Ulceration and hemor-

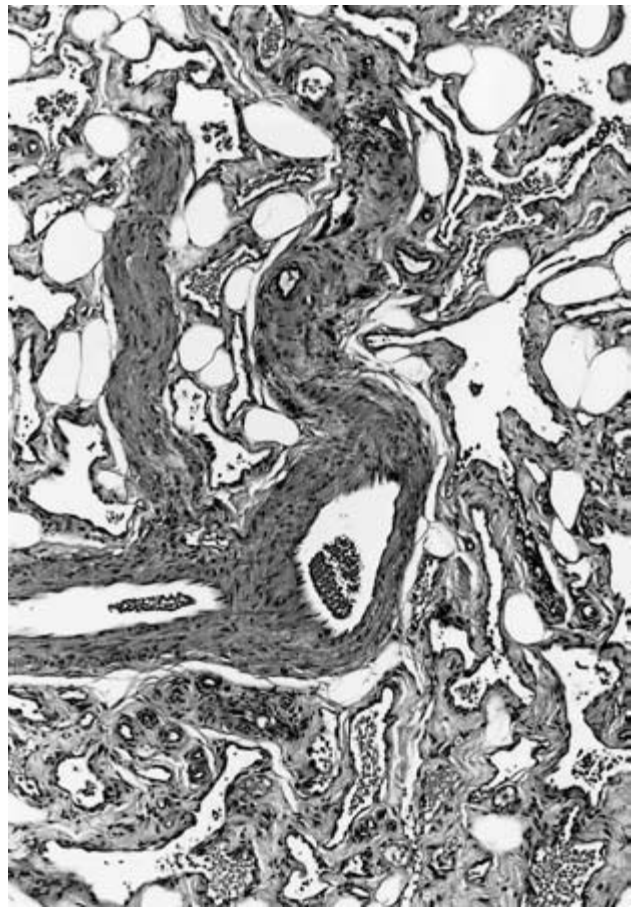


Fig. 28.14 Arteriovenous hemangioma in a dog comprising thick-walled arterial and thin-walled venous structures.

rhage are commonly present. The close association of the vascular proliferation with the hyperplastic epidermis is characteristic for angiokeratoma and allows differentiation from other vascular tumors.

Granulation tissue-type hemangioma

(Figures 28.16 and 28.17)

In humans, this lesion is also referred to as pyogenic granuloma or lobular capillary hemangioma (Calonje & Wilson-Jones, 1997; Weiss & Goldblum, 2001). The mass may be multilobulated and is mostly composed of small, branching, dilated capillary-type vessels; larger dilated vessels may also be present in some lesions, particularly in the center of lobular aggregates of capillaries. Vascular structures are lined by well-differentiated endothelial cells and filled with numerous red blood cells. The vascular spaces are separated by a fibrous stroma that is often edematous and contains variable numbers of mixed inflammatory cells; the degree of inflammation may be dependent upon the stage of evolution of the tumor and/or secondary ulceration. The overlying epidermis may be hyperplastic and variably ulcerated.

Granulation tissue-type hemangioma should be differentiated from true granulation tissue, from angiomatosis, particularly secondary to lymphedema (Klippel–Trenaunay-like syndrome), and from highly vascularized acrochordon (see Chapter 27). In dermal granulation tissue, the vessels are typically arranged perpendicularly to the skin surface. Angiomatosis secondary to lymphedema is not as circumscribed as granulation tissue-type hemangiomas. Moreover, the hypoplasia of deep

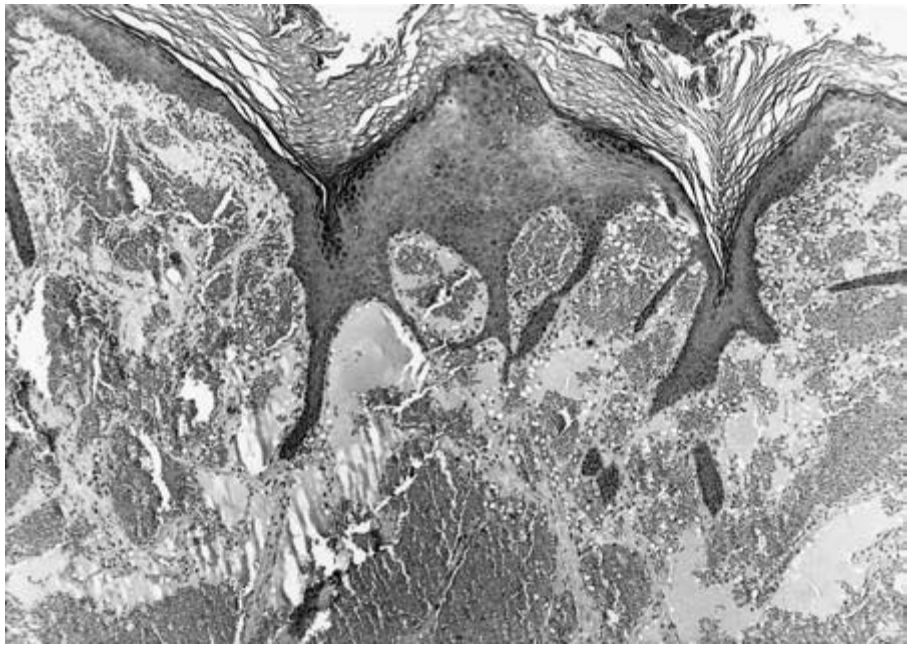


Fig. 28.15 Angiokeratoma in a dog. The vascular component of the lesion is identical to cavernous hemangioma. Note that the hyperplastic epidermis forms rete peg-like extensions, which appear to partially surround vascular structures in the superficial dermis.

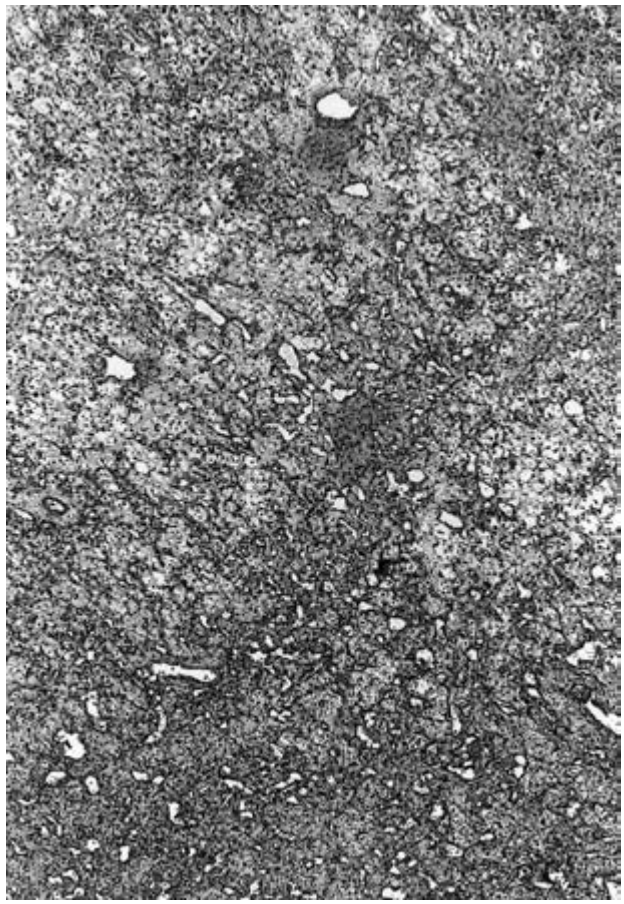


Fig. 28.16 Granulation tissue-type hemangioma in a dog. Larger vascular structures are interspersed with very small capillary-type vessels.

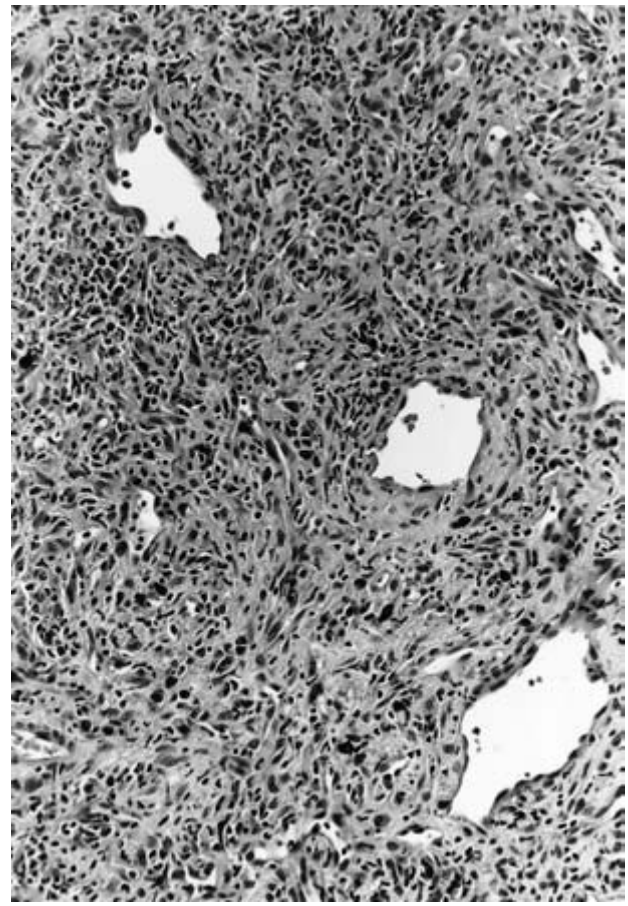


Fig. 28.17 Higher magnification of granulation tissue-type hemangioma in a dog. Small capillaries surrounding larger vessels are often collapsed. Note the dispersed pleocellular inflammatory infiltrate.

lymphatics and the presence of dilated superficial lymphatics separate angiomatosis secondary to lymphedema from granulation tissue-type hemangioma. The inflammatory component may be more pronounced in granulation tissue-type hemangioma when compared to angiomatosis secondary to lymphedema. In granulation tissue-type hemangioma, the vascular structures are arborizing and grouped into lobules. The vessels are not as numerous or uniform in highly vascularized acrochordon when compared to the proliferative vascular channels in granulation tissue-type hemangioma.

Spindle cell hemangioma (Figures 28.18 and 28.19)
In humans, this lesion is also referred to as spindle cell hemangioendothelioma (Requeña & Sangueza, 1997; Weiss & Goldblum, 2001). Lesions are characterized by variably sized blood-filled channels lined by fairly well differentiated endothelial cells. The vascular channels are separated from each other by septa comprising densely packed spindle cells with elongated, blunt ended nuclei. Based on studies of human tumors, these spindle cells are not of endothelial origin, but may represent fibroblasts or pericytes. Occasionally, the vascular spaces are collapsed, which results in areas of solid spindle cell proliferation. The spindle cell nuclei may be hyperchromatic, but mitotic figures are rare.

Spindle cell hemangiomas should be distinguished from hemangiosarcomas and scrotal-type vascular hamartomas. The endothelial cells lining the vascular channels of hemangiomas are well-differentiated, while hemangiosarcomas are characterized by cytologic atypia of endothelial cells and the presence of mitotic figures. Moreover, as immunohistochemistry may demonstrate (see below), the solid areas of proliferating spindle cells are not of endothelial cell origin, in contrast to the solid areas of hemangiosarcomas (Requeña & Sangueza, 1997). Both spindle cell hemangiomas and scrotal-type vascular hamartomas contain numerous spindle cells, which are either fibroblasts or pericytes. However, spindle cell hemangiomas are solitary nodules with haphazardly

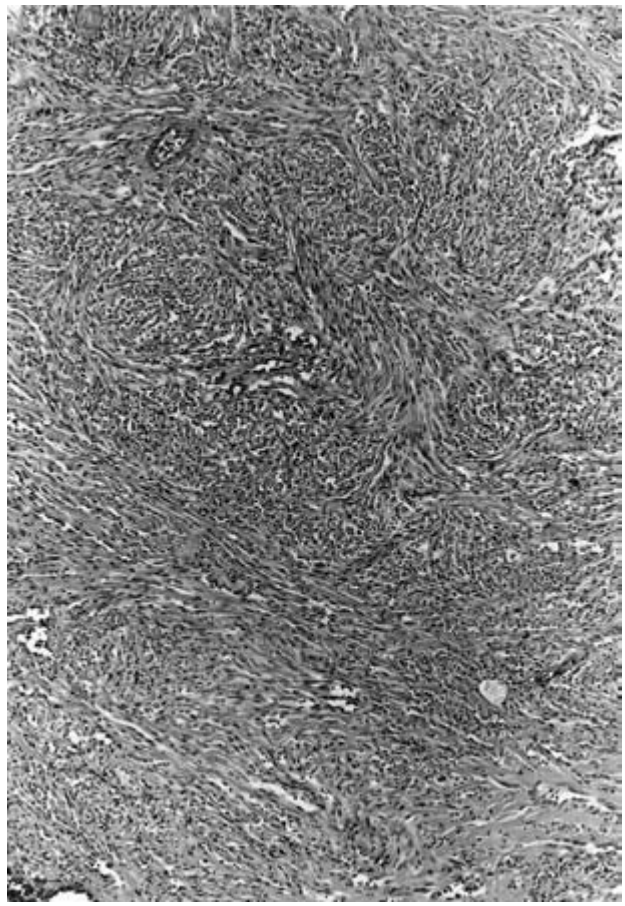


Fig. 28.18 Spindle cell hemangioma in a dog. Small slit-like vascular structures are embedded in a dense proliferation of spindle cells.

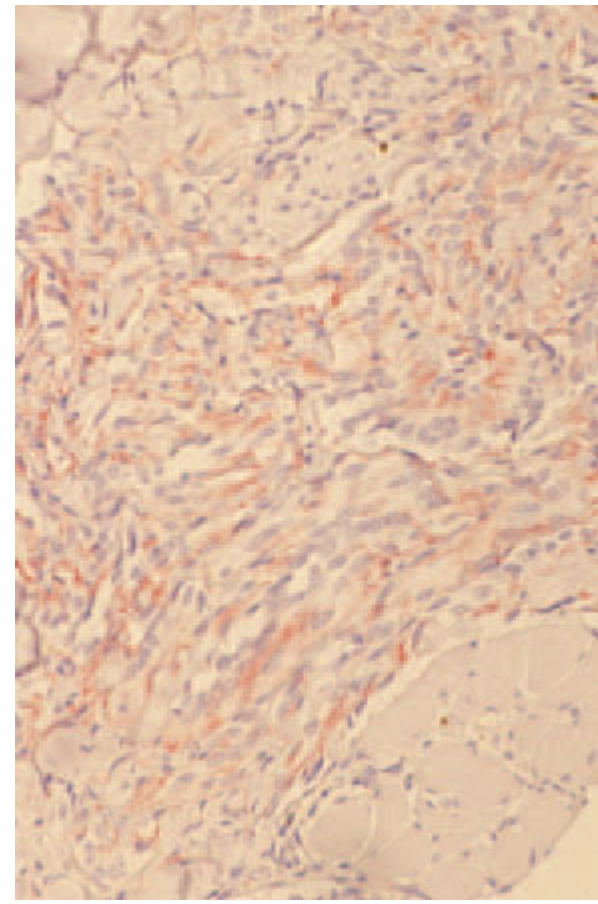


Fig. 28.19 Spindle cell hemangioma. Immunohistochemical stain with anti-CD31 colors endothelial cells; these are surrounded by negatively stained pericytes or fibroblasts (chromogen aminoethylcarbazole [AEC]).

arranged spindle cell bundles and vascular channels, while scrotal-type vascular hamartomas are composed of multiple nests and lobules of vascular structures accompanied by spindle cells tightly associated with the vascular channels.

Solar-induced dermal hemangioma

With persistent sun exposure, solar-induced hemangiomas likely progress along a continuum from vascular ectasia to benign and malignant neoplasia. These tumors tend to be less well circumscribed than other hemangiomas. Cytologic features resemble those of idiopathic hemangiomas, although vascular structures are more uneven in size and may not be completely enclosed. There may be early transition to a more aggressive appearance, characterized by atypia of endothelial cells and a tendency to form smaller vascular structures or solid clusters. The dermis adjacent to the neoplastic mass may contain clusters and plaque-like aggregates of proliferative, non-neoplastic blood vessels that may be telangiectatic. Solar fibrosis and elastosis are often seen in the surrounding dermis, lending support for solar induction (see Chapter 15). Squamous cell carcinoma (*in situ* or invasive) may occasionally occur in the vicinity of solar-induced hemangioma (see Chapter 22).

The accompanying solar lesions permit differentiation of solar-induced hemangioma from other vascular proliferations. Nuclear uniformity and absence of atypical mitotic figures are important features for differentiation of solar-induced hemangioma from solar-induced hemangiosarcoma; however, transitional lesions are not uncommon. The separation between benign and malignant forms of solar-induced vascular tumors may be difficult, as this condition likely represents a continuum.

Immunohistochemistry

The proliferating spindle cells between the vascular structures of spindle cell hemangiomas are vimentin-positive,

but lack typical endothelial expression of CD31, CD34 and factor VIII. These cells thus are not of endothelial origin, but most likely represent fibroblasts or pericytes. In humans, differentiation of vascular from lymphatic proliferations can be achieved by evaluating the lesions for expression of CD44 and podocalyxin versus lymphatic vessel endothelial receptor-1 (LYVE-1), podoplanin, and vascular endothelial growth factor receptor-3 (VEGFR-3). The latter are expressed only by lymphatic endothelial cells, and not by vascular endothelial cells. LYVE-1 expression in neoplastic lymphatics but not in blood vessels also has been documented in cats (Galeotti et al., 2004).

LYMPHANGIOMATOSIS

(Synonym: lymphangioma)

Lymphangiomas in humans have a prevalence of occurrence in infants and are believed to arise from a congenital failure of primitive lymphatic sacs to develop communications with the venous system (Weiss & Goldblum, 2001a). Hence, human lymphangiomas are considered to represent malformations rather than true neoplasms. The presence of malformed lymphatics, or a lack of communication with more central (downstream) vessels, leads to subsequent compensatory dilation of blocked lymphatic vessels. This process tends to support the presence of a malformation rather than neoplasia. To indicate the non-neoplastic etiology of these lesions, the term 'lymphangiomatosis' may be more accurate than lymphangioma. *De novo* dominant mutations have been suggested as an underlying cause for lymphatic malformations in humans (Breugem et al., 2001).

Histologically, lymphatic endothelial cells resemble vascular endothelial cells (Folpe & Gown, 2001; Weiss & Goldblum, 2001a,b). However, in contrast to blood vessels, lymphatic vessels have a discontinuous basement membrane when evaluated by electron microscopy. While lymphatic capillaries are lined by endothelial cells only, the collecting vessels are composed of endothelial cells with an incomplete layer of smooth muscle cells. The expression of lymphatic vessel endothelial receptor-1 (LYVE-1), vascular endothelial growth factor receptor-3 (VEGFR-3), and podoplanin is a feature of lymphatic endothelial cells only (Banerji et al., 1999; Weiss & Goldblum, 2001a). LYVE-1, a receptor for the extracellular matrix glycosaminoglycan hyaluron, is the equivalent of CD44 on vascular endothelia; vascular endothelia also express podocalyxin (Weiss & Goldblum, 2001c).

Lymphangiomas have been described in dogs and cats (Stambaugh et al., 1978; Turrel et al., 1988; Belanger et al., 1999). However, the occurrence of many of these lesions in young animals suggests a congenital malformation; thus the term 'lymphangiomatosis' is preferred. The lesions are usually poorly delineated and may be the result of constriction or lack of communication with more central lymphatic vessels. Some of the reported lymphangiosarcomas (see p. 753) in actuality also may represent lymphangiomatosis, as histologic differentiation is difficult.

Clinical features

Lymphangiomatosis is rare in both dogs and cats. Cutaneous and subcutaneous lesions present as fluctuant swellings that may measure up to 18 cm in diameter. Ulcers and tracts often drain serous fluid. Leakage of fluid may result in cutaneous vesiculation. Occasionally, smaller and more discrete lesions occur and may represent true 'lymphangiomas'. Some lesions may be polypoid. The small number of reported cases suggests a predilection for intertriginous areas, in particular the groin and rear leg (Stambaugh et al., 1978; Turrel et al., 1988; Belanger et al., 1999). Beagles were considered at risk in one small survey of lymphangiomas (Goldschmidt & Shofer, 1992). Based on several reports, most affected animals are less than 5 years of age (Stambaugh et al., 1978; Turrel et al., 1988; Belanger et al., 1999) and many have had a prolonged clinical course prior to presentation.

Lymphangiomatosis, although composed of banal lymphatics, is often recurrent and progressive. In one case, radiotherapy was used to successfully manage the condition (Turrel et al., 1988). In a puppy with multiple lymphangiomas, associated lymph node involvement was speculated to be a concurrent lymphatic malformation rather than metastasis; the animal survived after local surgical intervention (Belanger et al., 1999).

Histopathology (Figure 28.20)

Lymphangiomatosis is generally characterized by a poorly circumscribed mass involving the dermis, subcutis, or both. The lymphatic channels in lymphangiomatosis are composed of angular, dilated, and partially interconnected vascular structures lined by a single layer of uniform endothelial cells. The vascular channels contain small amounts of proteinaceous fluid and mixed mononuclear cells; erythrocytes are rarely observed. The endothelial cells lining the channels have minimal cytoplasm, elongated hyperchromatic nuclei, and inconspicuous nucleoli. Mitotic activity is minimal to absent. The connective tissue septa supporting the vascular structures frequently have an edematous or myxomatous appearance and contain a mild infiltrate of lymphocytes, plasma cells,

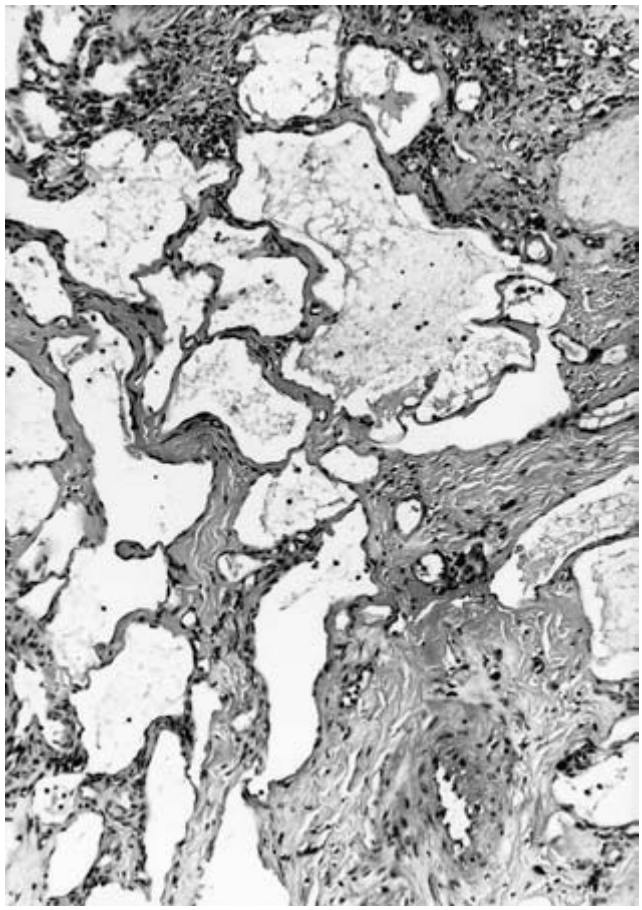


Fig. 28.20 Lymphangiomatosis in a dog. Cavernous, angular vascular spaces are lined by a single layer of small endothelial cells and do not contain erythrocytes. Note lymphoplasmacytic stromal infiltrate at top.

and small numbers of mast cells. The overlying epidermis may show acanthosis, spongiosis and, in some cases, spongiotic vesiculation due to chronic leakage of plasma proteins. Ulceration is a frequent secondary feature and results in marked granulation tissue formation.

Smaller lesions of lymphangiomatosis are occasionally seen. These are more discrete, often polypoid, and resemble erythrocyte-poor cavernous hemangiomas. These lesions likely represent true 'lymphangiomas'.

Lymphangiomatosis should be differentiated from progressive angiomatosis and from lymphangiosarcoma. In contrast to lymphangiomatosis, progressive angiomatosis is characterized by numerous red blood cells within the proliferating channels; the accompanying extracellular matrix lacks the mucinous appearance of lymphangiomatosis. It may be difficult to distinguish well-differentiated lymphangiosarcoma from lymphangiomatosis. Indeed, some reports of lymphangiosarcoma in young dogs may reflect this difficulty (see p. 753). The presence of pleomorphic lymphatic endothelial cells lining the vascular channels, focal lack of endothelial cells, some mitotic activity, blindly ending trabeculae, as well as markedly infiltrative growth, separate lymphangiosarcoma from lymphangiomatosis.

Smaller and discrete lesions of lymphangiomatosis (lymphangiomas) should be differentiated from relatively bloodless cavernous hemangiomas and markedly vascular acrochordons (see Chapter 27). Lymphangiomas are architecturally similar to cavernous hemangiomas, but usually are distinguished by the paucity of erythrocytes in the vascular spaces. Stromal edema and mucin, as well as lymphoplasmacytic infiltration, are prominent in lymphangiomas, while these features are not commonly observed in hemangiomas. The vessels in vascular acrochordons are less numerous when compared to lymphangiomas, and generally contain some red blood cells.

Immunohistochemistry

Lymphatic endothelial cell proliferations in humans express LYVE-1, podoplanin, and VEGFR-3; vascular endothelial cells lack the expression of these molecules, but express CD44 and podocalyxin instead. LYVE-1 expression in neoplastic lymphatics but not in blood vessels also has been documented in cats (Galeotti et al., 2004).

HEMANGIOSARCOMA

(Synonym: angiosarcoma)

Hemangiosarcomas, also referred to as hemangioendotheliomas in humans, are malignant neoplasms of vascular endothelial cells (Weiss & Goldblum, 2001a,b). Poorly differentiated hemangiosarcomas and lymphangiosarcomas often cannot be differentiated based on their morphologic features. In such cases the tumors are referred to as angiosarcomas. Hemangiosarcomas occur in both dogs and cats. Recognized variants include solar-induced haemangiosarcoma, and anaplastic and epithelioid (histiocytoid) angiosarcomas.

The etiology of hemangiosarcomas in humans is not known. Interestingly, many human angiosarcomas arise on the scalp and face of elderly patients, but a possible solar etiology is not discussed in reference texts. Similar to hemangiomas, canine hemangiosarcomas of glabrous and lightly pigmented skin appear to be solar induced (Hargis et al., 1992). Miller et al. (1992) suggested possible solar association for hemangiosarcomas in cats; these often occurred on white-haired regions of the ears

and face, in contrast to hemangiomas (see p. 741). Most hemangiosarcomas arise *de novo*, but malignant transformation within hemangiomas occurs in solar-associated lesions in dogs (Hargis et al., 1992).

Clinical features

Hemangiosarcomas account for slightly less than 1% of cutaneous and subcutaneous tumors in dogs and 2.8% in cats (Goldschmidt & Shofer, 1992). Hemangiosarcomas occur less frequently in dogs than hemangiomas. In cats, however, hemangiosarcomas are more frequent than their benign counterparts.

The majority of dermal hemangiosarcomas in dogs and cats present as ill-defined, red to dark blue plaques or nodules that are usually less than 2 cm in diameter. Hemangiosarcomas in chronically sun-exposed sites are frequently multiple in dogs. Subcutaneous hemangiosarcomas, which often involve the dermis secondarily, are poorly-circumscribed, dark red or blue-black, spongy masses that can measure up to 10 cm in diameter. Particularly in cats, hemangiosarcomas may resemble large ecchymoses or bruises that blanch transiently with pressure. Solid hemangiosarcomas may lack the typical purple-red color, due to their paucity of vascular channels and thus lower content of blood. Alopecia, thickened skin, hemorrhage, and ulceration are common features regardless of dermal or subcutaneous location.

Predilection sites for solar-induced hemangiosarcomas in dogs are the glabrous skin of the caudal ventral abdomen, inguinal region, medial thighs, and axillae, as seen with solar-induced hemangiomas and other sun-induced neoplasms. Nonsolar-induced canine hemangiosarcomas may develop at any site.

Feline hemangiosarcomas are frequently seen in the abdominal region; lesions also occur on the ears and head, as well as on the legs and paws (Miller et al., 1992; Goldschmidt & Hendrick, 2002). Hemangiosarcomas in one study were located in nonpigmented skin of the head and ears of cats, suggesting a relationship with solar exposure (Miller et al., 1992). It is possible that some of the feline hemangiosarcomas reported on legs and feet were actually progressive angiomatosis (see p. 735).

In the study of Hargis et al. (1992), Whippets, Bloodhounds, Salukis, and English Pointers had significantly increased prevalence of cutaneous vascular neoplasia in general; the survey of Goldschmidt and Shofer (1992) found Italian Greyhounds, Whippets, Irish Wolfhounds, Vizslas, American Bull Terriers, Beagles, and Golden Retrievers to be at increased risk for all hemangiosarcomas. Short-haired dogs with lightly pigmented skin, notably Whippets, Beagles, Dalmatians, American Bull Terriers, and Basset Hounds are likely predisposed to the development of solar-induced vascular neoplasms; this was supported by the tendency of these breeds to develop superficial (dermal) rather than subcutaneous vascular tumors, as well as a tendency to develop these tumors in sun-exposed regions (Hargis et al., 1992).

The average age of dogs and cats with all types of dermal and subcutaneous hemangiosarcomas in most surveys is 9 to 11 years (Pulley & Stannard, 1990; Goldschmidt & Shofer, 1992; Ward et al., 1994). Hemangiosarcomas were reported in cats between 9 and 17 years of age by Miller et al. (1992). A sex predilection has not been observed in cats or dogs (Goldschmidt & Shofer, 1992; Hargis et al., 1992; Ward et al., 1994).

Some reports of the biologic behavior and metastatic rate of hemangiosarcomas in dogs fail to separate tumors by primary anatomic site, thus implying that cutaneous hemangiosarcomas have a similarly aggressive biologic behavior to their visceral counterparts. Mortality rates up to 96% within 1 year have been reported (Brown et al., 1985). Other reports do not distinguish superficial from deep or solar from nonsolar induction. A study focusing on cutaneous and glossal hemangiosarcomas reported metastatic lesions in two out of ten dogs (Culbertson, 1982). In the study of Hargis et al. (1992), approximately 30% of dogs with solar-associated dermal or subcutaneous hemangiosarcoma died as a result of their tumors; euthanasia as a result of recurrent or additional skin tumors was common, but the clinical course of disease was long and extended up to 3 years. Confirmed metastasis was observed in fewer than 20% of dogs in that study; the lungs were most often affected (Hargis et al., 1992). Another report used a staging system based on increasing depth of the neoplasm (stages I to III) in 25 dogs, but did not distinguish solar versus nonsolar origin (Ward et al., 1994). Stage I tumors (confined to the dermis) were associated with significantly longer survival times than stage II and III tumors (subcutaneous and deep muscular invasion, respectively). Metastatic lesions in that study were seen in the draining lymph nodes and lungs.

Feline cutaneous hemangiosarcomas exhibit frequent local recurrence, but in most reports have a much lower incidence of metastasis than those of dogs (Carpenter et al., 1987; Miller et al., 1992). However, metastatic disease was reported in five cats with cutaneous hemangiosarcoma in one study (Kraje et al., 1999).

Histopathology

Hemangiosarcoma (Figures 28.21 and 28.22)

Hemangiosarcomas of the skin and subcutis show a continuum from well-differentiated lesions which are difficult to distinguish from hemangiomas, to highly anaplastic tumors (angiosarcomas) which require immunohistochemistry to confirm their endothelial cell origin (see

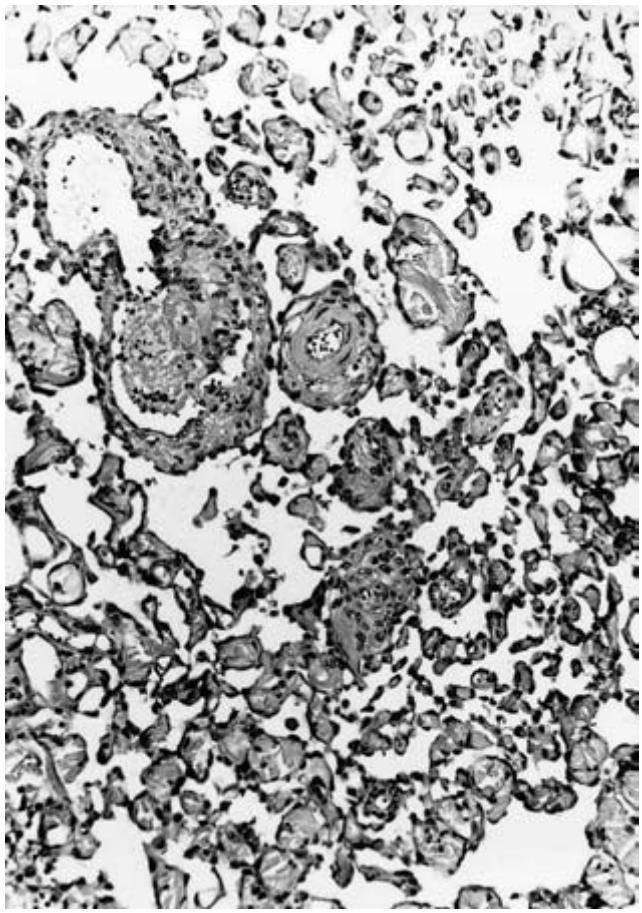


Fig. 28.21 Hemangiosarcoma in a dog. Endothelial cell nuclei are hyperchromatic and often protrude into vascular lumens. Note numerous blindly ending trabeculae lined by endothelial cells.

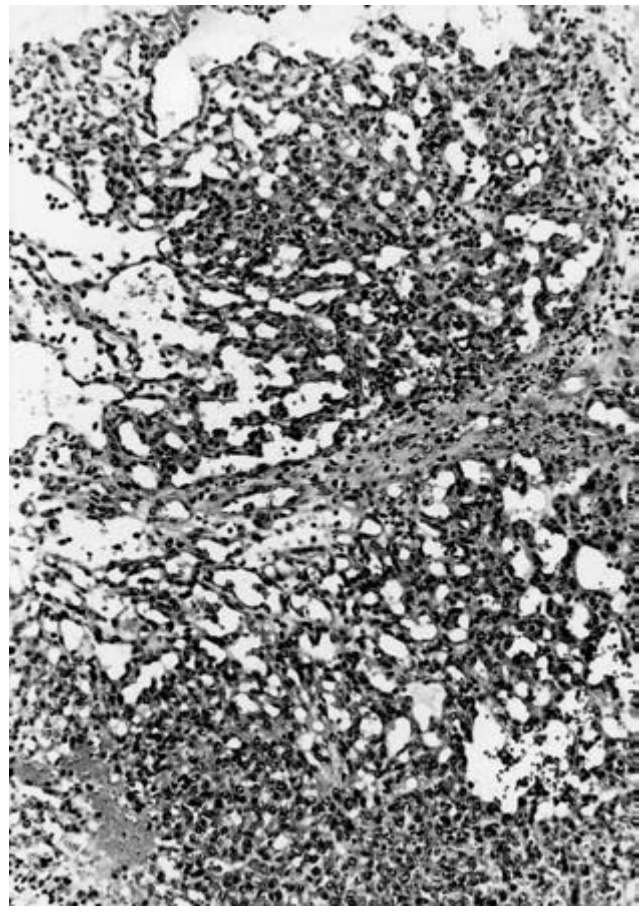


Fig. 28.22 Hemangiosarcoma in a dog. In this less well-differentiated example, some of the vascular structures are lined by multiple layers of endothelial cells. Note solid area of tumor cells at bottom.

below). Most cutaneous hemangiosarcomas have mild to severe acanthosis of the overlying epidermis. Ulceration, thrombosis, necrosis, and hemorrhage are common secondary features of larger hemangiosarcomas in dogs and cats regardless of location.

The majority of cutaneous hemangiosarcomas are well-differentiated neoplasms characterized by plump endothelial cells aligned on delicate collagen trabeculae or pre-existing dermal collagen bundles. The trabeculae form an anastomosing meshwork of blood-filled channels of varying size. The vascular spaces of hemangiosarcoma are not uniformly enclosed by endothelial cells, and blind-ended trabeculae are observed. Ragged peripheral tumor margins are created by infiltration and dissection of collagen bundles by the neoplasm. Tumor cells have minimal cytoplasm and enlarged hyperchromatic nuclei with inconspicuous nucleoli. Mitotic activity is low to moderate; atypical mitoses can usually be detected.

Piling up of tumor cells along basal laminae, epithelioid morphology, nuclear pleomorphism, nucleolar prominence, increased mitotic index, and partial loss of obvious vascular structures are features of hemangiosarcomas of increasing malignancy (or decreasing differentiation). These histopathologic features are observed more commonly in subcutaneous tumors.

Differential diagnoses for well-differentiated hemangiosarcoma include capillary hemangioma and progressive angiomatosis. Lymphangiosarcoma also may be considered for relatively bloodless hemangiosarcomas. In contrast to capillary hemangioma, the vascular spaces of hemangiosarcoma are not uniformly enclosed by endothelial cells. The progressive angiomatoses have multifocal to diffuse proliferations of infiltrating but well-defined vascular channels lined by well-differentiated endothelial cells. The presence of papillary endothelial hyperplasia supports a diagnosis of progressive angiomatosis; digital location is also highly suggestive. Infiltrative tumor margins with dissection of collagen bundles, large numbers of blindly-ending trabeculae, atypical mitoses, and cellular and nuclear pleomorphism are useful indica-

tors for hemangiosarcoma. Stromal edema, lymphoplasmacytic inflammation, and a paucity of red blood cells support a diagnosis of a lymphangiosarcoma over hemangiosarcoma.

Solar-induced hemangiosarcoma (Figure 28.23)

These largely exhibit features identical to nonsolar-induced hemangiosarcomas (see above) and share their differential diagnoses. The dermis adjacent to the neoplastic mass often contains clusters and plaque-like aggregates of proliferative or ectatic, non-neoplastic blood vessels (telangiectasia); concurrent solar-induced hemangioma may be present (see p. 741). There are often features of solar damage (elastosis and fibrosis) in the surrounding dermis (see Chapter 15). Squamous cell carcinoma (*in situ* or invasive) may occasionally occur in the vicinity of solar-induced hemangiosarcoma (see Chapter 22).



Fig. 28.23 Solar-induced hemangiosarcoma in a dog. Irregular vascular spaces dissect dermal collagen bundles resulting in ragged tumor margins. Note laminar homogenization of collagen indicative of solar fibrosis and elastosis as well as reactive vascular proliferation in the superficial dermis.

Angiosarcoma of vascular origin

These tumors are also referred to as anaplastic hemangiosarcomas. They are more frequent in the subcutis, but dermal masses may occasionally be seen. Angiosarcomas of vascular origin are poorly demarcated tumors, characterized by pleomorphic cells that pile up along basal lamina. Spindle cells arranged in interlacing bundles may be admixed with polygonal cells to form solid sheets. Often the masses lack obvious vascular differentiation, which may be manifested only by slit-like spaces that contain small numbers of erythrocytes. The tumor cells exhibit nuclear pleomorphism and nucleolar prominence. Mitotic activity is high and atypical mitotic figures are observed.

Angiosarcoma of vascular origin is difficult to separate from angiosarcoma of lymphatic origin. Stromal edema, lymphoplasmacytic infiltration, as well as electron microscopic demonstration of a discontinuous basement membrane, support a diagnosis of lymphatic origin. Anaplastic angiosarcomas with spindle cell predominance also need to be differentiated from fibrosarcomas and other spindle cell malignancies. Mixed spindle–polygonal angiosarcomas can resemble histiocytic sarcomas or even anaplastic carcinomas. Clefts containing rows of erythrocytes between the neoplastic cells are suggestive of vascular endothelial cell origin. Immunohistochemistry is often required for definitive differentiation of angiosarcoma (see below).

Epithelioid (histiocytoid) angiosarcoma

(Figures 28.24 through 28.26)

Some angiosarcomas in dogs may be composed predominantly of polygonal or plump spindle cells. These lesions resemble epithelioid or histiocytoid angiosarcomas in humans (Weiss & Goldblum, 2001a). The cells have abundant, pale eosinophilic cytoplasm and large vesicular nuclei with prominent nucleoli. The presence of blood-filled channels lined by these histiocytoid cells may mimic glandular structures with central hemorrhage. The endothelial origin of the tumor cells often needs to be confirmed by immunohistochemistry (see below). Mitotic activity is moderate to high, and occasional multinucleated tumor giant cells are present. Usually there are small foci of more typical endothelial differentiation.

Epithelioid angiosarcoma should be differentiated from anaplastic carcinomas, particularly those that feature hemorrhage. There are usually foci of cytologically more typical endothelial cells, facilitating the diagnosis of angiosarcoma. Also, the presence of blood is uncommon in luminal structures of carcinomas. Immunohistochemistry assists in confirming endothelial origin.

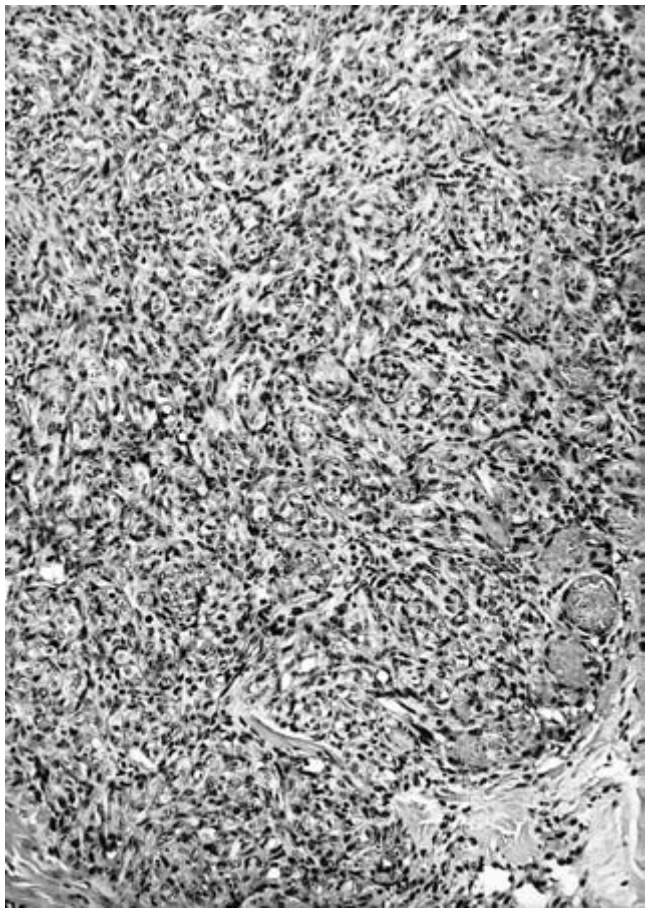


Fig. 28.24 Epithelioid (histiocytoid) angiosarcoma in a dog. The majority of the neoplasm is composed of nests of pale, polygonal and spindle cells. Vascular differentiation is most evident at the margin of the neoplasm at lower right.

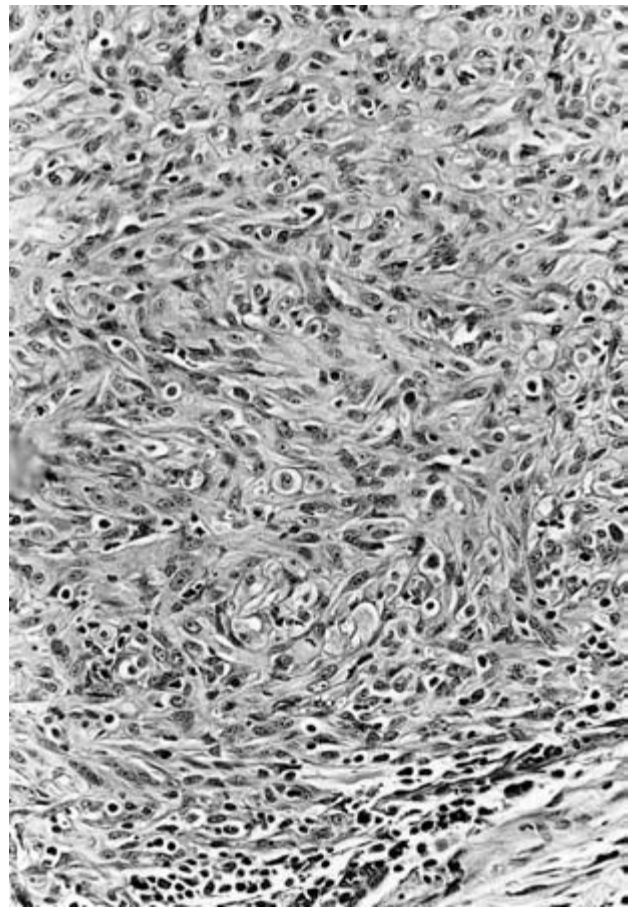


Fig. 28.25 Higher magnification of epithelioid (histiocytoid) angiosarcoma in a dog, demonstrating diffuse sheets of pale epithelioid cells that resemble histiocytes.

Immunohistochemistry

Poorly differentiated neoplastic vascular endothelial cells usually maintain their expression of CD31 and lectins; the expression of factor VIII may vary, and expression of CD34 is inconsistent (Augustin-Voss et al., 1990; Poblet et al., 1996; Arber et al., 1997). Differentiation of angiosarcoma of vascular origin from angiosarcoma of lymphatic origin in humans is based on expression of CD44 and podocalyxin by the former versus lymphatic vessel endothelial receptor-1 (LYVE-1), podoplanin, and vascular endothelial growth factor receptor-3 (VEGFR-3) by the latter. LYVE-1 expression in neoplastic lymphatics but not in blood vessels also has been documented in cats (Galeotti et al., 2004). Expression of CD31 and factor VIII separates the hemangiosarcomas and poorly differentiated angiosarcomas from fibrosarcomas (vimentin+) and histiocytic sarcomas (CD18+, CD45+, CD1+, CD11c+, MHC II+). Anaplastic carcinomas are positive for cytokeratins but do not express vimentin, CD31, or factor VIII.

LYMPHANGIOSARCOMA

(Synonym: angiosarcoma)

Lymphangiosarcomas are malignant neoplasms of lymphatic endothelial cells (Weiss & Goldblum, 2001a). Poorly differentiated lymphangiosarcoma often cannot be differentiated from hemangiosarcomas based on morphologic features, and are therefore referred to as angiosarcomas (Weiss & Goldblum, 2001a,b). Histologically, lymphatic endothelial cells resemble vascular endothelial cells (Weiss & Goldblum, 2001a,b; Folpe & Gown, 2001); immunohistochemistry is required for definitive differentiation in problematic lesions (see lymphangiomatosis, p. 748).

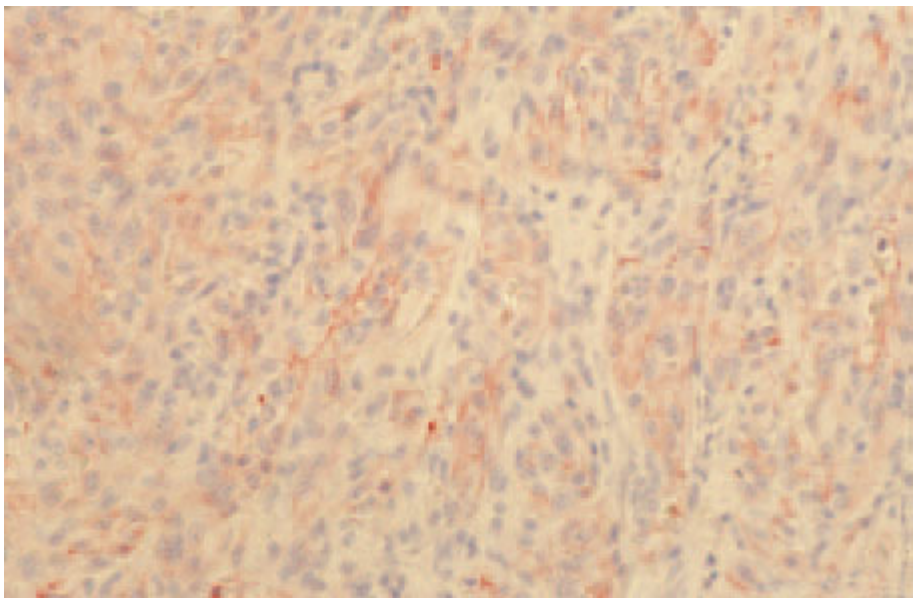


Fig. 28.26 Epithelioid (histiocytoid) angiosarcoma of Fig. 28.25. Immunohistochemical stain with anti-CD31 colors the histiocytoid cells of endothelial origin (chromogen aminoethylcarbazole [AEC]).

Lymphangiosarcomas occur in dogs and cats. Feline ventral abdominal angiosarcoma has not been entirely characterized to date, but electron microscopic evaluations suggest lymphatic origin (Hendrick et al., 1998).

The etiology of lymphangiosarcomas in humans and animals is not known. A congenital predisposition has been suggested in dogs. Although some reported cases of lymphangiosarcoma in young dogs actually may have represented lymphangiomatosis (see p. 748), metastatic lymphangiosarcoma has been reported in a puppy (Sagartz et al., 1996). Thus differentiation of lymphangiosarcoma from lymphangiomatosis may be difficult, particularly in young animals.

Clinical features

Lymphangiosarcoma is rare in dogs and cats, although several reports of small numbers of cases are present in the literature (Kelly et al., 1981; Franklin et al., 1984; Walsh & Abbot, 1984; Rudd et al., 1989; Swayne et al., 1989; Shiga et al., 1994; Sagartz et al., 1996; Fossum et al., 1998; Hinrichs et al., 1999; Galeotti et al., 2004). Lymphangiosarcomas present as large, diffuse, poorly demarcated, fluctuant swellings. Ulceration and serous drainage may be present. Reported locations are legs, ventral neck, and caudoventral abdomen; this is similar to the distribution pattern of lymphangiomatosis (see p. 748).

Lymphangiosarcomas have been diagnosed in young dogs as well as older animals (Kelly et al., 1981; Franklin et al., 1984; Rudd et al., 1989; Shiga et al., 1994; Fossum et al., 1998). The youngest reported case was in an 8-week-old puppy (Sagartz et al., 1996). The average age of cats with lymphangiosarcoma is 7 to 10 years (Walsh & Abbot, 1984; Carpenter et al., 1987; Swayne et al., 1989; Hinrichs et al., 1999; Galeotti et al., 2004). No breed or sex predispositions are reported.

Lymphangiosarcomas in cats exhibit frequent local recurrence (Carpenter et al., 1987). Metastasis to draining lymph nodes or distant organs such as the lungs may be found (Carpenter et al., 1987; Swayne et al., 1989; Hinrichs et al., 1999). In dogs, postsurgical recurrence and widespread visceral metastasis are common (Kelly et al., 1981; Franklin et al., 1984; Rudd et al., 1989). In the reported puppy, metastatic lesions to the draining lymph node and subsequently to a distant node occurred (Sagartz et al., 1996). However, it may be difficult to distinguish lymphangiosarcoma from lymphangiomatosis based on clinical and histological features if metastatic disease is not present. Some of the previously described cases of nonmetastatic lymphangiosarcomas may represent lymphangiomatosis (Shiga et al., 1994), particularly when found in young dogs (Fossum et al., 1998).

Histopathology (Figure 28.27)

Most lymphangiosarcomas are ill-defined but well differentiated neoplasms of the dermis and subcutis. The tumors are composed of plump spindle cells aligned in one or more layers along edematous collagenous trabeculae or pre-existing dermal collagen bundles. The trabeculae form an anastomosing meshwork of large, angular vascular spaces. Blindly ending trabeculae are frequently observed. Vascular structures dissect between dermal collagen bundles, subcutaneous lobules of adipocytes, and



Fig. 28.27 Lymphangiosarcoma in a cat. The dermis is diffusely infiltrated by irregular vascular spaces lined by a single layer of plump endothelial cells with hyperchromatic nuclei. Note paucity of erythrocytes and dissection of neoplastic endothelium between dermal collagen bundles.

fascial planes at the periphery, creating ragged tumor margins. The vascular spaces contain few to no erythrocytes, except in areas of ulceration and secondary hemorrhage. The sparse edematous stromal tissue is usually infiltrated by lymphocytes and plasma cells, and occasional hemosiderophages may be observed. The neoplastic endothelial cells may bulge into the vascular lumens. The tumor cells have pleomorphic, oval nuclei with variable nucleoli. The number of mitotic figures varies but they may be frequent (Sagartz et al., 1996). Lymphangiosarcomas on the caudal abdomen may incorporate and infiltrate inguinal lymph nodes.

The presence of pleomorphic lymphatic endothelial cells lining the vascular channels, focal lack of endothelial cells, blindly ending trabeculae, as well as markedly infiltrative growth, separates lymphangiosarcoma from lymphangiomatosis. Lymphangiosarcoma also must be differentiated from erythrocyte-poor hemangiosarcoma. The lack of red blood cells or very few red blood cells and presence of stromal edema with lymphoplasmacytic infiltration suggests lymphangiosarcoma over hemangiosarcoma. Evaluation of lymphangiosarcomas by electron microscopy reveals a discontinuous or absent basement membrane and numerous pinocytotic vesicles, while hemangiosarcomas are characterized by a continuous basement membrane.

Angiosarcoma of lymphatic origin

These tumors are also referred to as poorly differentiated lymphangiosarcomas. Lesions reported as feline ventral abdominal angiosarcoma are included in this group, as tumor cells lacked a continuous basement membrane (Hendrick et al., 1998; Goldschmidt & Hendrick, 2002). These neoplasms are characterized by a diffuse infiltration of endothelial cells, predominantly within the subcutis. Intraluminal red blood cells are sparse or absent. Often the masses lack obvious vascular differentiation. Spindle cells, arranged in interlacing bundles, may be admixed with polygonal cells to form solid sheets. The tumor cells exhibit nuclear pleomorphism and nucleolar prominence. Mitotic activity is high. The stroma in feline ventral abdominal angiosarcomas contains variable numbers of inflammatory cells and hemosiderophages (Hendrick et al., 1998; Goldschmidt & Hendrick, 2002).

Angiosarcomas of lymphatic origin lack a basement membrane or, alternatively, exhibit the presence of a discontinuous basement membrane on electron microscopic evaluation. Ultrastructurally, the pleomorphic tumor cells pile up along discontinuous basal lamina (Hendrick et al., 1998). These observations in conjunction with immunohistochemistry (see below) have identified the lesions as lymphatic in origin.

Angiosarcomas of lymphatic origin are difficult to separate from angiosarcoma of vascular origin. Stromal edema, lymphoplasmacytic infiltration, and electronic micrographic demonstration of a discontinuous basement membrane support the diagnosis of lymphatic origin; immunohistochemistry may also be of benefit. Anaplastic angiosarcomas with solid aggregates of spindle cells should be differentiated from fibrosarcomas and other spindle cell malignancies; this often requires immunohistochemistry.

Immunohistochemistry

Similar to neoplastic vascular endothelial cells, neoplastic lymphatic endothelial cells usually maintain their expression of CD31 and lectins; the expression of factor VIII may vary and expression of CD34 is inconsistent (Augustin-Voss et al., 1990; Poblet et al., 1996; Arber et al., 1997). In humans, differentiation of angiosarcoma of vascular origin from angiosarcoma of lymphatic origin is based on expression of CD44 and podocalyxin by the former versus lymphatic vessel endothelial receptor-1 (LYVE-1), podoplanin, and vascular endothelial growth factor receptor-3 (VEGFR-3) by the latter. LYVE-1 expression in neoplastic lymphatics but not in blood vessels also has recently been documented in cats (Galeotti et al., 2004). Expression of CD31 and factor VIII separates angiosarcomas of lymphatic origin from fibrosarcomas (vimentin+, CD31–, factor VIII–) and histiocytic sarcomas (CD18+, CD45+, CD1+, CD11c+, MHC II+).

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Chapter 29

Perivascular tumors

Perivascular tumors are also referred to as nonendothelial vascular tumors and arise from cells that support or invest blood vessels (Weiss & Goldblum, 2001). Perivascular tumors in humans include glomus tumors, hemangiopericytomas, and solitary fibrous tumors (Weiss & Goldblum, 2001). These tumors are uncommon and they may be easily misinterpreted as other mesenchymal proliferations. Solitary fibrous tumors and hemangiopericytomas may be part of a common family, and further studies are required to enable reliable differentiation (Weiss & Goldblum, 2001).

Glomus tumors have been reported in dogs and cats, and hemangiopericytomas have been recognized in dogs. Leiomyomas and leiomyosarcomas originating from vascular smooth muscle (angioleiomyoma, angioleiomyosarcoma) will be discussed with muscular tumors in Chapter 31.

GLOMUS TUMOR

Glomus tumors in humans include glomus tumor proper, glomangioma, glomangiomyoma, intravascular glomus tumors, and glomangiomatosis (Weiss & Goldblum, 2001). These subtypes of glomus tumors vary in the proportion of proliferating glomus cells and vascular structures. Glomus tumors mostly develop on digits and are often painful. With the exception of glomangiomatosis, glomus tumors in humans are considered benign.

Glomus tumors are neoplasms that arise from glomus cells, which are normally found in specialized arteriovenous shunts or anastomoses (Requeña & Sangueza, 1997). These arteriovenous anastomoses are numerous in distal acral areas where the majority of the glomus tumors occur in humans (Requeña & Sangueza, 1997; Weiss & Goldblum, 2001). Glomus cells are controlled by the sympathetic nervous system and regulate the flow within these cutaneous arteriovenous shunts, thereby influencing temperature regulation. Glomus cells are modified smooth muscle cells (Palungwachira et al., 2001). Thus, these vimentin-positive cells are rich in myofilaments and express α-smooth muscle actin and other muscle actin isoforms. Glomus cells also have a basal lamina that is positive for laminin and collagen IV (Folpe & Gown, 2001; Weiss & Goldblum, 2001).

Glomus tumors observed and reported in dogs and cats mostly resemble 'glomus tumor proper' in humans (Shinya et al., 1997; Uchida et al., 2002) and are composed of round cells. Spindle cell glomus tumors (glomangiomyomas) have also been observed. A recently reported intravascular leiomyosarcoma in a cat (Jacobsen & Valentine, 2000) exhibited clinical and morphologic features supportive of glomus cell origin and most likely represents an intravascular glomus tumor.

Clinical features

Glomus tumors are rare in dogs and cats (Shinya et al., 1997; Uchida et al., 2002). Only a few cases have been recognized by the authors. Glomus tumors are characterized by a solitary small nodule or mass, measuring up to 2 cm in diameter, and arising from the dermis or subcutis. Dermal glomus tumors may appear slightly bluish or purple in lightly pigmented skin. Unlike lesions in humans, glomus tumors in dogs and cats have not been reported to be painful. In humans, these nerve fibers contain substance P, which may explain the tenderness and paroxysmal pain reported (Weiss & Goldblum, 2001). Canine and feline glomus tumors tend to arise on lower extremities and digits (Shinya et al., 1997; Jacobsen & Valentine, 2000; Uchida et al., 2002). Multiple glomus tumors resembling glomangiomatosis in humans have not been observed in dogs or cats.

The small numbers of cases observed do not reveal any breed or sex predilections in dogs or cats. Complete surgical excision appears curative based on the limited follow-up available (Shinya et al., 1997; Uchida et al., 2002).

Histopathology (Figures 29.1 through 29.4)

Most canine and feline glomus tumors are characterized by well-demarcated, subcutaneous, or dermal masses

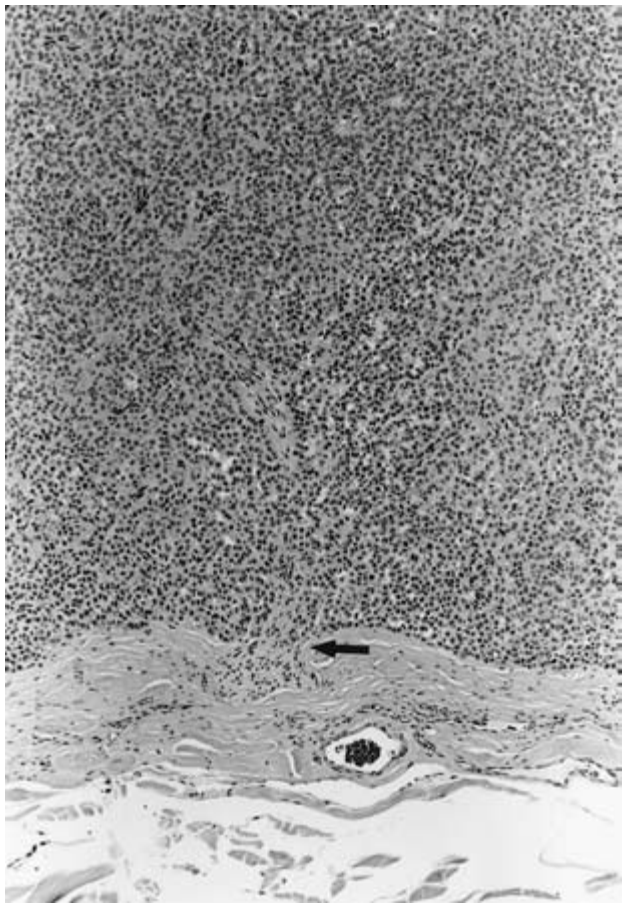


Fig. 29.1 Round cell type glomus tumor (glomus tumor proper) in a dog characterized by a well-demarcated encapsulated mass of round cells. There are numerous vascular structures associated with the capsule. Note the small nerve penetrating the tumor capsule and extending into the mass.

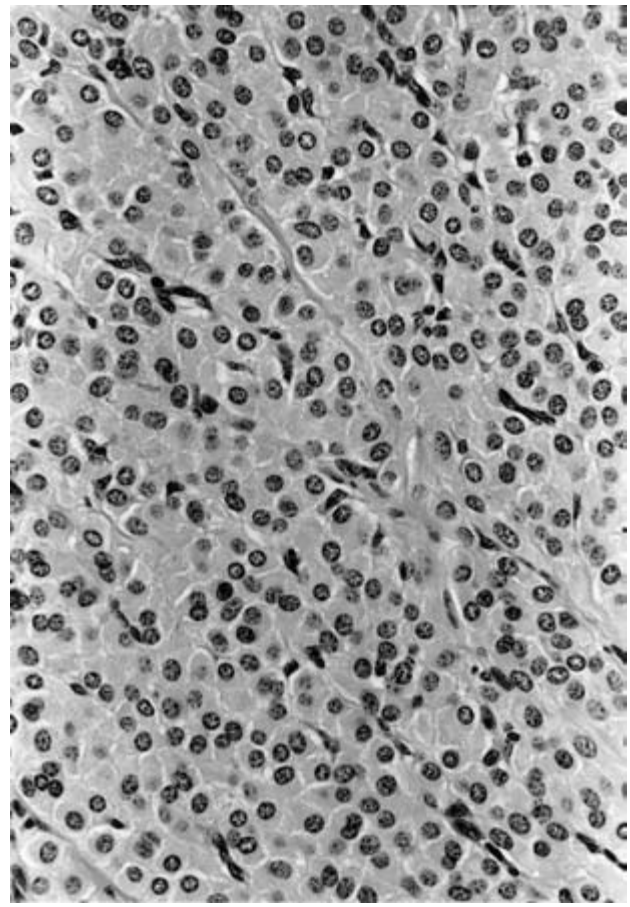


Fig. 29.2 Higher magnification of round cell type glomus tumor in a dog. Closely packed round cells have centrally located, clearly defined nuclei and a moderate amount of pale eosinophilic cytoplasm.

surrounded by compressed fibrous tissue. Some tumors have a fibrous capsule. Typically, there are numerous small nerve fibers and vessels associated with the mass, in particular at the tumor margin, and in the capsule surrounding the tumor. The nerve fibers tend to penetrate surrounding compressed fibrous tissue or the tumor capsule. The majority of the mass is usually composed of variable numbers of densely arranged round cells, and hence resembles glomus tumor proper in humans (Weiss & Goldblum, 2001) (round cell type). Admixed there may be variable numbers of slightly elongated, plump spindle cells. Rarely, the nodule is primarily composed of somewhat plump spindle cells resembling glomangiomyoma in humans (Weiss & Goldblum, 2001) (spindle cell type). Within the tumor mass there are numerous entrapped vascular structures, which may be compressed and appear as narrow cleft-like structures filled with red blood cells. The endothelial lining is not always obvious; some blood-filled channels may, in fact, be lined by the glomus cells, which palisade along the vascular space. A slightly mucinous stroma is occasionally seen.

The round tumor cells have scant to moderate pale eosinophilic cytoplasm and large round to oval, clearly defined nuclei. Spindle cells contain large elongated oval nuclei. Mitotic figures are rare. Each tumor cell or small groups of tumor cells are surrounded by a basement membrane, which can be demonstrated by periodic acid–Schiff (PAS) stain or electron microscopy. Electron microscopic evaluation of a canine glomus tumor revealed actin-like filaments, cytoplasmic dense bodies, pinocytotic vesicles, and glycogen granules (Shinya et al., 1997). Occasionally multinucleated giant cells may be present.

Glomus tumor proper, or round cell type, may need to be distinguished from Merkel cell tumors, and leukocytic round cell tumors (plasma cell tumors, nonepitheliotropic lymphomas, histiocytomas, mast cell tumors, and transmissible venereal tumors). In contrast to glomus tumors, Merkel cell tumors and leukocytic round cell tumors lack

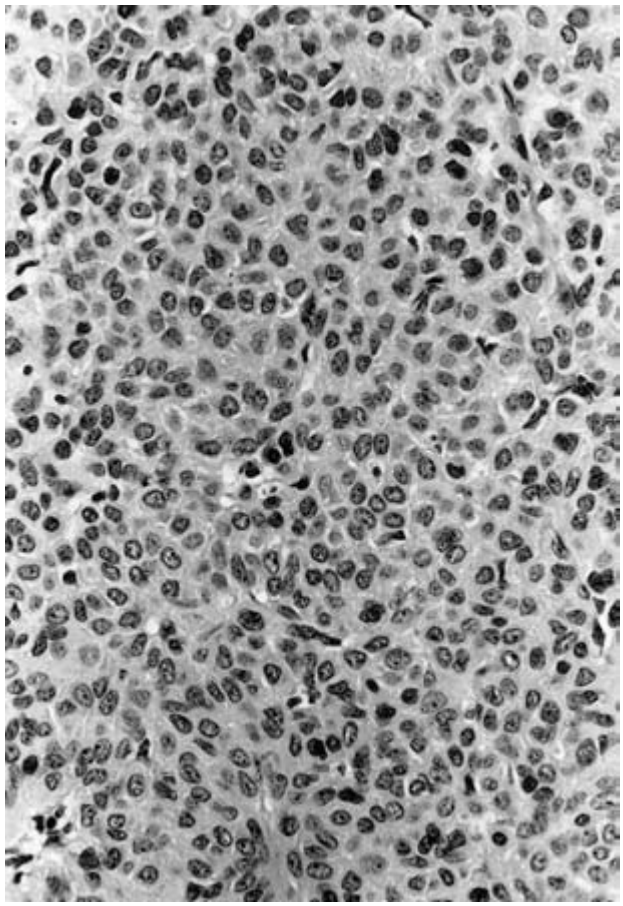


Fig. 29.3 Glomus tumor in a dog. In this example, occasional slightly elongated cells with oval nuclei are admixed with the round tumor cell population.

the association with larger vessels and nerve fibers. Merkel cell tumors and plasma cell tumors have densely packed cell aggregates, often referred to as 'packeting' of tumor cells, separated by fine collagenous stroma. While glomus tumors are characterized by a PAS-positive basement membrane surrounding the tumor cells, leukocytic round cell tumors lack a basement membrane. Plasma cell tumors usually are characterized by moderate pleomorphism of the tumor cells and tend to have eccentric nuclei, while round cell glomus tumors have centrally located, clearly defined nuclei. The dense cytoplasmic RNA in plasma cells stains magenta with methyl green pyronine (MGP) stain. Histiocytomas have a 'top heavy' configuration and in contrast to glomus cell tumors, often exhibit intraepidermal aggregates of tumor cells. Mast cells have cytoplasmic metachromatic granules, which can be identified by toluidine blue or Giemsa stains. Cytologic features of lymphomas and transmissible venereal tumors may be more difficult to differentiate from round cell glomus tumors and immunohistochemistry is required (see below).

Glomus tumors of spindle cell type may need to be differentiated from well-differentiated leiomyosarcoma, including piloleiomyosarcoma and angioleiomyosarcoma, as well as hemangiopericytoma. Piloleiomyosarcomas originate from the arrector pili muscles and, in contrast to glomus tumors, tend to entrap hair follicles and other adnexal structures, but lack the close association with vascular structures and nerve fibers. Angioleiomyosarcomas originate from the media of dermal blood vessels, and the tumors tend to blend into the muscle layer of the vascular walls. They lack the presence of numerous nerve

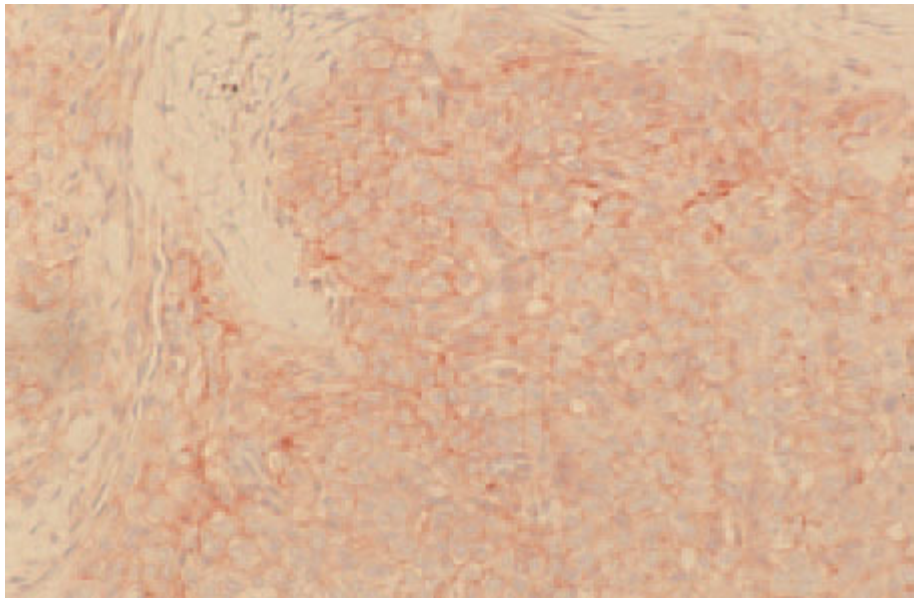


Fig. 29.4 Glomus tumor of Fig. 29.3. Immunohistochemistry with anti-collagen IV colors the basement membrane which surrounds single cells and groups of cells (chromogen aminoethylcarbazole [AEC]).

fibers, which is a common feature of glomus tumors. While glomus tumors tend to have a capsule, hemangiopericytomas are nonencapsulated and rather infiltrative tumors, and lack the presence of a basement membrane.

Intravascular glomus tumor

Some glomus tumors are surrounded by a large vascular structure, which may form a coherent endothelial lined channel at the periphery (Weiss & Goldblum, 2001). These features mimic the appearance of a large intravascular sarcoma. The recently reported intravascular leiomyosarcoma in a cat is consistent with an intravascular glomus tumor (Jacobsen & Valentine, 2000), as morphologic and immunophenotypic features indicate glomus cell origin (see below).

Immunohistochemistry

Glomus tumors retain the cytoplasmic expression of vimentin, α-smooth-muscle actin, and pan-muscle-specific actin of the normal glomus cell (Requeña & Sangueza, 1997; Breiteneder-Geleff et al., 1999). Single tumor cells or groups of tumor cells are surrounded by a collagen IV+ and laminin+ basement membrane. In contrast to glomus tumors, leiomyosarcomas consistently express desmin, as well as vimentin, α-smooth-muscle actin, and pan-muscle-specific actin. The previously reported intravascular leiomyosarcoma was desmin-negative, supporting glomus cell origin (Jacobsen & Valentine, 2000). Only on rare occasions do glomus tumor cells express desmin as well (Requeña & Sangueza, 1997; Breiteneder-Geleff et al., 1999).

The lack of expression of α-smooth-muscle actin and the lack of a collagen IV+ and laminin+ basement membrane separates hemangiopericytomas from glomus tumors. Neuroendocrine tumors such as Merkel cell tumors lack the expression of α-smooth-muscle actin and desmin, but are positive for chromogranin A and synaptophysin. Merkel cell tumors also express cytokeratin, especially CK20. Leukocytic round cell tumors (lymphoma, mast cell tumors, histiocytomas, plasma cell tumors, and transmissible venereal tumors) lack expression of α-smooth-muscle actin and desmin, and the tumor cells are not surrounded by a laminin+ and collagen IV+ basement membrane. Instead the leukocytic tumors express the common leukocyte antigens CD18 and CD45.

HEMANGIOPERICYTOMA

Hemangiopericytoma has been a controversial neoplasm in humans as well as in dogs (Perez et al., 1996; Weiss & Goldblum, 2001; Mazzei et al., 2002). These neoplasms have not been identified in cats. Recent studies indicate that hemangiopericytomas have been overdiagnosed in both humans and in dogs, as the diagnostic term 'hemangiopericytoma' is often used to denote the histologic pattern created by a variety of spindle cell tumors with a whorling pattern, rather than a specific tumor of pericytes (Perez et al., 1996; Williamson & Middleton, 1998; Weiss & Goldblum, 2001). The controversy derives from the difficulty in identifying pericytes by their morphology and immunophenotype. Hence, the diagnosis of hemangiopericytoma should only be made if extensive immunohistochemistry has ruled out another cell of origin (see below). It is therefore considered more accurate to use the more general morphologic term 'canine spindle cell tumor with whorling pattern' if immunohistochemistry has not been performed.

Pericytes are spindle cells surrounding blood vessels. Their morphologic features are virtually indistinguishable from endothelial cells, fibroblasts, and other spindle cells. Electron microscopic evaluation reveals a close association of pericytes with the periendothelial basement membrane, but the pericytes themselves are not surrounded by a basal lamina and hence are negative for laminin and collagen IV (Requeña & Sangueza, 1997; Weiss & Goldblum, 2001). Similar to other mesenchymal cells, pericytes express vimentin. However, they lack a characteristic immunophenotype, as additional proteins specific for pericytes have not been identified to date (Requeña & Sangueza, 1997; Folpe & Gown, 2001; Weiss & Goldblum, 2001).

Clinical features

Canine hemangiopericytomas have been reported by Goldschmidt (1985) to comprise 13.3% of all mesenchymal neoplasms in a large review. Additionally, they account for 7% of all canine skin tumors (Goldschmidt & Shofer, 1992). However, as in other reviews, the pericytic origin of this neoplasm has never been convincingly proven, despite ultrastructural studies (Xu, 1986). The high reported incidence may be the result of using the term 'hemangiopericytoma' to denote a histologic pattern rather than a specific tumor of pericytes (Perez et al., 1996; Affolter & Moore, 2002; Mazzei et al., 2002). Thus, the true incidence of canine hemangiopericytoma may be considerably lower.

'Canine spindle cell tumors with whorling pattern', which include hemangiopericytomas, are solitary, deep dermal and subcutaneous, multilobular, fairly well circumscribed masses with a firm or a slightly fatty consistency. The masses are frequently adhered to underlying soft tissue. Overlying skin may be alopecic, ulcerated, and hyperpigmented. Neoplasms of this type often favor the trunk or legs. The previously reported preference of hemangiopericytoma for the periarticular region of the

legs must be re-evaluated, as some of the previously diagnosed hemangiopericytomas were, in fact, histiocytic sarcomas (Affolter & Moore, 2002).

The average age of affected animals is 7 to 10 years (Bostock & Dye, 1980; Graves et al., 1988; Postorino et al., 1988). Large breed dogs are in general at greater risk; one survey included Siberian Huskies, Irish Setters, and German Shepherd Dogs, as well as mixed breeds (Goldschmidt & Shofer, 1992). A 2:1 female to male predominance has been observed (Goldschmidt & Shofer, 1992).

Hemangiopericytomas have been reported to exhibit frequent local recurrence with increasing invasiveness following successive surgeries; recurrence rates reported range from 26 to 38%, with recurrence intervals of 1 to 56 months (Graves et al., 1988; Postorino et al., 1988). This variation in reported incidence of recurrence may be due to inclusion of neoplasms of different cell origins and thus different biological behavior. In the authors' experience, the metastatic rate is very low; one study observed less than 1% metastases (Goldschmidt, 1985).

Histopathology (Figures 29.5 and 29.6)

Using morphologic guidelines from descriptions of human hemangiopericytomas, canine hemangiopericytomas are multilobular, unencapsulated subcutaneous and/or dermal masses comprising small spindle and polygonal cells. The cells are arranged as interlacing bundles, sheets, and concentric whorls in varying proportions. Hemangiopericytomas with large numbers of whorls have a classical 'fingerprint' pattern (Weiss & Goldblum, 2001). The whorls generally have a single capillary blood vessel at their centers. Spindle cells surrounding branching vascular structures, arranged in an 'antler-like' configuration, are a feature considered typical for hemangiopericytomas in humans (Requeña & Sangueza, 1997); this pattern has not been reported in dogs. Occasionally, the central vascular structures in canine hemangiopericytomas are collapsed and no longer recognizable as endothelial lined structures. The presence of these collapsed capillaries

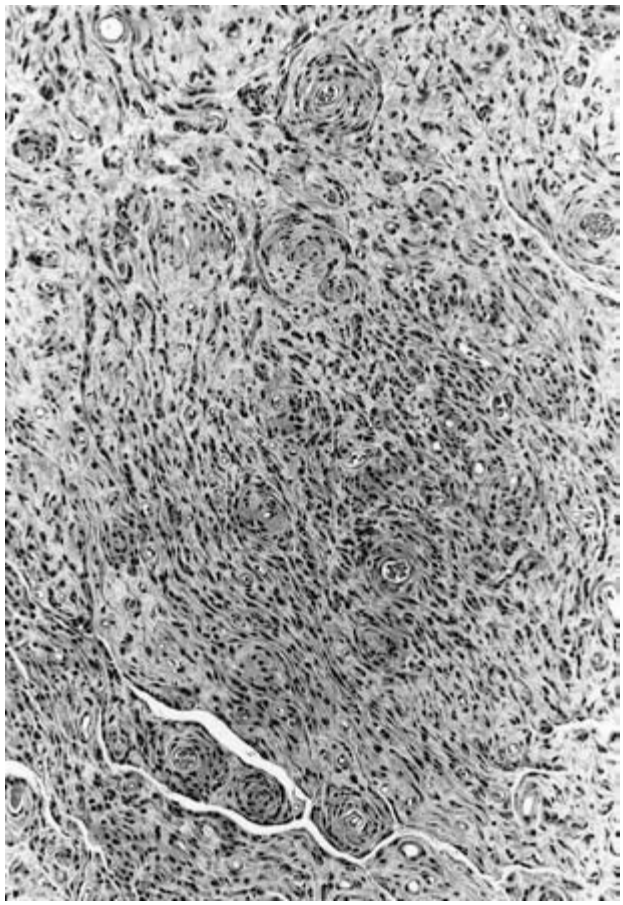


Fig. 29.5 Hemangiopericytoma in a dog. Proliferating spindle cells with elongated nuclei encircle small capillaries.

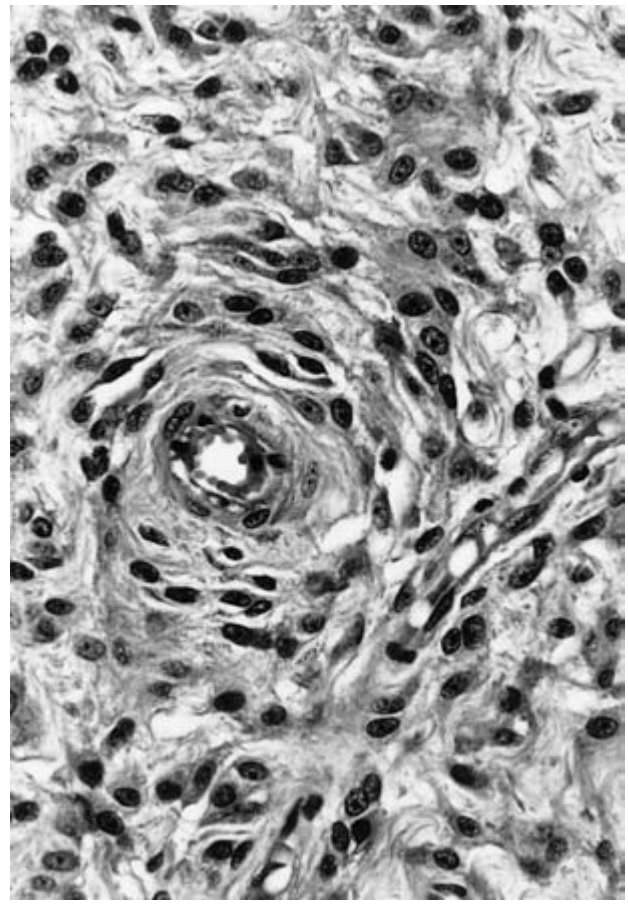


Fig. 29.6 Higher magnification of hemangiopericytoma in a dog. Central vessels are surrounded by spindle cells, which have identical morphology to the cells immediately surrounding the vascular structures (putative pericytes).

can only be identified by immunohistochemistry (see below).

At the periphery of most hemangiopericytomas, tendrils of tumor cells extend along fascial planes, between lipocytes, and around tendon sheaths. These small infiltrative extensions make clinical surgical assessment of tumor margins difficult. Zones of necrosis, hemorrhage, and fibrosis are common secondary features. Cellularity varies from moderately low to high, depending upon the quantity of stromal collagen and mucin. Stromal collagen is usually sparse and fibrillar. Lesions with abundant stromal mucin often appear as widely separated lobules and isolated islands of tumor tissue.

The tumor cells generally have poorly-defined, pale eosinophilic or amphophilic cytoplasm. The nuclei are oval to elongated, and uniformly pale with finely dispersed chromatin and small central nucleoli. Mitotic activity is usually low. Nuclear pleomorphism and mitotic index may be increased in recurrent lesions.

Differential diagnoses for true hemangiopericytoma include other mesenchymal 'spindle cell tumors with whorling pattern', such as peripheral nerve sheath tumors, fibrosarcomas, myofibroblastic fibrosarcomas, spindle cell histiocytic sarcomas, and spindle cell glomus tumors (glomangiomyomas). Differentiation of hemangiopericytoma from peripheral nerve sheath tumors can be difficult, as cytologic features may be strikingly similar. However, peripheral nerve sheath tumor cells are surrounded by a basement membrane, while the pericytes of hemangiopericytomas are not. Whorls present in peripheral nerve sheath tumors are not centered on vascular structures. In contrast to hemangiopericytomas, most peripheral nerve sheath tumors have interlacing wavy bundles of tumor cells (Antoni type A pattern), fusiform and serpentine nuclei, and variable palisading of tumor cells. Fibrosarcomas and myofibroblastic fibrosarcomas have similar cytoplasmic and nuclear features to hemangiopericytomas. The former may exhibit whorling of tumor cells around a collagenous center, but lack concentric perivascular whorls.

Spindle cell predominant histiocytic sarcomas are often composed of a mixture of spindle cells and round large individualized cells. Whorling of tumor cells may be seen, but in contrast to hemangiopericytomas, the whorls are not centered on small vascular structures. Spindle cell glomus tumors are characterized by tumor cells surrounding vascular structures, but may have a more prominent component of plumper spindle cells than hemangiopericytomas. In most instances the glomus tumor cells are rounder and have a central round nucleus; the tumor cells are also surrounded by a basement membrane. Glomus tumors also have numerous nerves and larger vascular structures, both within the tumor and in the capsule surrounding the mass. In contrast, hemangiopericytomas exhibit infiltrative growth and a lack of capsule formation; the vascular structures within the tumor may be collapsed.

Immunohistochemistry

Immunohistochemistry is not useful in the definitive diagnosis of hemangiopericytoma, as specific markers for pericytes do not exist. Instead immunohistochemistry may be useful in ruling out other 'spindle cell tumors with whorling pattern' that have a more characteristic immunophenotype. Hemangiopericytomas in humans express vimentin and CD34 (Rosai, 1996; Weiss & Goldblum, 2001). However, CD34 is seen only on a small subpopulation of cells, and most positive cells in the lesions are endothelial cells lining the small vascular channels (Rosai, 1996). The central collapsed capillaries can be demonstrated by the presence of factor VIII+, CD34+ endothelial cells.

Other diverse proteins occasionally documented in human tumors with morphology consistent with hemangiopericytoma are factor XIIIa, MHC II, α-smooth-muscle actin, and desmin (Rosai, 1996). These observations indicate that the diagnosis of hemangiopericytoma is more commonly used to denote a pattern of tumor cell arrangement rather than a specific tumor; this is further supported by the fact that these molecules have not been documented in normal pericytes. Similar to results in humans, retrospective phenotypic studies of previously diagnosed canine hemangiopericytomas indicate that a vast majority of these tumors originated from cells other than pericytes (Perez et al., 1996; Affolter & Moore, 2002; Mazzei et al., 2002).

Fibrosarcomas, peripheral nerve sheath tumors, and hemangiopericytomas all express vimentin. In the absence of other identifiable proteins, these tumors cannot be differentiated using immunohistochemistry. Peripheral nerve sheath tumors may express S100, glial fibrillary acidic protein (GFAP), and neuron-specific enolase (NSE). Both peripheral nerve sheath tumors and glomus tumors have a basal lamina, which can be identified by antilaminin and anticollagen IV antibodies. Glomus tumors express α-smooth muscle actin and may occasionally express desmin as well. Myofibroblastic fibrosarcomas also express α-smooth muscle actin in addition to vimentin. Histiocytic sarcomas are consistently positive for common leukocyte antigen CD45 and CD18, and they also express CD1, CD11c and MHC II.

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Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis, Second Edition
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Chapter 30

Lipocytic tumors

Lipocytic tumors include benign proliferations such as lipomatosis and lipomas, as well as malignant neoplasms such as liposarcomas (Messick & Radin, 1989; Goldschmidt & Shofer, 1992; Hendrick et al., 1998; Weiss & Goldblum, 2001a,b; Liggett et al., 2002). Infiltrative lipomas and infiltrative angiolipomas, although characterized by morphologic well-differentiated fatty tissue, have variable locally aggressive behavior (Goldschmidt & Shofer, 1992; Weiss & Goldblum, 2001a; Liggett et al., 2002).

Mature lipocytes, or adipocytes, are large and have small nuclei that are compressed against the cell membranes by the abundant cytoplasmic stores of neutral lipid (Banks, 1993). Lipoblasts, the lipocyte precursor cells, are small and have large, centrally located nuclei and few or multiple small cytoplasmic vacuoles (Banks, 1993); these cells may be indicative of malignant transformation. The cytoplasmic lipid can be demonstrated on frozen section using Sudan black or Sudan red stains. Lipocytes, like other mesenchymal cells, express vimentin. However, they lack expression of other known proteins specific for lipocytes, which makes definitive identification of poorly differentiated lipocytic neoplasms difficult.

LIPOMATOSIS

Lipomatosis refers to the multicentric proliferation of architecturally normal adipose tissue. Several syndromes have been described in humans, including nevus lipomatosus superficialis, diffuse lipomatosis, pelvic lipomatosis, adiposis dolorosa (Dercum's disease), familial multiple lipomatosis, and multiple symmetric lipomatosis (Madelung's disease) (Weiss & Goldblum, 2001). Lipomatosis is extremely rare in dogs and cats. A single case of canine lipomatosis has been documented that resembled multiple symmetric lipomatosis in humans (Gilbert et al., 1990). One case of lipomatosis has also been described in a cat (Carpenter et al., 1987).

Clinical features

The canine case of lipomatosis was reported in a 5-year-old female Dachshund that had progressively enlarging, pendulous, fatty skin folds involving the neck and trunk bilaterally (Gilbert et al., 1990). The skin was atrophic, partially alopecic, and multifocally ulcerated due to trauma. The feline case of lipomatosis was described in a 4-year-old cat; fatty skin folds were present symmetrically on the caudal thighs (Carpenter et al., 1987).

Histopathology

Lipomatosis in the canine case was characterized by diffuse thickening of the subcutis by mature adipose tissue (Gilbert et al., 1990). The overlying epidermis and dermis were mildly atrophic. The subcutaneous fat had a normal complement of fibrous septa, blood vessels, and nerves. The interlobular septa showed mild mucin deposition. The majority of lipocytes were cytologically normal. A small number of primitive mesenchymal cells and lipoblasts (lipocyte precursor cells) were present around blood vessels. The primitive mesenchymal cells were small and stellate and had dark, ovoid nuclei; the lipoblasts were stellate or polygonal and contained multiple small lipid vacuoles. The lipoblast nuclei were ovoid and hyperchromatic. The affected cat had infiltrations of benign adipose tissue with concurrent pansteatitis (Carpenter et al., 1987).

The primary differential diagnosis for lipomatosis is lipoma or normal adipose tissue, particularly for needle biopsy specimens. Lipomas are characterized by the absence of large vessels and nerve trunks, while lipomatosis generally has a normal complement of fibrous septa, blood vessels, and nerves. Clinicopathologic correlation is essential in the diagnosis of lipomatosis.

LIPOMA

Benign tumors of lipocytes include lipomas, fibrolipomas, chondrolipomas, angiolipomas, and angiofibrolipomas (Goldschmidt & Shofer, 1992; Hendrick et al., 1998; Weiss & Goldblum, 2001; Liggett et al., 2002). In addition, spindle cell lipomas have been rarely observed in dogs and are discussed separately (see p. 770).

Lipomas largely resemble normal adipose tissue. It has been proposed that canine and feline lipomas may represent foci of nodular hyperplasia or altered lipocyte metabolism rather than true neoplasms (Pulley & Stannard, 1990).

Clinical features

Lipomas are common in dogs and fairly common in cats (Bevier & Goldschmidt, 1981; Goldschmidt & Shofer, 1992). They account for approximately 9% of canine skin and subcutaneous tumors, based on a survey by one author (E.J.W.). The incidence in cats was approximately 5% (Carpenter et al., 1987; Goldschmidt & Shofer, 1992). The incidence rate of fibrolipoma and angiolipoma has not been documented; a single case of feline angiofibrolipoma has been described (Liggett et al., 2002). Rare chondrolipomas have been observed in dogs by the authors and are also described by Goldschmidt and Shofer (1992).

Lipomatous tumors present as well-circumscribed, ovoid, or discoid masses with a soft or rubbery consistency. Most masses are well circumscribed and have delicate fibrous capsules. In about 5% of cases multiple lipomas are observed (Goldschmidt & Shofer, 1992). Fibrolipomas and chondrolipomas may have a somewhat firmer consistency, and angiolipomas often have a red or blue hue when viewed through overlying skin. The majority of benign lipomatous tumors arise in the subcutaneous tissue and can attain sizes greater than 20 cm in diameter. The overlying skin is freely movable. Partial alopecia and epidermal atrophy may occur with larger lesions. Occasionally, lipomatous tumors develop in the deep dermis or superficial subcutis, especially in cats. These superficial lipomas usually measure less than 2 cm in diameter.

The majority of canine and feline lipomas occur on the trunk and legs (Pulley & Stannard, 1990; Goldschmidt & Shofer, 1992). Fibrolipomas in dogs often occur on temporal or intermandibular regions. Chondrolipomas in dogs occur most often on the pawpads.

The average age of affected dogs with benign lipomatous tumors is 8 to 9 years, and females are at increased risk (Pulley & Stannard, 1990; Goldschmidt & Shofer, 1992). Lipomas occur in all breeds of dogs. Labrador Retrievers, Doberman Pinschers, and Miniature Schnauzers are reported to be at increased risk based on one survey (Goldschmidt & Shofer, 1992), while additional breeds at risk, as compiled by Scott et al. (2001), include Cocker Spaniels, Dachshunds, and Weimaraners. Lipomas in cats occur most often in 7 to 13-year-old animals; Siamese cats are at increased risk based on one large survey, and there is no sex predilection (Goldschmidt & Shofer, 1992).

Histopathology

Lipoma (Figures 30.1 and 30.2)

In general, benign lipocytic tumors, typified by lipomas, are well-circumscribed dermal or subcutaneous nodules characterized by a proliferation of mature lipocytes that are virtually indistinguishable from their counterparts in normal fat. Lipomas often have a delicate capsule and a

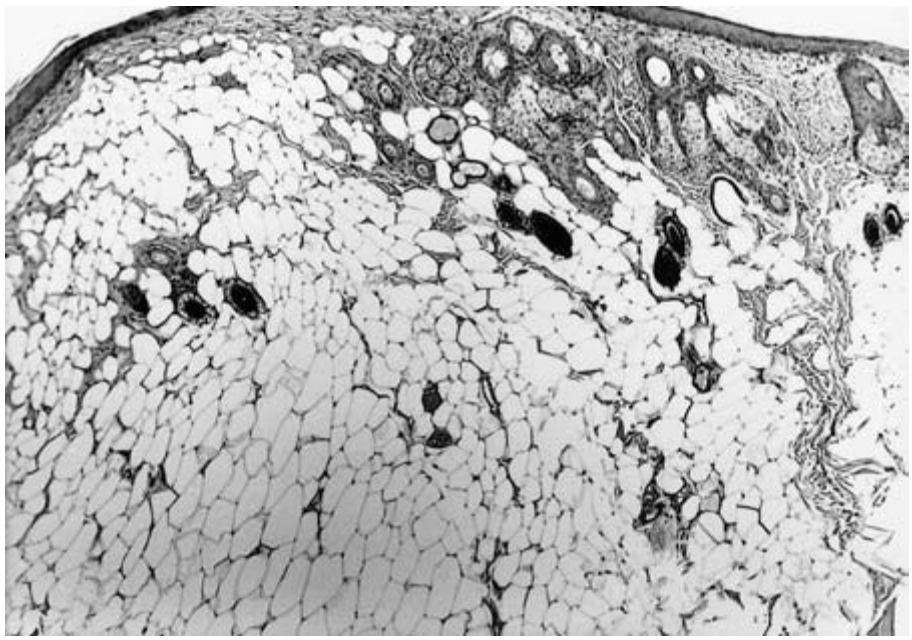


Fig. 30.1 Lipoma in a cat. A relatively discrete nodule of mature lipocytes involves the dermis and subcutis.

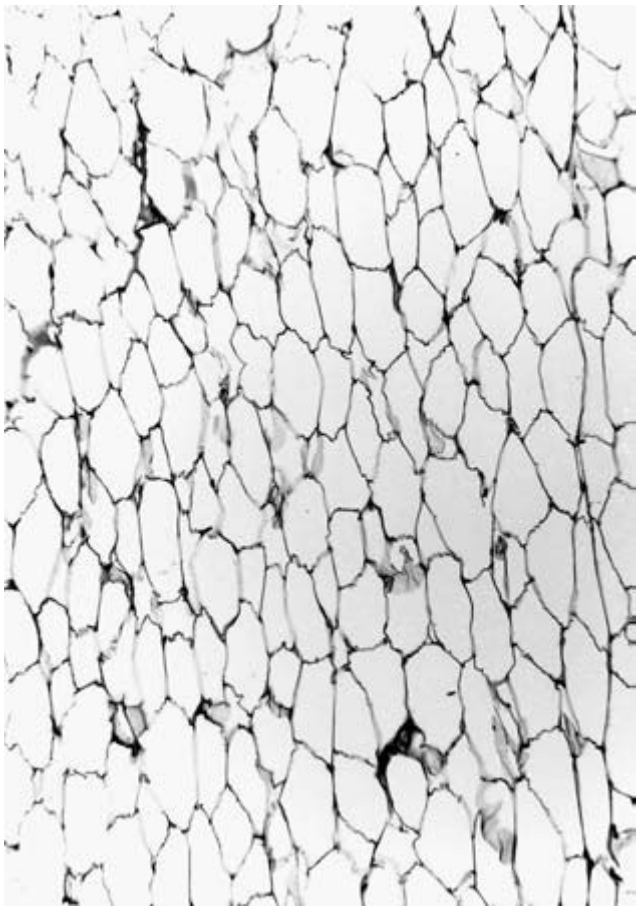


Fig. 30.2 Lipoma in a dog comprising uniform mature lipocytes; note that nuclei are barely discernible in most of the cells.



Fig. 30.3 Fibrolipoma in a dog. The mass of mature lipocytes is dissected by cell poor fibrous tissue composed of arborizing collagen bundles.

delicate capillary vasculature supported by thin strands of collagen. Lipocytes sometimes appear larger or have more variability in size than those of adjacent normal fat. Nuclei are small and compressed against the cell membranes by the abundant cytoplasmic stores of lipid. Mitotic figures are not observed. Ischemic degenerative changes may occur in large masses. Lipocyte necrosis is generally accompanied by hemorrhage, fibrosis, and a variable infiltrate of foamy macrophages. Saponification of necrotic fat is occasionally seen, characterized by light basophilic material within damaged lipocytes.

The primary differential diagnosis for uninflamed lipoma is normal adipose tissue, particularly for needle biopsy specimens. The absence of large vessels and nerve trunks is useful in distinguishing a lipoma from normal fat. Inflamed lipomas should be differentiated from foci of traumatic panniculitis or steatitis (see Chapter 21), particularly in cats, as these may resemble areas of ischemic degeneration in lipomas. Both have numerous foamy macrophages dispersed throughout the lesion. Peripheral encapsulation by mature granulation tissue is more indicative of a primary inflammatory or traumatic lesion of fat than an inflamed lipoma. In addition, mildy inflamed lipomas should be differentiated from atypical lipomas (see liposarcoma, p. 772). Inflamed fat contains lesional foamy macrophages, which may be difficult to differentiate from lipoblasts (lipocyte precursor cells). Occasional cellular atypia in the lipoblastic population of atypical lipomas may allow differentiation.

Fibrolipoma (Figure 30.3)

Fibrolipomas are characterized by the presence of sparse to moderate amounts of dissecting fibrous tissue within an otherwise typical lipoma. The fibrous component is cell poor and primarily characterized by accumulations of thick to finely fibrillar, arborizing collagen bundles.

The differential diagnosis is principally fibrotic adipose tissue occurring as an end-stage reaction to trauma or severe inflammation. In general, the fibrosis of scarring steatitis is more cellular than fibrolipoma, and contains

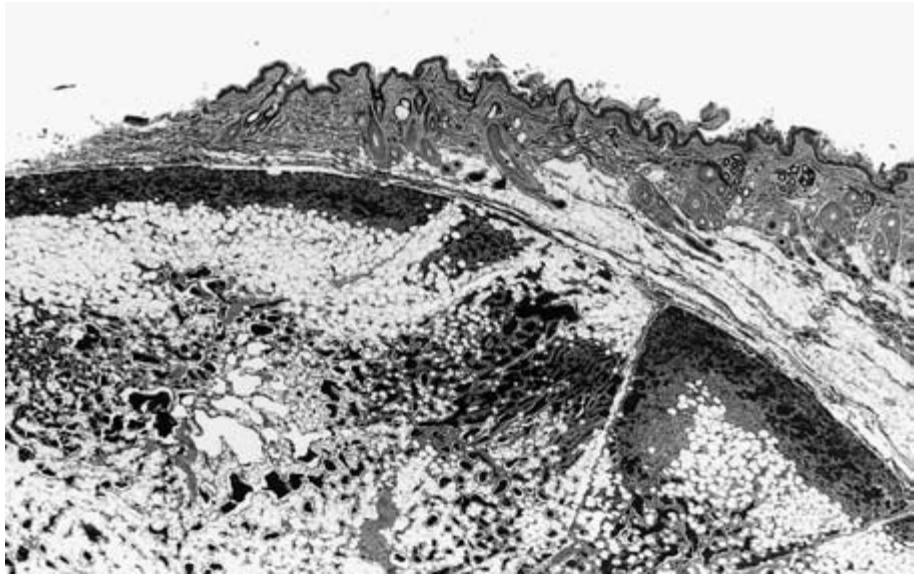


Fig. 30.4 Angiolipoma in a dog. The well-demarcated subcutaneous mass is composed of mature fatty tissue and variably sized, partially branching, thin-walled vascular structures.

evidence of current or chronic hemorrhage (hemosiderosis). In addition, atypical lipoma has areas of increased cellularity, and may require differentiation from fibrolipoma. The atypical lipoma has admixed lipoblasts, which, in contrast to fibroblasts, are round with round, centrally or slightly eccentrically located nuclei and cytoplasmic fat vacuoles.

Angiolipoma (Figure 30.4)

These tumors contain clusters of branching blood vessels that are enclosed and dispersed within an otherwise typical lipoma (Weiss & Goldblum, 2001). The blood vessels are lined by well-differentiated endothelial cells and embedded in a delicate fibrous stroma, which dissects the proliferating fatty tissue.

Angiolipoma must be differentiated from infiltrative hemangioma (see Chapter 28). The latter is characterized by a relatively discrete mass composed of large vascular channels, resembling cavernous hemangioma, surrounded by numerous small to medium-sized vascular channels that are dispersed within normal fatty tissue of the subcutis. In contrast, angiolipomas have multifocal, randomly distributed, branching vascular structures within a well-demarcated lipomatous mass.

Angiofibrolipoma (Figure 30.5)

This variant represents a combination of fibrolipoma and angiolipoma (Liggett et al., 2002). Angiofibrolipomas are characterized by bands of collagenous connective tissue accompanied by clusters of branching vessels, both of which dissect well-differentiated adipose tissue. This compound neoplasm is unique and diagnostically distinctive; differential diagnoses are not known.

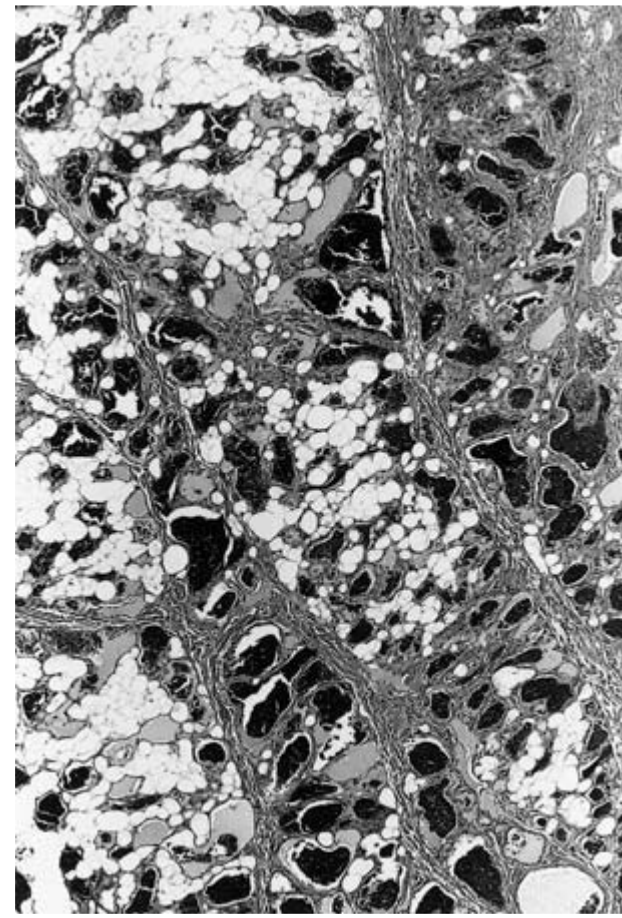


Fig. 30.5 Angiofibrolipoma in a dog composed of mature fatty tissue, branching collagen bundles, and admixed variably sized, thin-walled vascular structures.

Chondrolipoma (Figure 30.6)

This rare variant is characterized by the presence of scattered islands of well-differentiated cartilage within an otherwise typical lipoma. Small amounts of mucin and collagen are often found adjacent to the chondroid islands. This compound neoplasm is unique and diagnostically distinctive; differential diagnoses are not known.

SPINDLE CELL LIPOMA

Spindle cell lipomas in humans are characterized by replacement of mature fat by collagen-forming spindle cells (Enzinger & Harvey, 1975). Clinical features do not deviate from those of usual lipomas. Despite the dense cellularity, they are considered benign. Spindle cell lipomas lack expression of receptors for insulin growth factors I and II, which are usually seen in liposarcomas (Duve et al., 1995). This observation supports the benign behavior of these lesions. Spindle cell lipomas have not been reported in the veterinary literature; a few have been observed in dogs by the authors.

Clinical features

Spindle cell lipomas are rare in dogs and have not been recognized in cats. Similar to lipomas, spindle cell lipomas present as well-circumscribed, ovoid, or discoid masses with a soft or rubbery consistency. Canine spindle cell lipomas have been seen on the hip, elbow, ventral abdomen, inguinal region, mid-dorsal trunk, and on the forehead.

The tumor masses evaluated were excised from a Golden Retriever, a Golden Retriever mix, a Labrador Retriever, an Australian Shepherd mix, an Australian Heeler, an Airedale Terrier, a Boxer, and a Great Dane. The average age was 9 years, with a range of 5 to 14 years. Canine spindle cell lipomas, similar to their counterpart in humans, appear to be benign lesions, and complete surgical excision is curative.

Histopathology (Figure 30.7)

Spindle cell lipomas are well-circumscribed tumor masses that vary in their composition of mature adipose tissue

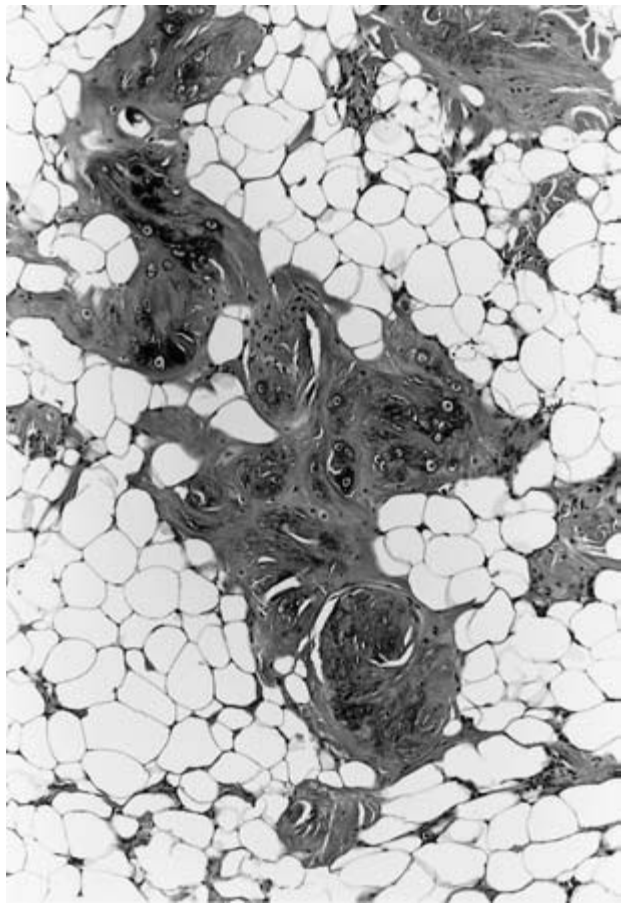


Fig. 30.6 Chrondrolipoma in a dog. This otherwise typical lipoma has multiple coalescing foci of proliferating chondrocytes embedded in cartilaginous matrix.

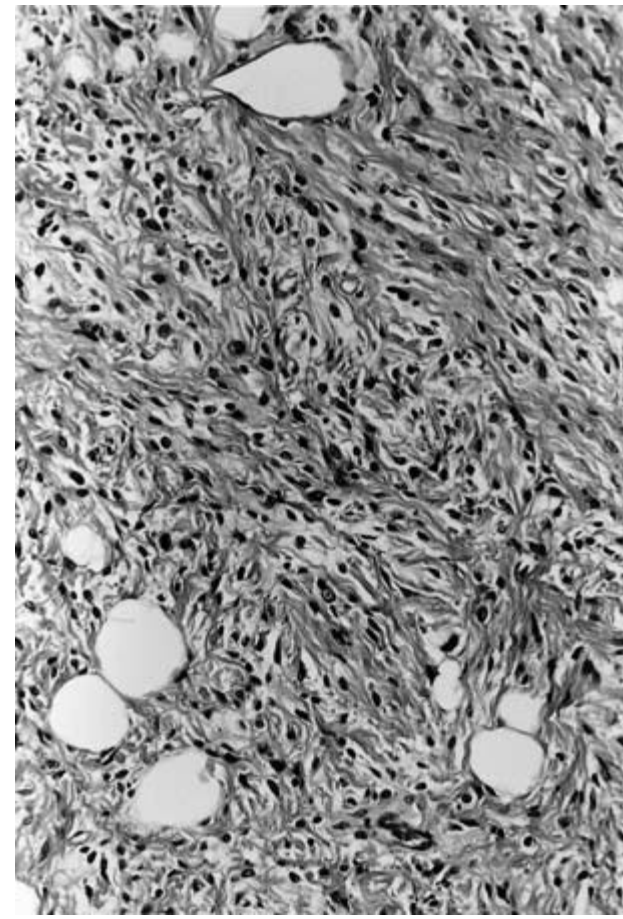


Fig. 30.7 Spindle cell lipoma in a dog. Mature lipocytes are surrounded by fairly uniform spindle cells accompanied by a collagenous stroma.

and spindle cells. Spindle cells are mostly arranged in short parallel bundles. Occasionally, palisading of the spindle cells is noted. These cells are admixed with well-differentiated proliferating adipocytes, which sometimes appear larger or have more variability in size than those of adjacent normal fat. The nuclei of the adipocytes are small and compressed against the cell membranes by the abundant cytoplasmic stores of neutral lipid.

The spindle cells are fairly uniform and have narrow cytoplasmic processes. The nuclei are narrow and elongated, and the nucleoli are inconspicuous. Rarely, giant cells may be present. The spindle cells deposit variable amounts of collagen and mucinous matrix. Blood vessels may be inconspicuous or prominent and arborizing (branched). Spindle cells may surround dilated, branching vascular structures, resulting in a pseudoangiomatous pattern. Osseous and cartilaginous metaplasia, features occasionally seen in spindle cell lipomas in humans (Weiss & Goldblum, 2001), have not been recognized in canine tumors.

Most spindle cell lipomas have a fair amount of fatty tissue and thus are not difficult to separate from other spindle cell tumors. Differential diagnoses for spindle cell lipoma with a minimal amount of adipose tissue are other spindle cell proliferations such as peripheral nerve sheath tumors, hemangiopericytomas, nodular fasciitis, fibrosarcomas, and leiomyosarcomas. In spindle cell lipomas the spindle cells are arranged in short parallel bundles, while peripheral nerve sheath tumors are composed of predominantly small spindle cells arranged in wavy bundles, streams, and concentric whorls (Antoni type A arrangement). Both tumors may contain a fair amount of myxoid stroma. In some cases it may be helpful to perform electron microscopy, as peripheral nerve sheath tumor cells are surrounded by a basal lamina, which can be demonstrated ultrastructurally. Some spindle cell lipomas are rich in branching vessels surrounded by spindle cells; differentiation from hemangiopericytoma may not be possible if these lipomas contain scant adipose tissue, even with immunohistochemistry (see below). Additional sections from the mass may aid in identification of zones of lipocytes. The irregular arrangement of large spindle cells separates nodular fasciitis from spindle cell lipoma. Moreover, nodular fasciitis may contain a reactive inflammatory infiltrate. Fibrosarcomas and leiomyosarcomas are highly cellular and do not contain admixed adipocytes. Leiomyosarcomas are characterized by spindle cells that contain plump elongated nuclei with blunt ends, while in spindle cell lipomas the nuclei are narrow and pointed.

Immunohistochemistry

Immunohistochemical studies have not been performed on canine spindle cell lipomas. Based on human studies, the fusiform cells in spindle cell lipoma should express vimentin and CD34, and occasionally S100. CD34 is a protein primarily expressed by embryonic cells of the hematopoietic system and vascular endothelial cells (see Chapter 28); however, it has been reported in a variety of spindle cell neoplasms, including spindle cell lipomas of humans (Cerelli & Wick, 2002). Spindle cell lipomas lack expression of the muscle proteins actin and desmin. In contrast to spindle cell lipoma, peripheral nerve sheath tumors have a basal lamina surrounding each tumor cell that can be demonstrated by immunohistochemistry for laminin and collagen IV. Moreover, peripheral nerve sheath tumors occasionally demonstrate glial fibrillary acidic protein (GFAP). Some cells in nodular fasciitis express α-smooth-muscle actin, indicating that they are of myofibroblastic origin. Leiomyosarcomas express α-smooth-muscle actin and desmin.

INFILTRATIVE LIPOMA

Infiltrating lipomas in humans, which include infiltrating angiolipomas, chiefly present as subcutaneous and intramuscular lesions (Weiss & Goldblum, 2001). Similar lesions are seen in dogs and cats (Gleiser et al., 1979; Esplin, 1984; McChesney et al., 1980; Liggett et al., 2002).

Clinical features

Infiltrative lipomas are uncommon in dogs and rare in cats (Gleiser et al., 1979; McChesney et al., 1980; Esplin, 1984). Infiltrative lipomas and infiltrative angiolipomas are large, poorly defined, deep subcutaneous and intramuscular swellings that are slightly firmer than banal lipomas. Most tumors arise in the deep soft tissues of the neck, trunk, and proximal legs (Pulley & Stannard 1990; Goldschmidt & Shofer, 1992). Leg lesions may produce pain or impair locomotion.

Affected animals are usually middle-aged or older, but young adults occasionally develop lipomas of this type. Females are predisposed (Pulley & Stannard 1990; Goldschmidt & Shofer, 1992). A study of 16 dogs described a median age of 6 years and a female to male ratio of 4:1 (Bergman et al., 1994). This study also reported a high incidence of infiltrative lipomas in Labrador Retrievers. Standard Schnauzers and Doberman Pinschers also are at increased risk (Goldschmidt & Shofer, 1992).

Infiltrative lipomas and angiolipomas do not undergo malignant transformation and possess no metastatic potential. However, they commonly require radical surgical excision, external beam irradiation, or a combination thereof, to prevent local recurrence (McEntee et al., 2000).

Histopathology (Figure 30.8)

Infiltrative lipoma is a diffusely invasive neoplasm involving the subcutis, skeletal muscle, and fascia. The tumor is unencapsulated, and margins are difficult to assess. The neoplasm is composed of sheets and trabeculae of mature lipocytes identical to those of simple lipoma; however, the mass markedly infiltrates the surrounding tissue. The tumor tissue spreads along fascial planes and into muscle bundles. The myofibers often become individualized and atrophic as they are entrapped by the encroaching adipose tissue. Although the adipose tissue appears poorly vascularized, degenerative changes are rarely observed.

The histopathologic appearance of infiltrative lipoma is unique in excisional biopsy specimens. Small amounts of normal fat are often present between muscle bundles in obese animals, and it may be difficult to render a definitive diagnosis of infiltrative lipoma in such patients if only core needle or small incisional biopsy samples are provided.

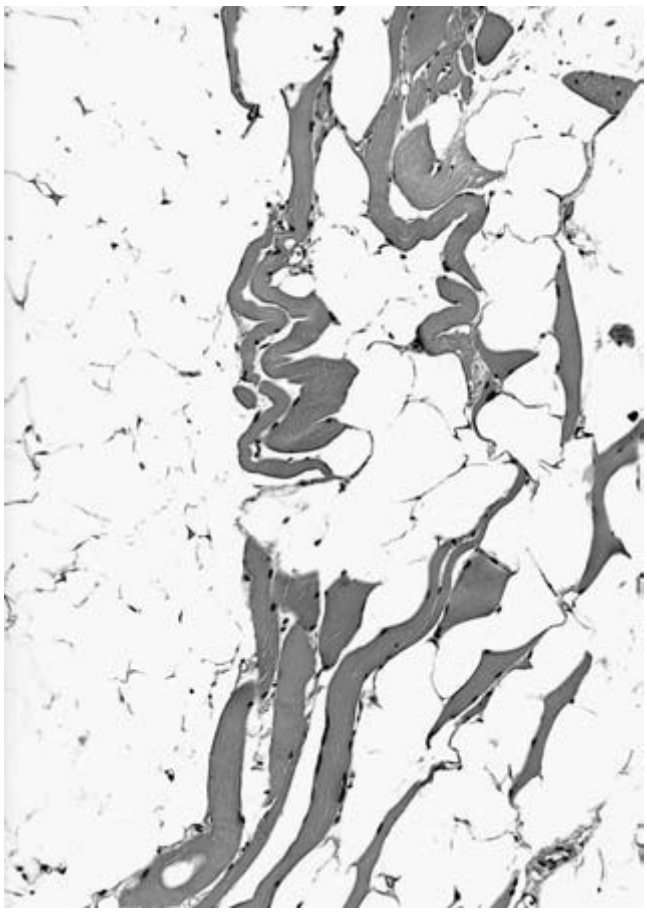


Fig. 30.8 Infiltrative lipoma in a dog. Mature lipocytes infiltrate between muscle bundles and individual muscle fibers.

Infiltrative angiolipoma

This subcutaneous lesion is composed of proliferating vascular structures, admixed with an infiltrative growth of well-differentiated fatty tissue as seen in infiltrating lipomas (Liggett et al., 2002). Infiltrative angiolipomas may penetrate underlying muscle. The proliferating vascular channels are lined by well-differentiated endothelial cells.

Infiltrating angiolipoma that affects muscle has been considered an entity that must be differentiated from intramuscular hemangioma (also called mixed intramuscular hemangioma; Liggett et al., 2002). However, this may be an issue of nomenclature, as both neoplasms feature proliferation of vessels as well as adipose tissue within muscle (Liggett et al., 2002). Intramuscular hemangiomas originate within the muscle, whereas infiltrative angiolipomas originate in the subcutaneous fat and invade the underlying muscle; it may be impossible to determine the exact origin in most cases.

Differentiation of infiltrative angiolipoma from infiltrative hemangioma and progressive angiomatosis may not be possible based on small core biopsies. Large excisional biopsies are necessary to appreciate the combined proliferation of vascular structures and fatty tissue seen in infiltrative angiolipoma. The vascular structures in angiolipomas are more consistently composed of thin-walled vessels lined by flat endothelial cells; arteriovenous structures often featured in angiomatosis are not observed.

LIPOSARCOMA

Liposarcoma is the most common malignant soft tissue tumor in humans (Weiss & Goldblum, 2001). Similar to the human classification, feline and canine malignant lipocytic tumors have been categorized as atypical lipoma, well-differentiated liposarcoma, myxoid liposarcoma, and pleomorphic (dedifferentiated) liposarcoma (Doster et al., 1986; Messick & Radin, 1989).

Ultrastructural evaluation suggests that canine liposarcomas evolve from precursor cells of white adipose tissue, also referred to as ordinary or unilocular adipose tissue, which is characterized by a signet ring appearance (Doster et al., 1986). The etiology of canine liposarcomas is largely unknown. Some strains of feline sarcoma virus have been associated with development of liposarcomas in kittens (Stephens et al., 1983).

Clinical features

Liposarcomas, which include atypical lipoma, are uncommon in dogs and very rare in cats; the incidence of canine and feline liposarcomas was less than 0.5% in one survey of all skin and subcutaneous tumors (Goldschmidt &

Shofer, 1992). The authors believe that liposarcomas are of much lower incidence in cats than in dogs; only a few feline cases have been reported (Carpenter et al., 1987; Tanimoto et al., 1987).

Liposarcomas are variably circumscribed, soft or fleshy masses that measure 2 cm or more in diameter. Most liposarcomas arise in the subcutis, but frequently involve the dermis secondarily (Goldschmidt & Shofer, 1992). With dermal involvement, the skin is thickened and often alopecic. Ulceration may occur in larger lesions. Most tumors involve the axial region and proximal legs (Goldschmidt & Shofer, 1992; Baez et al., 2004).

The average age of affected dogs is 9 to 10 years (Bevier & Goldschmidt, 1981; Doster et al., 1986; Baez et al., 2004); Shetland Sheepdogs and Beagles appear to be predisposed (Goldschmidt & Shofer, 1992). Sex predilections have not been observed. Too few cases of feline cutaneous liposarcoma have been reported to determine predilection data.

Biologic behavior of liposarcoma in humans is partially dependent upon the histopathologic subtype (Weiss & Goldblum, 2001); whereas atypical lipomas are considered of low-grade malignancy, dedifferentiated liposarcomas have a poor prognosis. Differences in behavior have not been conclusively shown in animals; however, in one large study, three of four dogs with metastatic disease at the time of surgery had pleomorphic liposarcomas (Baez et al., 2004). Recurrence of liposarcomas in dogs and cats following surgical excision has been considered a common event in some reviews (Theilen & Madewell, 1987), while Goldschmidt and Shofer (1992) considered it uncommon. A 28% recurrence rate among 43 dogs was reported; longest survival times were correlated with wide rather than marginal excision (Baez et al., 2004). The incidence of distant metastasis, however, is low in cats and dogs. Metastases of canine liposarcomas have been found in the lungs (Theilen & Madewell, 1987; Pulley & Stannard, 1990), but were reportedly rare at the time of surgery in a recent large report (Baez et al., 2004). Other locations for metastatic lesions are liver and bone (Theilen & Madewell, 1987).

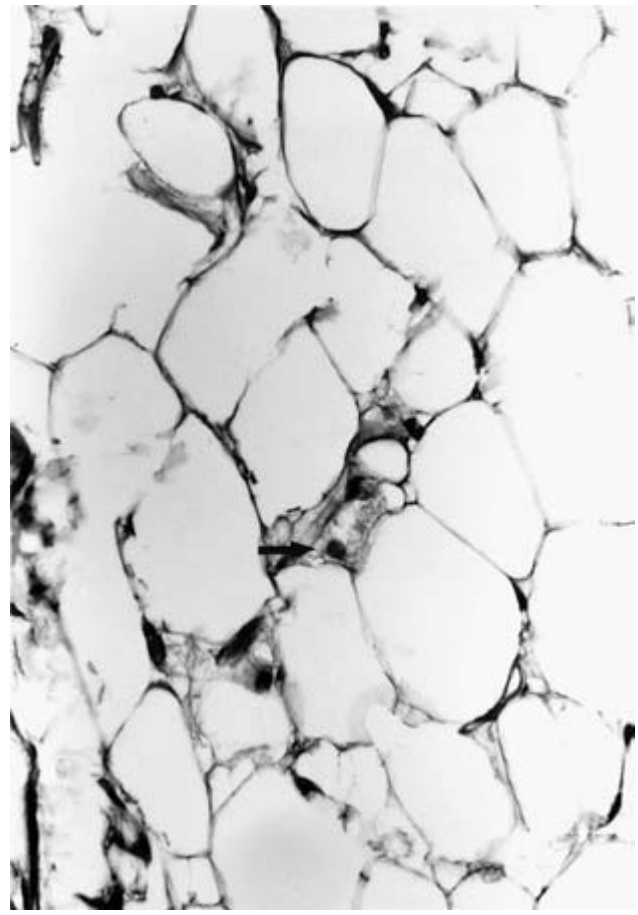


Fig. 30.9 Atypical lipoma in a dog. Admixed with mature fatty tissue there are scattered lipoblasts, characterized by small lipid vacuoles and small round nuclei (arrow).

Histopathology

Atypical lipoma (Figure 30.9)

The majority of these usually well-circumscribed but nonencapsulated masses are composed of well-differentiated lipocytes similar to lipomas. Sclerotic areas may be present. In comparison to lipoma there is subtle increased cellularity, and there are small numbers of individual or clustered lipoblasts dispersed amongst the well-differentiated lipocytes. Lipoblasts, the lipocyte precursor cells, are smaller, have large, centrally located nuclei and few small cytoplasmic vacuoles (Banks, 1993). Occasionally, mild pleomorphism, nuclear hyperchromatism, and rare mitotic figures are seen in these precursor cells. The presence of lipoblasts with occasional cellular atypia is considered an indication of an early transition to more aggressive behavior. Hence, atypical lipomas are best considered low-grade liposarcomas. One case of regional lymph node metastasis from a very large atypical lipoma in the front leg of a dog has been observed by the authors.

Atypical lipomas should be differentiated from mildly inflamed lipomas, from foci of mildly inflamed adipose tissue (steatitis), and from fibrolipomas. Inflamed fat contains lesional foamy macrophages, which may be difficult to differentiate from lipoblasts. Atypia and mitotic activity of lipoblasts may allow differentiation. In contrast to atypical lipomas, fibrolipomas have strands of fibrous tissue in an otherwise typical lipoma and no evidence of lipoblasts.

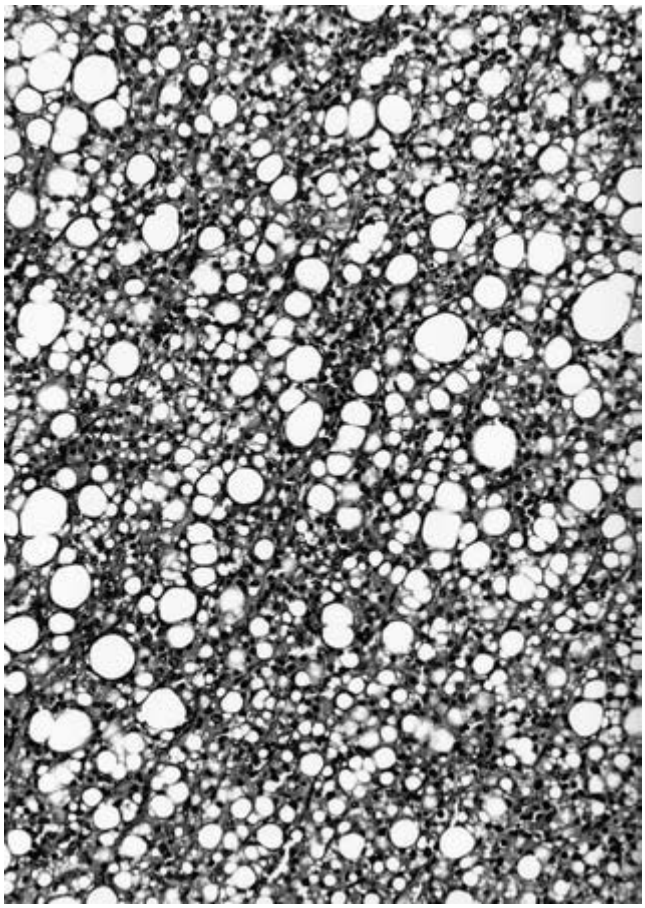


Fig. 30.10 Well-differentiated liposarcoma in a dog. Polygonal cells are arranged in solid sheets and contain lipid vacuoles of varying size.

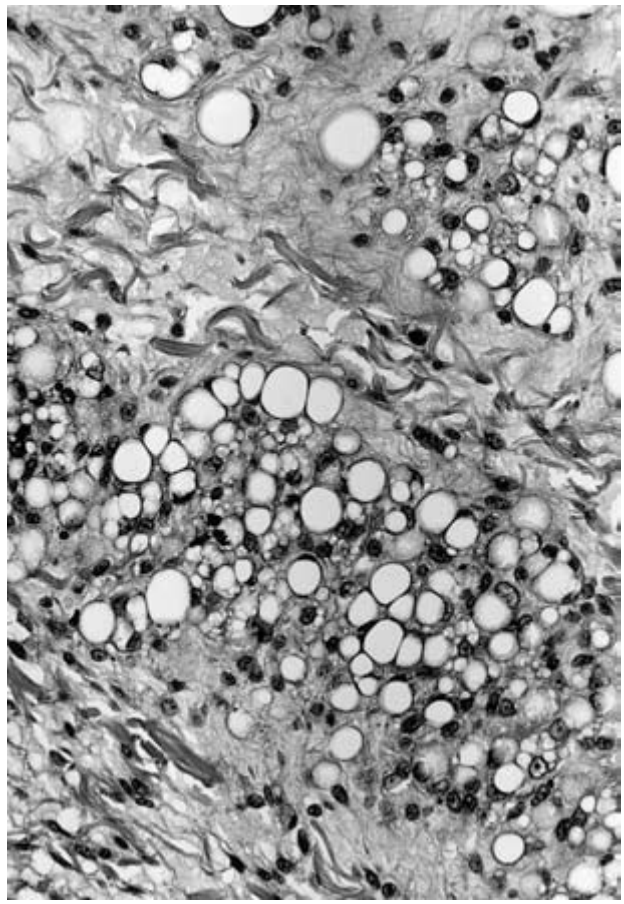


Fig. 30.11 Higher magnification of liposarcoma in a dog. The mass is dominated by lipoblasts containing numerous small lipid vacuoles; note admixed mature lipocytes.

Well-differentiated liposarcoma (Figures 30.10 and 30.11)
This is the most common histopathologic subtype of liposarcoma. Multilobular, fairly well-circumscribed, but unencapsulated neoplasms arise from the subcutis and often infiltrate the dermis. The masses comprise large, round to polygonal cells arranged in solid sheets. Stromal collagen production is not observed. Occasionally, there is a component of admixed spindle cells embedded in myxoid stroma.

The majority of tumor cells have abundant cytoplasm and variable numbers of easily recognizable intracytoplasmic lipid droplets. Moderate numbers of cells have single large lipid vacuoles, resulting in peripheral nuclear displacement as in mature lipocytes. Other cells resemble lipoblasts (lipocyte precursors), and contain central nuclei and small numbers of delicate lipid droplets. Lipoblastic nuclei are large and pleomorphic; they are often round with marginated chromatin and prominent nucleoli. Mitotic activity is low, but most of the mitoses are atypical. Hemorrhage, necrosis, fibrosis, and ulceration are secondary features.

In general, the differential diagnosis of liposarcoma is not problematic. The presence of well-differentiated lipocytes and moderate numbers of lipoblasts usually separates well-differentiated liposarcomas from other mesenchymal malignancies.

Myxoid liposarcoma (Figures 30.12 and 30.13)
This is a less common variant of liposarcoma, characterized by a background of mucin (Messick & Radin, 1989). The masses are unencapsulated with poorly defined margins. They are composed of a mixture of lipocytes, lipoblasts, spindle cells, and stellate cells. The myxoid ground substance, demonstrable with Alcian blue stain at pH 2.5, may be intermingled with small numbers of collagen fibrils. A delicate anastomosing capillary vasculature is present. Lipocytes are fairly well differentiated and usually have single large cytoplasmic lipid vacuoles. There are variable numbers of lipoblasts, usually few, as well as

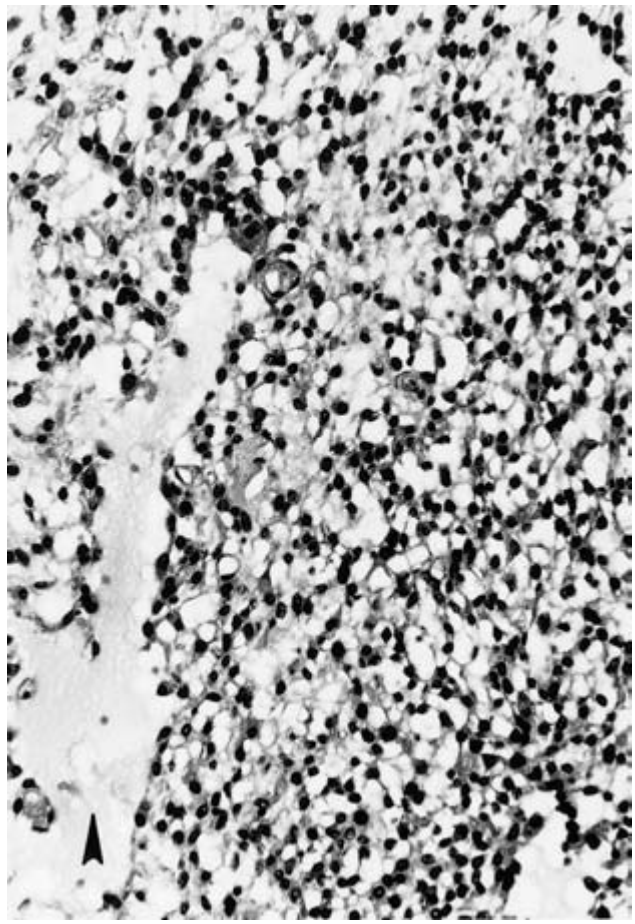


Fig. 30.12 Myxoid liposarcoma in a dog. There is a bubbly appearance of the stroma and single lipid vacuoles in many of the tumor cells. Note mucin lake at left (arrow).

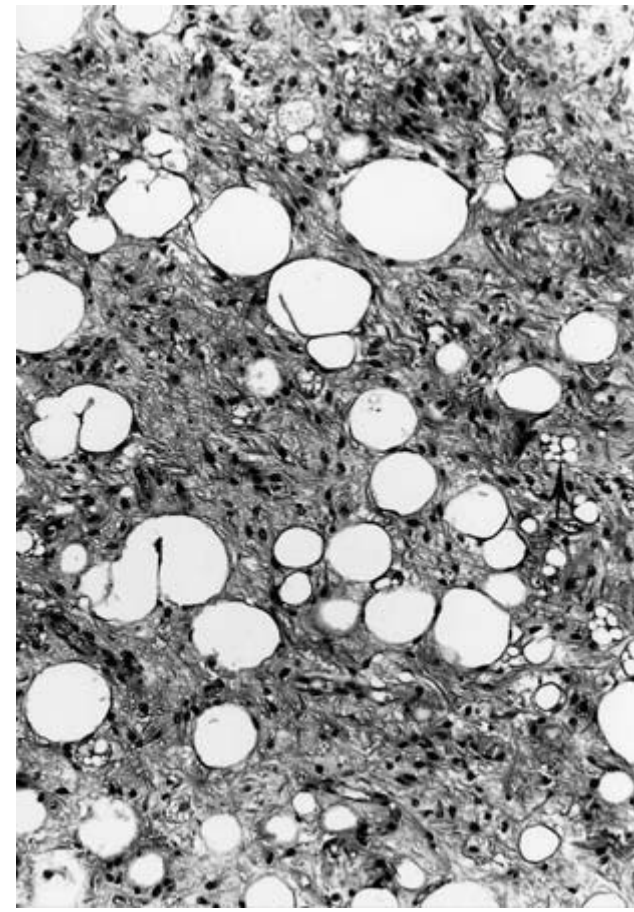


Fig. 30.13 Myxoid liposarcoma in a dog. Spindle and stellate cells predominate in this example and are distributed haphazardly through a stroma of mucin and collagen fibers. Note scattered mature lipocytes with single large vacuoles and lipoblasts (arrow at right) with multiple small vacuoles.

occasional multinucleated cells. Stellate and spindle cells are arranged haphazardly or in interlacing bundles; in some areas they may predominate. Nuclear features of the spindle cell population resemble those of fibrosarcoma or myxosarcoma (see Chapter 27). These spindle cells have few cytoplasmic lipid droplets or may lack any evidence of lipid storage.

Differential diagnoses for myxoid liposarcoma include myxoid variants of other spindle cell malignancies, e.g. myxosarcoma and myxoid peripheral nerve sheath tumors. If cells of obvious lipocyte lineage are sparse or absent, differentiation of myxoid liposarcomas from these sarcomas may not be possible based on histomorphology. Oil red O stains on frozen sections may help to identify intracytoplasmic fat within the tumor cells.

Pleomorphic liposarcoma (Figure 30.14)

This rare variant of liposarcoma is characterized by tumor cells that vary markedly in size and shape. Multinucleated giant cells are common, and comprise tumor cells or reactive leukocytic giant cells. Stromal production of mucin or collagen is not observed. The cells have abundant eosinophilic cytoplasm that may appear glassy or foamy. Distinct lipid vacuoles are usually recognizable in small numbers of neoplastic cells (lipoblasts). Nuclei also exhibit marked variability in size, shape, and chromatin pattern. Nuclear hyperchromatism is common and nucleoli are prominent. Many mitoses are present, and atypical mitoses are common.

Pleomorphic liposarcomas with scant lipoblasts may be difficult to differentiate from other pleomorphic mesenchymal malignancies, particularly histiocytic sarcomas (see Chapter 35). Pleomorphic liposarcomas with numerous multinucleated giant cells may present as anaplastic sarcomas with giant cells (see Chapter 33).

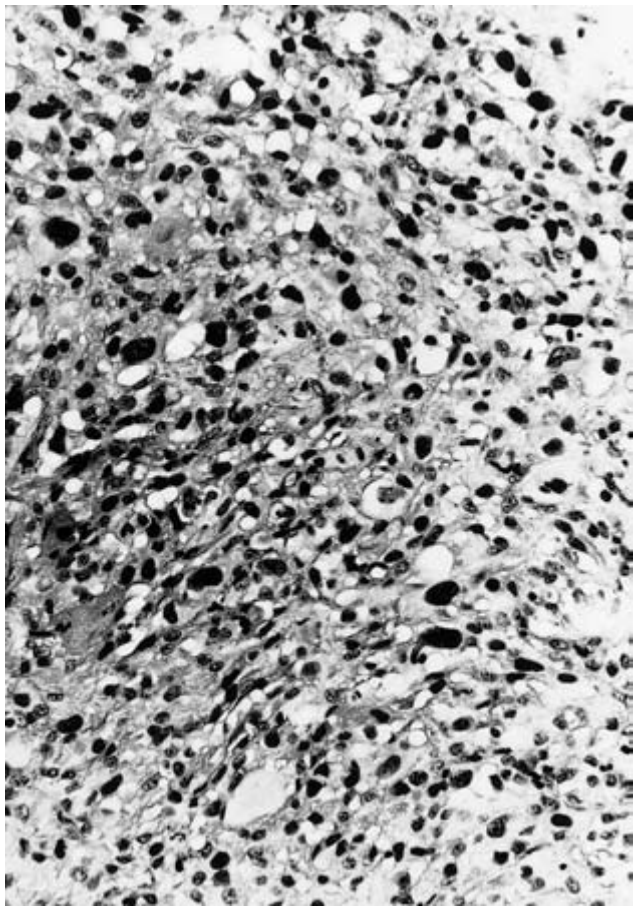


Fig. 30.14 Pleomorphic liposarcoma in a dog. Solid sheets of highly pleomorphic polygonal cells exhibit variable lipid vacuolation. Note markedly enlarged, hyperchromatic nuclei.

Immunohistochemistry

Immunohistochemistry generally is not useful in the identification of liposarcomas or in their differentiation from other mesenchymal malignancies. Lipocytes, like other mesenchymal cells, express vimentin but do not express other known surface or cytoplasmic proteins specific for this cell type. Therefore, immunohistochemistry does not allow differentiation between myxosarcoma and myxoid liposarcoma, for example, or between pleomorphic liposarcoma and other undifferentiated mesenchymal malignancies. Differentiation of myxoid liposarcoma from the myxoid variant of peripheral nerve sheath tumor also may be problematic, as neoplastic lipocytes occasionally express S100, and peripheral nerve sheath tumors are not consistently positive for S100. Some nerve sheath tumors, in contrast to lipocytic neoplasms, express glial fibrillary acidic protein (GFAP). In contrast to liposarcoma, peripheral nerve sheath tumors have a basal lamina surrounding each tumor cell that can be demonstrated by immunohistochemistry for laminin and collagen IV. Pleomorphic liposarcomas can be differentiated from histiocytic sarcomas by their lack of expression of common leukocyte markers (CD45, CD18).

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Chapter 31

Smooth muscle and skeletal muscle tumors

Muscle tumors of the skin are usually composed of smooth muscle; both leiomyoma and leiomyosarcoma have been described (Weiss & Goldblum, 2001a,b). Skeletal muscle proliferations include skeletal muscle hamartoma, rhabdomyoma, and rhabdomyosarcoma (Weiss & Goldblum, 2001c,d). All of these tumors, with the exception of rhabdomyoma, are observed in dogs and/or cats.

Under the influence of transforming growth factor-beta (TGF-β) and granulocyte–monocyte colony stimulating factor (GM-CSF), fibroblasts may transform into myofibroblasts (Schuerch et al., 1997) that display myoblastic features. Proliferations of myofibroblasts are discussed with fibrosarcomas (myofibroblastic fibrosarcomas; see Chapter 27).

Both smooth and skeletal muscles express the intermediate filaments vimentin, actin, and desmin (Folpe & Gown, 2001). Muscle isoforms of actin include α-smooth-muscle actin, expressed by smooth muscle cells and myofibroblasts, and pan-muscle actin, expressed by smooth muscle, myofibroblasts, and skeletal muscle. Desmin, although fairly characteristic of muscle cells, is occasionally also expressed by nonmuscle cells, including fibroblastic reticulum cells in the lymph node, submesothelial fibroblasts, and endometrial stromal cells. Skeletal muscle cells can be differentiated from smooth muscle cells by their expression of myoglobin, myogenic transcription factors, and lack of expression of α-smooth-muscle actin, as well as by electron microscopic documentation of striation (Folpe & Gown, 2001).

LEIOMYOMA

Cutaneous leiomyomas may arise from vascular smooth muscle, arrector pili muscle (piloleiomyoma), or from deep dermal smooth muscle of the genital region (Goldschmidt & Shofer, 1992; van der Wall, 1981; Weiss & Goldblum, 2001; Liu & Mikaelian, 2003). Some tumors of vascular smooth muscle also have a vasoproliferative component; these are termed angioleiomyomas. The perifollicular dermis harbors the mid-dermal vascular plexuses and the bulk of the arrector pili muscles. This may explain why dermal leiomyomas are often closely associated with adnexal structures.

Cutaneous leiomyomas (including piloleiomyomas) occur in both cats and dogs. Angioleiomyoma has been reported in a cat (Liu & Mikaelian, 2003). Some dermal smooth muscle proliferations may represent smooth muscle hamartomas rather than true leiomyomas. Putative hamartomas of arrector pili muscle have been described in the dog (Liu & Mikaelian, 2003); however, the histologic description did not diverge significantly from leiomyoma. In contrast to the nodular lesions described by Liu and Mikaelian (2003), smooth muscle hamartomas in humans are poorly-delineated plaques containing enlarged, disoriented, but discrete muscle bundles that are usually admixed with large hair follicles (Ragsdale, 1997). Nodular benign smooth muscle proliferations arising from arrector pili muscle will be discussed as piloleiomyomas in this text.

One report describes bilateral rhabdomyomas on the convex surface of the pinnae in four white cats (Roth, 1990). It is the authors' opinion that these lesions are more consistent with leiomyomas.

Clinical features

Smooth muscle tumors of the skin are very rare in dogs (Bevier & Goldschmidt, 1981; Goldschmidt, 1985). Leiomyomas have been reported in feline skin, but there is no data for their incidence (Finnie et al., 1995; Cooper & Valentine, 2002; Liu & Mikaelian, 2003).

Cutaneous leiomyomas are solitary, well-circumscribed, firm, round to ovoid nodules that are less than 2 cm in diameter. They mostly occur on the vulva, perineal area, groin, head, and back. Piloleiomyomas in dogs have been recognized on the dorsal trunk, legs, and head (Liu & Mikaelian, 2003). Interestingly, leiomyomas have not been reported in the scrotum, which contains abundant smooth muscle. Feline piloleiomyomas have been observed in the skin of the thigh and the dorsal muzzle (Liu & Mikaelian, 2003). Age and breed predilections for smooth muscle proliferations have not been documented.

Histopathology

Typical leiomyomas are small, circumscribed, but unencapsulated dermal nodules composed of long, plump spindle cells arranged in interlacing fascicles. There is little or no collagenous stroma. Frequently there are one or several adnexal structures enclosed in the mass, and the interlacing muscle fascicles tightly surround entrapped hair follicles and glands. The spindle cells have abundant pink cytoplasm with perinuclear vacuolation. These perinuclear vacuoles contain glycogen, which can be demonstrated with a periodic acid–Schiff (PAS) stain. Nuclei are bland and elongated; they are blunt-ended and have frequent chromatin crossbars. A twisted appearance may characterize some nuclei. Mitotic figures are usually not present. Leiomyomas stain yellow with van Gieson's stain. Masson's trichrome stain colors smooth muscle red, and longitudinal cytoplasmic striation may be apparent. Rarely, the tumors are secondarily ulcerated and inflamed.

Leiomyomas may be confused with fibromas. In contrast to leiomyomas, fibromas contain obvious interstitial collagen, and the nuclei of fibroblasts tend to be more tapered rather than blunt-ended as in leiomyomas. The collagen in fibromas stains red with van Gieson's stain and blue with Masson's trichrome stain. These special stains are usually sufficient to differentiate between fibroma and leiomyoma, if needed.

Piloleiomyoma (Figure 31.1)

These leiomyomas arise from the arrector pili muscles. The connection of the neoplasm to pre-existing arrector pili muscles is reportedly fairly evident in dogs, while it may be difficult to see in cats (Liu & Mikaelian, 2003). Osseous metaplasia has been observed in one cat with multiple piloleiomyomas (Finnie et al., 1995). The connection with the arrector pili muscles differentiates piloleiomyoma from other leiomyomas or from dermal fibromas.

Angioleiomyoma

As described in a single cat, this well-delineated tumor is composed of packed, interlacing bundles of smooth muscle fibers originating from vessel walls. The muscle bundles are composed of plump spindle cells with indistinct cell borders. The vessels within the mass are also proliferative (Liu & Mikaelian, 2003). Occasionally, the vascular spaces are very thin and cleft-like. The tumor cells blend imperceptibly into the muscle layer of the vascular walls. The endothelial cells lining the vessels of origin lack evidence of atypia (Liu & Mikaelian, 2003). The association with blood vessels differentiates angioleiomyoma from other leiomyomas or from dermal fibromas.



Fig. 31.1 Piloleiomyoma in a dog arising from the arrector pili muscle (arrow). (Case material courtesy S.M. Liu.)

Immunohistochemistry

Smooth muscle is vimentin-positive, as are other mesenchymal tissues. The expression of desmin and α-smooth-muscle actin assists in the identification of smooth muscle origin. Fibromas lack expression of desmin and α-smooth-muscle actin (Andreasen & Mahaffey, 1987).

LEIOMYOSARCOMA

Leiomyosarcoma in humans includes myxoid, epithelioid, and pleomorphic variants (Weiss & Goldblum, 2001). Cutaneous leiomyosarcomas have been reported in both dogs and cats, but myxoid and epithelioid variants have not been identified in those species (Brodey, 1970; Cooper & Valentine, 2002). Canine and feline leiomyosarcomas may originate from arrector pili muscles (piloleiomyosarcoma) or from vessel walls (angioleiomyosarcoma) (Carpenter et al., 1987; Liu & Mikaelian, 2003). Pleomorphic variants are also recognized; some of these resemble anaplastic sarcomas with giant cells (see Chapter 33).

Cutaneous malignant smooth muscle tumors of dogs and cats may be underdiagnosed due to their resemblance to far more common spindle-cell tumors such as fibrosarcomas, peripheral nerve sheath tumors, and histiocytic sarcomas. An intravascular leiomyosarcoma has been reported in a digit of a cat (Jacobsen & Valentine, 2000); the authors believe that this lesion is more consistent with a glomus tumor (see Chapter 29).

Clinical features

Leiomyosarcomas of the skin are rare in dogs and cats. Canine and feline leiomyosarcomas are small, nonulcerated, predominantly dermal tumors. Leiomyosarcomas of the perineal areas occur in cats and dogs (Cooper & Valentine, 2002). Piloleiomyosarcomas have been observed on the trunk, legs, and lip in dogs, and on the thigh in a cat (Liu & Mikaelian, 2003). Angioleiomyosarcomas were reported on the face of one cat and on the extremities, including pawpads, in dogs (Liu & Mikaelian, 2003).

Breed and age predilections are not available. Leiomyosarcomas are locally invasive and tend to recur after incomplete excision. Metastatic lesions have not been reported (Liu & Mikaelian, 2003).

Histopathology

Leiomyosarcoma (Figure 31.2)
In general, leiomyosarcomas are variably circumscribed but unencapsulated dermal neoplasms that may extend into the subcutis. The overlying epidermis may be hyperplastic or ulcerated. There is minimal stromal collagen.

Most recognized leiomyosarcomas are well differentiated and are composed of long, plump spindle cells arranged in bundles. The neoplastic cells have abundant eosinophilic cytoplasm or a clear appearance due to variable cytoplasmic vacuolation. Nuclei are of medium size; the majority retain the typical blunt-ended, elongated configuration of typical smooth muscle cells. Some nuclei appear twisted. Nucleoli are small. The chromatin is stippled or marginated, and chromatin crossbars can usually be detected. Occasionally, moderate anisocytosis and anisokaryosis are seen. Mitotic activity is low to moderate. Similar to their benign counterpart, leiomyosarcomas stain yellow with van Gieson's stain. Masson's trichrome stain colors the neoplastic cells red and often reveals a longitudinal cytoplasmic striation.

In contrast to leiomyomas, leiomyosarcomas are characterized by an expansive and invasive growth pattern, higher cellularity, and cellular atypia. The differential diagnosis of cutaneous leiomyosarcoma may be difficult due the histopathologic similarity to other spindle cell tumors with scant stroma, such as fibrosarcomas, myofibroblastic fibrosarcomas, spindle cell predominant histiocytic sarcomas, and malignant peripheral nerve sheath tumors. Even blunt-ended or twisted nuclear morphology may not be reliably predictive of smooth muscle origin; in a small study of several tumors with typical smooth muscle morphology, the authors were unable to confirm smooth muscle origin using immunohistochemistry (see below).

Fibrosarcoma and myofibroblastic fibrosarcoma contain variable amounts of collagen, which stains red with van Gieson's stain and blue with Masson's trichrome stain. In contrast to well-differentiated leiomyosarcomas, most histiocytic sarcomas contain some individualized round cells with abundant cytoplasm, as well as giant cells, admixed with the spindle cells. Distinction between histiocytic sarcoma and potential epithelioid variants (as seen in humans) of leiomyosarcoma would require

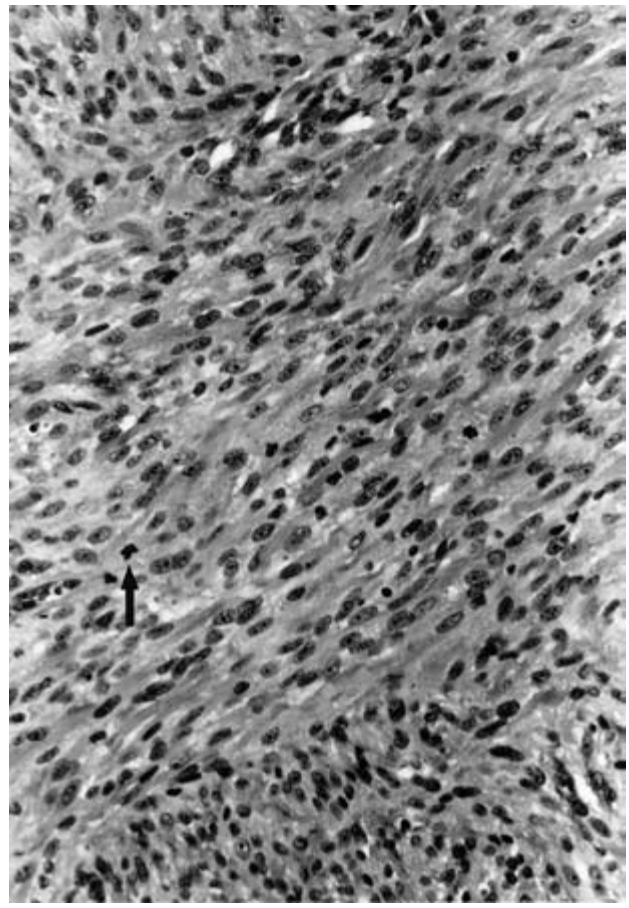


Fig. 31.2 Leiomyosarcoma in a dog confirmed by immunohistochemistry. The tumor cells have elongated, blunt-ended nuclei and often one nucleolus. There is moderate anisokaryosis and occasional mitotic figures (arrow) are present. (Case material courtesy S.M. Liu.)

immunohistochemistry (see below). Malignant peripheral nerve sheath tumors are composed of smaller spindle cells with fusiform or serpentine nuclei. The cells may be arranged in palisades, or they may be embedded in a mucinous matrix; these patterns are not observed with well-differentiated leiomyosarcoma.

Piloleiomyosarcoma (Figure 31.3)

These tumor nodules resemble piloleiomyomas (see p. 778) and connect to pre-existing arrector pili muscles (Liu & Mikaelian, 2003). Adnexal appendages may be entrapped within the tumor mass (Liu & Mikaelian, 2003). In contrast to their benign counterparts, piloleiomyosarcomas are composed of more pleomorphic, plump spindle cells, which occasionally show nuclear palisading and packeting. Central areas of necrosis, inflammation secondary to ulceration, and ruptured follicles may be present. A mitotic rate of 2 or more per 10 high power fields (40×) has been reported (Liu & Mikaelian, 2003).

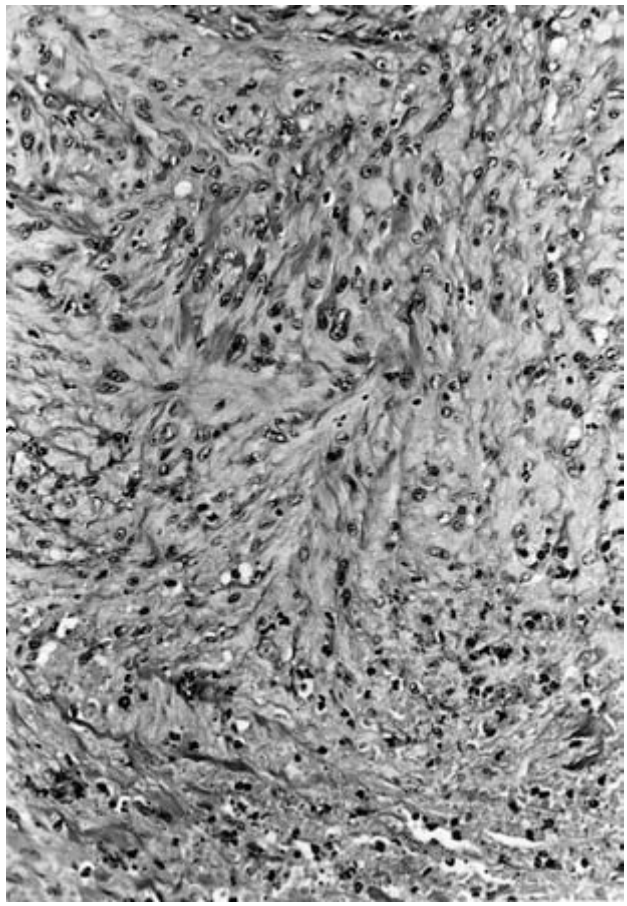


Fig. 31.3 Pleomorphic piloleiomyosarcoma in a dog confirmed by immunohistochemistry. The pleomorphic spindle cells are arranged in interlacing bundles. There is prominent anisokaryosis. Note the focus of necrosis at bottom. (Case material courtesy S.M. Liu.)

Differential diagnoses of piloleiomyosarcoma are those of routine leiomyosarcoma (see above). However, in contrast to piloleiomyosarcomas, other mesenchymal neoplasms do not connect to pre-existing arrector pili muscles.

Angioleiomyosarcoma

Angioleiomyosarcomas are closely connected with vascular structures and originate from the muscular media of pre-existing dermal blood vessels. The tumor cells blend into the muscle layer of the vascular walls. Closely packed interlacing bundles of plump spindle cells surround capillaries, veins, arterioles, arteries, or thin cleft-like vascular spaces. The tumor cells resemble those of routine leiomyosarcomas.

Differential diagnoses of angioleiomyosarcoma are similar to those of leiomyosarcoma (see above). In contrast to angioleiomyosarcoma, these other mesenchymal tumors do not connect to the wall of pre-existing blood vessels. In addition, angioleiomyosarcomas may require differentiation from spindle cell glomus cell tumors. Glomus tumors entrap numerous endothelial-lined capillary-like vascular structures, and often small nerves are seen along the margin of the tumor. Angioleiomyosarcomas are composed of smooth muscle cells proliferating from the muscular layer of intralesional vessels.

Pleomorphic leiomyosarcoma

These tumors are poorly demarcated and are invasive into the surrounding tissues. They are composed of plump spindle cells with abundant eosinophilic cytoplasm and large vesicular, oval to elongated, blunt-ended nuclei with marginated and occasionally stippled chromatin. In comparison to routine leiomyosarcomas, pleomorphic leiomyosarcomas are characterized by moderate to marked anisocytosis and anisokaryosis of the tumor cells. The mitotic activity is moderate to high and bizarre mitotic figures may be seen. There may be variable numbers of elongated and occasionally stellate multinucleated tumor giant cells. These giant cells may have prominent anisokaryosis. In addition, there may be multinucleated giant cells with more monomorphic round nuclei. The latter include tumor giant cells as well as reactive giant cells of leukocytic origin. Pleomorphic, poorly differentiated leiomyosarcomas, particularly those with numerous giant cells, may present as anaplastic sarcomas with giant cells (see Chapter 33).

The principal differential diagnosis for pleomorphic leiomyosarcoma is rhabdomyosarcoma. Cross-striations, which can be visualized by phosphotungstic acid–hematoxylin (PTAH) stain or electron microscopy, separate rhabdomyosarcomas from pleomorphic leiomyosarcomas. In addition, pleomorphic leiomyosarcomas

need to be differentiated from poorly differentiated fibrosarcomas and myofibroblastic fibrosarcomas, as well as histiocytic sarcomas. Immunohistochemistry is often required to determine the cell of origin as all are pleomorphic and may feature giant cells (see below). Fibrosarcomas and myofibroblastic fibrosarcomas are composed of spindle cells with elongated and more pointed nuclei, while leiomyosarcomas generally have blunt-ended nuclei; however, nuclear morphology often is not reliably predictive (see above). Moreover, fibrosarcomas and myofibroblastic fibrosarcomas produce variable collagen, which stains red with van Gieson's stain and blue with Masson's trichrome stain; this is in contrast to the scant or absent stroma seen in leiomyosarcomas. The presence of large, round, cytoplasm-rich tumor cells admixed with plump spindle-shaped tumor cells suggests histiocytic sarcoma; immunohistochemistry may be required.

Immunohistochemistry

Like other mesenchymal tumors, leiomyosarcomas are positive for vimentin. The expression of desmin and α-smooth-muscle actin identifies smooth muscle origin (Andreasen & Mahaffey, 1987). In contrast, fibrosarcomas, peripheral nerve sheath tumors, and histiocytic sarcomas lack expression of α-smooth-muscle actin and desmin. In contrast to muscle tumors, some peripheral nerve sheath tumors may be positive for S100 and express glial fibrillary acidic protein (GFAP) and neuron-specific enolase (NSE). Histiocytic sarcomas consistently express common leukocyte antigens CD45 and CD18, and as dendritic antigen presenting cells they are also positive for CD1, CD11c, and MHC II. In contrast to leiomyosarcomas, rhabmyosarcomas lack expression of α-smooth-muscle actin but express pan-muscle actin and myoglobin. Myofibroblastic fibrosarcomas and glomus tumors coexpress vimentin and α-smooth-muscle actin; occasionally they may also express desmin. In those desmin-positive cases, immunohistochemical differentiation from leiomyosarcomas and angioleiomyosarcomas may not be possible.

CANINE SKELETAL MUSCLE HAMARTOMA

Skeletal muscle hamartomas, also referred to as striated muscle hamartomas, are rare lesions predominantly seen on the face and neck of newborn children (Weiss & Goldblum, 2001). Some children have other congenital anomalies associated with these hamartomas. Skeletal muscle hamartomas of the skin have not been reported in dogs and cats. The authors have observed a few cases in dogs.

Clinical features

The limited number of skeletal muscle hamartomas seen in dogs presented as small firm dermal or subcutaneous nodules with intact overlying epidermis. Based on the small number of cases observed, there were no sex or breed predispositions. Lesions were found in young dogs.

Histopathology (Figures 31.4 and 31.5)

Canine skeletal hamartomas are composed of multifocal nodules of small skeletal muscle fibers that are haphazardly distributed throughout the dermis. The fibers may be embedded in a collagenous stroma and surrounded by adnexal structures and adipose tissue. The overlying epidermis is normal. Skeletal muscle hamartomas in humans may show central calcification (Weiss & Goldblum, 2001), a feature not seen in the canine equivalent. Canine skeletal muscle hamartomas have unique histologic features and are easy to differentiate from other benign mesenchymal proliferations.

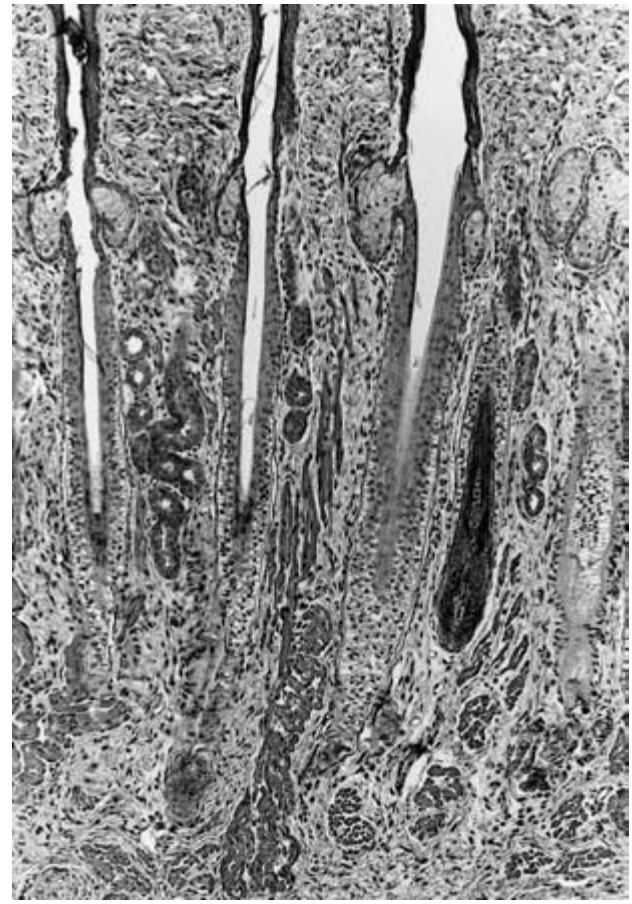


Fig. 31.4 Skeletal muscle hamartoma in a dog. Groups of darkly stained normal skeletal muscle fibers are embedded in the collagenous stroma of the interfollicular dermis.

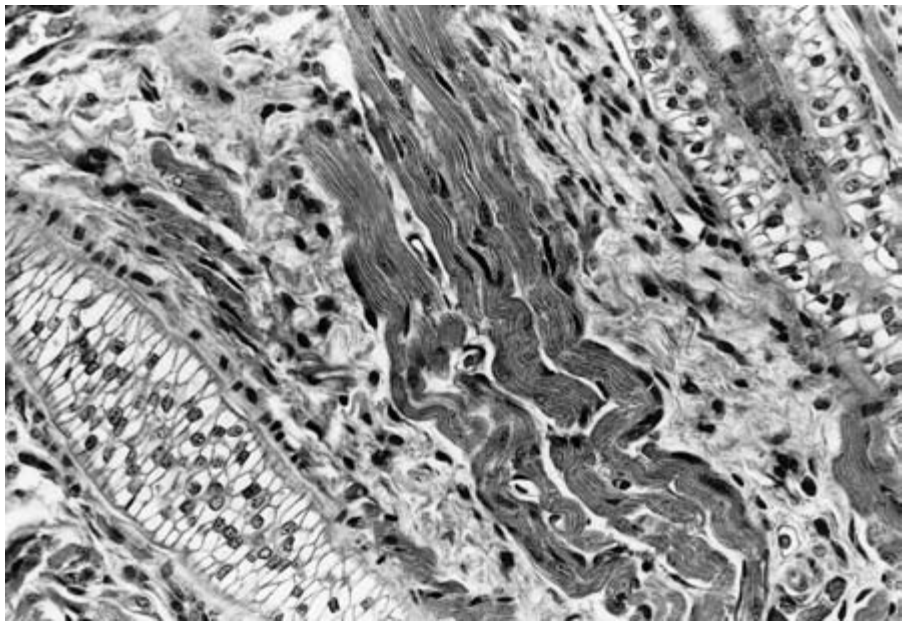


Fig. 31.5 Higher magnification of skeletal muscle hamartoma of Fig. 31.4 showing normal morphology of the skeletal muscle fibers.

RHABDOMYOSARCOMA

Primary cutaneous rhabdomyosarcomas in humans are extremely rare. More commonly, the dermis and subcutis may be secondarily infiltrated by an aggressive rhabdomyosarcoma arising from underlying tissue (Weiss & Goldblum, 2001). Rhabdomyosarcomas occur in cats (Macy & Bergman, 1995). One canine cutaneous rhabdomyosarcoma has been seen by one of the authors (E.J.W.).

Clinical features

Cutaneous rhabdomyosarcoma is extremely rare in cats. Most rhabdomyosarcomas in feline skin develop at the site of previous injection or vaccination (Macy & Bergman, 1995); the complex features of vaccine-induced sarcomas are discussed in Chapter 33. Rhabdomyosarcomas vary in size and may measure up to several centimeters in diameter. They are firm, poorly demarcated, often multilobulated masses, which arise in the deep subcutis and the underlying skeletal muscles. Due to tumor invasion into the dermis and subcutis, the skin is firmly adhered to the mass. Alopecia and ulceration are common.

Age and breed predilections are not known. The canine rhabdomyosarcoma was observed on the ventrolateral thorax of an 8-year-old Vizsla. The tumor recurred twice, but metastases were not observed.

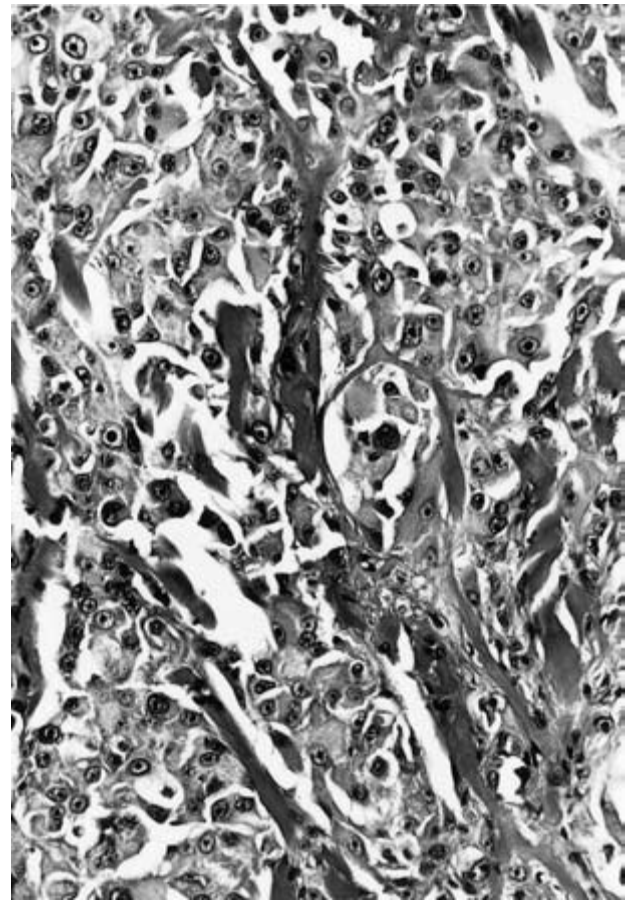


Fig. 31.6 Rhabdomyosarcoma in a dog. Pleomorphic plump spindle cells are associated with rudimentary, fragmented, darkly stained muscle fibers.

Histopathology (Figures 31.6 and 31.7)

Rhabdomyosarcomas are characterized by poorly demarcated subcutaneous masses that may extend into the

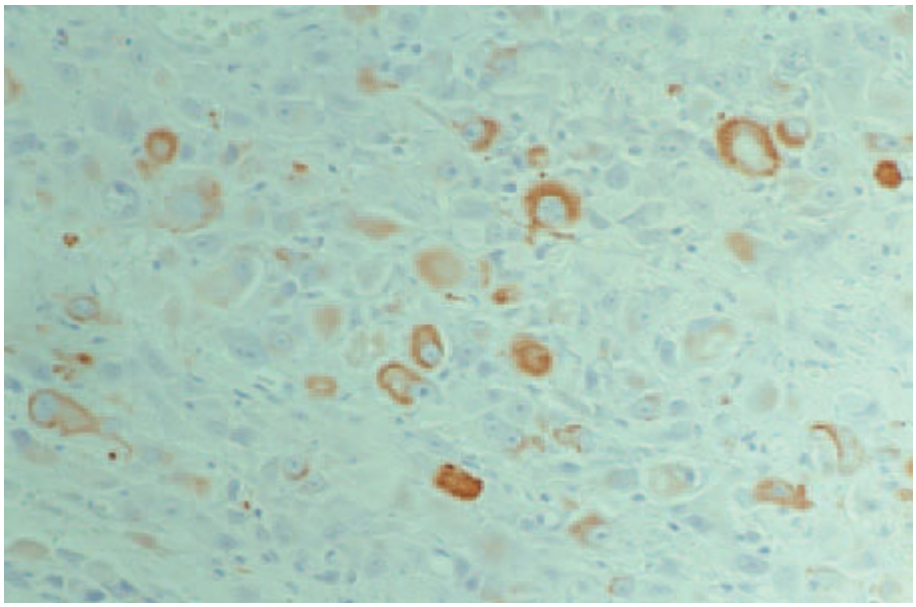


Fig. 31.7 Rhabdomyosarcoma of Fig. 31.6. Immunohistochemistry for desmin confirms the muscle origin of this sarcoma (chromogen aminoethylcarbazole [AEC]); α-smooth-muscle actin staining was negative.

dermis and the underlying skeletal muscles. Larger tumors often have areas of necrosis and an associated infiltrate of neutrophils. Pleomorphic spindle cells are arranged in irregular, partially interlacing bundles and occasional whorls. Neoplastic cells often trail into fiber-like structures. The spindle-shaped tumor cells have ovoid to elongated and vesicular nuclei with blunt ends and one or more prominent nucleoli, and variable eosinophilic cytoplasm. Occasionally, a mixture of vesicular and hyperchromatic nuclei is noted. The mitotic rate is highly variable, and atypical, bizarre mitotic figures may be observed. Multinucleated giant cells may be present, including both tumor giant cells and reactive leukocytic giant cells. Multinucleated tumor cells may have elongated nuclei arranged in a row. Highly pleomorphic, poorly differentiated rhabdomyosarcomas with abundant giant cells may present as anaplastic sarcomas with giant cells (see Chapter 33). Phosphotungstic acid–hematoxylin (PTAH) staining may reveal delicate cross-striations, also demonstrated by electron microscopy.

Rhabdomyosarcomas may be difficult to differentiate from other mesenchymal malignancies in which pleomorphism is present, including pleomorphic leiomyosarcomas, poorly differentiated fibrosarcomas and myofibroblastic fibrosarcomas, as well as histiocytic sarcomas. Moreover, poorly differentiated rhabdomyosarcomas may present as anaplastic sarcomas with giant cells (see Chapter 33). Leiomyosarcomas lack the cross-striations of skeletal muscle that are visualized by PTAH-stain or electron microscopy. Fibrosarcomas and myofibroblastic fibrosarcomas are composed of spindle cells with elongated and more pointed nuclei, while rhabdomyosarcomas have elongated blunt-ended nuclei; however, nuclear morphology often is not reliably predictive of cell type. Moreover, fibrosarcomas and myofibroblastic fibrosarcomas often produce a variable amount of collagen, which stains red with van Gieson's stain and blue with Masson's trichrome stain; this is in contrast to the scant or absent stroma seen in rhabdomyosarcoma. In contrast to rhabdomyosarcomas, histiocytic sarcomas are composed of a mixture of plumper spindle cells, arranged in dense bundles, as well as more individualized round cells with abundant cytoplasm.

Immunohistochemistry

Rhabdomyosarcomas express vimentin, pan-muscle actin, desmin, and myoglobin, but lack expression of α-smooth-muscle actin (Brown, 1987; Martin de las Mulas et al., 1992). In contrast to rhabdomyosarcomas, leiomyosarcomas lack expression of myoglobin, but express α-smooth-muscle actin instead. Myofibroblastic fibrosarcomas express α-smooth-muscle actin and some may coexpress desmin, but they consistently lack expression of myoglobin. Fibrosarcomas and histiocytic sarcomas express vimentin, but lack expression of any muscle-specific proteins. Histiocytic sarcomas are of leukocytic origin, and hence express the common leukocyte antigen CD45 and CD18 as well as CD1, CD11c, and MHC II.

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Chapter 32

Neural and perineural tumors

Nerves and nerve sheath cells originate from the neuroectoderm or neural crest (Weiss & Goldblum, 2001a,b). Cells forming the peripheral nerve sheath may produce collagen, and hence have characteristics similar to fibroblasts. Peripheral nerve sheath cells, in particular Schwann cells, are surrounded by a basal lamina that can be demonstrated by electron microscopy or by immunohistochemistry. Neural and perineural tumors include traumatic neuroma, and benign and malignant peripheral nerve sheath tumors.

Merkel cells form mechanoreceptors in conjunction with nerve terminals. The exact origin of Merkel cells has been debated (Kidd et al., 1971; Hashimoto, 1972; Ortonne & Darmon, 1985; Saurat et al., 1988; Saxod, 1996). Most recent evidence confirms neural crest origin for mammalian Merkel cells (Szeder et al., 2003); thus, Merkel cell tumors are included in this chapter.

TRAUMATIC NEUROMA

(Synonym: tail dock neuroma)

Neuromas are exuberant but non-neoplastic proliferations of nerve tissue (Weiss & Goldblum, 2001). They are a manifestation of traumatic or surgical nerve transsection followed by disorganized proliferation of the proximal nerve stump due to poor apposition or absence of the distal nerve segment. They are reported in many species and occur in a variety of anatomic locations. Neuromas in dogs are mostly seen as a sequel to cosmetic caudectomy; these are referred to as tail dock neuromas (Gross & Carr, 1990). Traumatic neuromas have not been reported in cats.

Clinical features

Neuromas in dogs are rare. Tail dock neuromas present as painful, alopecic, hyperpigmented, lichenified lesions of the docked tip of the tail. The underlying connective tissue is thickened and firm, and there is focal adhesion between the connective tissue and the skin.

Affected animals are less than 4 years of age and often have a prolonged history of severe self-trauma to the tail tip. Five of six dogs in the original report of Gross & Carr (1990) were Cocker Spaniels; this suggests a possible breed predilection.

Histopathology (Figure 32.1)

Tail dock neuromas are characterized by multiple small nerve bundles that are arranged individually and in clusters. These foci of proliferating neural tissue are randomly distributed through dense connective tissue, which is composed of thick collagen bundles with minimal cellularity, resembling scar tissue. The fibrous tissue extends throughout the dermis and through the subcutis to the periosteum of the caudal coccygeal vertebra. Axons within the nerve bundles are thinly myelinated, and the perineurium appears slightly thickened. The histological appearance of tail dock neuroma is unique; there are no known differential diagnoses.

MERKEL CELL TUMOR

(Synonym: neuroendocrine carcinoma)

Merkel cell tumors, which are also referred to as Merkel cell carcinomas, neuroendocrine carcinomas, or trabecular carcinomas, are fairly uncommon solitary round cell tumors of the skin and mucous membrane in humans (Lever & Schaumburg-Lever, 1990; Reed & Argenyi, 1997; Kerl & Hoffman-Wellenhof, 2003). The exact origin of the Merkel cell has been debated in the literature. Merkel cells express cytokeratin (CK) 20 and some desmosomal proteins, and they have tonofilament-like structures that converge upon the desmosomal structures (Kidd et al., 1971; Hashimoto, 1972; Ortonne & Darmon, 1985; Saurat et al., 1988). These observations indicate epithelial characteristics; Merkel cell tumors have also been referred to as cutaneous small cell undifferentiated carcinomas (Reed & Argenyi, 1997).

Origin from the neural crest has been proposed, char-

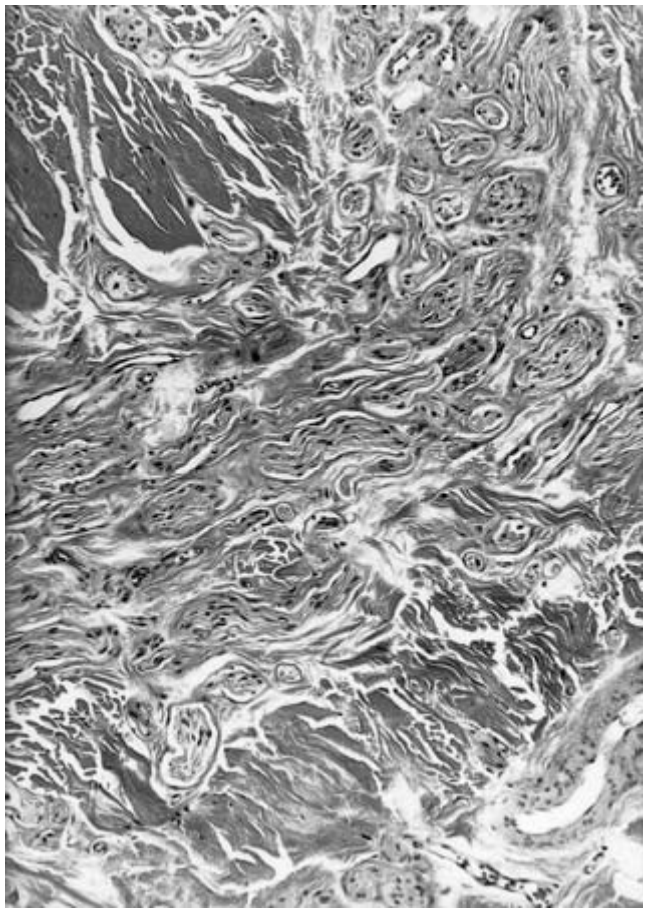


Fig. 32.1 Traumatic (tail dock) neuroma in a dog. Numerous small nerve bundles are distributed haphazardly through thick collagen resembling scar tissue.

acterizing Merkel cells as neuroendocrine cells and cells of the amine precursor uptake and decarboxylation (APUD) system (Saxod, 1996). The following findings support this hypothesis: Merkel cells have membrane-bound dense-core granules; they express neuron-specific enolase (NSE), chromogranin A, and synaptophysin (Folpe & Gown, 2001; DeLellis & Shin, 2002); and they also often connect with structures identified as a mitochondria-rich, nonmyelinated axon terminals (Hashimoto, 1972). Most recently, marked Merkel cells in whiskers and interfollicular skin of transgenic mice were found to express beta-galactosidase, confirming Merkel cells as neural crest descendants (Szeder et al., 2003).

Merkel cell tumors have been described in dogs and cats (Glick et al., 1983; Whiteley & Leininger, 1987; Konno et al., 1998; Patnaik et al., 2001; Bagnasco et al., 2003). Some of the early descriptions of Merkel cell tumor in these two species may, in fact, be of neoplasms of other origins, as cutaneous round cell tumors are difficult to differentiate based on morphologic features only. Accurate differentiation requires electron microscopic evaluation and immunohistochemistry (see below).

Clinical features

Merkel cell tumors are rare in dogs and cats. The tumor nodules are characterized by firm, intradermal, flesh-colored, or red nodules or plaques measuring up to 1.5 cm in diameter. The overlying skin may be alopecic. There are no known predilection sites in the skin; lesions also may occur in the oral cavity.

Merkel cell tumors are mostly seen in older dogs, ranging from 7 to 14 years (Glick et al., 1983; Whiteley & Leininger, 1987; Konno et al., 1998). The two feline cases were described in an 8-year-old and an 18-year-old (Patnaik et al., 2001; Bagnasco et al., 2003). The small number of cases published does not permit reliable conclusions regarding breed predilections.

In contrast to Merkel cell tumor in humans, most cases of canine Merkel cell tumors reported appear to have benign behavior (Whiteley & Leininger, 1987) and surgical excision is curative. While behavior was benign in one feline report (Bagnasco et al., 2003), in a second cat there was recurrence and pulmonary metastasis (Patnaik et al., 2001).

Histopathology (Figures 32.2 through 32.4)

In general, Merkel cell tumors are intradermal nonencapsulated masses that often extend into the subcutaneous tissue. Epidermis and follicular structures are not invaded. The tumor may be composed of solid nests and clusters of fairly monomorphic round cells surrounded by a delicate fibrovascular stroma to create packets. Cords and trabeculae of cells may be prominent, more closely resembling human Merkel cell tumors. The round tumor cells are characterized by a moderate amount of pale eosinophilic cytoplasm and centrally located, round or oval nuclei with a sharply defined nuclear membrane. The chromatin is evenly dispersed, or occasionally finely clumped and marginated. The nucleoli are small or inconspicuous. Cellular atypia is rare, and mitotic figures are occasionally seen.

On electron microscopy, the tumor cells have loosely arranged, often perinuclear intermediate filaments, rudimentary desmosomal structures, interdigitating cellular projections, and membrane-bound dense core granules, which are mainly concentrated in the cytoplasmic processes (Whiteley & Leininger, 1987). Grimelius argyrophilic stain colors the cytoplasm of variable numbers of tumor cells, as seen in other neuroendocrine tumors.

Differential diagnosis for Merkel cell tumors includes other cutaneous round cell tumors, such as plasmacytomas, mast cell tumors, balloon cell melanocytomas,

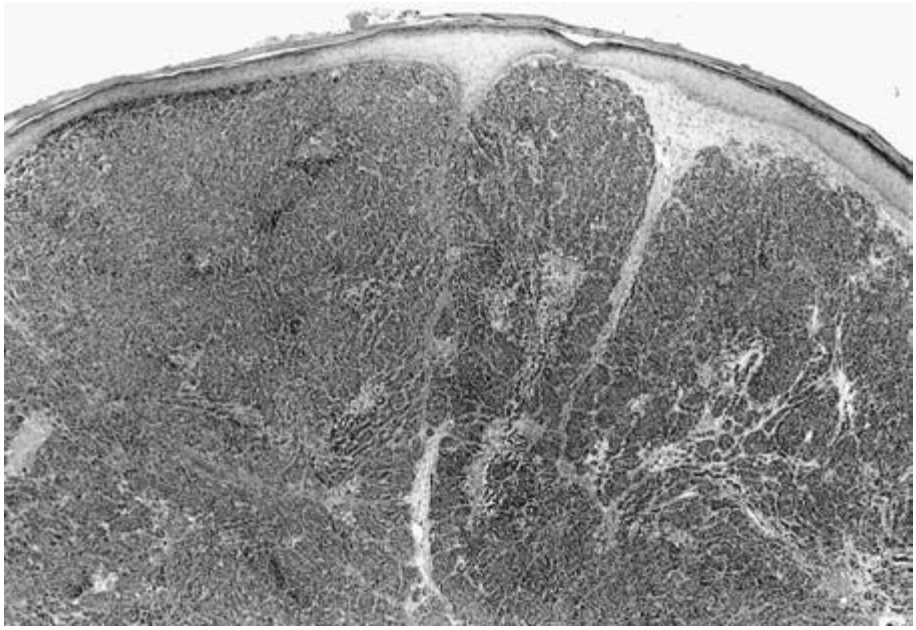


Fig. 32.2 Merkel cell tumor in a cat composed of small dark cells in nests and packets. (Case material courtesy F. Abramo.)

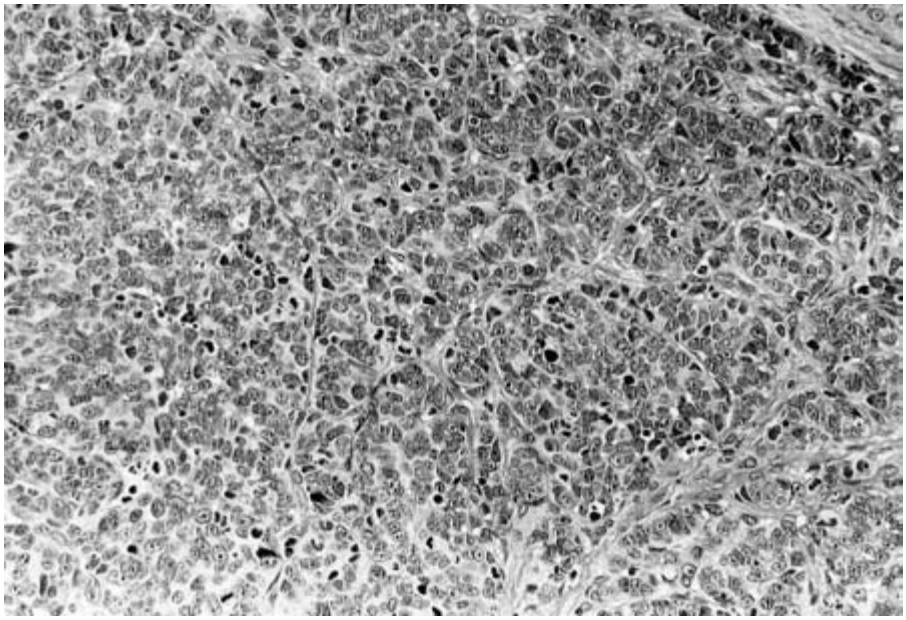


Fig. 32.3 Higher magnification of Merkel cell tumor in Fig. 32.2 showing packets of cells separated by a delicate fibrovascular stroma. The cells have round to oval nuclei with finely clumped chromatin.

round cell glomus tumors, histiocytomas, transmissible venereal tumors, and nonepitheliotropic lymphomas. Morphologic features and special stains may partially assist in differentiation, but often immunohistochemistry is required to identify the cell of origin (see below). Both nonepitheliotropic lymphoma and transmissible venereal tumors may be most difficult to differentiate from Merkel cell tumors based on morphologic features alone. Except for plasmacytomas, glomus tumors, and, to a lesser extent, transmissible venereal tumors, other round cell tumors are not arranged in packets. In contrast to Merkel cell tumors, plasmacytomas are composed of a more pleomorphic cell population characterized by eccentrically located nuclei and more basophilic cytoplasm; in addition, small to moderate numbers of multinucleated tumor cells are usually present. Mast cell tumors are characterized by intracytoplasmic metachromatic granules, which can be demonstrated by toluidine blue or Giemsa stains. Balloon cell melanocytomas are characterized by round cells that have a larger amount of clear cytoplasm when compared to Merkel cell tumors. Moreover, the presence of melanin, often requiring Fontana–Masson

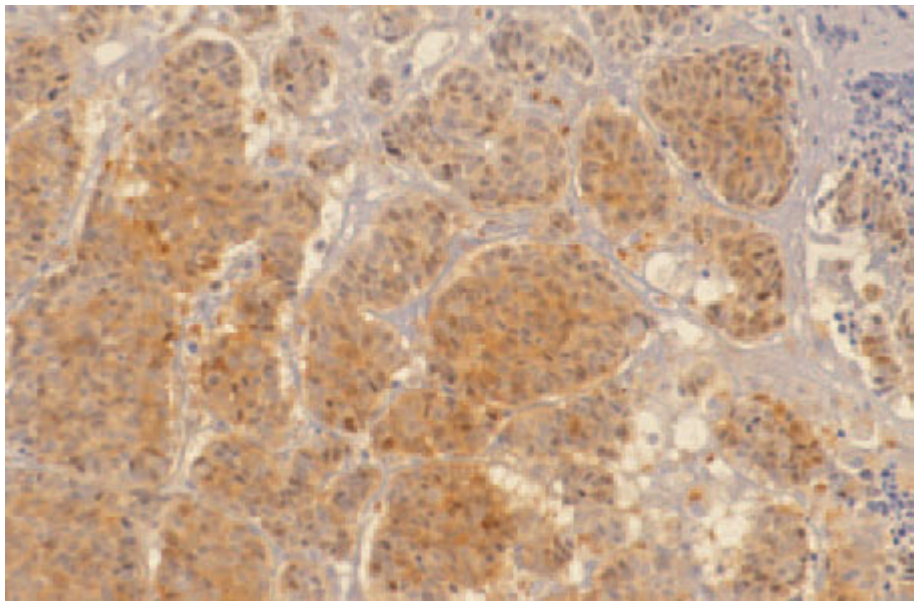


Fig. 32.4 Merkel cell tumor of Fig. 32.2. Immunohistochemistry with neuron-specific enolase (NSE) demonstrates positive cytoplasmic reactivity (chromogen diaminobenzidine [DAB]).

staining, differentiates melanocytomas from Merkel cell tumors. In contrast to Merkel cell tumors, glomus tumors are usually well circumscribed and associated with numerous vascular structures and nerves. Histiocytomas are often characterized by intraepidermal tumor cell aggregates, a feature not observed in Merkel cell tumors. During regression, both histiocytomas and transmissible venereal tumors have marked lymphocytic infiltration, a feature not seen in Merkel cell tumors.

Immunohistochemistry

Canine and feline Merkel cell tumors are positive for CK20 (detected with pancytokeratin stains), chromogranin A, and neuron-specific enolase (NSE) (Konno et al., 1998; Patnaik et al., 2001; Bagnasco et al., 2003). Feline and canine Merkel cell tumors have not been evaluated for expression of *c-kit* receptor; this receptor for stem cell factor is expressed by human Merkel cell tumors (Su et al., 2002).

Canine and feline Merkel cell tumors lack expression of the common leukocyte markers CD45 and CD18, which allows differentiation of Merkel cell tumors from leukocytic round cell tumors, including lymphoma, plasmacytoma, histiocytoma, mast cell tumor, and transmissible venereal tumor. Melanocytomas and glomus tumors lack expression of cytokeratins and chromogranin A. Melanocytomas express vimentin instead, and may be positive for melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), tyrosinase, S100, HMB-45/gp100, tyrosine-related protein-2 (TRP-2) or melanoma isoform of microphthalmia transcription factor (MITF-M). In contrast to Merkel cell tumors, glomus tumors express α-smooth-muscle actin and may occasionally also express desmin.

BENIGN PERIPHERAL NERVE SHEATH TUMOR

(Synonyms: schwannoma, neurofibroma)

Benign peripheral nerve sheath tumors in humans are often subclassified as schwannoma, neurothekeoma, neurofibroma, neurofibromatosis, and perineuroma (Weiss & Goldblum, 2001). This classification is based upon such features as presence or absence of encapsulation, amount and type of stroma, and presumed cell of origin (Weiss & Goldblum, 2001).

With the exception of benign myxoid peripheral nerve sheath tumors in dogs, which resemble myxoid schwannoma or neurothekeoma in humans, there is no clear-cut histopathologic subclassification of peripheral nerve sheath tumors in dogs and cats. Most benign canine and feline peripheral nerve sheath tumors have been presumed to be of Schwann cell origin (Cordy, 1990; Summers et al., 1992). There is a basal lamina surrounding single cells and groups of tumor cells, demonstrated by electron microscopy and immunohistochemistry (see below), which supports this hypothesis. As clinical and morphologic similarities amongst the proposed subclassifications outweigh the differences (Goldschmidt & Hendrick, 2002; Koestner & Higgins, 2002), the authors prefer to classify most of these tumors under the general name of peripheral nerve sheath tumor.

Clinical features

Benign cutaneous peripheral nerve sheath tumors are uncommon neoplasms in dogs and cats. However, the exact incidence of these tumors is difficult to evaluate as they have marked histopathologic and immunophenotypic similarities with other spindle cell tumors. Hence, they may be underdiagnosed or overdiagnosed, depending on the bias of the pathologist. Based on one large survey, the combined incidence of benign and malignant neural tumors is reported to be 0.5% in dogs and 1.4% in cats (Goldschmidt & Shofer, 1992).

In dogs, peripheral nerve sheath tumors usually present as circumscribed, lobulated cutaneous masses of variable consistency. They are generally 2 to 3 cm in diameter, but occasionally may measure up to 5 cm. They most often develop in the subcutaneous tissue and may expand into the dermis. The overlying skin may be atrophic and alopecic, and ulceration is uncommon. Lesions are most commonly located on the trunk and distal legs. Myxoid peripheral nerve sheath tumors (myxoid schwannomas) have been observed on the digits of dogs only. In cats, cutaneous peripheral nerve sheath tumors are usually smaller intradermal nodules located on the head and neck.

Affected animals are middle-aged or older; the mean age in dogs is 7.3 to 8.3 years (Bradley et al., 1982; Goldschmidt & Shofer, 1992). The mean age in cat is reported to be 9 years (Goldschmidt & Shofer, 1992). There is no breed predilection reported for these tumors. One source found a 3 : 1 female predominance for feline benign neural tumors, but the total number of cases was small (Goldschmidt & Shofer, 1992). Benign peripheral nerve sheath tumors may recur after incomplete excision.

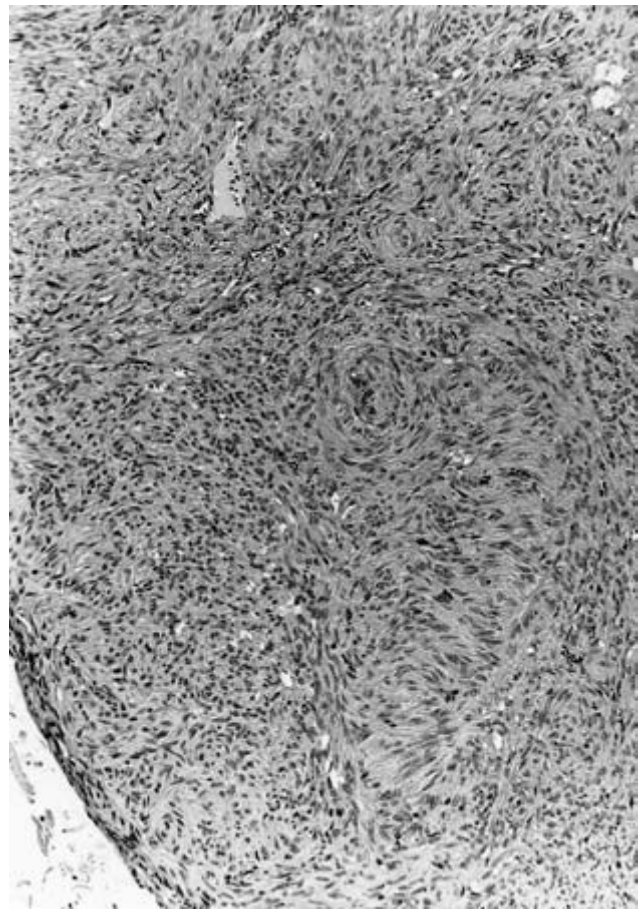


Fig. 32.5 Benign peripheral nerve sheath tumor in a dog. Spindle cells are arranged in palisades and partial whorls. Note the delicate collagenous stroma.

Histopathology

Benign peripheral nerve sheath tumor

(Figures 32.5 and 32.6)

These may be delineated by a delicate capsule, or they may present as unencapsulated, variably demarcated masses. The latter are mainly subcutaneous and occasionally have delicate projections of tumor tissue extending into adjacent fat and along fascial planes. This explains the recurrence often observed with peripheral nerve sheath tumors. Benign dermal nerve sheath tumors often extend to the dermal–epidermal junction, as observed in neurofibromatosis in humans (Weiss & Goldblum, 2001). At the periphery of smaller neoplasms, small nerve branches may be detected.

In dogs, benign peripheral nerve sheath tumors are composed of predominantly small spindle cells embedded in a delicate collagenous stroma. Cells have ovoid, fusiform or serpentine nuclei, which are small and euchromatic, and pale, poorly defined cytoplasm. Nucleoli are inconspicuous. Occasional nuclear hyperchromatism is seen and mitotic figures are rare. Electron microscopy shows that the basal lamina around the tumor cells is often thickened and folded. The neoplastic cells are arranged in wavy bundles, streams, and concentric whorls. Whorls are occasionally around blood vessels. The latter most likely represent an attempt to reduplicate tactile receptor structures. This pattern is referred to as Antoni type A (Weiss & Goldblum, 2001). Palisading and herringbone patterns appear less common than in schwannomas of humans (Koester & Higgins, 2002), but if present, they are very characteristic. Moreover, formation of Verocay bodies, as described in human tumors, characterized by a double row of palisading tumor cells, is rare. Some areas of the neoplasms may contain polygonal cells with small dark nuclei, loosely distributed in a fibrillar and mucinous matrix. This growth pattern is referred to as Antoni type B. Occasionally, tumors with a

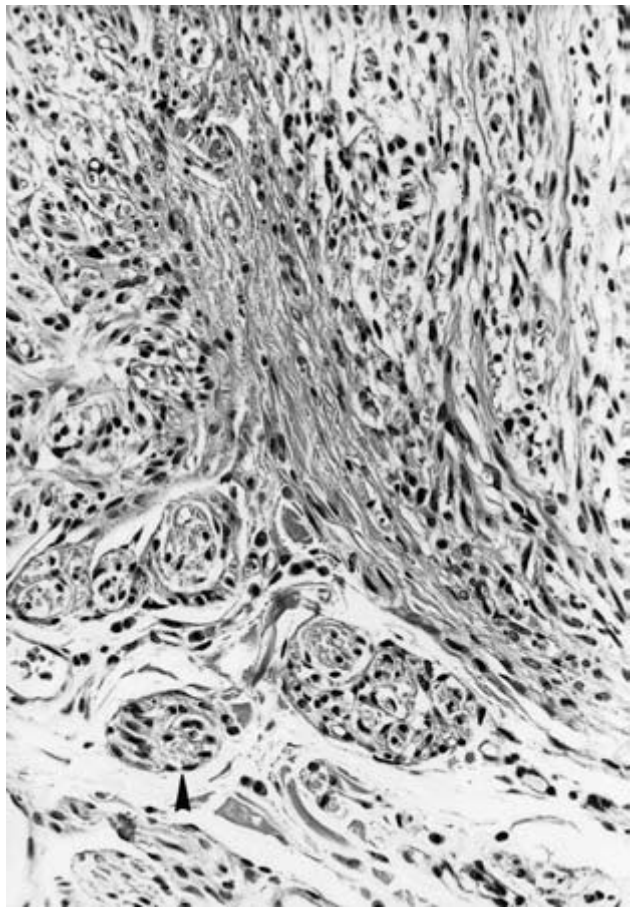


Fig. 32.6 Higher magnification of benign peripheral nerve sheath tumor in a cat. Spindle cells are arranged in bundles. Note small normal nerve bundles (arrow) at the periphery of the tumor at bottom.

plexiform architecture occur, characterized by discrete lobules interspersed with broad, winding trabeculae of spindle cells. These resemble plexiform neurofibroma in humans (Weiss & Goldblum, 2001).

In cats, benign peripheral nerve sheath tumors have morphologic features similar to their canine counterparts. However, they tend to be less cellular and are characterized by more abundant collagenous and mucoid matrix. The tumors are mostly composed of elongated spindle cells, which form fascicles. Admixed are areas of either Antoni type A or type B patterns. Palisading is more common than in canine peripheral nerve sheath tumors (Koester & Higgins, 2002). A reactive lymphoid infiltrate is common.

Benign peripheral nerve sheath tumors are separated from malignant nerve sheath tumors by the presence of a fairly monomorphic cell population and a relative absence of mitotic figures. Marked branching invasion of the underlying soft tissue is usually absent in benign lesions, while infiltrative proliferation of tumor cells along fascial planes and nerves is frequently seen with malignant peripheral nerve sheath tumors.

Hemangiopericytoma and benign peripheral nerve sheath tumors may be very similar architecturally and difficult to differentiate. Concentric whorling around central branching capillaries is a feature of hemangiopericytoma. However, concentric circling around central small vessels may also occasionally be seen with benign peripheral nerve sheath tumors. In comparison to peripheral nerve sheath tumors, hemangiopericytomas are often more cellular. A predominance of fusiform and serpentine nuclei with smaller nucleoli is more consistent with the diagnosis of a peripheral nerve sheath tumor, while hemangiopericytomas have round to oval nuclei.

Additional differential diagnoses for benign peripheral nerve sheath tumors include fibroma, fibrosarcoma, spindle cell lipoma, and dermatofibroma. Fibromas are less cellular and lack palisading and marked whorling of cells. The stromal collagen is coarser and more abundant. Fibrosarcomas have mitotic activity, and atypical mitoses may be seen. Fibrosarcomas also lack palisading and marked whorling of cells, and stromal collagen is usually coarser. Both peripheral nerve sheath tumors and spindle cell lipomas contain myxoid stroma, but most spindle cell lipomas have a fair amount of admixed adipose tissue. The spindle cells of spindle cell lipoma are not arranged in whorls and they do not palisade. Dermatofibromas and benign superficial peripheral nerve sheath tumors have similar cellularity and architecture. Dermatofibromas can usually be distinguished by their ragged margins and entrapment of pre-existing dermal collagen bundles by the proliferating fibrocytes; dermatofibromas may also be partially mineralized.

Myxoid peripheral nerve sheath tumor

(Figure 32.7)

Myxoid peripheral nerve sheath tumors have a multilobular configuration with small spindle and stellate cells forming loose, concentric swirls in an abundant background of mucin (acid mucopolysaccharides). These lobular structures, delineated by delicate bundles of collagen, are strongly reminiscent of Pacinian corpuscles. Cytologic features are as described for typical benign peripheral nerve sheath tumors.

The differential diagnoses for myxoid peripheral nerve sheath tumor are myxoma and low-grade myxosarcoma. These tumors share a moderate to marked amount of stroma containing acid mucopolysaccharides. In contrast to benign peripheral nerve sheath tumors, formation of a lobular pattern and large, concentric whorls of the tumor cells are not seen with myxomas and low-grade myxosarcomas. Narrow serpentine nuclei, if present, are more consistent with peripheral nerve sheath origin, while

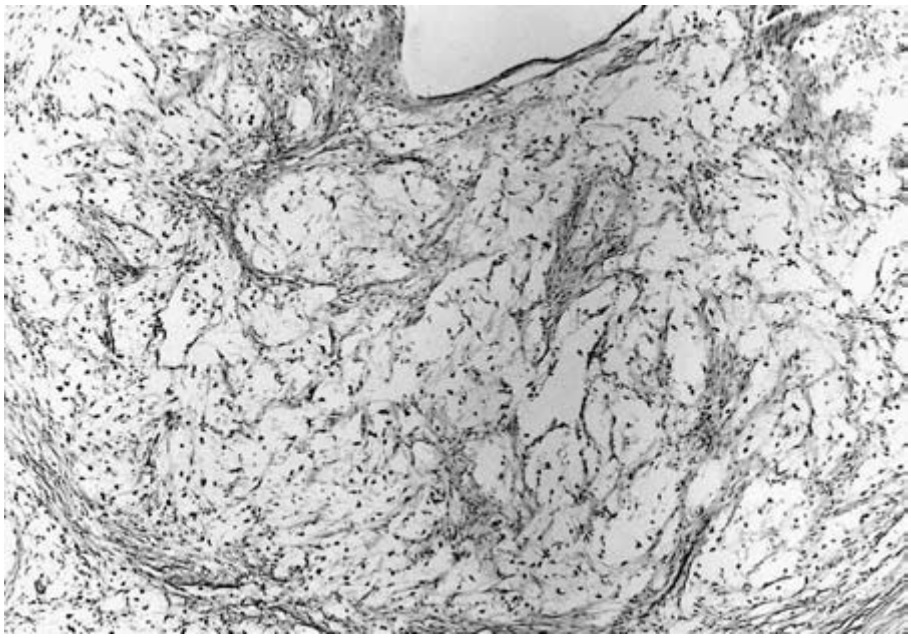


Fig. 32.7 Benign myxoid peripheral nerve sheath tumor from the digit of a dog. Stellate and spindle cells tend to form loose whorls in an abundant myxoid stroma. Note the multilobular architecture created by collagen bundles.

hyperchromatic nuclei and mitotic figures can usually be identified in myxosarcomas.

Immunohistochemistry

Immunohistochemistry of benign peripheral nerve sheath tumors in dogs and cats is not as diagnostically reliable as in humans (Weiss & Goldblum, 2001). Canine and feline benign peripheral nerve sheath tumors consistently express vimentin. However, they vary significantly in their expression of glial fibrillary acidic protein (GFAP) and S100 (Koester & Higgins, 2002). However, the often thickened and folded basal lamina is positive for laminin and collagen IV.

In the absence of positive staining for S100 and GFAP, it may be difficult to differentiate benign peripheral nerve sheath tumors from fibromas, dermatofibromas, spindle cell lipomas, low-grade fibrosarcomas, or hemangiopericytomas. Also, some spindle cell lipomas, as determined in humans, may express S100, which also confounds differentiation. However, in contrast to peripheral nerve sheath tumors, these other tumors have no basal lamina, and hence are negative for laminin and collagen IV.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

(Synonyms: malignant schwannoma, neurofibrosarcoma)

Malignant peripheral nerve sheath tumors in humans may be subclassified as malignant schwannoma and neurofibrosarcoma (Weiss & Goldblum, 2001). Malignant transformation of benign peripheral nerve sheath tumors has been described in humans (Weiss & Goldblum, 2001).

Similar to their benign counterparts (see p. 789) malignant canine and feline peripheral nerve sheath tumors have been presumed to be mainly of Schwann cell origin (George et al., 1989; Cordy, 1990; Summers et al., 1992). There is a basal lamina surrounding single cells and groups of cells, demonstrated by electron microscopy or by immunohistochemistry (see below) which supports this hypothesis. As clinical and morphologic similarities outweigh the differences in proposed subclassifications (Goldschmidt & Hendrick, 2002; Koestner & Higgins, 2002) the authors prefer to classify these tumors under the general name of malignant peripheral nerve sheath tumors.

Clinical features

Malignant peripheral nerve sheath tumors appear to be uncommon in dogs and cats. Based on one large survey, the combined incidence of benign and malignant neural tumors is reported to be 0.5% in dogs and 1.4% in cats (Goldschmidt & Shofer, 1992). The exact incidence is difficult to evaluate, however, as they have marked histopathologic similarities to other spindle cell neoplasms such as fibrosarcoma, myxosarcoma, hemangiopericytoma, spindle cell amelanotic melanoma, and histiocytic sarcoma, and thus may be underdiagnosed or overdiagnosed.

Malignant peripheral nerve sheath tumors have similar clinical features to their benign counterparts (see p. 789). In dogs, they predominantly arise in the subcutis and may

extend into the dermis; most masses measure more than 2 cm in diameter, are poorly defined, and are usually firmly adhered to underlying soft tissue. In cats, they are often smaller and intradermal. The overlying skin may be atrophic and alopecic; ulceration is uncommon.

Canine malignant peripheral nerve sheath tumors are mostly located on the trunk or extremities, while feline tumors are mostly observed on the head and neck. Several feline malignant peripheral nerve sheath tumors have been seen in the periorbital area by one author (E.J.W.).

Mean age of affected dogs is 9 years and in cats 11 years (Goldschmidt & Shofer, 1992); that survey also reported a predisposition in Golden Retrievers and a 3:2 female predominance in cats. Malignant nerve sheath tumors tend to recur after surgical excision. The incidence of recurrence is higher in cats than in dogs. Metastases, however, are uncommon (Kuntz et al., 1997; Goldschmidt & Hendrick, 2002), but have been observed in the lungs and lymph nodes (Kuntz et al., 1997). One survey showed that none of the dogs with tumors distal to the knee or elbow developed metastasis (Kuntz et al., 1997).

Histopathology (Figures 32.8 through 32.10)

In dogs, malignant peripheral nerve sheath tumors are unencapsulated, mostly subcutaneous masses that exhibit infiltrative growth into deeper tissues including adjacent fat and fascial planes. Frequently, small branches or finger-like tendrils of tumor cells invade the underlying soft tissue and proliferate along fascial planes and nerve sheaths. This growth pattern explains the recurrence often observed with peripheral nerve sheath tumors. The less common dermal tumors often extend to the dermal–epidermal junction, similar to neurofibrosarcoma in humans (Weiss & Goldblum, 2001). Nerve fibers may be entrapped within the tumor mass and small nerve branches are often seen at the periphery of smaller neoplasms. Occasionally, small numbers of tumor cells can

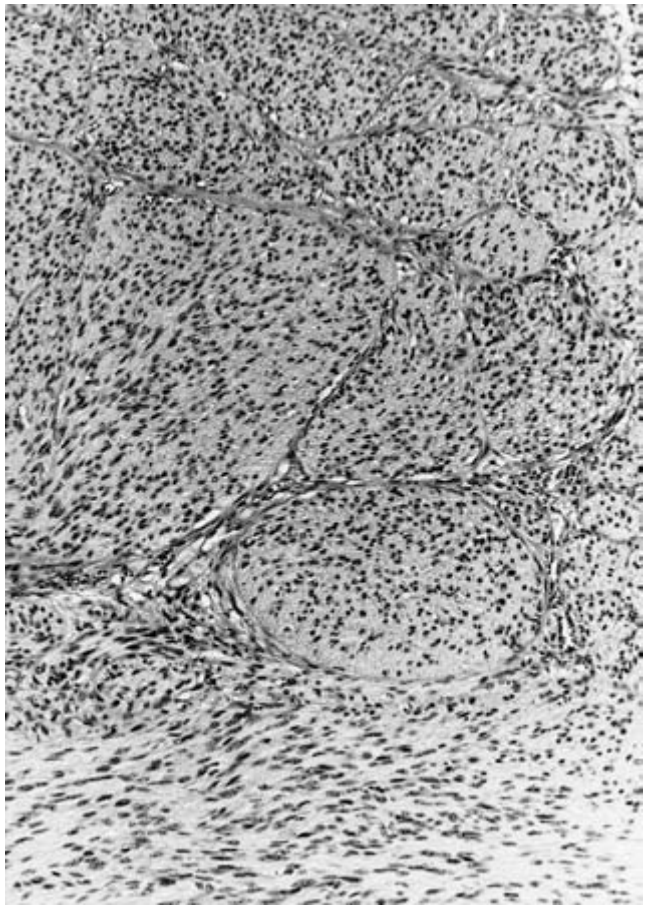


Fig. 32.8 Malignant peripheral nerve sheath tumor in a cat. Spindle cells are arranged in bundles and partial whorls. Note vesicular nuclei and small nucleoli.

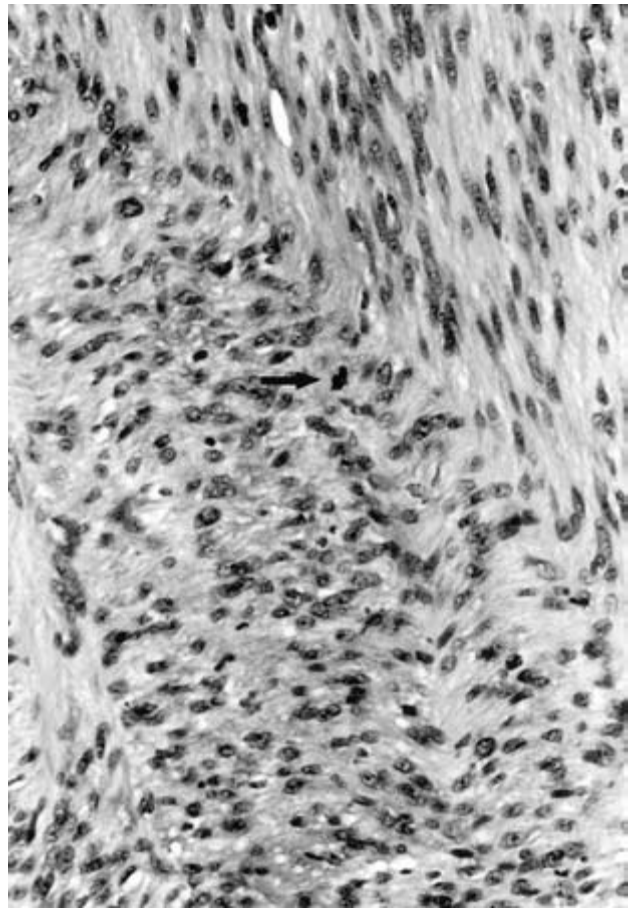


Fig. 32.9 Higher magnification of malignant peripheral nerve sheath tumor in a dog. The tumor cells have larger and less pointed nuclei than in benign peripheral nerve sheath tumors (see Fig. 32.6). Note mitotic figure (arrow).



Fig. 32.10 Malignant peripheral nerve sheath tumor in a dog. The tumor mass contains a large zone of chondro-osseous metaplasia.

be seen within nerve fascicles at some distance from the primary mass.

Canine malignant peripheral nerve sheath tumors have morphologic features similar to benign peripheral nerve sheath tumors (see p. 789). In general, malignant tumors have higher cellularity, and neural patterns may be subtle. Hence, pronounced Antoni types A and B patterns (see p. 790) are often less evident. The tumor cells are embedded in a delicate collagenous stroma. Zones of necrosis and sclerosis may be present. Myxoid change of the stroma may occur, and occasionally the extracellular matrix exhibits focal cartilaginous or osseous differentiation.

The tumor masses comprise variably pleomorphic, plump spindle cells arranged mostly in interlacing bundles, while palisading and whorls, indicating reduplication of tactile receptor structures, are less pronounced than in benign tumors. The spindle-shaped tumor cells have pale, poorly defined cytoplasm, and moderately enlarged, vesicular nuclei that vary from fusiform to ovoid to serpentine. Anisokaryosis may be prominent. The mitotic activity is moderate and has been reported as 5 mitoses per 10 high power fields (40×) (Kuntz et al., 1997). Atypical mitoses may be present.

Malignant peripheral nerve sheath tumors differ from benign nerve sheath tumors by a more pleomorphic cell population, increased mitotic activity, less pronounced neural patterns, and infiltrative growth. Further differential diagnoses for malignant peripheral nerve sheath tumors include fibrosarcoma and myxosarcoma, hemangiopericytoma, spindle cell amelanotic melanoma, and histiocytic sarcoma. In comparison to malignant peripheral nerve sheath tumors, fibrosarcomas may have a fair number of tumor giant cells, and palisading is not seen. Similar to myxosarcoma, malignant peripheral nerve sheath tumors may contain myxoid stroma. Myxosarcomas have a larger amount of myxoid stroma, the tumor cells are haphazardly arranged within the extracellular matrix, and neural patterns are not observed.

Hemangiopericytomas and malignant peripheral nerve sheath tumors may be strikingly similar. While malignant peripheral nerve sheath tumors are characterized by fusiform and serpentine nuclei with smaller nucleoli, hemangiopericytomas have rather round to oval nuclei; also, their cellular whorls are clearly centered on capillaries. Amelanotic spindle cell melanomas may exhibit neural patterns such as whorling and occasional palisading. In contrast to peripheral nerve sheath tumors, spindle cell melanomas often have some degree of junctional activity with the overlying epidermis or follicular epithelium, as well as minimal melanin, which may be documented by Fontana–Masson stain. In the absence of junctional activity and melanin, differentiation of amelanotic melanomas with neural patterns and malignant peripheral nerve sheath tumors may not be possible, even with immunohistochemistry (see below). Most histiocytic sarcomas are composed of both spindle cells and large round cells; multinucleated tumor giant cells are relatively common in contrast to malignant peripheral nerve sheath tumors.

Immunohistochemistry

Immunohistochemistry of peripheral nerve sheath tumors in dogs and cats is not as diagnostically reliable as in humans (Weiss & Goldblum, 2001). Only expression of vimentin is consistently seen, while expression of glial fibrillary acidic protein (GFAP) and S100 is variable (Koester & Higgins, 2002). However, the thickened basal lamina around the tumor cells can be demonstrated by immunohistochemistry for laminin and collagen IV, both basement membrane components.

In the absence of positive staining for S100 and GFAP, it may be difficult to differentiate malignant peripheral nerve sheath tumors from fibrosarcomas, myxosarcomas, and hemangiopericytomas. However, in contrast to

peripheral nerve sheath tumors, these tumors have no basal lamina, and hence are negative for laminin or collagen IV. Similar to malignant nerve sheath tumors, malignant melanomas may express S100. However, in contrast to nerve sheath tumors, melanomas may be positive for melanoma-associated antigen recognized by T cells (MART-1), melanoma-associated antigen (Melan-A), HMB-45/gp100, tyrosinase, tyrosinase related protein-2 (TRP-2) or melanoma isoform of microphthalmia transcription factor (MITF-M). Expression of leukocytic markers such as the common leukocyte proteins CD45 and CD18, as well as expression of CD1, CD11c and MHC II, separates histiocytic sarcomas from malignant peripheral nerve sheath tumors.

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Chapter 33

Other mesenchymal tumors

VACCINE-INDUCED SARCOMA

(Synonym: injection-induced sarcoma)

Sarcoma as a complication of vaccination has not been reported in humans, but is well documented in cats (Hendrick & Goldschmidt, 1991; Dubielzig et al., 1993; Hendrick & Brooks, 1994). Vaccine-induced sarcomas have been mostly associated with killed rabies and killed feline leukemia virus (FeLV) vaccines (Macy & Hendrick, 1996). A direct role for virus has not been shown; in one study feline immunodeficiency virus (FIV), FeLV, papillomavirus, polyomavirus, or herpesvirus could not be identified by polymerase chain reaction (PCR) analysis of 50 vaccine-induced sarcomas (Kidney et al., 2001). In a report of a large multicenter study (Kass et al., 2003) there was no obvious association between development of vaccine-induced sarcoma and brand or manufacturer within a vaccine antigen class; the report, however, suggested an association with administration of long-acting medications, such as long-acting penicillin and methyl prednisolone acetate.

Both killed rabies and FeLV vaccines contain an aluminum adjuvant (Macy & Hendrick, 1996). Aluminum has previously been linked to chronic inflammation and the formation of granulomas at vaccine injection sites (Hendrick & Dunagan, 1991). However, although most vaccines in the large study of Kass et al. (2003) were adjuvanted, there was no significant difference in incidence of sarcoma between adjuvanted and nonadjuvanted products.

Vaccine-induced sarcomas are believed to evolve from primitive mesenchymal cells within the inflammatory reaction (Macy & Hendrick, 1996). The study of Gobar & Kass (2002) has shown that the risk of development of sarcomas secondary to inflammation increases if local inflammation fails to resolve after 4 months. Various cytokines and growth factors may play a crucial role in the development and differentiation of these sarcomas (Couto et al., 2002). For example, myofibroblastic differentiation may be guided by the influence of transforming growth factor-beta (TGF-β) and granulocyte–monocyte colony stimulating factor (GM-CSF), both of which are produced by lesional macrophages (Schuerch et al., 1997).

Vaccine-induced sarcomas derive from fibroblastic, myofibroblastic, myoblastic, osteoblastic, and chrondroblastic origins (Dubielzig et al., 1993; Macy & Bergman, 1995; Macy & Hendrick, 1996; Couto et al., 2002). Occasionally, sarcomas may also arise from histiocytes; one of the authors (V.K.A.) has recognized histiocytic sarcoma of dendritic cell origin at a previous vaccine injection site. Hence, fibrosarcomas, myxosarcomas, myofibroblastic fibrosarcomas, rhabdomyosarcomas, osteosarcomas, chondrosarcomas, and histiocytic sarcomas all may be recognized in the setting of vaccine induction. More than one type may coexist in a given tumor. In some cases, the tumors are composed of primitive tumor cells, and specific lineage cannot be assigned. Some of these primitive vaccine-induced sarcomas have numerous multinucleated giant cells and likely were previously classified as anaplastic sarcomas with giant cells or 'malignant fibrous histiocytomas' (see p. 806).

Clinical features

The prevalence of vaccine-induced sarcomas has been reported as approximately one to two cases per 10 000 rabies or FeLV vaccinations (Macy & Hendrick, 1996; Gobar & Kass, 2002). The tumors vary in size and may measure several centimeters in diameter. They are firm, poorly demarcated, often multilobulated masses that usually arise in the subcutis or in skeletal muscle. A central large cavity filled with clear fluid often is observed on cut section. Alopecia and ulceration are common. The tumor masses are seen at common injection sites, such as the dorsal neck, interscapular region, dorsolateral thorax, hindleg, and dorsal lumbar region. Occasionally, typical vaccine-induced sarcomas are seen more ventrally; gravitational drift of vaccine product is the likely cause for these aberrant locations.

The average age for cats with vaccine-induced sarcoma is about 10 years (Kass et al., 2003), and the highest peaks of incidence have been seen in cats 6 to 7 and 10 to 11

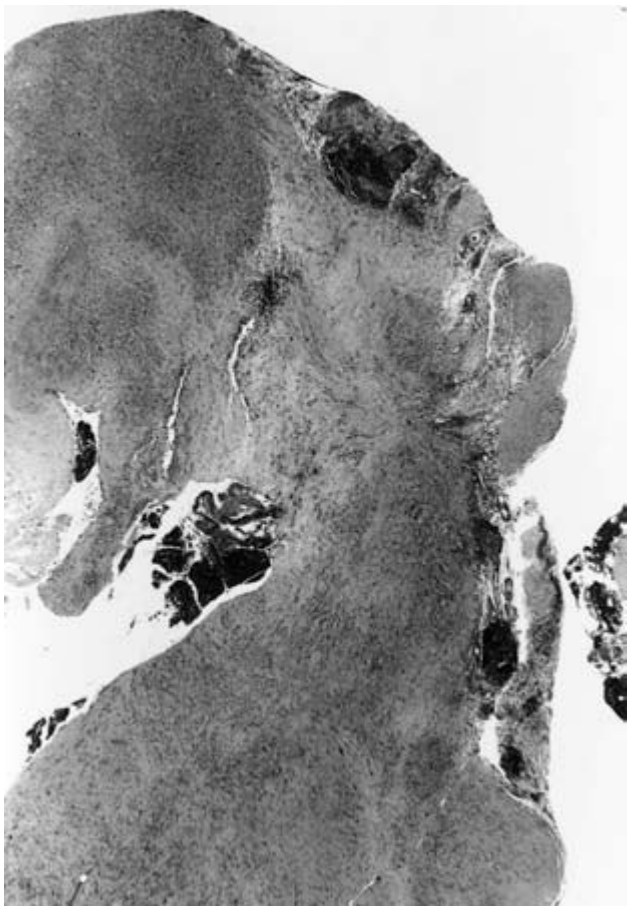


Fig. 33.1 Vaccine-induced sarcoma (fibrosarcoma) in a cat. The poorly circumscribed mass has a central cavity and multifocal nodular lymphocytic infiltrates along the right margin.



Fig. 33.2 Higher magnification of Fig. 33.1. The neoplastic spindle cells are associated with a reactive lymphocytic infiltrate that is dispersed throughout the tumor mass and in an aggregate along the tumor margin at bottom.

years of age (Kass et al., 1993). However, the overall risk for developing a vaccine-induced sarcoma seems to decrease with increasing age (Doddy et al., 1996). A higher incidence in females has been reported in two studies (Tennant 2000; Kass et al., 2003). Breed predilections have not been reported (Kass et al., 1993).

Vaccine-induced sarcomas are locally invasive and aggressive neoplasms, and complete surgical excision is often difficult. The incidence of recurrence is therefore high, and metastasis to draining lymph nodes does occur. Metastasis to other organ systems, such as the lungs, has been reported as well (Briscoe et al., 1998). Prolonged survival time is closely related to early surgical intervention and radical excision. Survival times of up to 576 days after surgery have been reported (Hershey et al., 2000).

Histopathology (Figures 33.1 through 33.6)

Vaccine-induced sarcomas may be of fibroblastic, myofibroblastic, myoblastic, chrondroblastic, osteoblastic, and/or histiocytic origin. Independent of the cell of origin, vaccine-induced sarcomas are poorly demarcated subcutaneous masses that extend into the dermis and the underlying skeletal muscle. Vaccine-induced sarcomas tend to be characterized by the presence of less differentiated tumor cells, increased numbers of bizarre mitotic figures, and more numerous tumor giant cells compared to their nonvaccine-induced counterparts. Aggregates of large macrophages with intracytoplasmic blue-gray material (probable vaccine adjuvant) may still be present within or at the margins of the tumor. Areas of tumor necrosis containing neutrophils are common. Necrosis leads to cavitation, which may be predominantly central or multifocal. Margins of these cavitations are composed of necrotic tumor tissue.

Vaccine-induced sarcomas typically contain a reactive lymphoid infiltrate that may be severe. It is mainly observed along the margins but may be present throughout the tumor. The lymphoid infiltrate often is arranged

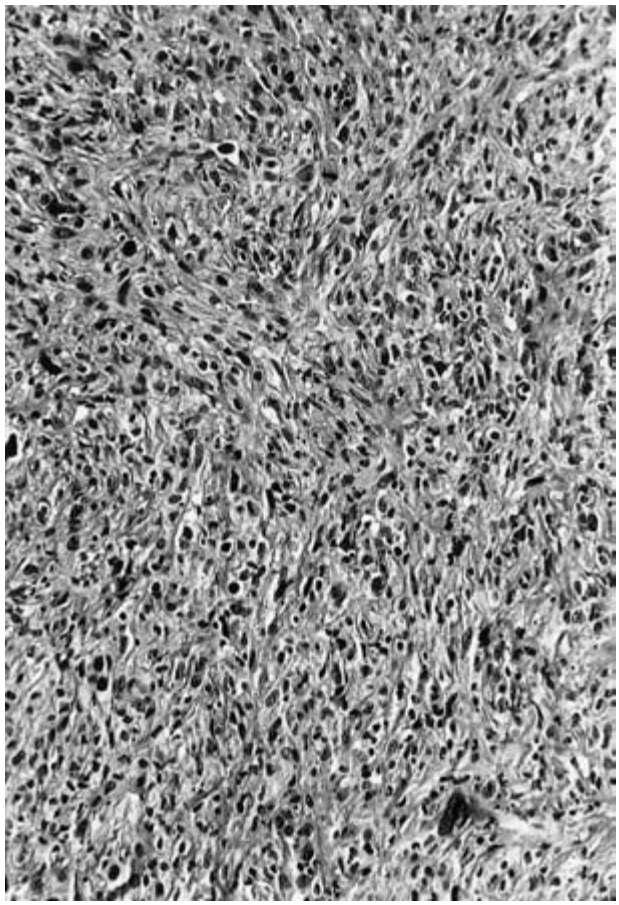


Fig. 33.3 High magnification of vaccine-induced sarcoma (fibrosarcoma) in a cat composed of interlacing bundles of spindle cells. There are occasional giant cells.

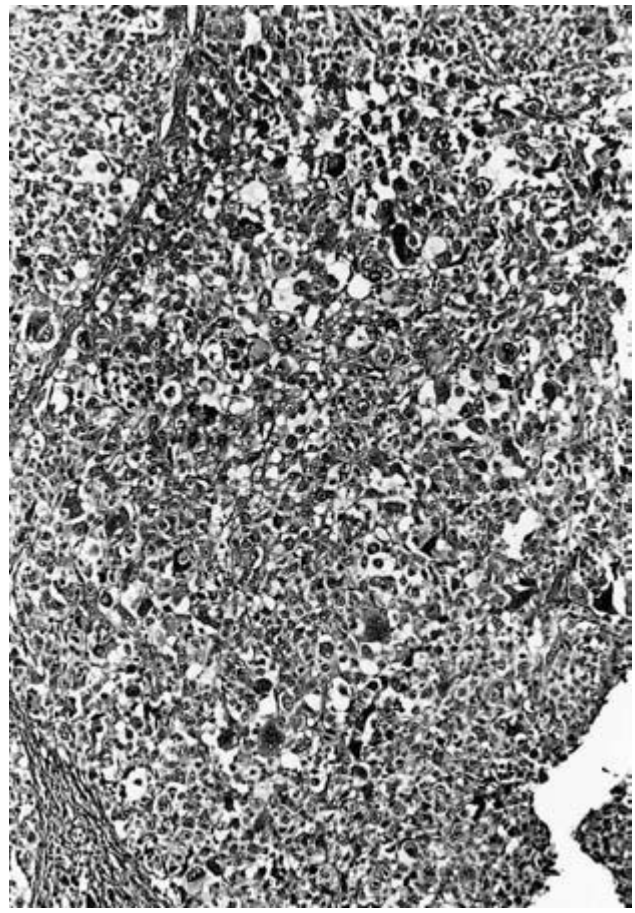


Fig. 33.4 Vaccine-induced sarcoma (histiocytic sarcoma) in a cat. There is marked anisocytosis and anisokaryosis of the tumor cells and numerous multinucleated cells are present.

in dense aggregates and may form follicular structures. The intensity of the lymphoid infiltrates does not correlate with the degree of differentiation of the tumor cell population (Couto et al., 2002).

In many cases neoplastic cells are fairly pleomorphic and primitive, and the specific mesenchymal cell of origin can only be determined by special stains and immunohistochemistry (see below). In general, the tumor cells are spindle-shaped and arranged in irregular, partially interlacing bundles. Occasional whorls may be seen. Alternatively, very plump spindle cells or round cells with histiocytoid characteristics may be observed. Most spindle cells have large ovoid to fusiform and vesicular nuclei with one or several prominent nucleoli. The round cells have round to oval, large vesicular nuclei usually located in the center of the cell. The mitotic rate is variable and has been reported as up to 2 per high power field (40×) (Couto et al., 2002). Atypical, bizarre mitotic figures are frequent. Multinucleated giant cells are relatively common. Some have regular monomorphic, round nuclei and lack mitotic figures, while others have marked anisokaryosis and bizarre mitoses. These two morphologically distinct populations of multinucleated giant cells are of tumor cell as well as reactive histiocytic origin (Couto et al., 2002). The number of pleomorphic multinucleated tumor cells appears to correlate with cytological features of increased malignancy.

Variable extracellular matrix is observed. Tumors of fibroblastic origin may have ample collagen, while sarcomas of muscle origin have scant collagenous stroma. The authors have seen one case of vaccine-associated keloidal fibrosarcoma (see Chapter 27). Osteoid deposition is seen in vaccine-induced osteosarcomas. Non-neoplastic osseous metaplasia may occasionally be found in tumors not of osteoblastic origin; this may be a sequela to tissue hypoxia. With chondroid differentiation, chondroblastic cells are located within lacunae and are surrounded by a partially hyalinized myxoid stroma.

Special stains may help to assign the cell of origin to some vaccine-induced sarcomas. For example, phospho-

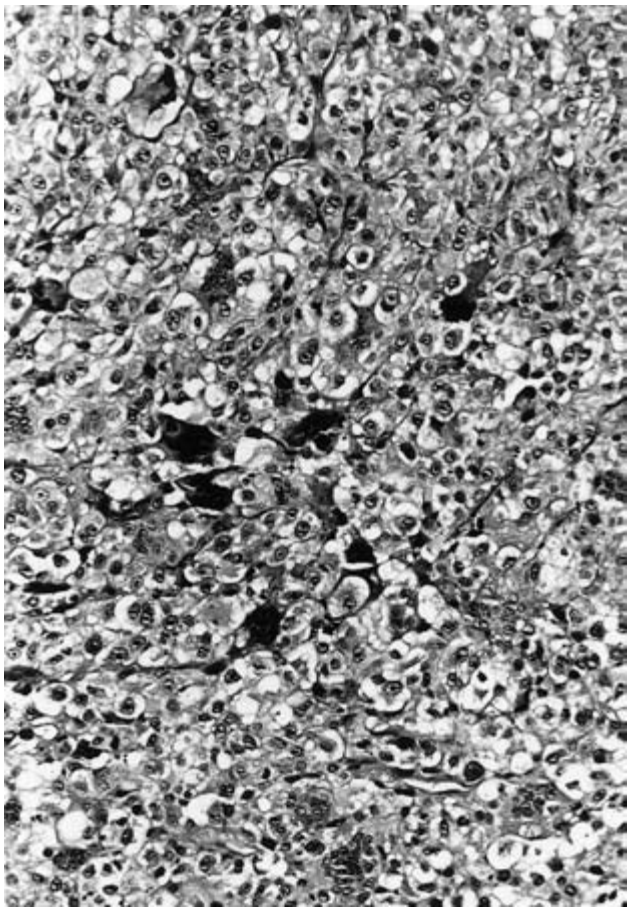


Fig. 33.5 Higher magnification of vaccine-induced sarcoma (histiocytic sarcoma) in a cat, composed of large round cells with round nuclei, prominent nucleoli, and abundant vacuolated cytoplasm. Occasional giant cells are noted.

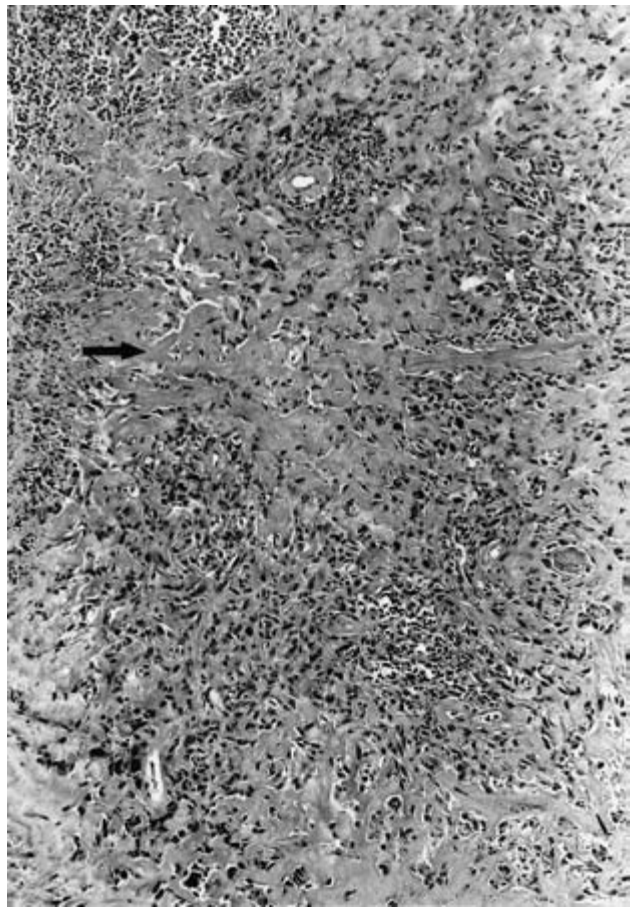


Fig. 33.6 Vaccine-induced sarcoma (osteosarcoma) in a cat demonstrating production of homogeneous, amorphous osteoid (arrow).

tungstic acidic–hematoxylin (PTAH) enhances the appearance of cross striations, and hence can identify skeletal muscle origin. However, immunohistochemistry is often required (see below).

Differentiation of the various morphologic subtypes of vaccine-induced sarcomas from their nonvaccine induced counterparts is not always possible. Anaplasia is more pronounced in vaccine-induced tumors. Primitive forms of vaccine-induced sarcomas with numerous giant cells likely were previously classified as anaplastic sarcoma with giant cells, and are essentially indistinguishable from that entity (see p. 806). Lymphocytic inflammation is not specific to vaccine-induced sarcoma but may be present in nonvaccine-induced sarcomas as well (Doddy et al., 1996). However, the lymphoid infiltration tends to be more intense in vaccine-induced sarcomas, and may fortuitously be accompanied by basophilic vaccine product within macrophages. Definitive identification of vaccine association usually is based principally upon the clinical history and location of the tumor masses.

Immunohistochemistry

All tumors are positive for vimentin, which confirms mesenchymal origin. Immunohistochemistry for vimentin, α-smooth-muscle actin, pan-muscle actin, desmin, S100, and leukocyte antigens (CD45 and CD18) may allow subclassification of the tumor cell population (Table 33.1). Multinucleated giant cells are of variable immunophenotype. Tumor multinucleated giant cells express an immunophenotype identical to the tumor cell population. Reactive multinucleated giant cells express the common leukocyte antigen CD45 and CD18, and thus are most likely of histiocytic origin.

TRANSMISSIBLE VENEREAL TUMOR

Transmissible venereal tumor (TVT), occasionally also referred to as Sticker tumor or venereal granuloma, has been recognized only in dogs. It is transmitted by viable tumor cells spread from infected dogs or bitches during coitus, or by licking or rubbing. Transmissible venereal tumors can therefore spread fairly rapidly where

Table 33.1 Immunophenotype of vaccine-induced sarcomas.

Cell origin	Vimentin	Smooth-actin	Desmin	S100	CD45; CD18	Osteocalcin	Osteonectin
Fibroblasts	+	–	–	–	–	–	–
Myofibroblasts	+	+	–/(+)	–	–	–	–
Rhabdomyoblasts	+	–	+	–	–	–	–
Chondrocytes	+	–	–	–/(+)	–	–	–
Osteoblasts	+	–	–	–	–	+	+
Histiocytes	+	–	–	–	+	–	–

dogs are allowed to roam freely, or in active breeding colonies.

Although the lesions have been recognized for many years, the exact origin of this tumor remains unknown. The karyotype of TVT cells is consistently composed of 58 or 59 chromosomes, which differs from the 78 chromosomes of normal canine cells (Weber et al., 1965). A consistent unique genetic marker within the oncogene c-*myc* has been documented in TVT cells (Katzir et al., 1987; Amariglio et al., 1991). An inverted transposable element inserted into the c-*myc* gene has been identified by polymerase chain reaction (PCR) studies.

The tumor cells express vimentin and are of mesenchymal origin (Pereira et al., 2000), and have been identified as canine leukocytes (Moore, P.F. & Affolter, V.K., unpublished data, 2003). Some studies suggest a histiocytic origin (Mozos et al., 1996; Marchal et al., 1997); including a report in which intracytoplasmic *Leishmania* sp. amastigotes were described (Albanese et al., 2002); however, the immunophenotype of the infected cells and the tumor cells was not determined in that report, and thus the presence of infected reactive histiocytes, admixed within the tumor cell population cannot be ruled out. Extensive immunophenotyping of TVTs on snap-frozen tissue samples has failed to confirm a histiocytic origin (Moore, P.F. & Affolter, V.K., unpublished data, 2003).

Clinical features

The exact incidence of TVTs is not known. Transmissible venereal tumors are mainly seen where dogs are intensely bred or within wild dog populations (Nielsen & Kennedy, 1990). The tumors vary in size from small nodules to large masses that measure up to 10 cm in diameter. Transmissible venereal tumors present as either nodular, pedunculated, or papillary and multilobular, ill-defined cutaneous masses. The surface is often ulcerated. The consistency of these tumors varies, and they may be soft and friable or semifirm.

Lesions are mainly observed on genital skin or mucosa. However, lesions may develop anywhere in the skin, in the oral cavity, or within nasal and conjunctival mucosa. Extragenital subcutaneous masses with overlying scar tissue can occasionally be seen, indicating transmission through traumatized skin.

Transmissible venereal tumors can develop at any age. No breed or sex predilections have been described.

Early lesions exhibit rapid growth. A subsequent decreased rate of growth may indicate a developing immune response (Cohen & Steel, 1972). Spontaneous regression can occur, and the recovered dogs acquire humoral and cellular immunity that protects against development of subsequent tumors (Beschorner et al., 1979; Mizuno et al., 1989). Additional cutaneous tumors are usually induced by traumatic implantation (Goldschmidt & Hendrick, 2002). Metastasis to draining lymph nodes is common and mainly involves the superficial inguinal lymph nodes in males and superficial inguinal and external iliac lymph nodes in females. The development of distant metastasis involving internal organs has been associated with immune suppression, such as concurrent viral diseases. Metastatic lesions have been described in the lungs, liver, pancreas, tonsils, brain, pituitary gland, and eyes (Nielsen & Kennedy, 1990).

Histopathology (Figures 33.7 and 33.8)

Transmissible venereal tumors are characterized by poorly demarcated dermal and subcutaneous masses composed of sheets and rows of round or polyhedral cells with indistinct cell borders. The tumor cell population is supported by a fine fibrovascular stroma. On rare occasions there may be intraepithelial tumor cell aggregates. The tumor cells have large round granular to vesicular nuclei and a large single nucleolus. There is a moderate amount of pale, eosinophilic cytoplasm. The marked cytoplasmic vacuolization, which is highly characteristic in aspirates and imprints of these tumors, is often inconspicuous or absent in tissue sections. Mitotic figures are numerous, and as many as 6 to 8 per high power field (40×) may be observed. There is often necrosis of the surface as well as foci throughout the tumor mass. A reactive infiltrate of lymphocytes with fewer plasma cells, macrophages, and neutrophils may be seen; this infiltrate is scant during the progressive growth of the early stage, and is most prominent in regressing lesions.

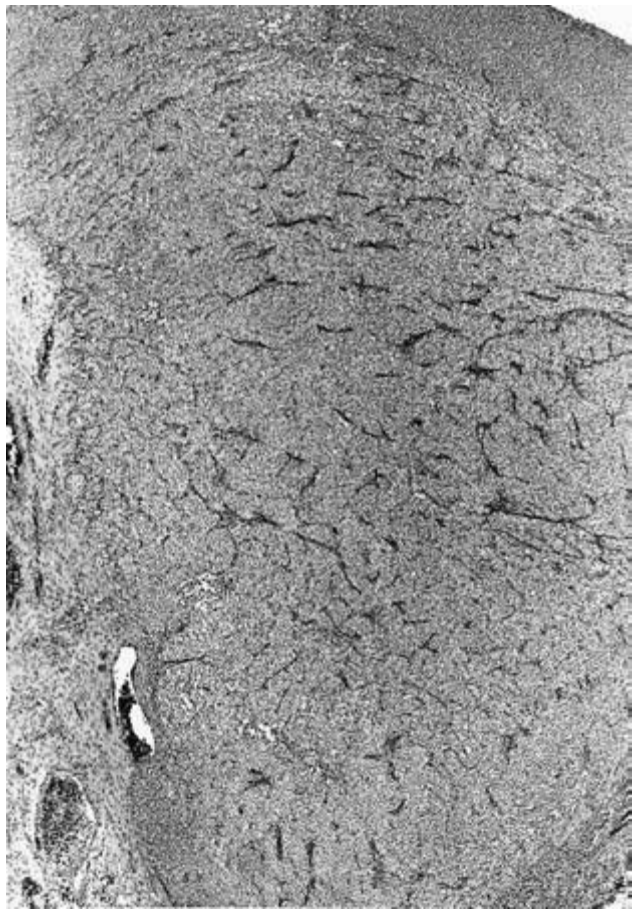


Fig. 33.7 Transmissible venereal tumor in a dog composed of round cells supported by a delicate fibrovascular stroma.

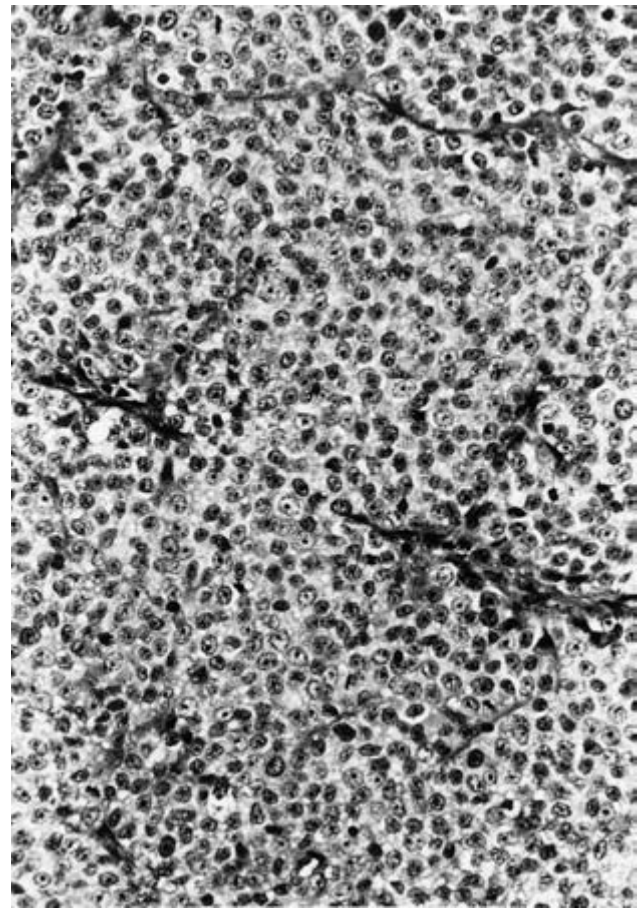


Fig. 33.8 Higher magnification of transmissible venereal tumor in a dog. The round tumor cells have round, clearly defined, finely granular to vesicular nuclei, often distinct single nucleoli, and a moderate amount of pale, occasionally vacuolated cytoplasm.

Transmissible venereal tumors are often indistinguishable from many other canine round cell tumors based on morphologic features only. These include canine histiocytomas, nonepitheliotropic large cell lymphomas, mast cell tumors, plasmacytomas, balloon cell melanocytomas, and Merkel cell tumors. Cytoplasmic vacuolization, if prominent enough to appear in tissue sections, assists in separating TVTs from other round cell tumors.

Histiocytomas may exhibit epitheliotropism, which is very rarely seen in TVTs. The proliferating Langerhans cells of histiocytomas often have slightly indented nuclei, while TVTs tend to have monomorphic, large, round nuclei. Neoplastic lymphocytes may have large, round to ovoid or folded and cleaved nuclei with finely stippled or marginated chromatin. Mast cell tumors are characterized by intracytoplasmic granules. In poorly granulated mast cell tumors, the metachromatic granules may be visualized by toluidine blue or Giemsa stains. In contrast to TVTs, lymphomas and mast cell tumors may contain a moderate to marked eosinophilic infiltrate. Plasmacytomas are often characterized by more anisocytosis and anisokaryosis than seen in TVTs; binucleated and multinucleated tumor cells are common. The dense cytoplasmic RNA in plasma cells stains magenta with methyl green pyronine (MGP) stain. In contrast to TVTs, balloon cell melanocytomas are often characterized by packeting of the tumor cells, and there may be occasional spindle cells. Fontana–Masson's stain also may identify small amounts of melanin. Electron microscopy reveals the presence of dense core secretory granules and desmosomal structures in Merkel cell tumors; the argyrophilic cytoplasmic granules can be demonstrated with Grimelius stain. In contrast to TVTs, Merkel cell tumors are characterized by distinct packeting of the tumor cells, which is typical for neuroendocrine neoplasms.

Immunohistochemistry

Expression of CD45 and CD45RA can be demonstrated in TVTs, indicating leukocytic origin (Moore, P.F. &

Affolter, V.K., unpublished data, 2003). The only other protein consistently expressed by the tumor cells is CD49d, a β1-integrin involved with ligation of cells to the extracellular matrix and endothelial cells (Moore, P.F. & Affolter, V.K., unpublished data, 2003). Some lesions are reported to be positive for alpha-1-antitrypsin and lysozyme, and a histiocytic origin has been suggested (Mozos et al., 1996). However, evaluation of snap-frozen tissue samples and flow cytometry on solubilized tumors has consistently failed to show expression of the glycoproteins characteristic for histiocytes (macrophages or dendritic cells), such as CD11b, CD11c, CD1, and MHC II (Moore, P.F. & Affolter, V.K., unpublished data, 2003). These results do not support the hypothesis of a histiocytic origin for TVTs.

In contrast to TVTs, other leukocytic round cell tumors express additional leukocytic cell markers. Cutaneous lymphomas usually express the T cell marker CD3. Histiocytomas are positive for CD18, CD11c, CD1, MHC II, and E-cadherin, a phenotype consistent with Langerhans cells (see also Chapter 35). Mast cell origin may be confirmed by positive staining for tryptase and KIT. Plasmacytomas are positive for CD45 and CD45RA, immunoglobulins and immunoglobulin light chains; about 80% of the tumors express CD79a. Amelanotic melanocytic tumors and Merkel cell tumors lack expression of leukocyte markers CD18 and CD45. Positive staining with S100, melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), HMB-45/gp100, melanoma isoform of microphthalmia transcription factor (MITF-M), tyrosinase, or tyrosine-related protein-2 (TRP-2) may confirm melanocytic origin. Merkel cell tumors express neuron specific enolase (NSE), synaptophysin, chromogranin A, and cytokeratin 20 (detected with pancytokeratin stains).

GANGLION

(Synonym: ganglion cyst)

Ganglions or ganglion cysts are myxoid tumorous masses containing unilocular or multilocular cysts (Weiss & Goldblum, 2001). In humans, ganglions of the subcutaneous tissues tend to occur in close proximity to joints or tendon sheaths, primarily on the hands and feet. Although ganglions may be attached to joint capsules or tendon sheaths, they do not connect with the synovial lining (Weiss & Goldblum, 2001; Pool & Thompson, 2002). This separates ganglions from synovial cysts. Subcutaneous ganglions are seen in dogs, but they have not been reported in cats (Cho et al., 2000; Pool & Thompson, 2002). However, one author (E.J.W.) has seen two cases in cats.

The pathogenesis of ganglions is poorly understood. Previously suggested mechanisms involving rupture of synovial membranes are no longer considered valid. However, about half of the humans affected have a history of previous trauma at the site, an observation that would support damage to joint capsules or tendon sheaths. Most cases in dogs are incidental findings, and a direct association with previous trauma cannot usually be established. The development of ganglion cysts has been interpreted as metaplasia of fibroblasts to mucin-secreting cells (Cho et al., 2000).

Clinical features

Subcutaneous ganglions are rarely seen in dogs and cats. Subcutaneous ganglions are soft and ill-defined masses that may measure up to several centimeters. As they contain unilocular or multilocular cavities, they may fluctuate on palpation. The cysts contain a yellowish mucinous fluid on cut section, and the walls of the cavities may form internal shiny folds. Similar to humans, ganglions in dogs and cats mostly develop in the vicinity of joints, in particular the elbow and stifle (Cho et al., 2000; Pool & Thompson, 2002).

There are no breed or sex predilections for ganglions in dogs and cats. The lesions have been reported in dogs as young as 4 months of age (Cho et al., 2000). Ganglions are benign lesions and complete excision is curative. They may recur locally if excision is incomplete.

Histopathology (Figures 33.9 and 33.10)

At an early stage, ganglions are characterized by a localized accumulation of myxoid material in the subcutis and deep dermis. With progression, unilocular or multilocular, thick-walled cavities develop, which contain bluish-gray mucinous material. There is no epithelial or synovial cell lining (Cho et al., 2000). The cavities are lined by fibroblasts, and the wall is composed of inner myxomatously and outer fibromatous regions. The inner myxomatous layer is characterized by loosely arranged spindle and stellate cells embedded in abundant myxoid stroma. Moderate anisokaryosis may be seen. Mitotic figures are rare. Electron microscopy of these cells reveal abundant rough endoplasmic reticulum and Golgi apparatus; both may be markedly dilated and contain fine granular material, indicating degenerative change (Cho et al., 2000). The outer layer is composed of irregularly arranged fibroblasts, a collagenous stroma, and marked neovascularization resembling granulation tissue. The content of the cavities and the myxoid portion of the wall both stain positively for acid mucin (blue) with Alcian blue–periodic acid–Schiff (PAS) stains (pH 2.5) (Cho et al., 2000). Depending on the location of the ganglion, there are components of either joint capsule or tendon sheath in the surrounding tissue.

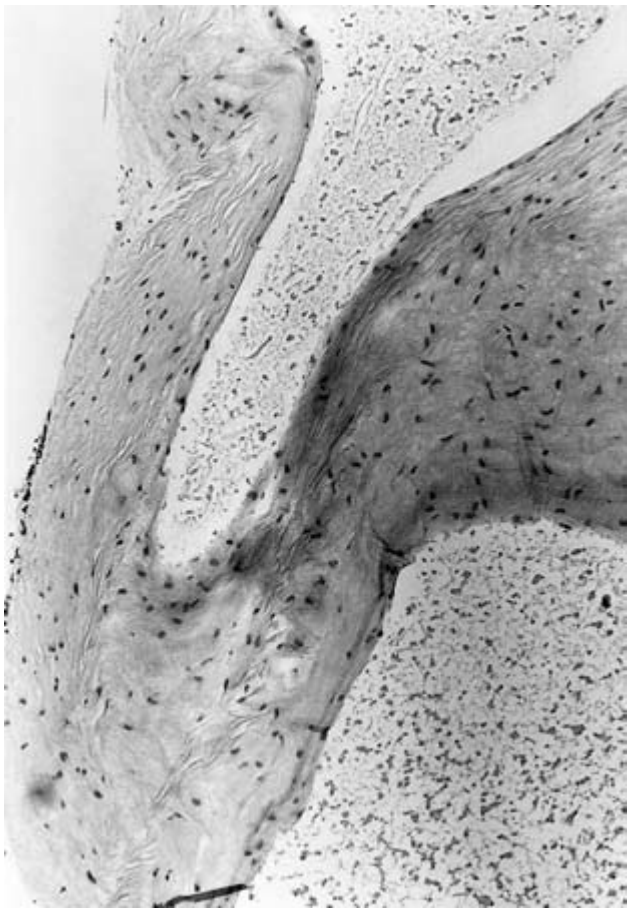


Fig. 33.9 Ganglion in a dog. The central cavity is surrounded by a thick-walled capsule of myxoid fibrous tissue.

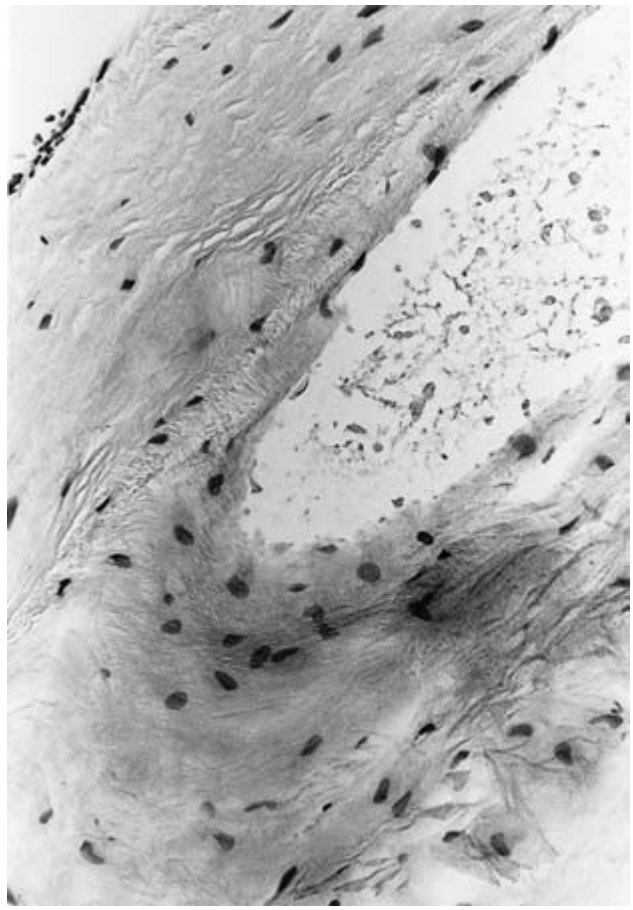


Fig. 33.10 Higher magnification of Fig. 33.9. There is an abrupt transition from the cavity to the capsule. No epithelial lining is seen.

Ganglions need to be differentiated from myxomas, localized mucinosis, or synovial cysts. Early stages of ganglion resemble myxoma; both are characterized by loosely arranged fibroblasts producing mucin. However, with progression, ganglions develop cavitations, a feature not seen in myxomas. Localized mucinosis is characterized by an accumulation of hypocellular mucin separating preexisting collagen bundles; cavitation is absent. Synovial cysts are characterized by similar myxoid tissue surrounding a central cystic space; these cysts, however, are lined by synovial cells.

GRANULAR CELL TUMOR

(Synonyms: granular cell myoblastoma, granular cell schwannoma)

Granular cell tumor in humans, previously referred to as granular cell myoblastoma, was first considered to be of muscular origin (Weiss & Goldblum, 2001). One study demonstrated positive staining for alpha-1-antitrypsin and alpha-1-antichymotrypsin, two antiproteinases present in macrophages (Ulrich et al., 1987). However, these proteases are also found in other leukocytic cells from the bone marrow as well as in epithelial cells from the gastrointestinal tract, pancreas, and liver (Ulrich et al., 1987). Recent immunohistologic data from human granular cell tumors indicate expression of S100, neuron specific enolase (NSE), and various myelin proteins; tumor cells are surrounded by a laminin-positive basement membrane (Weiss & Goldblum, 2001). These results suggest a neural origin for granular cell tumors in humans.

Granular cell tumors of the skin, oral cavity, and central nervous system have been recognized in cats and dogs (Beck et al., 1986; Cordy, 1990; Goldschmidt & Shofer, 1992). Although histologic features resemble the morphologic characteristics of its counterpart in humans, the exact origin of the proliferating cells remains unknown. Except for their expression of vimentin, which supports a mesenchymal origin, immunohistologic and ultrastructural studies do not support a unique cell of origin for all the granular cell tumors examined (Geyer at al., 1992;

Patnaik, 1993; Higgins et al., 2001). Some canine granular cell tumors appear to be of neural origin (Geyer et al., 1992; Rallis et al., 2001), while others lack the immunophenotype and basement membrane that would support neural derivation (Higgins et al., 2001; Cooper & Valentine, 2002; Head et al., 2002). Two studies have demonstrated membrane bound autophagic vesicles containing cellular debris by electron microscopy in some tumors, a feature that would suggest histiocytic origin (Geyer et al., 1992; Higgins et al., 2001). Alpha-1-antitrypsin and alpha-1-antichymotrypsin have been observed in some canine tumors (Higgins et al., 2001), as seen in macrophages as well as other cell types in humans (Ulrich et al., 1987). Immunohistochemistry with more specific leukocyte markers (see below) has failed to confirm histiocytic origin. Seemingly, granular cell tumor is a morphologic designation for tumors in dogs and cats that have similar cytologic features but likely various cellular origins.

Clinical features

Granular cell tumors of all sites are uncommon in dogs and rare in cats (Cooper & Valentine, 2002); these neoplasms are considered very rare in the skin and subcutis of these species. Granular cell tumors are mostly well-defined solitary masses. Occasionally they are larger and poorly circumscribed. In dogs they mostly develop in the oral cavity, in particular on the tongue and palate, but may also occur on the lips, the ears, other locations of the skin, as well as in internal organs (Wyand & Wolke, 1968; Geyer et al., 1992; Patnaik, 1993). In cats, granular cell tumors have been reported in the tongue, the palate, the digits, and on the vulva (Rallis et al., 2001; Cooper & Valentine, 2002).

No breed or sex predilections have been documented for either species. The mean age in dogs is 8 to 9 years (Head et al., 2002). The mean age of affected cats has not been reported.

Feline and canine granular cell tumors exhibit slow expansive growth, and surgical excision usually is curative. Only one canine case has been reported with metastatic lesions in the lung, heart, and diaphragm (Beck et al., 1986).

Histopathology (Figures 33.11 and 33.12)

Granular cell tumors are characterized by variably circumscribed, nonencapsulated masses composed of sheets, cords, or nests of large, round to polygonal cells divided by collagen that may be delicate and fibrillar, or thick and hyalinized. The overlying epithelium is often markedly hyperplastic. The tumor cells have well-defined cell borders, and a moderate amount of pale, eosinophilic cytoplasm. There are delicate, eosinophilic and periodic acid–Schiff (PAS) positive, diastase resistant (nonglycogen) granules. In some reports, electron microscopic evaluation identified these granules as membrane bound autophagic vesicles containing cellular debris (Geyer et al., 1992; Higgins et al., 2001). The round nuclei are usually small, central, or eccentric, and may contain one or two distinct nucleoli. Mitotic figures are rare.

Granular cell tumors are distinctive and differential diagnosis is not highly problematic. Well-differentiated

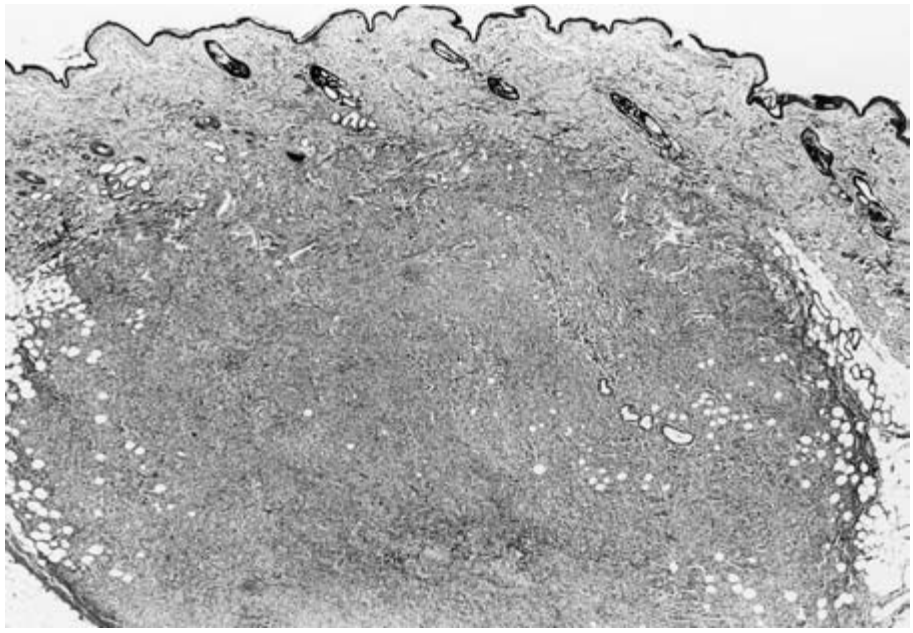


Fig. 33.11 Granular cell tumor in a dog. The deep dermal and subcutaneous mass is nonencapsulated.

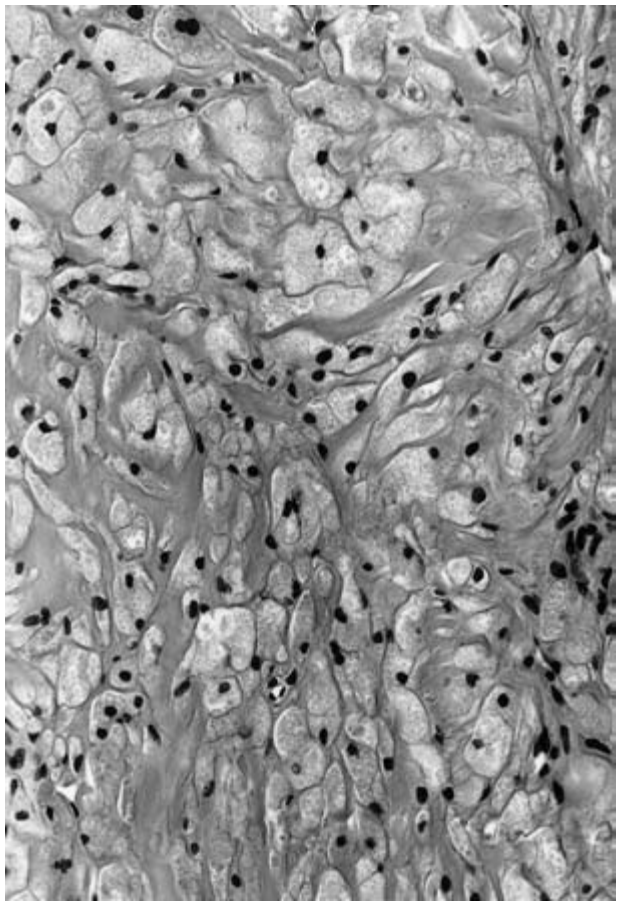


Fig. 33.12 Higher magnification of granular cell tumor in a dog. The individualized large round cells have central round to oval, dense nuclei and abundant pale granular cytoplasm.

histiocytic sarcoma and balloon cell melanocytoma may need to be considered. In contrast to granular cell tumors, well-differentiated histiocytic sarcomas are usually composed of individualized round tumor cells with admixed spindle-shaped tumor cells. The cytoplasm lacks the granular appearance of granular cell tumors. The round to oval nuclei are often indented or twisted, while nuclei of granular cell tumors are consistently round. Fontana–Masson's stain may identify small amounts of melanin in balloon cell melanocytomas, and a small number of more spindle-shaped tumor cells may be admixed.

Immunohistochemistry

Several studies reveal a variable immunophenotype of granular cell tumors. Some tumors have been reported to be positive for alpha-1-antitrypsin, alpha-1-antichymotrypsin, and lysozyme (Higgins et al., 2001), suggesting histiocytic origin. However, these markers are not specific for histiocytic cells (see above). Further, a histiocytic origin could not be confirmed in two cases examined, as tumor cells lacked expression of the common leukocyte markers CD18 and CD45 (Moore, P.F. & Affolter, V.K., unpublished data, 2003). Some canine granular cell tumors express S100 and neuron-specific enolase (NSE), and a neural origin has been suggested (Geyer et al., 1992). Expression of S100 was reported in one canine granular cell tumor of the brain (Patnaik, 1993), but neural origin of the granular cell tumor in the brain of another dog could not be confirmed as tumor cells only partially expressed S100 and lacked a basal lamina, a feature observed with neural origin (Higgins et al., 2001). Moreover, canine and feline granular cell tumors have reportedly lacked expression of glial fibrillary acidic protein (GFAP) (Geyer et al., 1992; Higgins et al., 2001), another neural marker. Some canine and feline granular cell tumors have expressed α-smooth muscle actin or desmin (Patnaik, 1993; Rallis et al., 2001), suggesting muscle origin. These highly variable findings indicate that canine and feline granular cell tumors likely are of different cell origins.

Differentially, histiocytic sarcomas are composed of dendritic antigen presenting cells, which express the common leukocyte markers CD45 and CD18 as well as CD1, CD11c and MHC II, in contrast to granular cell tumors. Histiocytic sarcomas lack expression of α-smooth muscle actin, desmin, NSE, GFAP, or S100. Positive staining with melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), HMB-45/gp100, tyrosinase, melanoma isoform of microphthalmia transcription factor (MITF-M), or tyrosine-related protein-2 (TRP-2) may assist in confirming melanocytic origin.

ANAPLASTIC SARCOMA WITH GIANT CELLS

(Synonym: malignant fibrous histiocytoma, giant cell tumor of soft tissue, spindle cell tumor of soft parts)

'Malignant fibrous histiocytoma' is a term that was first proposed in the human literature. It encompasses a group of soft tissue neoplasms characterized by spindle cells in a storiform (cartwheel) growth pattern that are admixed with histiocytoid cells in varying proportions (Ozzello et al., 1963). This group of tumors includes low-grade to high-grade malignancies that, based on their predominant morphologic features, have been divided into storiform-pleomorphic, myxoid, giant cell, and inflammatory subtypes (Weiss & Enzinger, 1978; Heenan, 1997; Weiss & Goldblum, 2001). These tumors were originally believed to derive from a monocyte/macrophage cell that could undergo transition to a 'facultative' fibroblast. Immunophenotyping has since indicated that these

human tumors represent a potpourri of various mesenchymal tumors with histologic similarities (Mirra et al., 1977; Kindblom et al., 1982; Dehner, 1988; Heenan, 1997; Weiss & Goldblum, 2001). Some anaplastic sarcomas arising from primitive mesenchymal cells may have potential for epithelial differentiation, and hence express both vimentin and cytokeratins. These have been described as epithelioid sarcomas (Enzinger, 1970).

The nomenclature of malignant fibrous histiocytoma did not find its way into the veterinary literature until 1979 when a small series of neoplasms in dogs and cats were reported with morphologic features similar to malignant fibrous histiocytomas in humans (Gleiser et al., 1979). Numerous case reports and review articles have been published since (Bevier & Goldschmidt, 1981; Confer et al., 1981; Macy & Reynolds, 1981; Renlund & Pritzker, 1984; Hendrick et al., 1992; Kerlin & Hendrick, 1996).

The diagnosis of malignant fibrous histiocytoma has always been controversial in veterinary medicine. Goldschmidt and Shofer (1992) preferred 'giant cell tumor of soft tissue' for this neoplasm. More recent studies clearly demonstrate that 'malignant fibrous histiocytoma' is actually a group of sarcomas of various cellular origins, and may represent anaplastic variants of fibrosarcoma, myofibroblastic fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, synovial cell sarcoma, and histiocytic sarcoma (Thoolen et al., 1992; Pace et al., 1994; Kerlin & Hendrick, 1996; Kramer et al., 1998; Affolter & Moore, 2002; Couto et al., 2002). Vaccine-induced sarcoma, which also is of variable mesenchymal origin (see p. 797), may present as an anaplastic sarcoma with giant cells. 'Malignant fibrous histiocytoma' thus is considered a descriptive morphologic term which does not reflect the cellular origin of the lesions. Essentially, the term implies the erroneous existence of a 'fibrous histiocyte'.

The study of Williamson and Middleton (1998) emphasizes the difficulties of separating poorly differentiated spindle cell tumors in dogs, and hence proposes the use of 'spindle cell tumors of canine soft parts', unless the cell of origin can be determined based on immunohistochemistry. Similar to that study, the authors choose to use the more descriptive and generic term 'anaplastic sarcoma with giant cells' to designate these poorly differentiated mesenchymal neoplasms of various origins. In essence, if the specific origin cannot be determined by morphology and immunohistochemistry, it is appropriate to designate the neoplasm as an anaplastic sarcoma with giant cells. Otherwise these neoplasms should be designated as poorly differentiated sarcomas of their specific origin (fibrosarcoma, myofibroblastic fibrosarcoma (see Chapter 27), liposarcoma (see Chapter 30), leiomyosarcoma, rhabdomyosarcoma (see Chapter 31), or histiocytic sarcoma (see Chapter 35).

Clinical features

True anaplastic sarcomas with giant cells are uncommon. Goldschmidt and Shofer (1992) report the incidence of 'giant cell tumors of soft tissue' as less than 0.5% in dogs and 0.9% in cats of all cutaneous neoplasms. Canine and feline anaplastic sarcomas with giant cells present similarly to their more well-differentiated counterparts. Solitary, large, firm, poorly circumscribed, subcutaneous, and dermal masses are usually observed. Alopecia and ulceration of the overlying epidermis may be present. Legs and shoulders are the most common sites.

The average age for anaplastic sarcomas with giant cells is 8 years in dogs and 10 years in cats (Goldschmidt & Shofer, 1992). Occasionally, lesions are seen in very young animals (Pires, 1997). Goldschmidt and Shofer (1992) report that females are more frequently affected than males at a ratio of 2:1. There are no known breed predilections for either cats or dogs.

The description of the behavior of feline and canine anaplastic sarcomas with giant cells (malignant fibrous histiocytomas) varies among different reports. Locally invasive tumors with no or low metastatic potential, as well as highly aggressive tumors with metastases to draining lymph nodes and other organs systems are described (Garma-Avina, 1987; Allen & Duncan, 1988; Gibson et al., 1989; Thoolen et al., 1992; Waters et al., 1994; Kerlin & Hendrick, 1996; Booth et al., 1998; Affolter & Moore, 2002). Behavioral differences may reflect the different cellular origin of these neoplasms.

Histopathology (Figures 33.13 through 33.17)

Canine and feline cutaneous anaplastic sarcomas with giant cells are unencapsulated, poorly defined tumor masses that are mostly localized to the subcutis. Dermal extension may occur secondarily. Variable amounts of collagen may be present, and the collagenous stroma may be hyalinized in some areas. Ulceration, necrosis, hemorrhage, and sclerosis are common secondary features. The tumor cell population is composed of variable numbers of spindle cells, large round cells (referred to as 'histiocytoid' cells), and multinucleated giant cells.

Plump spindle-shaped tumor cells form dense bundles or sheets. They may be arranged in a storiform pattern ('storiform' is derived from the Latin *storea*, meaning rope mat). Individual units comprising the 'mats' allegedly resemble spokes radiating from a central point. Occasionally, the cells may be arranged around vessels. The spindle cells have scant and poorly defined cytoplasm, and either uniform elongated nuclei with pointed

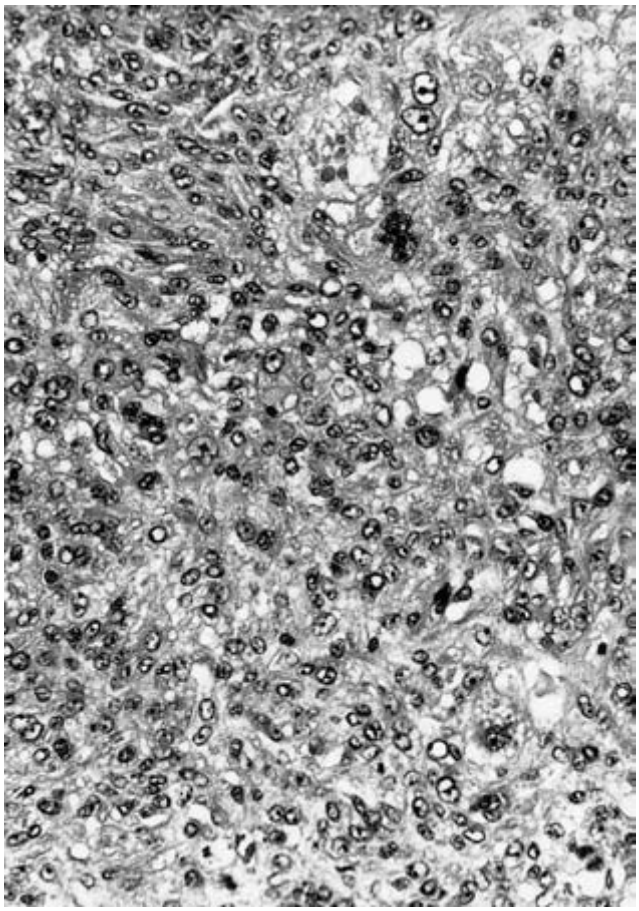


Fig. 33.13 Anaplastic sarcoma with giant cells in a dog featuring pleomorphic round to plump spindle cells with marked anisokaryosis. Note the lipid vacuolation of the histiocytoid cells.

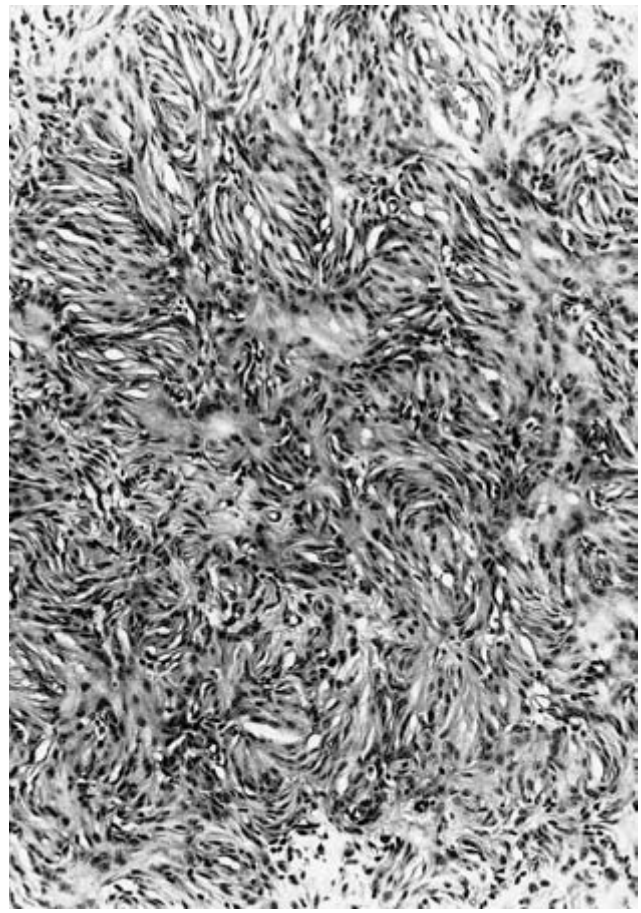


Fig. 33.14 Anaplastic sarcoma with giant cells in a dog. Spindle cells are arranged in repetitive storiform patterns; giant cells are absent in this view.

or blunt ends, or large oval nuclei. The nuclei have highly atypical features, including variable chromatin patterns, eccentric position, and frequent cytoplasmic invaginations. Mitotic activity varies and may be very high. Bizarre mitotic figures are common.

The presence of histiocytoid tumor cells varies between and within tumors, and may be very prominent in some areas. The histiocytoid cell population is mainly composed of large round cells with differing morphologies. Some histiocytoid tumor cells have round to oval, often pleomorphic, vesicular nuclei and a moderate to abundant amount of pale eosinophilic cytoplasm. Mitotic activity and degree of mitotic atypia vary in this population. Admixed there are also variable numbers of a second population of round cells with fairly monomorphic, round and indented nuclei and intracytoplasmic lipid vacuoles or intracellular hemosiderin; these may represent tumor cells or reactive histiocytes with phagocytic activity. Differentiation between tumor cells and reactive histiocytes requires immunohistochemistry (see below).

Multinucleated giant cells have a large amount of eosinophilic cytoplasm and may have up to 30 nuclei. In particular, abundant giant cells are common in anaplastic sarcomas of cats. The nuclei of some of these giant cells may be small and hyperchromatic, and there generally is no evidence of mitosis. This group of multinucleated giant cells may represent reactive histiocytic giant cells. Other multinucleated giant cells have marked anisokaryosis, moderate to marked mitotic activity, and occasional bizarre mitotic figures. Most of these more pleomorphic giant cells are of tumor cell origin. It may be important to differentiate between neoplastic and reactive multinucleated giant cells in these neoplasms, as the presence of neoplastic giant cells is considered a sign of poor prognosis in human medicine, while the presence of reactive multinucleated histiocytic giant cells may indicate a developing antitumor immune response (Josten & Rudolph, 1997). Immunohistochemistry allows differentiation between reactive and neoplastic multinucleated giant cells (see below).

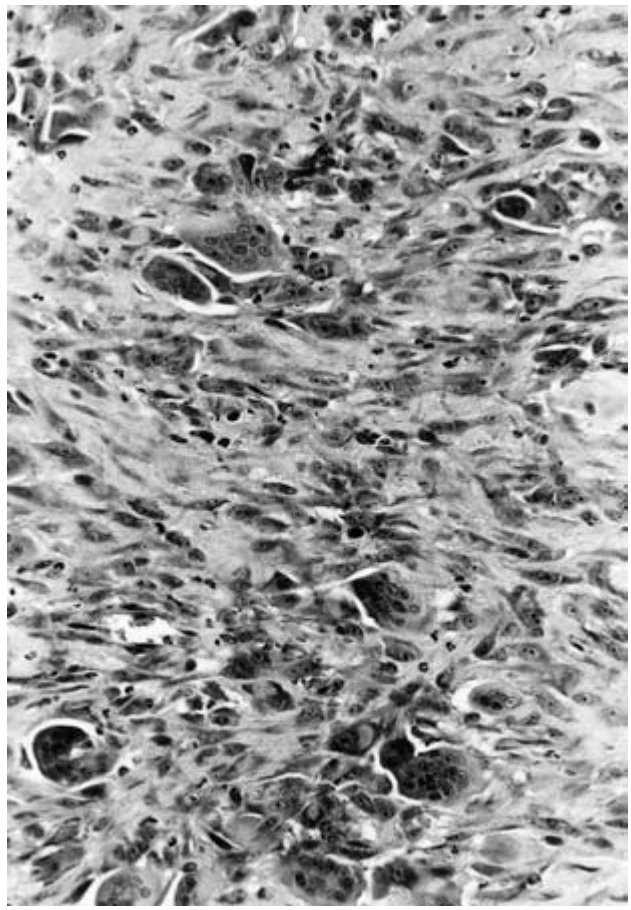


Fig. 33.15 Anaplastic sarcoma with giant cells in a dog composed of haphazardly arranged anaplastic spindle cells. The accompanying giant cells have fairly monomorphic nuclei and no evidence of mitosis, suggestive of reactive histiocytic origin.

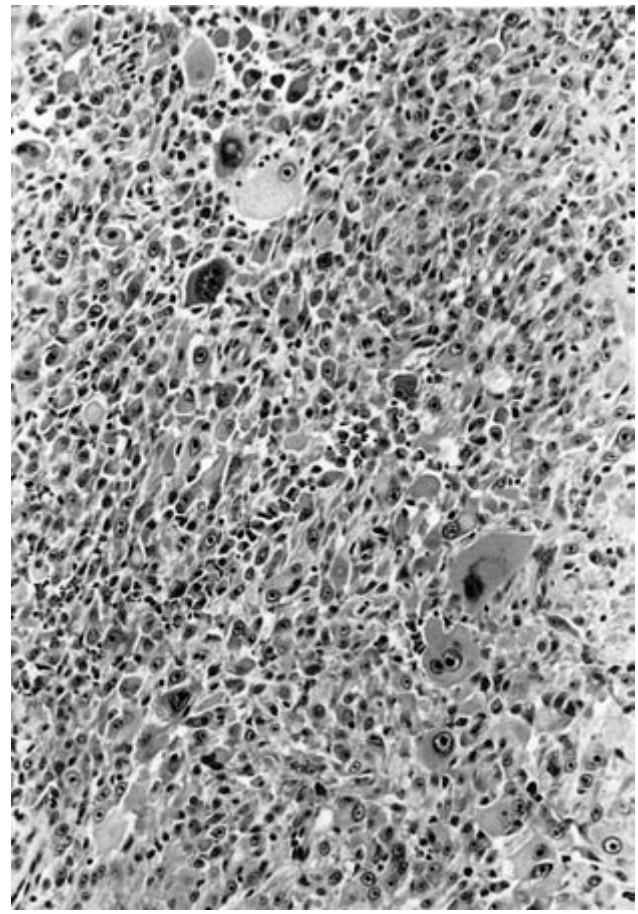


Fig. 33.16 Anaplastic sarcoma with giant cells in a dog. The round to spindled neoplastic cells are associated with pleomorphic multinucleated tumor cells with bizarre, large nuclei; compare these tumor giant cells with those of Fig. 33.15.

The presence of numerous giant cells is fairly characteristic for this morphologic group of tumors, but essentially 'anaplastic sarcoma with giant cells' is a diagnosis of default. Differential diagnosis should involve an attempt to identify other specific poorly differentiated sarcomas with giant cells (fibrosarcoma, myofibroblastic fibrosarcoma (see Chapter 27), liposarcoma (see Chapter 30), leiomyosarcoma, rhabdomyosarcoma (see Chapter 31), or histiocytic sarcoma (see Chapter 35). Occasionally, some areas within a tumor are composed of more distinctive architectural patterns and differentiated tumor cells, both suggesting a particular cell of origin. In such cases immunohistochemistry also may help to confirm a specific cell type. In those cases, the diagnosis of anaplastic sarcoma with giant cells should be avoided, and the tumor designated more specifically.

Anaplastic sarcomas with giant cells may also need to be differentiated from poorly differentiated osteosarcomas with giant cells, and anaplastic carcinomas. Osteosarcomas usually contain variable osteoid deposits between some of the tumor cells, and mineralization of the osteoid may occur. Moreover, osteoclasts are positive for tartrate-resistant acid phosphatase (TRAP), while multinucleated tumor giant cells of anaplastic sarcomas and reactive multinucleated giant cells are negative for TRAP (Josten & Rudolph, 1997). Anaplastic carcinomas may exhibit plump spindle cells, but in contrast to anaplastic sarcomas, occasionally may have cytoplasmic mucin. Also, anaplastic carcinomas may have small foci of tubular or acinar structures. Immunohistochemistry may be required.

Immunohistochemistry

As with all mesenchymal tumors, anaplastic sarcomas with giant cells are positive for vimentin. A panel of antibodies, including α-smooth-muscle actin, pan-muscle actin, desmin, leukocyte markers, osteonectin, osteocal-

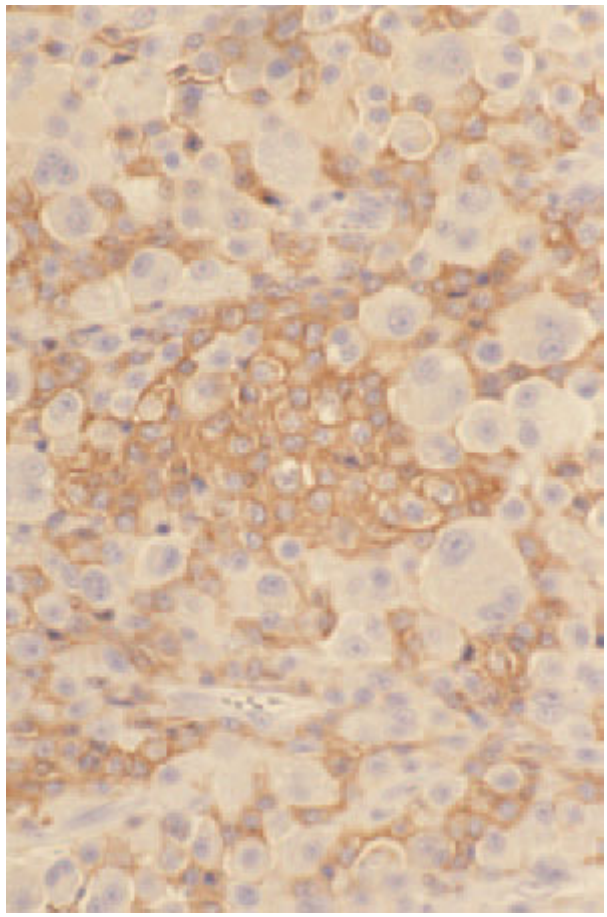


Fig. 33.17 Anaplastic histiocytic sarcoma in a cat. This neoplasm was initially diagnosed as an anaplastic sarcoma with giant cells; immunohistochemistry with anti-CD18 antibody confirms the leukocytic origin (chromogen diaminobenzidine [DAB]).

cin, and cytokeratins may permit identification of anaplastic variants of fibrosarcoma, myofibroblastic fibrosarcoma (see Chapter 27), liposarcoma (see Chapter 30), leiomyosarcoma, rhabdomyosarcoma (see Chapter 31), and histiocytic sarcoma (see Chapter 35). Anaplastic carcinomas generally retain broad expression of cytokeratin intermediate filaments, while minimal patchy expression of cytokeratins is only occasionally seen in anaplastic sarcomas. Anaplastic carcinomas may also express the carcinoembryonic antigen (CEA), although the utility of this marker in veterinary pathology has not been well documented. The default diagnosis of anaplastic sarcoma with giant cells should be made if immunophenotypic evaluation fails to exhibit expression of specific markers, and hence fails to identify a specific mesenchymal cell of origin.

Immunohistochemistry has identified two giant cell populations in anaplastic sarcomas with giant cells. Neoplastic multinucleated giant cells express an immunophenotype identical to the single nucleated tumor cells, while reactive multinucleated giant cells are of leukocytic origin and thus express CD18 and CD45. Moreover, neoplastic multinucleated giant cells tend to be strongly positive for MIB1, which recognizes the nuclear nonhistone protein Ki67 that is associated with cell growth and division. The high Ki67 labeling index indicates marked proliferative activity (Josten & Rudolph, 1997). In contrast, reactive multinucleated histiocytic giant cells, similar to osteoclasts, lack mitotic activity and are negative for MIB1 (Josten & Rudolph, 1997).

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Chapter 34

Melanocytic tumors

The classification of human melanocytic tumors is complex, and confusion has been engendered by the use of such terms as 'congenital nevus', 'acquired nevus', and 'nevus cell' (Lever & Schaumburg-Lever, 1990). The so-called 'nevus cells' in human pathology are melanocytes with slight histopathologic and biochemical alterations (Lever & Schaumburg-Lever, 1990). The terms 'nevus' and 'nevus cells' will be avoided by the authors except for comparative purposes.

In the past, different classification systems have been used for canine and feline melanocytic proliferations. The term 'melanoma' has been variably employed in veterinary nomenclature systems. Some classifications have used the term 'melanoma' to designate both benign and malignant neoplasms (Goldschmidt & Shofer, 1992), while others have limited it to malignant neoplastic proliferations (Pulley & Stannard, 1990). As in *Veterinary Dermatopathology* (Walder & Gross, 1992), and in accordance with the revised World Health Organization classification system (Goldschmidt et al., 1998), the authors use the term 'melanocytoma' to encompass all variants of congenital and acquired benign neoplasms arising from melanocytes; 'melanoma' is used synonymously with malignant melanoma.

Melanocytes are neuroectodermal cells. During fetal development, melanoblasts migrate from the neural crest to the epidermis and the hair bulbs, where they differentiate into mature cells. Homing signals, which direct the migration of melanoblasts to their destination, have not been identified to date (Sulaimon & Kitchell, 2003). Some melanoblasts may be retained in the dermis and mature to dermal melanocytes. Melanocytic proliferations may therefore arise from melanocytes in the epidermis, the dermis, or the adnexa.

While intraepidermal neoplastic melanocytes retain their expression of E-cadherin, dermal tumor cells no longer express it (Tang et al., 1994). Immunohistochemistry for E-cadherin is therefore not useful in the diagnosis of dermal melanocytic tumors. Melanocytes contain melanosomes, melanin granules, and tyrosinase. They also express S100, melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), the melanoma isoform of microphthalmia transcription factor (MITF-M), the enzyme tyrosinase, and gp100 (HMB-45) (Radford et al., 1996; Barrio, 1998; Busam et al., 1998, 2001; Jungbluth et al., 2000; Orchard, 2000; Berset et al., 2001). Melan-A and MART-1 antibodies recognize the same antigen, CD63 (Hemler, 2002). However, according to a small pilot study of several canine melanocytic tumors by one of the authors (V.K.A.), Melan-A and MART-1 are not consistently both positive in individual cases, and hence may have different specificities. In addition to Melan-A and MART-1, S100 (α unit), S100 ($\alpha\beta$ units), and tyrosinase gave the most promising results in the same study. Further, the study of Choi and Kusewitt (2003) reports that the tyrosinase-related protein-2 (TRP-2) appears to be retained in many amelanotic melanomas in dogs. Antibodies specific for MITF-M are currently being evaluated for their usefulness in diagnosis of canine and feline melanocytic tumors. It appears that this protein is strongly expressed in both canine and feline melanomas (Wojcieszyn, J., personal communication, 2003).

Dermal melanocytes must be differentiated from melanin-phagocytizing histiocytes, referred to as melanophages. The latter are often admixed with proliferating melanocytes. While melanocytes contain finely dispersed melanin granules, melanophages are distended with phagocytized coarse melanin granules of varying size. Electron microscopy demonstrates the presence of cross-striation in the melanosomes of melanocytes, whereas macrophages contain melanin in secondary lysosomes (Dardick, 1996).

UV light radiation has a significant influence on the development of some melanocytic tumors in humans (Longstreth, 1988; Langley et al., 2003). This has not been recognized in dogs and cats. A possible link between naturally occurring feline uveal melanomas and the presence of feline leukemia virus/feline sascoma virus (FeLV/FeSV) has been described (Stiles et al., 1999); however, the presence of viral DNA has not been reported in cutaneous melanocytic proliferations in cats. Loss of

expression of the tumor suppressor gene product p53, which induces the pancyclin-dependent kinase inhibitor p21/Waf-1, has been identified in benign canine melanocytic tumors (Ritt et al., 1998). As a result the tumor cells continuously divide and proliferate. The expression of KIT, the product of the proto-oncogene *c-kit*, plays an important role in the normal development of melanocytes in humans (Fleischman, 1992). Moreover, the loss of expression of KIT has been associated with metastatic behavior of melanomas in humans (Natali et al., 1992). In contrast, the importance of KIT in the normal development of feline and canine melanocytes and its involvement in melanocytic neoplasia has not been demonstrated to date (Sulaimon & Kitchell, 2003).

LENTIGO

Lentigo is a melanocytic proliferation best interpreted as intraepidermal melanocytic hyperplasia of well differentiated melanocytes (Elder & Elenitsas, 1997; Grichnik et al., 2003). Lentigo simplex in humans is characterized by a few small, scattered macules, while lentiginosis profusa features innumerable small macules (Elder & Elenitsas, 1997; Grichnik et al., 2003). The pathogenesis of lentigo simplex and lentiginosis profusa is not known; however, lentigo simplex may be regarded as an incipient or evolving junctional melanocytoma (Elder & Elenitsas, 1997). Solar lentigines develop mainly in older people and are, therefore, also referred to as senile lentigines (Elder & Elenitsas, 1997).

Lesions analogous to human lentigo simplex occur in dogs and in cats (Scott, 1987; Scott et al., 2001) and lentiginosis profusa has been documented in cats (Scott, 1987; Nash & Paulsen, 1990). Lesions originally reported as canine lentiginosis profusa (Briggs, 1985) were reclassified as pigmented epidermal nevi in *Veterinary Dermatopathology* (Walder & Gross, 1992); however, recent studies indicate that these lesions are induced by papillomavirus (Nagata, 1995) and are better referred to as pigmented viral plaques (see Chapter 22). Clinical photographs in some reference texts illustrating 'multiple lentigines' or 'tar spots' on the abdomen of dogs also are more consistent with pigmented viral plaques.

Clinical features

Based on the small number of cases reported, there are no incidence data for lentigo simplex in dogs and cats or lentiginosis profusa in cats. The authors believe that they are common, but are infrequently biopsied. Lentigines are well-demarcated, black, macular, or slightly raised, well-circumscribed lesions with a smooth surface. In cats, the lesions increase in size and number and then become stable. In dogs, they are often incidental findings, and their natural progression is unknown. They are usually less than 5 mm in diameter.

Lentigines may be solitary or multiple (lentigo simplex) or, occasionally numerous (lentiginosis profusa). The lesions in cats occur predominantly on the head, often on lips, eyelid margins, nasal planum, and pinnae (Scott, 1987; Scott et al., 2001). Lentigines in dogs occur almost exclusively on the nipples (Kraft & Frese, 1976). Multiple lesions with early lentiginous change were observed by the authors in a 12-year-old Golden Retriever that presented with multiple macular pigmented foci with scale.

In cats, lentigines tend to appear early in life, affecting animals less than 1 year of age. This suggests a congenital etiology. There are no breed predilections in cats, but affected animals have orange, cream, red, tricolor, or silver haircoats (Scott, 1987). Lesions in dogs occur in older animals, and there are no known breed predispositions.

Histopathology (Figures 34.1 and 34.2)

Lentigines are discrete, sharply demarcated, plaque-like lesions characterized by minimal to mild, irregular epidermal hyperplasia and marked hyperpigmentation (Elder & Elenitsas, 1997; Grichnik et al., 2003). The lesions contain increased numbers of deeply pigmented melanocytes. In addition, the epidermal keratinocytes are markedly hyperpigmented, which may partially obscure the presence of melanocytic hyperplasia. Numerous melanocytes are usually distributed as single cells among the basal epithelial cells and may be more concentrated along elongated rete ridge-like extensions, often in 'drip' configurations. The melanocytes are enlarged due to engorgement with melanin, but are otherwise normal. Dermal–epidermal clusters of melanocytes may occasionally be present, and small numbers of melanophages may accumulate in the superficial dermis.

The differential diagnoses for lentigo are ephelids (freckles) and pigmented viral plaques (see Chapter 22). Lentigines are grossly macular and are characterized microscopically by melanocyte hyperplasia, epidermal hyperpigmentation, and irregular epidermal hyperplasia. Ephelids are also macular, but show discrete areas of hyperpigmentation only, with no hyperplasia of melanocytes or keratinocytes. Pigmented viral plaques also lack melanocyte hyperplasia but exhibit epidermal hyperplasia, often in a scalloped pattern, with prominent hyperpigmentation, hypergranulosis, and hyperkeratosis; koilocytosis may be present. Intralesional papillomavirus can be demonstrated by immunohistochemistry (see Chapter 22).

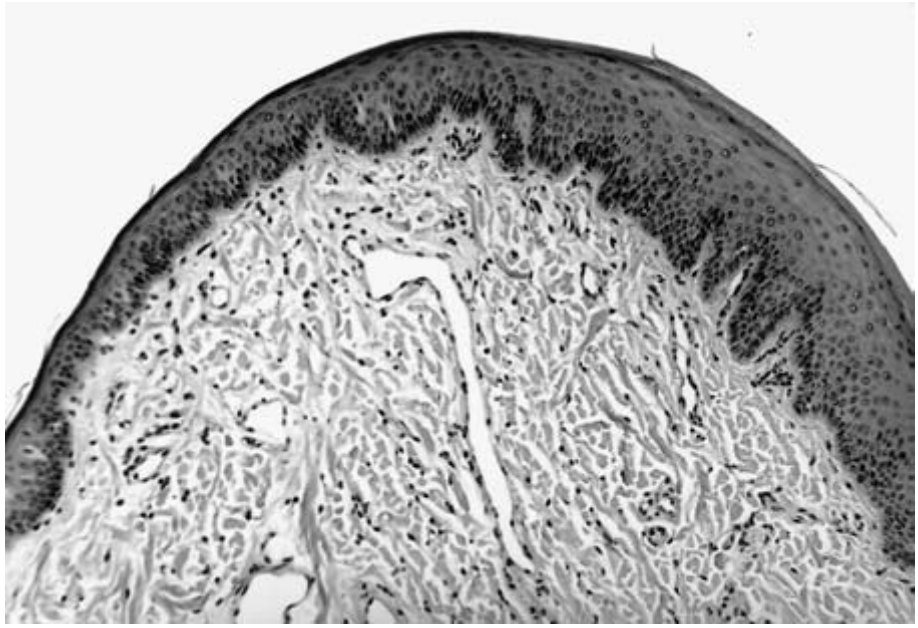


Fig. 34.1 Lentigo in a cat. Densely-pigmented melanocytes are accumulated in the basal cell layer of the lip margin. Note that epithelial hyperplasia is minimal.

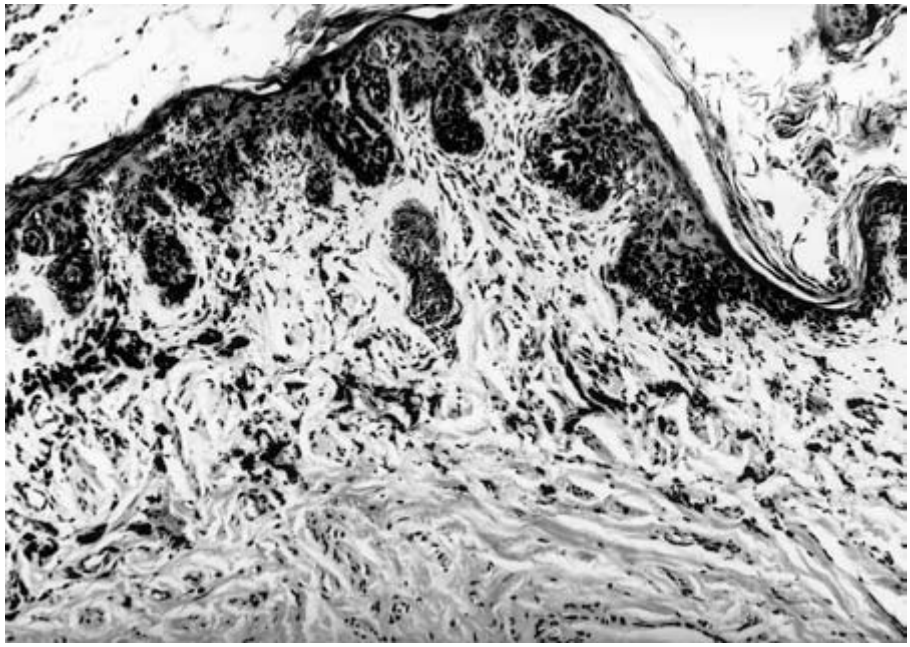


Fig. 34.2 Lentigo in the nipple of a dog. Densely-pigmented melanocytes are concentrated along rete ridge-like extensions of the hyperplastic epidermis. Hyperpigmentation extends into the stratum corneum. Note stellate melanocytes and plump melanophages in the underlying dermis.

MELANOCYTOMA

(Synonym: benign melanoma)

Cutaneous melanocytomas include all variants of congenital and acquired benign neoplasms arising from melanocytes. Melanocytomas are traditionally subdivided into junctional, compound, and dermal types in humans, according to the location of the proliferating melanocytes within the skin (Elder & Elenitsas, 1997). Melanocytomas include dermal, compound, and balloon cell melanocytomas in dogs and cats, as well as multiple dysplastic melanocytoma syndrome in dogs.

Clinical features

Melanocytomas are common in dogs and account for 3% to 4% of skin tumors (Conroy, 1983; Goldschmidt & Shofer, 1992). The ratio of cutaneous melanocytomas to malignant melanomas is reported in these surveys as 2:1

(Conroy, 1983) and 4:1 (Goldschmidt & Shofer, 1992). Melanocytomas are uncommon in cats, comprising only 0.6% to 1.3% of all skin tumors (Carpenter et al., 1987; Goldschmidt & Shofer, 1992). The frequency of feline melanocytomas documented in the literature ranges from 32% to 58% of all melanocytic proliferations (Macy & Reynolds, 1981; Carpenter et al., 1987; Goldschmidt & Shofer, 1992; Goldschmidt et al., 1993). Balloon cell melanocytoma is rare (Walder, 2000).

Junctional (intraepidermal) melanocytomas occur theoretically in dogs and cats, but have not been described. This may be because solitary macular lesions are difficult to detect on haired skin and are unlikely to be biopsied even when present on glabrous skin. Hence, canine and feline lesions are likely only biopsied when junctional melanocytomas have progressed into compound melanomas, a process documented in other species (Elder & Elenitsas, 1997).

Compound (intraepidermal and dermal) melanocytomas resemble compound melanocytic nevi in humans. They are the most common type of melanocytoma observed in dogs. One retrospective study found that compound melanocytomas accounted for 71% of feline melanocytomas (Miller et al., 1993).

Dermal melanocytomas are similar to the human cellular blue nevus or common blue nevus. Dermal melanocytomas are common in dogs. The majority of the feline benign melanocytic tumors described by Carpenter et al. (1987) were dermal melanocytomas, while Miller et al. (1993) listed 29% of feline melanocytomas in this category.

It is important to note that wide variation in incidence data is likely a result of lack of standardized diagnostic criteria for malignancy in melanocytic neoplasms; controversies persist in both human and veterinary medicine. Some investigators equate 'benign behavior', i.e. lack of recurrence or metastasis, with a benign neoplasm; this approach is misleading, as it discounts the possibility of a malignant neoplasm that has been surgically cured.

Compound melanocytomas present as solitary, circumscribed, brown to black, alopecic nodules that are usually less than 1 cm in diameter. The nodules may be smooth or slightly papillated, and vary from papular, dome-shaped, and plaque-like to pedunculated in configuration. Ulceration is uncommon.

Dermal melanocytomas present as solitary, circumscribed, alopecic, fleshy, dome-shaped masses that are 0.5 to 4.0 cm in diameter. The lesions generally appear blue-black when viewed through lightly pigmented skin, but they may also appear dark brown to black due to hyperpigmentation of the overlying epidermis. In cases of balloon cell dermal melanocytoma, the dermal nodule may have a cream or tan color.

Canine melanocytomas in general may occur anywhere on the body. In cats, benign melanocytic lesions favor the head, particularly the pinnae (Goldschmidt et al., 1993; Miller et al., 1993). Canine compound melanocytomas occur most often on the trunk and head, especially on the eyelids and muzzle. They may occur as pedunculated lesions on the lips. Dermal melanocytomas are most often truncal in location in dogs, and they occasionally occur on the extremities, particularly between the digits.

The average age of dogs with melanocytomas in the study of Bolon et al. (1990) was 8.1 years, but dogs as young as 1.5 years were affected. The peak occurrence is reported by Goldschmidt & Hendrick (2002) to be between 5 and 11 years in dogs, and 4 and 13 years in cats; the average is 9 years for both species (Goldschmidt & Shofer, 1992). A higher incidence for all melanocytic neoplasms is documented in canine breeds with dark pigmentation of the skin: dogs at higher risk are Scottish, Airedale and Boston Terriers; Miniature and Standard Schnauzers; Doberman Pinschers; Vizslas; Golden and Chesapeake Bay Retrievers; Irish Setters; Chow Chows; Boxers; and Cocker and Springer Spaniels (Conroy, 1967; Bolon et al., 1990; Goldschmidt & Hendrick, 2002; Scott et al., 2001 [compilation]). A predilection for males was observed by Conroy (1983), but this observation has not been confirmed by others. A higher incidence (65%) of melanocytomas was seen in female cats; 35% of cats with melanocytic proliferations in general had black or gray coat color (Goldschmidt et al., 1993).

Clinical criteria used to differentiate between benign and malignant melanocytic neoplasms are not sharply defined in dogs and cats. Location of the tumor has been considered important in regard to the clinical behavior. Melanocytic tumors of the nailbeds, mucocutaneous junctions, and oral mucosa are generally malignant; lesions on haired skin, including lips and digits, are more likely to be benign. Histologically benign melanocytic tumors have been seen on the labial mucocutaneous junction and oral mucosa; a clinicopathologic study is underway to investigate the biological behavior of these lesions (Esplin, 2003). In a retrospective survey of melanocytic neoplasms in dogs, four of 52 dogs with apparently benign histologic lesions developed metastases or inoperable recurrences (Bostock, 1979). In a more recent report, all of 77 neoplasms considered histologically benign did exhibit benign behavior (Bolon, 1990), suggesting that more stringent histologic criteria allow more accurate prognostication.

Malignant transformation occurs in a small percentage of benign melanocytic tumors in humans (Grichnik et al., 2003). This phenomenon has not been well documented in animals, but it may occur occasionally (Conroy, 1983) and has been observed by the authors. A recent case report describes malignant transformation of a congenital melanocytoma with subsequent metastasis in a 5-year-old Golden Retriever (Valentine et al., 1999).

Multiple dysplastic melanocytoma syndrome

The authors have observed a few cases of multiple (synchronous and metachronous) melanocytic tumors in dogs that were benign in their early stages but subsequently developed cytologic features of malignancy when allowed to increase in size. One dog, a spayed female Chow Chow, developed hundreds of these lesions over a period of 13 years. Most lesions were removed in early stages. Metastasis did not occur. This entity has some similarities to the dysplastic nevus syndrome in humans, which may occur in the context of malignant melanomas or as a separate entity (Elder & Elenitsas, 1997; Salopek, 2002). If surgically removed at an early stage, multiple dysplastic melanocytomas have a good prognosis and recurrence is not observed. However, new lesions may develop elsewhere on the body over time.

Histopathology

In general, melanocytomas are symmetrical, circumscribed, but unencapsulated masses. Melanocytomas have a variety of histopathologic patterns and are composed of spindle cells, round to polygonal cells, epithelioid cells, dendritic cells, or balloon cells; these cell types all may occur either alone or in combination. Spindle cell-predominant morphology was statistically associated with benignity in one study (71% melanocytomas in contrast to 29% melanomas) (Goldschmidt et al., 1993). Approximately two-thirds of canine melanocytomas have combined spindle and epithelioid morphology.

Spindle melanocytes have pale, poorly defined cytoplasm. These fusiform cells are usually arranged in small nests, or form whorls and serpentine bundles, simulating neural structures; this is not unexpected in light of the embryologic derivation of melanocytes from the neural crest. Round to polygonal cells are usually arranged in sheets and dense packets; the packets are separated by a very scant stroma. Epithelioid cells are rounded, have a large amount of pale eosinophilic cytoplasm, and are arranged in sheets and larger nests. Cell boundaries of epithelioid melanocytes may be difficult to discern. Dendritic melanocytes have a highly angular shape, sometimes with long cytoplasmic processes, and are usually arranged in small nests. Balloon melanocytes are large round cells that have abundant, very pale cytoplasm (see below).

In general, melanocytoma cells have slightly enlarged, vesicular nuclei and small or inconspicuous nucleoli. Nuclear shape may vary slightly from round to oval depending on the type of tumor cell. Balloon cell nuclei are smaller, uniform, and ovoid. Mitotic figures are rare in all cell types, and mitotic atypia is not observed.

The amount of melanin in individual tumor cells varies; the granules are small and uniform in size within a given tumor cell. Spindle, round to polygonal, and balloon cells often have sparsely-distributed melanin pigmentation. Large epithelioid tumor cells and dendritic cells tend to be heavily pigmented. With the exception of balloon cell melanocytomas, the vast majority of feline and canine melanocytomas have moderate to marked melanin pigmentation overall, at least in the superficial portions of the tumors. Fontana–Masson stain will usually confirm the presence of scant cytoplasmic melanin in poorly pigmented tumors. An abundance of melanin granules may obscure nuclear features. Bleaching of the tissue section with permanganate or oxalic acid will allow evaluation

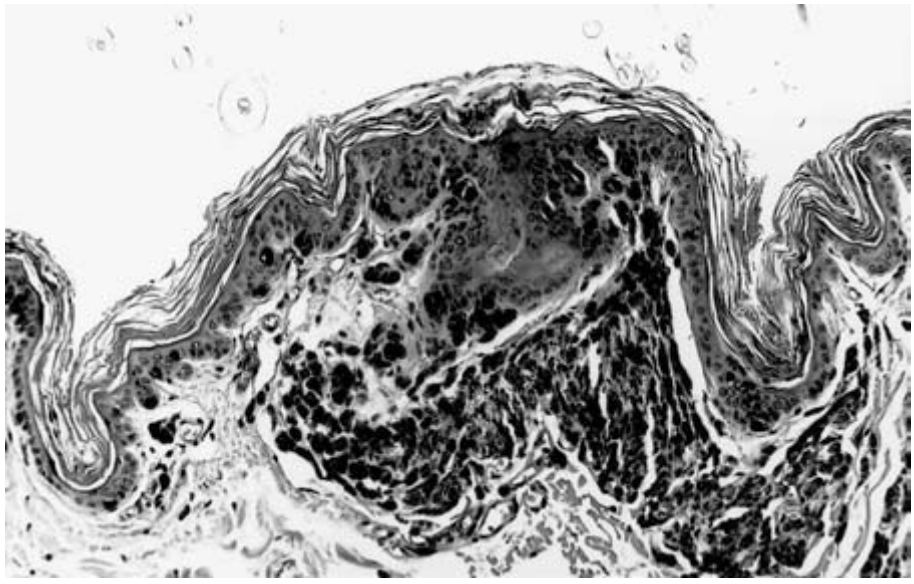


Fig. 34.3 Compound melanocytoma in a dog composed of heavily pigmented epithelioid melanocytes arranged in nests and clusters. Note the relative symmetry of both dermal and epidermal components.

of cellular morphology if investigation for cytologic features of malignancy is needed.

In most melanocytomas, the overlying epidermis is hyperpigmented, regardless of the presence or absence of intraepidermal clusters of neoplastic melanocytes. There may be secondary ulceration due to trauma. Typically, melanocytomas have a scant to occasionally moderate stromal collagen. Variable numbers of melanophages are often grouped in small clusters. Small foci of necrosis may be present in large tumors. A reactive population of lymphocytes and plasma cells suggests a secondary host immunologic response, particularly in the absence of traumatic features such as ulceration. Traumatic ulceration is accompanied by an influx of neutrophils.

Compound melanocytoma (Figures 34.3 and 34.4)
These tumors are often wedge-shaped in configuration and include a junctional and dermal component. Numerous, densely packed tumor cells are present in the dermis. Variable numbers of tumor cells accumulate in clusters

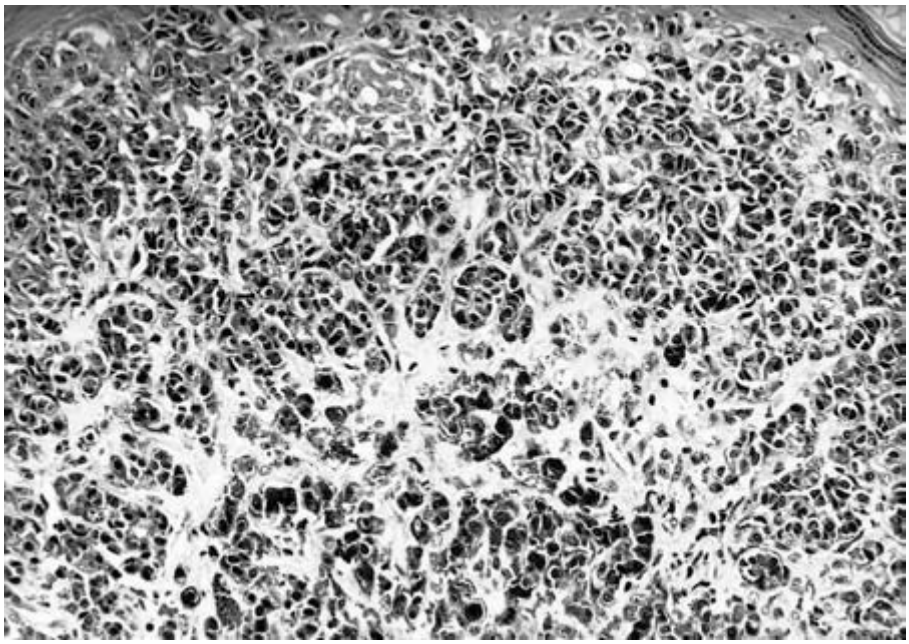


Fig. 34.4 Higher magnification of compound melanocytoma in a dog. Epithelioid cells containing moderate melanin pigment are arranged in nests and clusters within the dermis and along the dermal–epidermal junction. Nuclei are relatively small and uniform.

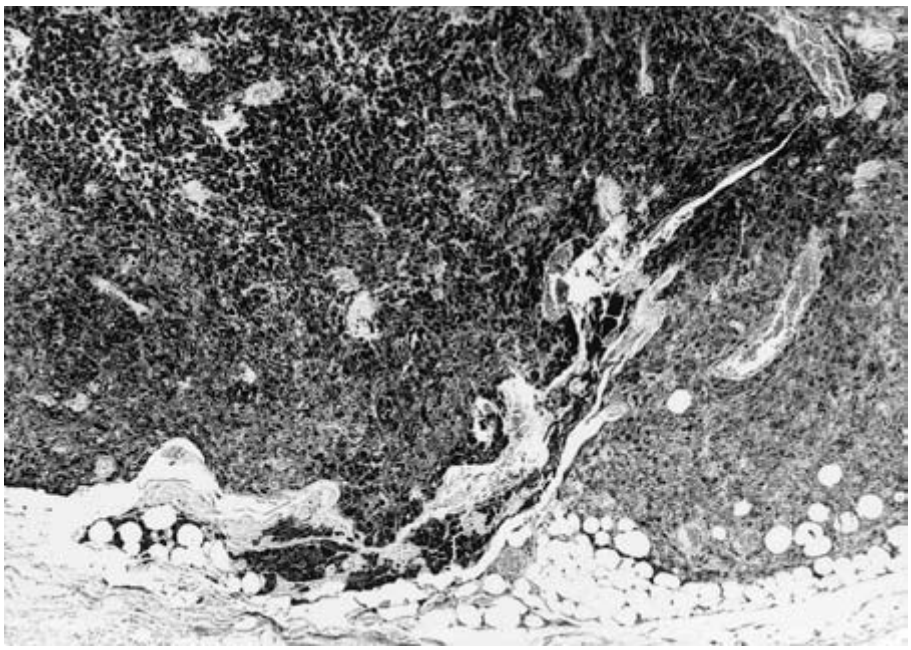


Fig. 34.5 Dermal melanocytoma in a dog. A large, well-circumscribed mass of heavily pigmented cells encroaches upon the subcutaneous fat.

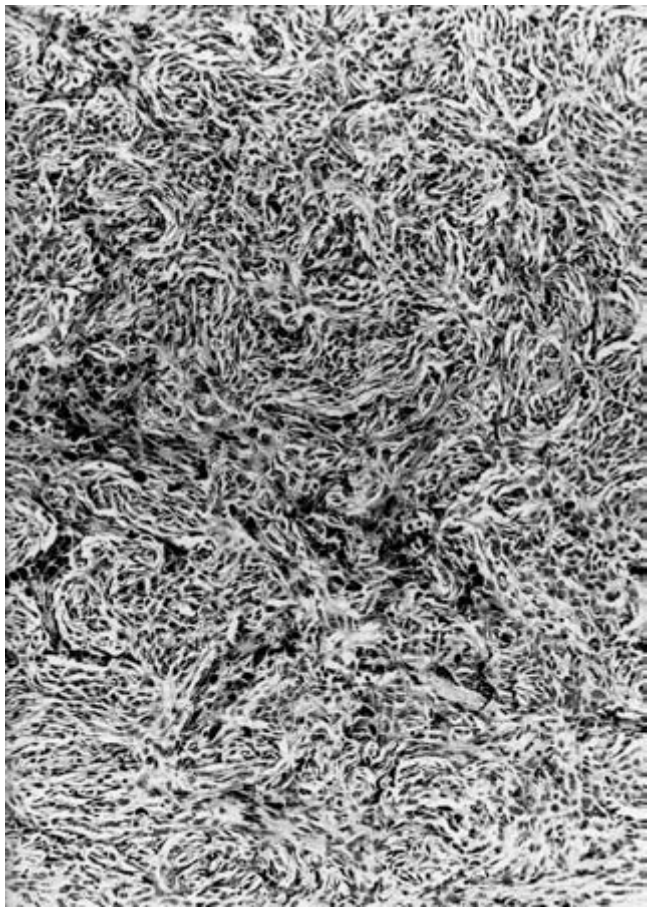


Fig. 34.6 Dermal melanocytoma in a dog. Sparsely pigmented fusiform cells arranged in whorls and nests are interspersed with heavily-pigmented epithelioid cells and melanophages.

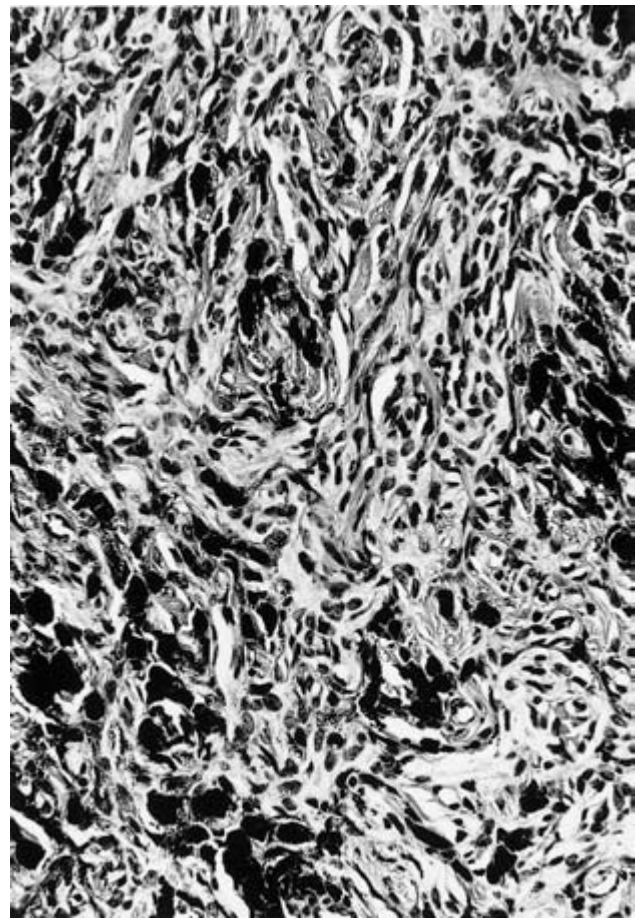


Fig. 34.7 Higher magnification of dermal melanocytoma of Fig. 34.6, showing uniform, ovoid nuclei and inconspicuous nucleoli. Note small bundles and nests reminiscent of neural tumors.

and nests within the epidermis along the dermal–epidermal junction and similarly in the outer follicular wall. This pattern is referred to as 'junctional activity'. Intraepidermal tumor aggregates may be prominent. Some neoplasms have melanocytic nests localized in the superficial dermis with sparing of the overlying epidermis; it is presumed that these nests have migrated downward from their previous location in the epidermis, as is observed in the life cycle of human pigmented nevi (Elder & Elenitsas, 1997; Grichnik et al., 2003). This suggests that some canine and feline compound melanocytomas may represent a progressive stage of clinically inapparent junctional melanocytoma, a process well recognized in other species.

Dermal melanocytoma (Figures 34.5 through 34.8)
These tumors are strictly intradermal in location. An unaffected Grenz zone is present in the superficial dermis, clearly separating the tumor cell population from the overlying epidermis. Larger tumors may encroach upon the subcutis. Most dermal melanocytomas are composed of spindle cells arranged in bundles, nests and whorls. Dermal melanocytomas are moderately cellular and generally lack stromal collagen. Melanophages are often distributed throughout the tumor nodule or arranged in aggregates. Occasional mitotic figures may be seen (less than 1 per 10 high power fields), but mitotic atypia is not observed.

Some dermal melanocytomas are composed of epithelioid or dendritic cells that are heavily pigmented. These tumor nodules have a small amount of stromal collagen. Nuclear morphology may be obscured by the large amount of pigment. Bleaching of the tissue section with permanganate or oxalic acid will allow evaluation of cellular morphology if investigation for cytologic features of malignancy is needed. Although nuclei may be large, there is minimal nuclear pleomorphism.

Differentiation of melanocytoma from malignant melanoma can be difficult in some cases. Categorization by cytologic criteria, including cell type, mitotic rate, and

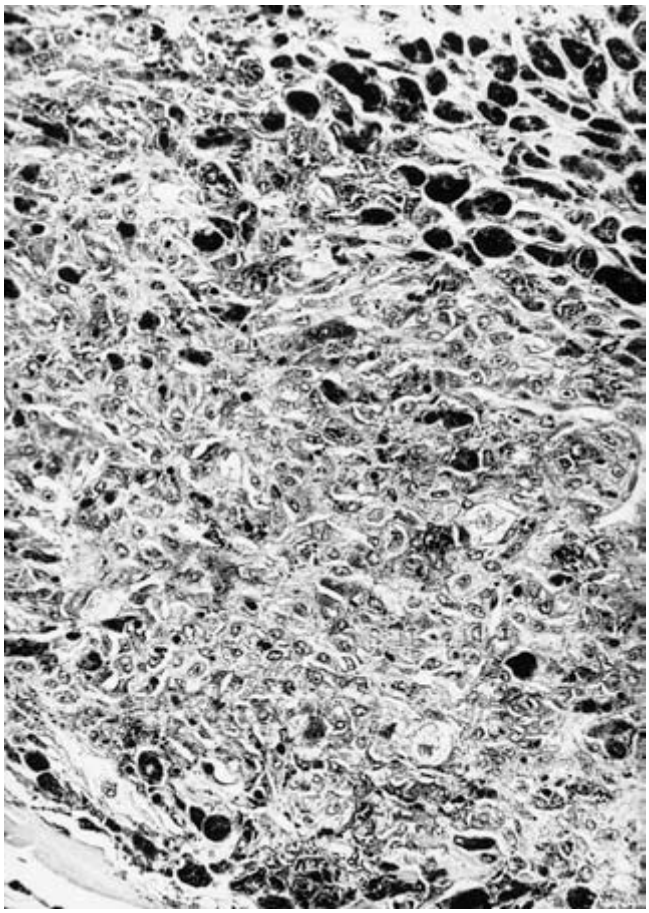


Fig. 34.8 Dermal melanocytoma in a dog dominated by moderately pigmented epithelioid cells in sheets and nests. Nuclei are large and vesicular, but uniform. Note coarse melanin granules in melanophages at top right.

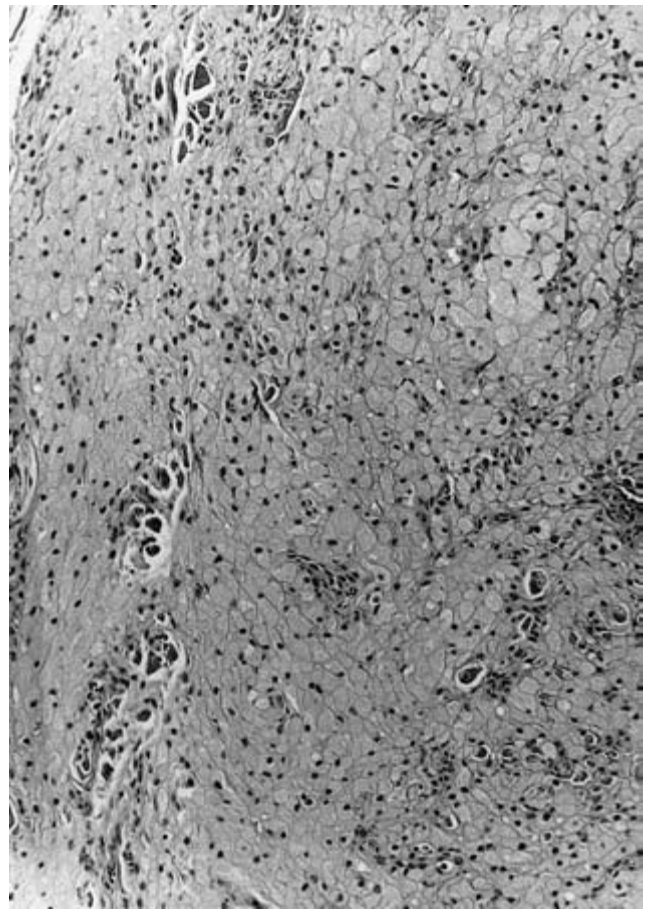


Fig. 34.9 Balloon cell melanocytoma in a dog. Solid sheets of large, polygonal cells have finely granular pigmentation. Nuclei are small and dark.

degree of pigmentation, varies markedly among different surveys. Most reviews fail to report a reliable connection between the presence of a specific cell type and behavior of the melanocytic tumors. Architectural symmetry and well-defined tumor margins are indicators of a benign lesion despite the large size of a tumor mass. Compound malignant melanomas often have aggregates of melanocytic cells at higher levels (pagetoid pattern) of the epidermis, while in melanocytomas the melanocyte aggregates tend to be limited to the lower part of the epidermis. The presence of numerous individual melanocytes in the basal cell layer, mimicking a lentiginous pattern, is also suggestive of malignancy. Although the nuclei of melanocytomas may be large and have prominent nucleoli, relative nuclear uniformity is observed. A mitotic index of fewer than 2 per 10 high-power fields has been considered to support benign biologic behavior in most melanocytic tumors in dogs (Bostock, 1979). In contrast, the value of mitotic activity to predict the outcome of feline melanocytomas versus their malignant counterparts is less clear (Goldschmidt et al., 1993; Smith et al., 2002). The proliferation index and the growth fraction are additional indicators of the biologic behavior of many neoplasms, and may assist in differentiating between melanocytomas and melanomas (Roels et al., 1999) (see immunohistochemistry, below).

Spindle cell-predominant melanocytomas with sparse pigmentation and marked neural growth patterns may be difficult to differentiate from dermal benign peripheral nerve sheath tumors. The presence of melanin granules, which may require Fontana–Masson staining for detection, assists in confirming the diagnosis.

Balloon cell melanocytoma (Figures 34.9 and 34.10)
Balloon cell change is considered a degenerative process induced by coalescence of melanosomes in conjunction with abnormal melanogenesis in the tumor cells (Sondergaard et al., 1980; Gupta et al., 1985); scattered balloon cells may be found in otherwise typical com-

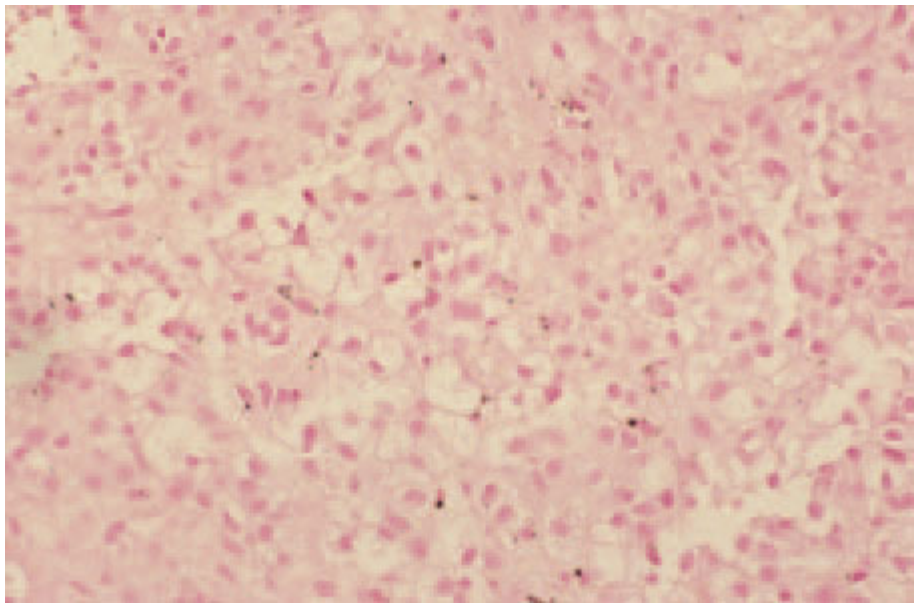


Fig. 34.10 Balloon cell melanocytoma in a dog. Fontana–Masson stain demonstrates occasional dark brown melanin pigment in the tumor cells.

pound and dermal melanocytomas. Balloon cell melanocytomas are most often dermal. They are composed predominantly of large round cells, although small numbers of fusiform or polygonal melanocytes are often present. The abundant and pale cytoplasm of the balloon cells generally has a finely granular quality. Dust-like melanin granules may be detected in small numbers, usually requiring Fontana–Masson staining. However, balloon cell melanocytomas often lack readily visible pigmentation, and immunohistochemistry may aid in their identification (see below). Nuclei are small, uniform, and ovoid; mitotic figures are rarely observed.

Balloon cell melanocytomas should be differentiated from leukocytic round cell tumors, particularly if pigment is scant and/or difficult to demonstrate. Differential diagnoses include large cell (clear cell) lymphoma, canine cutaneous histiocytoma, plasmacytoma, poorly granulated mast cell tumor, and transmissible venereal tumor. In contrast to melanocytomas, leukocytic round cell tumors lack the presence of admixed fusiform tumor cells. The nuclei of leukocytic round cell tumors tend to be larger than those of balloon cell melanocytoma. Plasma cell tumors have variable numbers of multinucleated tumor cells, a feature not observed in balloon cell melanocytomas. The dense cytoplasmic RNA in plasma cells stains magenta with methyl green pyronine (MGP). Mast cells usually contain some cytoplasmic granules that are metachromatic (purple) with toluidine blue or Giemsa stains.

Multiple dysplastic melanocytoma syndrome

These lesions mostly resemble compound melanocytomas on low magnification. However, cytologic atypia and mitotic figures are present; their incidence increases in larger lesions. Some of the proliferating melanocytes have irregularly shaped and enlarged hyperchromatic nuclei. Differential diagnoses are as for compound melanocytomas (see above); the presence of numerous tumors and variable cytologic atypia allow differentiation.

Immunohistochemistry

Neoplastic melanocytes may retain the expression of proteins S100, melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), HMB-45/gp100, melanoma isoform of microphthalmia transcription factor (MITF-M), tyrosinase-related protein-2 (TRP-2), and tyrosinase. Their presence can be demonstrated by using antibodies specific for these proteins. The usefulness of these cell markers used individually in the identification of poorly pigmented melanocytic proliferations in cats and dogs is still under debate (Sanduski et al., 1985; Cangul et al., 1999; Sulaimon et al., 1999, 2002; Ramos-Vara et al., 2000, 2002; Koenig et al., 2001; Laprie et al., 2001; Choi & Kusewitt, 2003). Studies evaluating the presence of Melan-A, MART-1, HMB-45/gp100, and neuron-specific enolase (NSE), as well as other markers, have mainly focused on identification of amelanotic malignant melanomas (see p. 825).

One particular clone of S100 (S100a) was successfully used to identify balloon cell melanocytic tumors (Walder, 2000). Balloon cell melanocytomas are differentiated from leukocytic round cell tumors (histiocytomas, lymphoma, mast cell tumors, plasmacytomas, and transmissible venereal tumors) by the expression of the common leukocyte antigen CD45 in the latter.

Identification of nuclear proteins associated with cell growth and division can be used as indicators of malignancy, and thus may be helpful in differentiating melanocytomas from melanomas. Particularly, the nonhistone protein Ki67 and the proliferating cell nuclear antigen (PCNA), a nuclear protein essential for correct DNA polymerase function, assist in separating benign from malignant melanocytic tumors. The proliferation index (defined as percentage of PCNA positive nuclear area) was 2.8% in canine melanocytomas versus 54% in malignant melanomas (Roels et al., 1999). Feline melanocytomas have a proliferation index of 6%, while their malignant counterparts have an index of 26% (Roels et al., 1999). The growth fraction (defined as percentage of Ki67-positive nuclear area) was 0.21% for canine melanocytomas and 21% for canine malignant melanomas (Roels et al., 1999). Feline melanocytomas have a growth fraction of 0.36% versus 16.6% in feline malignant melanomas (Roels et al., 1999).

MELANOCYTOMA–ACANTHOMA

This neoplasm has no exact human analogue. Pigmented seborrheic keratosis in humans, a lesion characterized by a proliferative epidermis with admixed multifocal aggregates of intraepidermal melanocytes, is occasionally referred to as melanoacanthoma (Silver & Ho, 2003). Desmoplastic trichoepitheliomas with concurrent intradermal nevi are also described in the human literature; it has been suggested that this represents a complex neoplasm rather than a 'collision' tumor, i.e. two distinct neoplasms occurring at the same anatomic site (Rahbari & Mehregan, 1975; Brownstein & Starink, 1987; Keen, 1996).

Canine melanocytoma–acanthomas are mixed tumors that are composed of a benign melanocytic proliferation, resembling compound melanocytoma, and a benign epithelial proliferation. A dermal melanocytoma–acanthoma has been immunophenotyped in a German Shepherd Dog (Espinosa de los Monteros et al., 2000), identifying the presence of keratinocytes and melanocytes. The epithelial component usually appears follicular and resembles an isthmus-type tricholemmoma or infundibular keratinizing acanthoma (see Chapter 23). Studies using low and high molecular weight keratins to identify the exact origin of the epithelial component of melanocytoma–acanthoma have not yet been performed. The authors have chosen the general appellation 'acanthoma' until the epithelial portion can be clearly classified.

The pathogenesis of canine melanocytoma–acanthoma is not known. It is still unclear whether both cell components are truly neoplastic. The close interaction between keratinocytes and melanocytes has been well established and is often referred to as the 'epidermal melanin unit' or the 'follicular melanin unit' (Sulaimon & Kitchell, 2003). As a result, the neoplastic cell population could initiate a reactive proliferation of the second cellular component. Keratinocytes produce melanocyte-stimulating hormone alpha (MSH-α) and hence may, in combination with kinase activation or release of basic fibroblast growth factor (bFGF), initiate melanocyte proliferation (De Luca et al., 1993; Luger et al., 1993; Schauer et al., 1994). Alternatively, melanocytes are known to release transforming growth factor (TGF), which can bind to receptors for epidermal growth factor (EGF) on keratinocytes. The result of this interaction would be a reactive proliferation of keratinocytes (Marquardt et al., 1983). Prominent or even pseudoepitheliomatous epidermal hyperplasia is a well-documented occurrence in human melanocytic nevi and, less commonly, in malignant melanomas (Scott et al., 1989; Kamino et al., 1990; Dorji et al., 2002; Mott et al., 2002). Also, bidirectional hor-

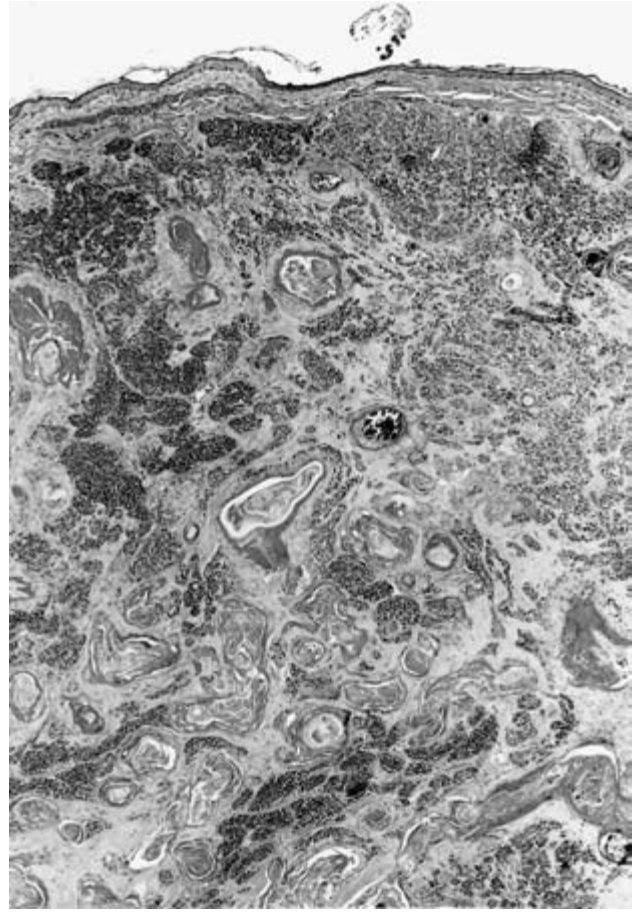


Fig. 34.11 Melanocytoma–acanthoma in a dog. Multiple cystic structures lined by keratinizing squamous epithelium are associated with nests of variably pigmented melanocytes.

monal and/or cytokine interactions could be operant in these neoplasms.

The authors have also observed a single case of melanocytoma associated with a proliferation of sweat glands in a dog (see below). The pathomechanism of this lesion remains unclear; however, those proposed for the development of melanocytoma–acanthoma may also have driven this lesion.

Clinical features

Melanocytoma–acanthoma is a rare neoplasm of dogs. It has not been recognized in cats. Melanocytoma–acanthomas are solitary, circumscribed, pigmented, dome-shaped nodules that measure less than 1 cm in diameter. Only a small number of cases have been observed, and age, breed and site predilections are as yet undetermined.

The lesions have predominantly expansive growth, and surgery is curative. However, several cases of malignant melanoma arising in melanocytoma–acanthoma have been seen by the authors.

Histopathology (Figures 34.11 through 34.16)

Melanocytoma–acanthomas are well-circumscribed, unencapsulated dermal nodules that are focally contiguous with the epidermis. The epithelial component is characterized by anastomosing trabeculae of fairly small keratinocytes with peripheral palisading. There are cystic structures of varying size containing amorphous or laminated keratin. The majority of cystic structures keratinize without a granular cell layer. These features are consistent with follicular origin of the epithelial component and suggest isthmus differentiation (see Chapter 23). There are occasional larger cysts that demonstrate infundibular keratinization, characterized by presence of keratohyalin granules.

Numerous nests and clusters of polygonal or spindled

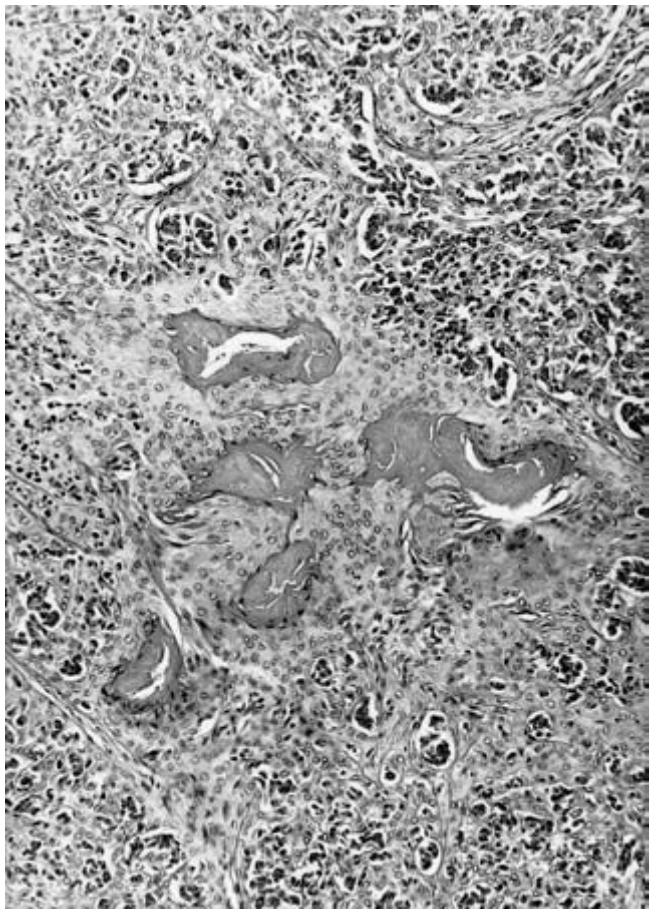


Fig. 34.12 Higher magnification of melanocytoma–acanthoma in a dog. Islands of small, pale keratinocytes have central cysts filled with amorphous keratin. Clusters of small melanocytes are present in the stroma and within the epithelium.

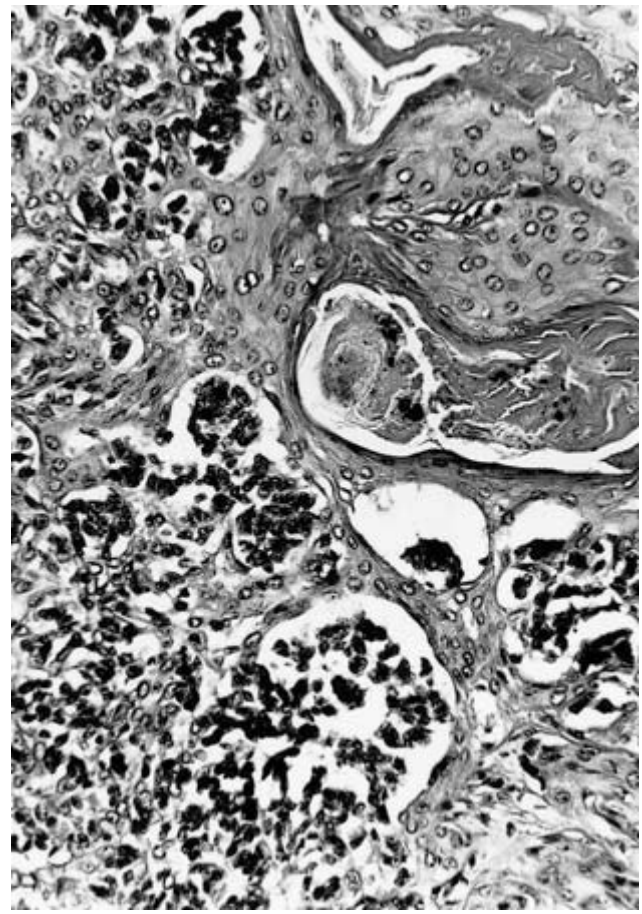


Fig. 34.13 Higher magnification of melanocytoma–acanthoma of Fig. 34.12 demonstrating intraepithelial nests of melanocytes with uniform, ovoid nuclei. Note tricholemmal-type keratinization of cystic structure and clumps of melanin within the cyst.

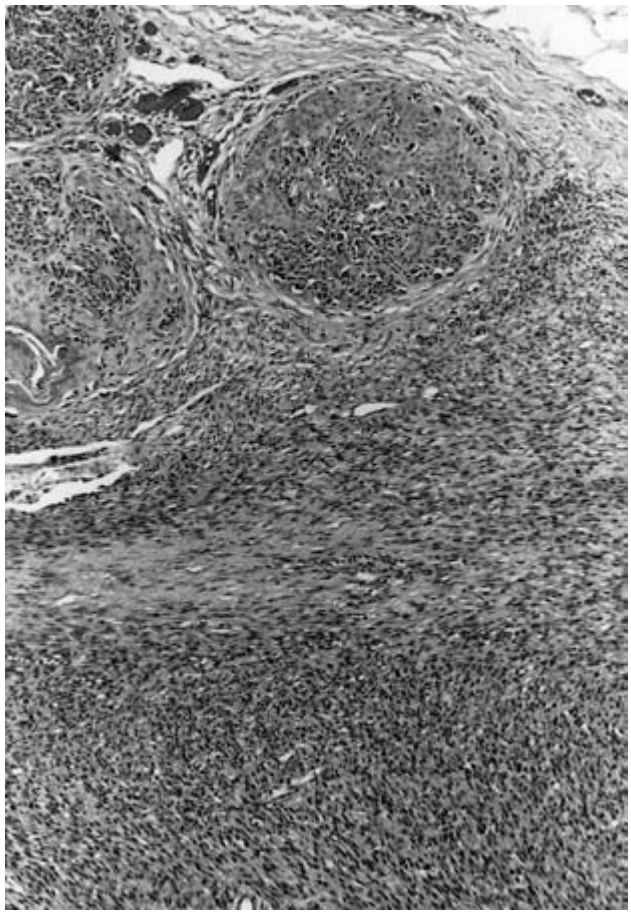


Fig. 34.14 Spindle cell melanoma arising from a melanocytoma–acanthoma in a dog. A large mass composed of mainly spindled melanocytes in the lower portion lies adjacent to a melanocytoma–acanthoma at top.

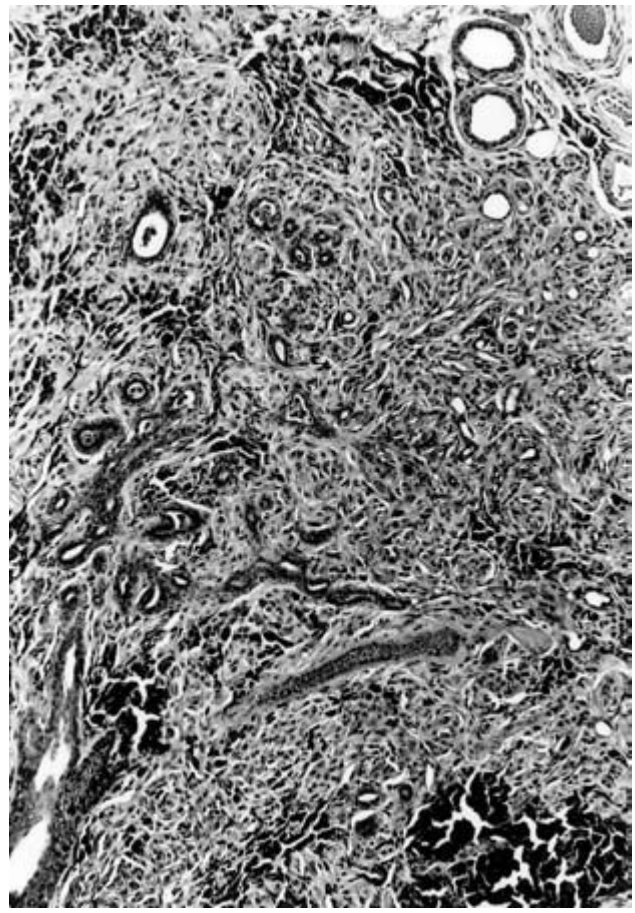


Fig. 34.15 Melanocytoma associated with sweat gland proliferation in a dog. Dermal sheets and nests of pigmented polygonal and spindled melanocytes entrap numerous irregular sweat glands.

melanocytes are distributed along the periphery of the epithelial trabeculae and cysts, simulating junctional activity. The keratinocytes and cyst contents show patchy areas of clumped melanization. There is a sparse collagenous stroma that is filled with clusters of melanocytes and melanophages, analogous to the dermal component of a compound melanocytoma (see p. 815).

The majority of keratinocytes have moderate, glassy, pale pink cytoplasm. Nuclei are bland and ovoid, and nucleoli are inconspicuous. Mitotic activity is minimal. Scattered individual dyskeratotic cells, characterized by shrinkage and brightly eosinophilic cytoplasm, are also noted. Rarely, moderate pleomorphism of the keratinocytes and local invasive growth indicate possible early malignant transformation of the epithelial component; alternatively, this may be reactive pseudoepitheliomatous hyperplasia.

The melanocytes have minimal to moderate cytoplasm and moderate to abundant melanin granules. Some of the small melanocytes may be sparsely pigmented and very difficult to distinguish from basaloid keratinocytes. Nuclei are small, ovoid, and euchromatic. Nucleoli are inconspicuous, and mitotic figures are not observed. In rare instances, malignant transformation of the melanocytic cell population has been noted, characterized by denser proliferations of spindled and polygonal melanocytes with anisokaryosis. An obvious mass of melanocytes may develop adjacent to and contiguous with the melanocytoma–acanthoma. Occasionally, the former shows features of malignancy such as cytologic atypia and mitotic figures.

A melanocytoma associated with proliferation of sweat glands has been observed in one dog. The majority of the tumor nodule was composed of variably pigmented, fairly monomorphic, predominantly spindled melanocytes with admixed dispersed melanophages. Entrapped within the melanocytoma was one area of irregular, branching hyperplastic glandular structures consistent with apocrine

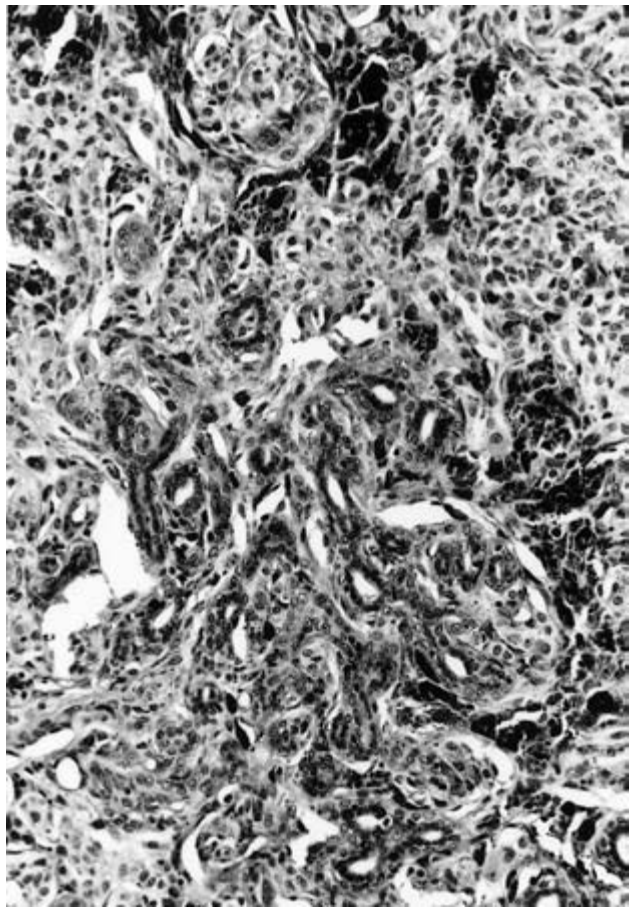


Fig. 34.16 Higher magnification of melanocytoma of Fig. 34.15. Predominantly polygonal, variably pigmented melanocytes accompany numerous proliferating sweat glands.

sweat glands. Occasionally, there were papillated structures protruding into the glandular lumina.

Melanocytoma–acanthoma is unique, and differential diagnosis is not problematic. The consistent close interrelationship of the melanocytic and epithelial components of melanocytoma–acanthoma differentiates it from a random overlap of two neoplasms, i.e. a 'collision' tumor, such as a compound melanocytoma with tricholemmoma or trichoepithelioma (see Chapter 23).

MELANOMA

(Synonym: malignant melanoma)

In humans, malignant melanomas often transform from pre-existing benign melanocytic proliferations (Grichnik et al., 2003). The influence of UV radiation in the pathogenesis of malignant transformation has been well documented in humans (Longstreth, 1988; Langley et al., 2003). However, the etiopathogenesis of canine and feline melanoma is not well understood. Malignant transformation of benign melanocytic proliferations of dogs has been reported (Conroy, 1983; Valentine et al., 1999). The incidence of this malignant transformation is not known, however, and the progression has not been associated with UV radiation.

Canine and feline malignant melanocytic tumors include melanomas with junctional activity and dermal melanomas. The latter group includes balloon cell melanomas, spindle cell melanomas, and feline giant epithelioid melanomas. Purely intraepidermal melanomas, described as superficial spreading melanoma or lentigo maligna in humans, have not been reported in dogs and cats. However, the authors have seen a case of multiple intraepidermal proliferations of atypical melanocytes in a dog consistent with a diagnosis of superficial spreading melanoma; the lesions were associated with a melanoma with junctional activity. Moreover, the authors also have observed a case of apparent malignant transformation in a lentigo consistent with a diagnosis of lentigo maligna. This raises the question of whether early radial growth phase melanomas may be missed in dogs and cats, as lesions may not be biopsied until a vertical growth phase produces an obvious mass.

Clinical features

In dogs, melanomas accounted for 0.8% (Goldschmidt & Shofer, 1992) and 2% (Conroy, 1983) of all skin tumors in two large surveys, and represented 19% and 33% of the total cutaneous melanocytic neoplasms in these surveys, respectively. Melanomas are less common in cats, comprising only 0.4% to 2.8% of all skin tumors (Carpenter et al., 1987; Goldschmidt & Shofer, 1992). In cats, between 42% and 68% of all cutaneous melanocytic proliferations exhibit malignant behavior (Macy & Reynolds, 1981; Carpenter et al., 1987; Goldschmidt & Shofer, 1992; Goldschmidt et al., 1993). It is important to note that wide variations in data are likely a result of lack of standardized diagnostic criteria for malignancy in melanocytic neoplasms; controversies persist in both human and veterinary medicine. Some investigators equate 'benign behavior', i.e. lack of recurrence or metastasis, with a benign neoplasm; this approach is misleading, as it discounts the possibility of a malignant neoplasm that has been surgically cured.

Melanomas range in size from several millimeters to as large as 10 cm in diameter; the majority of lesions are 1 to 3 cm in diameter. Most neoplasms are sessile, but occasional melanomas are polypoid or plaque-like. Melanomas appear gray, brown, or black, depending upon the extent of melanin production, presence of junctional activity, and presence of reactive hyperpigmenta-

tion of the overlying epidermis. Ulceration is common, particularly in larger lesions.

The head (particularly lips and eyelids) and legs (including nailbeds) are the most frequently reported locations for cutaneous melanomas in dogs (Goldschmidt & Shofer, 1992). They also occur on the trunk. Based upon the small number of described cases in cats, the head, thorax, and tail are preferential sites (Goldschmidt et al., 1993; Miller et al., 1993); in one study, eyelid melanocytic tumors were invariably malignant (Goldschmidt et al., 1993).

Cutaneous melanoma is mostly seen in older animals. The average age in dogs is between 9 and 11 years, and in cats between 8 and 12 years (Goldschmidt & Hendrick, 2002). However, in both species cutaneous melanomas may develop in animals as young as 2 years of age. Dogs with heavily pigmented skin, such as black Cocker Spaniels; Scottish, Boston, and Airedale Terriers; Schnauzers; Doberman Pinschers; Irish Setters; Vizslas; Golden and Chesapeake Bay Retrievers; Irish Setters; Chow Chows; and Boxers are predisposed to all melanocytic neoplasms (Bolon et al., 1990; Scott et al., 2001 [compilation]; Goldschmidt & Hendrick, 2002). Cats with black or gray haircoats are reported to be predisposed to melanocytic tumors in general (Goldschmidt et al., 1993; Goldschmidt & Hendrick, 2002). There are no sex predilections reported for cutaneous melanomas in dogs or cats. Giant cell epithelioid melanomas occur only in cats.

Clinical criteria used to differentiate between benign and malignant melanocytic neoplasms are not sharply defined in dogs and cats. Location of the tumor has been considered important in regard to the clinical behavior. Melanocytic tumors of the nailbeds, mucocutaneous junctions, and oral mucosa are generally malignant; lesions on haired skin, including lips and digits, are more likely to be benign. The large majority of melanomas in dogs and cats are primarily dermal in location; thus, the complex human prognostic schemes based on depth of dermal invasion from intraepidermal melanomas (Clark's level, Breslow thickness) do not apply. Moreover, the loss of expression of KIT, a factor indicating progression to a metastatic phenotype in melanomas in humans (Natali et al., 1992), has not been demonstrated in dogs or cats to date (Sulaimon & Kitchell, 2003). Large tumor size has been reported to correlate significantly with aggressive biologic behavior (Theilen & Madewell, 1987). Conversely, tumor size in the study of Bostock (1979) was found not to be of prognostic value.

The proliferation index and the growth fraction are additional indicators of the biologic behavior of many neoplasms, and may assist in differentiating between melanocytomas and melanomas (Roels et al., 1999; Laprie et al., 2001) (see immunohistochemistry, below). In the report of Laprie et al. (2001), 22% of the dogs developed recurrence and/or metastasis within 2 years, and significantly reduced survival time correlated with both mitotic index and proliferation markers. In a small retrospective study on canine balloon cell melanomas, no recurrences or metastases were documented, suggesting that this variant has indolent biologic behavior (Walder, 2000).

The study of Bolon et al. (1990) reported a 35% surgical cure rate for histopathologically malignant canine melanocytic tumors; the remaining 65% recurred and/or metastasized. However, lesions from nailbed and labial mucocutaneous junction were included in the data, probably increasing the number of unfavorable outcomes; metastases to regional lymph nodes and lungs occurred in 13% of those cases. Nailbed melanomas in dogs were reported by Marino et al. (1995) to have a 58% incidence of metastasis and a 13% 2-year survival rate. Two of five cats with cutaneous melanoma had multiple recurrences and satellite metastases (the development of multiple small cutaneous nodules around a primary melanoma), and one cat developed extensive visceral metastasis (Patnaik, 1988).

Histopathology

In general, melanomas are fairly well circumscribed but unencapsulated neoplasms that may involve epidermis and dermis or dermis alone; large tumor masses may extend to the subcutis. The overlying epidermis may be hyperpigmented, regardless of the presence or absence of intraepidermal clusters or nests of neoplastic melanocytes (junctional activity). Melanomas tend to be asymmetrical. The asymmetry may be most readily recognizable in the epidermal component of junctional tumors. Ulceration and necrosis are common features, particularly in larger masses. Pigmentary incontinence as a result of tumor cell necrosis is common, and numerous melanophages may be distributed throughout the neoplasm. Stromal collagen is minimal to moderate and occasionally exhibits chondroid and/or osseous metaplasia. Some tumors possess a myxoid stroma. A reactive population of lymphocytes and plasma cells may be present peripherally.

Melanoma cells display a marked diversity of cytologic features, as they share common embryologic roots with both neural and epithelial tissues. As in melanocytoma (see p. 815) the cell types observed include spindle cells, round to polygonal cells, dendritic cells, epithelioid cells, and balloon cells. Ganglion cell and multinucleated giant cell forms also may be observed. Most canine melanomas comprise varying proportions of spindle cells and round to polygonal cells. Pure spindle cell melanomas and pure epithelioid melanomas occur less frequently, as do balloon cell melanomas. The majority of retrospective studies, however, indicate that different cell types

are not of prognostic significance in canine and feline melanocytic tumors (Conroy, 1967; Bostock, 1979; Macy & Reynolds, 1981; Bolon et al., 1990; Miller et al., 1993).

Spindle melanocytes have poorly defined cytoplasm. These fusiform cells are usually arranged in interlacing bundles, partial whorls and nests. These morphologic features resemble neural structures; this is not unexpected in light of the embryologic derivation of melanocytes from the neural crest. The nuclei are plump and fusiform; moderate to marked nuclear pleomorphism is seen. Chromatin patterns vary from tumor to tumor and often within a given neoplasm. Nucleoli are present and may be prominent. Round to polygonal cells are arranged in sheets and dense packets of cells; the packets are separated by a scant stroma. Dendritic cells have a highly angular stellate shape, often with long cytoplasmic processes, and plump oval to elongated nuclei. Epithelioid cells have a large amount of pale eosinophilic cytoplasm, often with indistinct cell borders; the cells are arranged in sheets and larger nests. Both round to polygonal and epithelioid cells have large ovoid nuclei. Similar to their spindle-shaped counterparts, they may exhibit marked anisokaryosis, variable chromatin patterns, and prominent nucleoli. Balloon melanoma cells are large with clear cytoplasm (see below). Occasionally, tumors contain small numbers of ganglion-like cells characterized by abundant, angular cytoplasm and large, eccentric, often hyperchromatic nuclei. Mitotic activity in melanomas is usually 3 or greater per 10 high power fields (40×), and mitotic atypia is present. Low-grade or well-differentiated melanomas also occur; these have a lower mitotic index, and architectural and cytologic features of malignancy may be subtle.

The cytoplasm of most melanoma cells is pale and the degree of pigmentation varies from abundant to undetectable both within a given neoplasm and amongst neoplasms. No consistent degree or pattern of melanin pigmentation occurs within a given melanoma. The abundance of melanin granules in some melanomas tends to obscure nuclear features; thus, bleaching of the tissue section with potassium permanganate or oxalic acid may be required to evaluate cellular and nuclear morphology. The cytoplasm of amelanotic melanomas often has a gray or muddy purplish-gray, granular quality. Fontana–Masson staining may confirm the presence of cytoplasmic melanin in some poorly pigmented tumors.

Dermal melanomas (Figures 34.17 through 34.22)
These tumor masses lack junctional activity, but often extend deeply into the subcutaneous tissue. Although a specific cell type may predominate, most tumors will exhibit a mixture of spindle cells, round to polygonal cells, and/or epithelioid cells. Spindle cells are often poorly pigmented. Round to polygonal and epithelioid cells tend to have moderate to abundant melanin, but may be sparsely pigmented in amelanotic forms.

The primary differential diagnosis of dermal melanoma is melanocytoma, particularly for smaller neoplasms. Moderate to marked nuclear pleomorphism, nucleolar prominence, a mitotic rate of 3 or greater per 10 high power fields (40×), presence of atypical mitoses, asymmetry of the tumor nodule, and marked lymphoplasma-

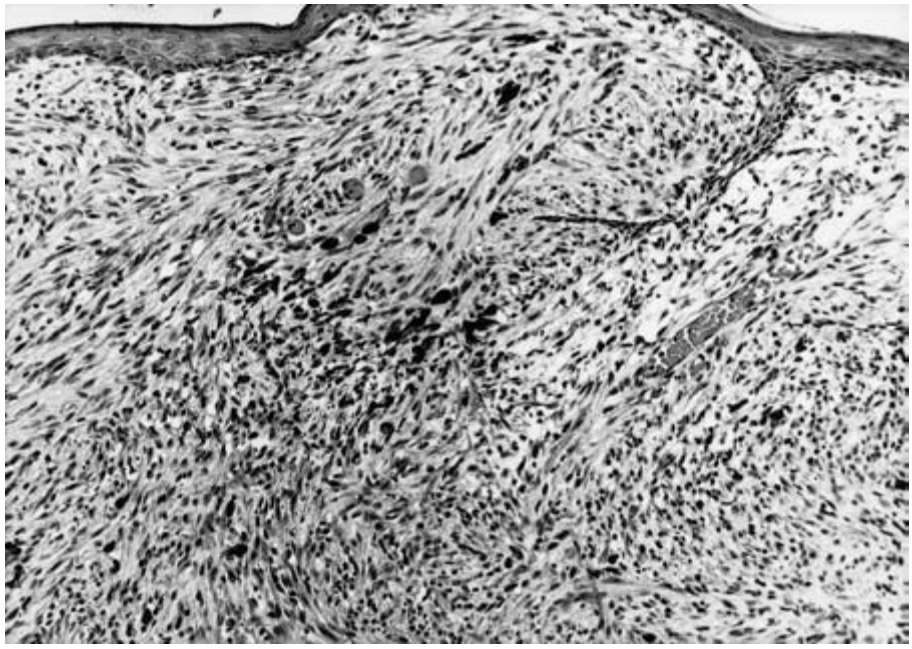


Fig. 34.17 Dermal melanoma in a dog composed predominantly of non-pigmented spindle cells arranged in interlacing bundles. Small numbers of heavily pigmented cells are present. Note that an intraepidermal component is not evident.

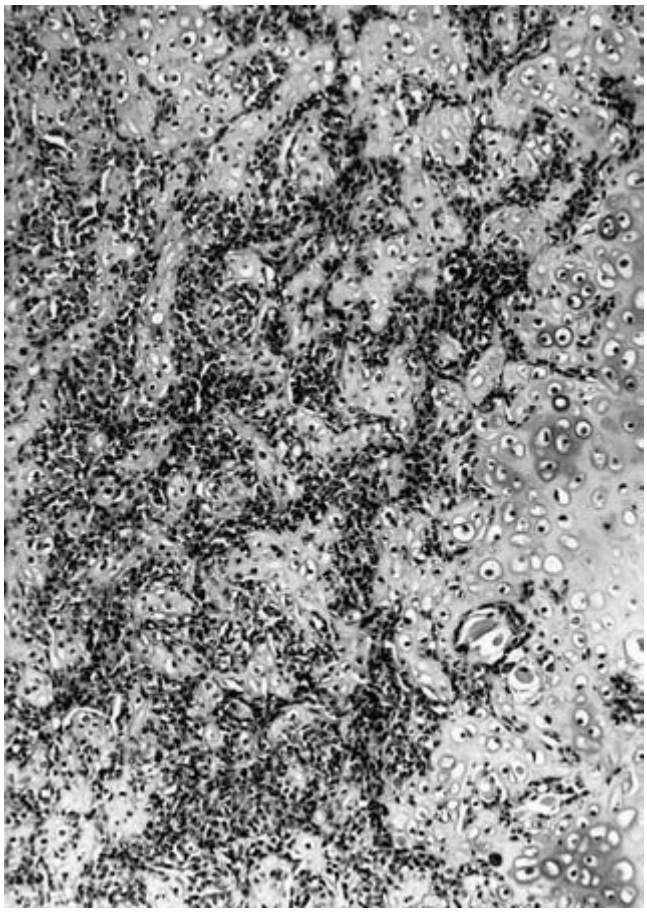


Fig. 34.18 Dermal malignant melanoma with chondroid metaplasia in a dog. Nests and trabeculae of darkly pigmented, polygonal melanocytes are interspersed with zones of well-differentiated cartilage.

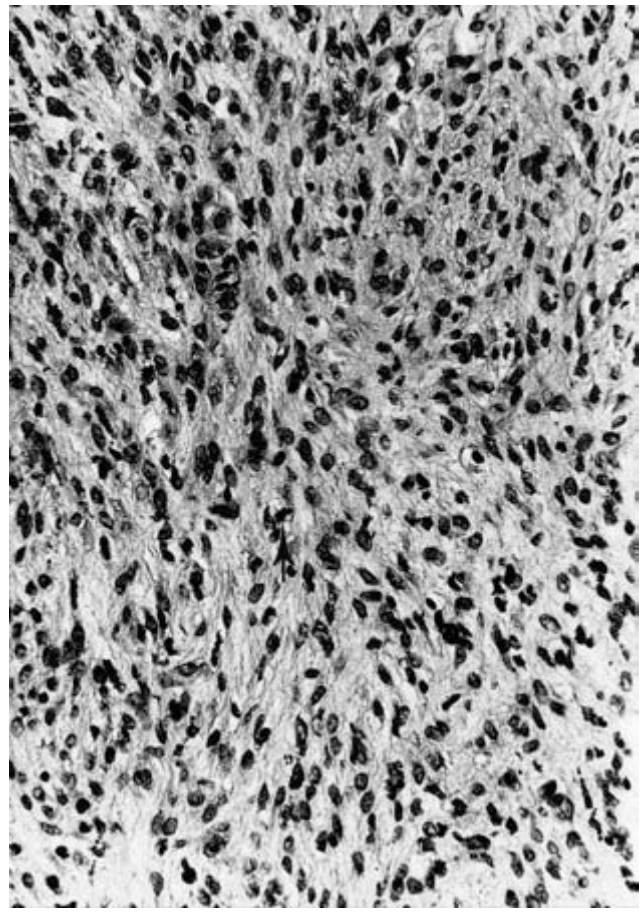


Fig. 34.19 Higher magnification of malignant dermal melanoma in a dog featuring moderate nuclear enlargement and pleomorphism.

cytic inflammation are features which support a diagnosis of melanoma (Bostock, 1979; Bolon et al., 1990; Goldschmidt et al., 1993; Miller et al., 1993). A predominance of epithelioid tumor cells, multinucleated melanocytes, and prominent tumor necrosis indicate malignancy of melanocytic tumors in cats (Goldschmidt et al., 1993; Miller et al., 1993). Identification of the proliferation index and the growth fraction also assists in differentiating between melanocytomas and melanomas (see immunohistochemistry, below) (Roels et al., 1999).

Dermal amelanotic melanomas that are composed of round melanocytes should be differentiated from leukocytic round cell tumors, including nonepitheliotropic lymphomas, plasma cell tumors, poorly granulated mast cell tumors, transmissible venereal tumors and Merkel cell tumors. In particular, plasma cell tumors, and Merkel cell tumors may most closely mimic amelanotic melanomas as these are usually characterized by packeting and nesting of tumor cells. Multilobular nuclei are more common in plasmacytomas. Also, the dense cytoplasmic RNA stains magenta with methyl green pyronine (MGP) stain. In contrast to amelanotic melanomas, transmissible venereal tumors have finely vacuolated tumor cells. Amelanotic epithelioid dermal melanomas may mimic anaplastic carcinomas. If Fontana–Masson staining fails to reveal melanin, immunohistochemistry may be required (see below).

Melanomas with junctional activity

Many melanomas, particularly those of the nailbed and lip, have demonstrable 'junctional activity', i.e. the presence of tumor cells at the dermal–epidermal junction, as well as at higher levels of the epidermis. The intraepidermal component is composed predominantly of epithelioid melanocytes arranged individually or in nests and clusters. Distribution of numerous melanocytes through all levels of the epidermis is referred to as a 'pagetoid' pattern. Numerous individual neoplastic melanocytes

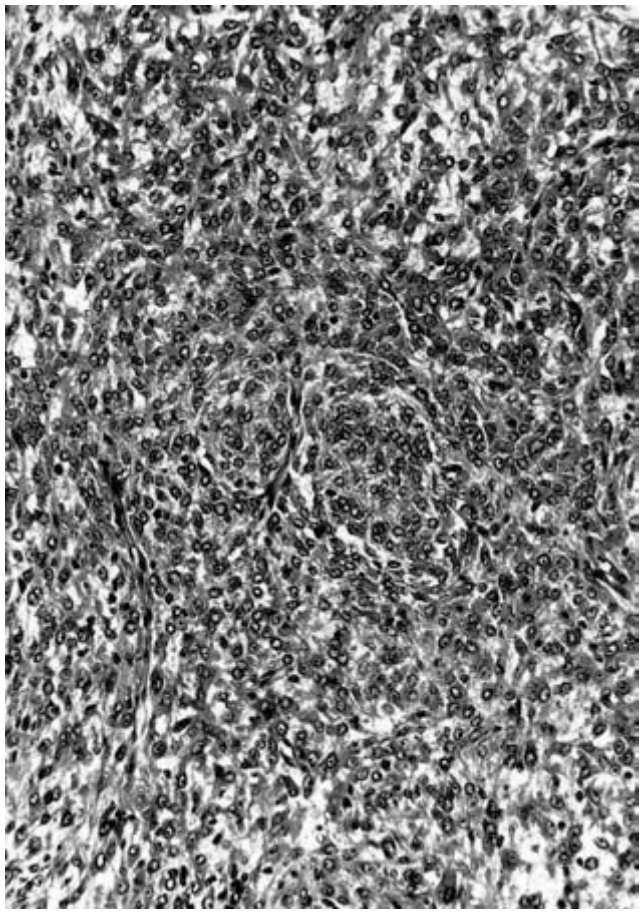


Fig. 34.20 Dermal melanoma in a dog. Polygonal poorly pigmented cells are arranged in sheets and nests, and have vacuolated and granular cytoplasm.

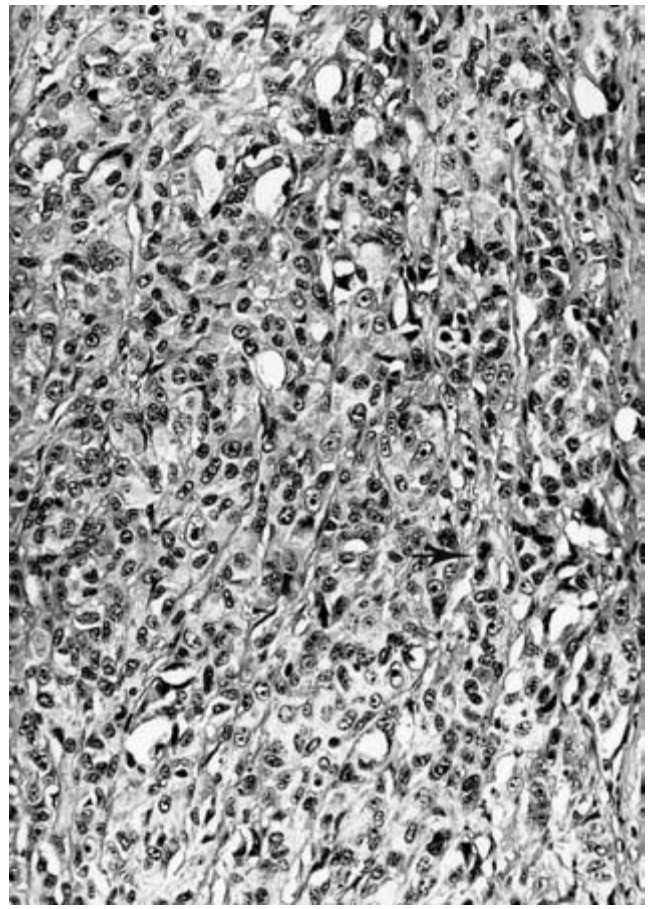


Fig. 34.21 Dermal melanoma in a dog. Highly pleomorphic spindle cells and polygonal cells are arranged in nests. Nuclei are markedly enlarged and have prominent nucleoli. Note mitotic figures (arrow).

present within the basal cell layer only, which is also referred to as an 'atypical lentiginous infiltrate', is another feature that may be seen in melanomas. Intraepidermal melanocytes often contain more melanin pigment than the cells of the dermal component.

In one dog with junctional melanoma, the authors observed purely intraepidermal accumulations of neoplastic melanocytes in additional biopsies. Large, round, poorly pigmented melanocytes were seen as single cells and as aggregates throughout the epidermis (pagetoid distribution). These features are characteristic of superficial spreading melanoma in humans (Rosai, 1996). The melanocytic origin of these cells was confirmed with immunohistochemistry (see below).

The authors also observed a small lesion in a dog consistent with lentigo maligna in humans (Rosai, 1996). The lesion was architecturally similar to a benign lentigo (see p. 814), but had small aggregates of atypical melanocytes arranged along the basal cell layer and concentrated in markedly elongated rete ridges.

The differential diagnoses for pigmented melanomas with junctional activity mirror those of dermal melanomas (see above). The differential diagnoses for amelanotic melanomas with junctional activity include epitheliotropic T cell lymphoma and canine cutaneous histiocytoma with intraepidermal tumor cell aggregates. Most melanomas with junctional activity have some melanin pigmentation, which helps to differentiate them from round cell tumors with intraepidermal tumor cell aggregates. The presence of mixed spindle and polygonal tumor cells also indicates melanocytic origin, as histiocytomas and lymphomas are characterized by a relatively monomorphic round cell population.

Spindle cell and desmoplastic melanomas

(Figures 34.23 through 34.25)

This subgroup of dermal melanomas is composed predominantly of spindled melanocytes. The vast majority are amelanotic, and cells are arranged in bundles or palisades, mimicking tumors of neural origin. Admixed there

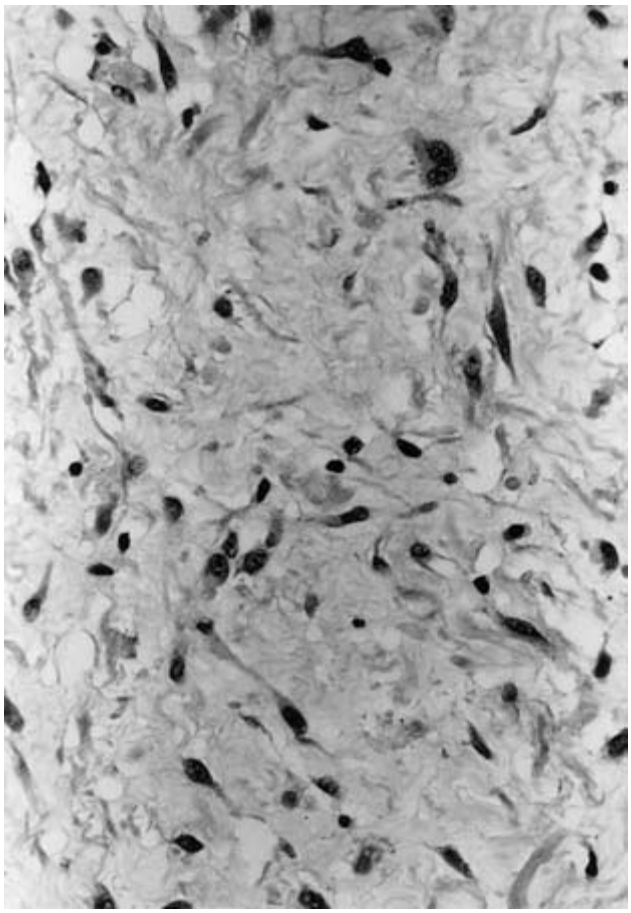


Fig. 34.22 Amelanotic spindle cell dermal melanoma in a dog. Spindle to stellate cells are embedded in a loose stroma; compare with densely organized spindle cell melanoma of Fig. 34.14.

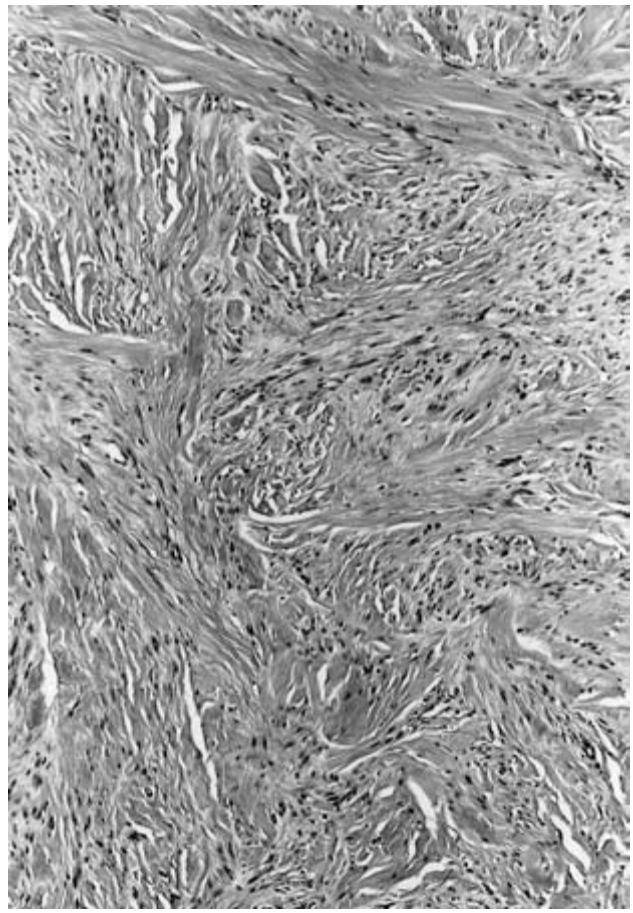


Fig. 34.23 Desmoplastic melanoma in a dog. Note prominent fibroblastic component and abundant collagen. Single tumor cells lie amongst the fibroblastic population (see Fig. 34.25).

are stellate (dendritic) cells. The spindled melanocytes may be densely packed, or arranged loosely within abundant pale stroma. As melanin granules are extremely sparse, a Fontana–Masson stain usually is necessary to detect the presence of melanin granules. Occasionally, there is a prominent fibroblastic component associated with the spindle shaped melanocytes, and collagen may become more abundant than the tumor cells. These lesions, which can resemble nodular scars or fibromas, are also referred to as 'desmoplastic melanoma' in the human literature (Elder & Elenitsas, 1997). Desmoplastic melanomas tend to have small areas of lentiginous change (individual atypical melanocytes in the overlying basilar epidermis) or junctional activity (nested melanocytes in the lower epidermis) associated with the dermal mass. Step sections may be required to find this highly diagnostic intraepithelial component.

Differentiation of fibrosarcoma and nerve sheath tumors from amelanotic spindle cell dermal melanomas may not be possible based on morphologic features. Desmoplastic spindle cell melanomas are particularly difficult to distinguish from benign or non-neoplastic collagenous masses. Careful search for small numbers of atypical pigmented cells in the dermis and overlying epidermis (lentiginous change or junctional activity) is needed, using step sectioning if necessary. Immunohistochemistry usually is required for definitive diagnosis (see below).

Balloon cell melanoma (clear cell melanoma)

Balloon cell change is considered a degenerative change induced by coalescence of melanosomes in conjunction with abnormal melanogenesis in the tumor cells (Sondergaard et al., 1980; Gupta et al., 1985). This subtype of dermal melanoma has a multilobular architecture and does not possess an intraepidermal component (Diters & Walsh, 1984; van der Linde-Sipman et al., 1997). The cells are large and have clear or slightly eosinophilic cytoplasm. The majority of cells have an epithelioid conformation, but small zones of spindling may be detected. Most balloon cell melanomas are



Fig. 34.24 Higher magnification of desmoplastic melanoma of Fig. 34.23. The overlying epidermis is hyperplastic and harbors a focal nest of pigmented melanocytes (junctional activity) (arrow).

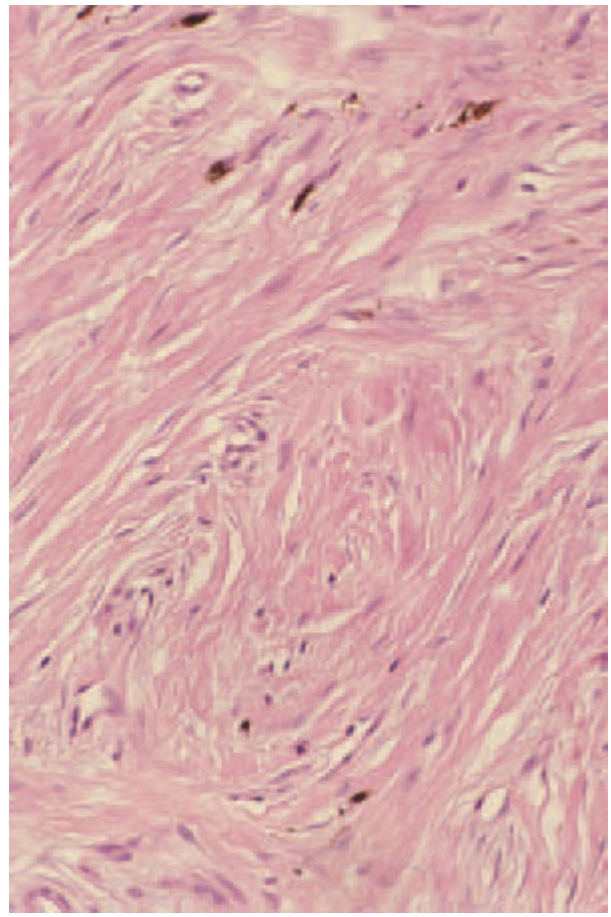


Fig. 34.25 Desmoplastic melanoma of Fig. 34.23. Fontana–Masson stain demonstrates dark brown melanin in some of the spindled neoplastic melanocytes, which are entrapped within the dense fibrous tissue.

amelanotic. Dust-like melanin granules similar to those of balloon cell melanocytoma may be present in a few tumor cells, and Fontana–Masson staining may be required for their demonstration. Nuclei are large and vesicular, and have prominent nucleoli. Mitotic activity is relatively low.

Differential diagnoses for balloon cell melanomas are large cell variants of leukocytic round cell tumors (poorly-differentiated mast cell tumors, histiocytic sarcomas, and large cell lymphomas), and clear cell apocrine ductular carcinoma. Toluidine blue or Giemsa stain may permit identification of the metachromatic granules of mast cell tumors. Histiocytic sarcomas may comprise a predominantly round cell population with large amounts of pale cytoplasm; however, most have admixed spindle cells as well. Large cell (clear cell) lymphomas may have a large amount of fairly clear cytoplasm and may not be distinguishable from balloon cell melanomas based on morphologic features. Small to moderate amounts of melanin pigment are often present in clear cell apocrine ductular carcinoma, increasing the possibility for misdiagnosis. In clear cell apocrine ductular carcinoma, the clear cells are arranged in solid islands with central cystic degeneration, or may line tubular structures. Epidermal or follicular contiguity and residual hyperplastic follicular papillary mesenchymal bodies are additional features of this rare variant of sweat gland carcinoma (see Chapter 25). Immunohistochemistry may be needed to differentiate among clear cell tumors (see below).

Giant epithelioid melanoma (Figure 34.26)

Melanomas in cats are often composed of epithelioid cells, and occasional giant epithelioid forms are seen (Goldschmidt et al., 1993). This subtype of dermal melanoma is composed of large cells with a glassy, eosinophilic cytoplasm. They have large nuclei, which vary in shape from ovoid to fusiform, and may contain large nucleoli. Marked to moderate anisokaryosis is seen, and the chromatin pattern varies among tumors and within a particular tumor mass. Margination of chro-

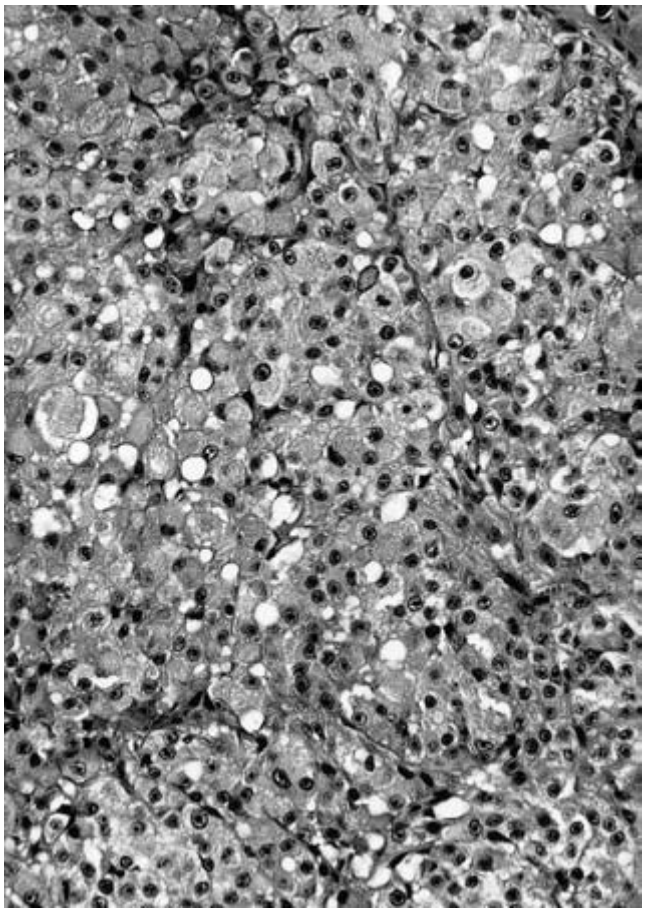


Fig. 34.26 Giant epithelioid melanoma in a cat. Large epithelioid cells have abundant, glassy or finely granulated cytoplasm. Nuclei are large and have prominent nucleoli.

matin or finely stippled chromatin may be seen. The mitotic activity is 3 or more per 10 high-power fields, and mitotic atypia is present.

Similar to balloon cell melanomas, poorly pigmented feline giant epithelioid melanomas may need to be differentiated from leukocytic round cell proliferations, particularly pleomorphic mast cell tumors or feline progressive dendritic cell histiocytosis (see Chapter 35). Immunohistochemistry will facilitate differentiation (see below).

Immunohistochemistry

Melanoma cells often retain expression of characteristic proteins. In humans, a panel of antibodies specific for S100, melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), E-cadherin, tyrosinase, HMB45/gp100, and melanoma isoform of microphthalmia transcription factor (MITF-M) is used to identify melanocytic origin (Barrio, 1998; Busam et al., 1998, 2001; Radford et al., 1996; Orchard, 2000; Berset et al., 2001). However, the usefulness of these markers used individually in identifying feline and canine amelanotic melanomas is still under debate (Sanduski et al., 1985; Cangul et al., 1999, 2001; Sulaimon et al., 1999; Ramos-Vara et al., 2000, 2002; Koenig et al., 2001; Laprie et al., 2001; Hoinghaus et al., 2002; Sulaimon et al., 2002; Choi & Kusewitt, 2003). Different specificities among the various clones of these immunostain reagents accounts for some of the inconsistencies in reported staining results. The S100a clone (which is unrelated to the αβ subunits of S100 protein) was successfully used to identify balloon cell melanomas (Walder, 2000). HMB45 was successfully demonstrated in melanomas after pretreatment of tissue samples with $KMnO_4$–oxalic acid (Sulaimon et al., 1999). It appears that MITF-M is strongly expressed in canine and feline melanomas (Wojcieszyn, J., personal communication, 2003). Expression of neuron-specific enolase (NSE) has been reported as well (Smith et al., 2002). A recent study shows that 50% of canine amelanotic melanomas evaluated retained the expression of tyrosinase-related protein-2 (TRP-2) (Choi & Kusewitt, 2003). Melan-A, MART-1, S100 (α unit), S100 (αβ units), and tyrosinase gave promising results in a small pilot study performed by one of the authors in dogs (V.K.A.). However, none of the individual antibodies gave a consistent and reliably positive result in all the cases evaluated. Hence, the entire panel ideally should be applied to any questionable case, which may be financially restrictive.

Identification of nuclear proteins associated with cell growth and division, including Ki67 (a nonhistone protein) and proliferating cell nuclear antigen (PCNA) (a nuclear protein essential for correct DNA polymerase function) can be used as indicators of malignancy and thus may be helpful in differentiating melanocytomas from melanomas. The proliferation index (defined as percentage of PCNA-positive nuclear area) of canine melanomas was 54% compared to 2.8% in melanocytomas (Roels et al., 1999). The predictive value of the proliferation index in regard to clinical behavior of canine melanomas has been reported as 97% (Laprie et al., 2001). Feline melanomas have a proliferation index of 26%, while melanocytomas have an index of 6% (Roels et al., 1999). The growth fraction (defined as percentage of Ki67-positive nuclear area) was 21% for canine melanomas versus 0.21% for melanocytomas (Roels et al., 1999). Feline melanomas have a growth fraction of 16.6% versus 0.36% in melanocytomas (Roels et al., 1999).

In the differentiation of spindle cell amelanotic melanomas from fibrosarcomas and peripheral nerve sheath tumors, both fibrosarcomas and peripheral nerve sheath tumors express vimentin but are negative for Melan-A,

MART-1, S100, HMB-45/gp100, MITF-M, tyrosinase, and TRP-2.

In contrast to amelanotic melanomas of round cell type, balloon cell type, and giant epithelioid type in cats, leukocytic round cell tumors (including histiocytomas and histiocytic sarcomas in dogs, and progressive dendritic cell histiocytosis in cats), express the common leukocyte antigens CD45 and CD18. The expression of cytokeratins generally separates carcinomas from amelanotic epithelioid melanomas or balloon cell melanomas in dogs; however, weak or focal cytokeratin staining is reported in a small proportion of melanomas (Dabbs, 2002). To complicate the picture, clear cell apocrine ductular carcinoma can express vimentin as well as Melan-A and MART-1 (see Chapter 25); however, only apocrine ductular carcinomas are positive for CAM5.2.

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Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis, Second Edition
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Chapter 35

Histiocytic tumors

Histiocytic proliferative diseases in humans include reactive and neoplastic proliferations of either dendritic antigen presenting cells or macrophages (Favara et al., 1997; Schmitz & Favara, 1998). Histiocytes are CD45+, CD18+ leukocytes that originate from a CD34+ precursor cell in the bone marrow. Upon differentiation guided by a variety of cytokines and stem cell factors, the precursor cells develop into phenotypically separate cell lineages with different tissue distribution and function (Table 35.1) (Affolter & Moore, 2002a). Macrophages are primarily involved with phagocytosis and intracellular digestion of foreign antigens. Dendritic antigen presenting cells are poorly phagocytic; they specialize in processing and presenting antigens, and hence express the antigen presenting molecules CD1, MHC II, and MHC I.

Dendritic cells are a diverse group, and can be divided into sublineages based on their phenotype and location (Table 35.1) (Affolter & Moore, 2002a). The dendritic cells involved in proliferative histiocytic diseases affecting the skin are either of Langerhans cell origin or of interstitial/dermal dendritic cell origin. Langerhans cells harbor in the epidermis and follicular epithelium, while interstitial/dermal dendritic cells are located in the perivascular dermis.

Some leukocyte proteins are variably expressed by macrophages versus dendritic cells and therefore allow differentiation between these two sublineages of histiocytes. A limited panel of antibodies currently is available for immunophenotyping histiocytic cells in formalin-fixed, paraffin-embedded tissues. Immunophenotypic differentiation between macrophages and dendritic cells currently requires fresh-frozen tissue samples (Table 35.1) (Moore et al., 1998).

A variety of reactive and neoplastic histiocytic diseases, including proliferations of dendritic cells and macrophages, have been recognized in dogs and cats (Affolter & Moore, 2000a). Canine dendritic cell neoplasms include solitary and multiple histiocytomas, as well as localized and disseminated histiocytic sarcoma (Moore et al., 1996; Affolter & Moore, 2002b). Reactive histiocytosis, also of dendritic cell origin, is considered to be a reactive inflammatory process in dogs that is most suggestive of an immune regulatory dysfunction and not a true neoplasm (Affolter & Moore, 2000b); it is therefore discussed with noninfectious nodular and diffuse granulomatous and pyogranulomatous diseases (see Chapter 13). Proliferations of dendritic cell origin are uncommon in cats; most seen to date have been considered neoplastic and have been categorized as progressive dendritic cell histiocytosis or histiocytic sarcoma (Affolter & Moore, 2000a). Primary cutaneous neoplasms of macrophages have not been identified in dogs and cats.

REACTIVE FIBROHISTIOCYTIC NODULE

(Synonyms: benign fibrous histiocytoma, juvenile xanthogranuloma, fibroxanthoma)

Benign fibrohistiocytic proliferations in humans include a variety of processes composed of mixed fibroblasts and histiocytes (Rosai, 1996; Weiss & Goldblum, 2001). Lesions with a predominance of histiocytic cells are also referred to as benign fibrous histiocytoma, juvenile xanthogranuloma, and papular xanthoma (Rosai, 1996; Weiss & Goldblum, 2001; Breier et al., 2002). Human dermatofibromas are also included in this group; however, feline and canine dermatofibromas are primarily composed of fibroblasts and fibrocytes (see Chapter 27). Canine fibrohistiocytic nodules have similar but not identical characteristics to juvenile xanthogranuloma in humans, which comprise nonLangerhans cell histiocytes (Weiss & Goldblum, 2001). Although, in humans, fibrohistiocytic nodules are considered to be reactive proliferations rather than true neoplasms, the term 'benign fibrous histiocytoma' is still used.

Reactive fibrohistiocytic nodules occur in dogs. Based on the human literature, they were previously referred to as 'benign fibrous histiocytomas' in *Veterinary Dermatopathology* (Walder & Gross, 1992). The term 'benign fibrous histiocytoma' now is considered inaccurate as it implies the existence of a 'fibrous histiocyte', i.e. a hybrid cell of fibroblastic and histiocytic origin. A small

Cell type	Phenotype in	
	Fresh-frozen tissue	Formalin-fixed tissue
Macrophages	CD45, CD18 CD11b, MHCII, CD68	CD45, CD18
Antigen presenting DC	CD45, CD18 CD1, CD11c, MHCII, CD11b, ICAM-1	CD45, CD18
Langerhans cells	E-cadherin	E-cadherin
interstitial (dermal) DC	CD90	
activated dermal DC	CD4	

Table 35.1 Phenotypic characteristics of macrophages and antigen presenting dendritic cells (DC).

pilot study by one author (V.K.A.) indicates that most canine fibrohistiocytic nodules are predominated by CD45+, CD18+ histiocytes, and have admixed vimentin-positive fibroblasts. The authors therefore prefer the descriptive term 'fibrohistiocytic nodule'.

The etiology of canine fibrohistiocytic nodules is unknown. As all samples evaluated by immunohistochemistry to date were submitted in formalin, it is currently not known whether the lesional histiocytes are macrophages or dendritic cells. The presence of lipid-type vacuoles in many of the cells suggests that they are phagocytic macrophages. The benign morphology and biological behavior, and the presence of a mixed cell population suggest a reactive process.

Clinical features

Reactive fibrohistiocytic nodules are uncommon in dogs. These are solitary or occasionally multiple firm cutaneous nodules, measuring less than 1 cm in diameter. They may be partially alopecic. Lesions occur most often on the face, scrotum, and legs, but other sites may be affected.

Most affected dogs are less than 3 years of age. In contrast to juvenile xanthogranulomas in humans, which often occur in infants, reactive fibrohistiocytic nodules have not been reported in puppies. Neither breed nor sex predilections have been observed.

It is not known if spontaneous regression occurs (a feature of juvenile xanthogranuloma of humans), as most reactive fibrohistiocytic nodules are solitary and diagnosed after surgical excision. Reactive fibrohistiocytic nodules have a good prognosis, as recurrence following surgical excision has not been observed.

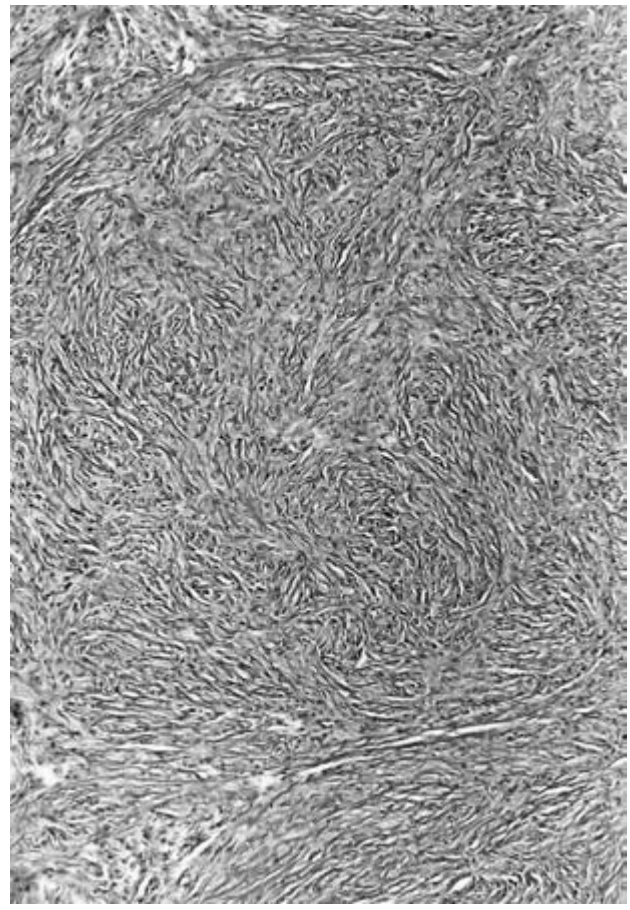


Fig. 35.1 Reactive fibrohistiocytic nodule in a dog composed of intermingled spindle cells and larger round cells.

Histopathology (Figures 35.1 through 35.5)

Fibrohistiocytic nodules are circumscribed, nonencapsulated dermal nodules composed predominantly of histiocytic cells arranged in solid sheets. The lesions commonly have a wedge-shaped or base-narrow configuration. The cellular infiltrate usually extends to the dermal–epidermal junction, and the overlying epithelium often is hyperplastic. A sparse collagenous matrix, occasionally composed of partially hyalinized collagen bundles, most likely represents residual dermal collagen.

Large round to polygonal histiocytic cells have abundant, pale eosinophilic cytoplasm that may contain vari-

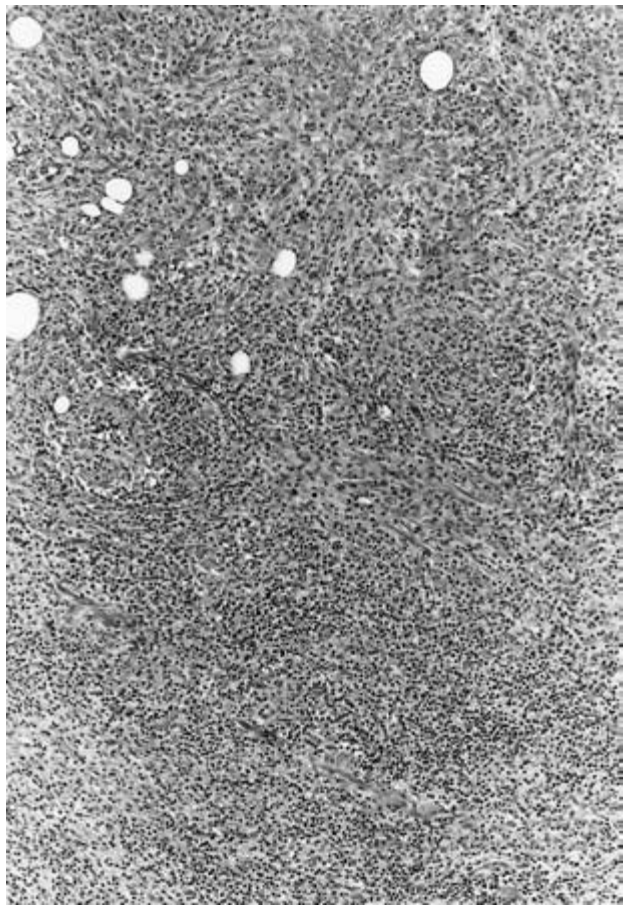


Fig. 35.2 Reactive fibrohistiocytic nodule in a dog with diffuse lymphocytic inflammation.

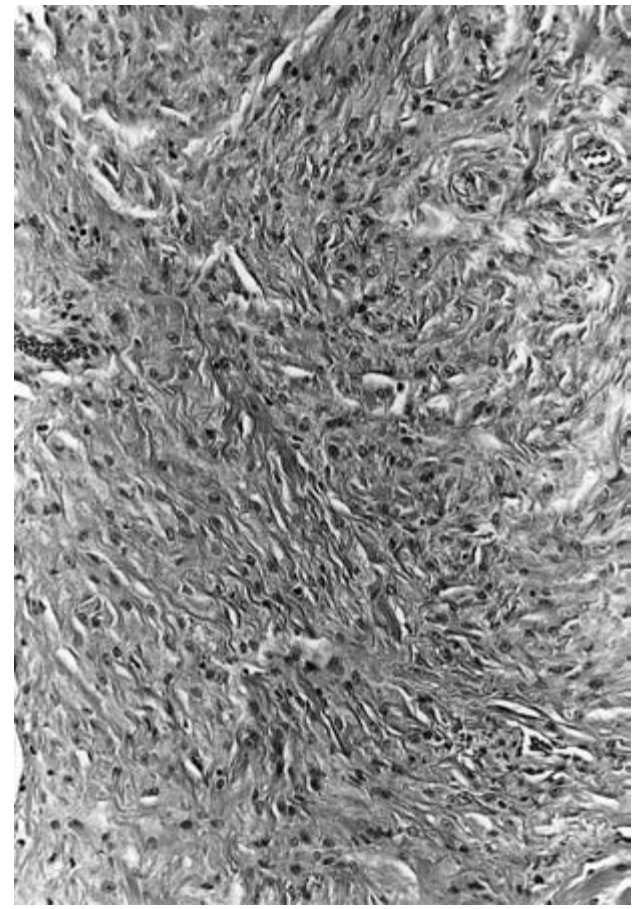


Fig. 35.3 Higher magnification of reactive fibrohistiocytic nodule in a dog. Pale round cells with poorly defined boundaries are intermingled with spindle cells.

able numbers of delicate vacuoles with smooth contours, consistent with lipid. The nuclei are small and vary from round or oval to irregular. Nucleoli are inconspicuous, and mitotic figures are observed infrequently. Occasional multinucleated cells are present. Admixed are plump spindle cells that also are histiocytic based on immunohistochemistry (see below). These spindle cells have oval to slightly elongated nuclei with marginated chromatin. Some spindle cells are narrower and more elongate, consistent with fibrocytic origin, and have pointed nuclei with finely dispersed chromatin. Lymphocytic infiltrates are either dispersed throughout the mass or are arranged in aggregates. Neutrophils and eosinophils are usually present in small numbers.

Differential diagnoses for benign fibrohistiocytic nodules include cutaneous histiocytomas, cutaneous xanthomas, reactive histiocytosis, and other infectious and noninfectious granulomatous processes. The histiocytes of canine cutaneous histiocytoma have less cytoplasm and do not exhibit cytoplasmic lipidization. Moreover, histiocytomas often have epitheliotropism and lack admixed spindle cells. Cutaneous xanthomas associated with abnormalities of lipid metabolism are usually multiple and have histiocytic cells with markedly foamy cytoplasm. Late lesions of reactive histiocytosis may exhibit vacuolization of the lesional dendritic cells, which may make differentiation from fibrohistiocytic nodules more difficult. However, reactive histiocytosis is a multicentric disease that is characterized by a multinodular to diffuse, pleocellular infiltrate that predominates in the deep dermis rather than the superficial dermis, and tends to be markedly angiocentric. Granulomatous inflammation, either infectious or sterile, commonly has a multinodular to coalescing configuration and is composed of a markedly pleocellular cell population with larger numbers of neutrophils.

Immunohistochemistry

Reactive fibrohistiocytic nodules are predominated by CD45+, CD18+ histiocytes; these include the round cell population as well as the plump spindle cells. Additional differentiation between macrophages and dendritic cells

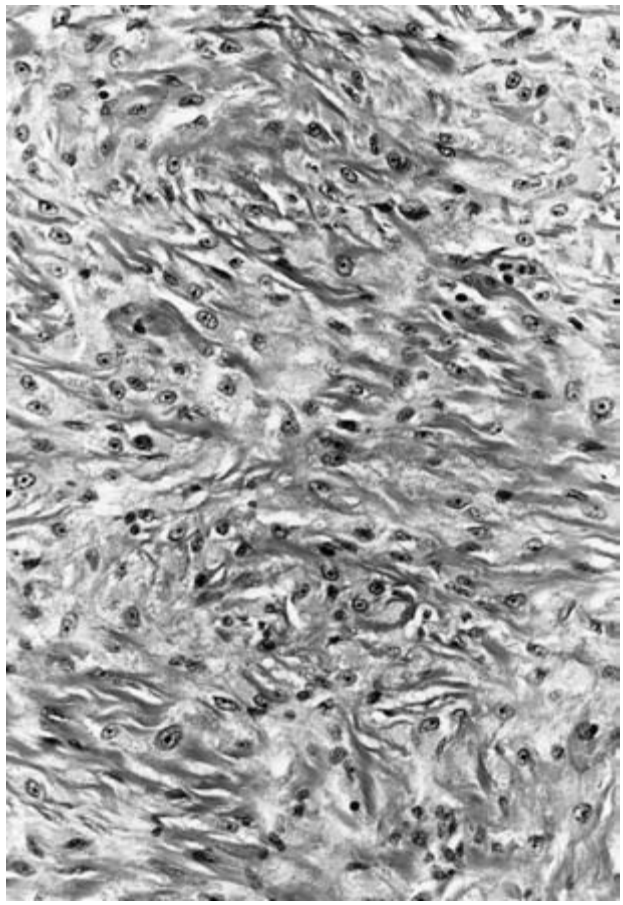


Fig. 35.4 High magnification of reactive fibrohistiocytic nodule in a dog demonstrating large finely vacuolated histiocytic cells; note fewer admixed spindle cells comprising both histiocytes and fibroblasts.

has been precluded by the lack of fresh tissue samples. The occasionally observed multinucleated cells are histiocytes and also express CD45 and CD18. The admixed slender spindle cells express vimentin, but lack expression of leukocyte markers and hence are consistent with fibrocytes. The lymphocytic infiltrate is composed of CD3+ T cells. Immunohistochemistry is of limited help in the differentiation of fibrohistiocytic nodules from differential lesions (see above), as the exact immunophenotype of the histiocytic sublineage in fibrohistiocytic nodules is not known.

CANINE CUTANEOUS HISTIOCYTOMA

Histiocytomas are composed of Langerhans cells (Table 35.1). Proliferations of Langerhans cells vary in humans and include several clinical presentations (Munn & Chu, 1998). The lesions may be limited to the skin, such as in congenital histiocytoma and Hashimoto–Pritzker disease (Munn & Chu, 1998; Schmitz & Favara, 1998). Often several organ systems are affected in humans, including skin (80% of cases), bone, lymph nodes, spleen, liver, thymus, bone marrow, lung, and central nervous system, as in Hand–Schuller–Christian disease or Letterer–Siwe disease (Munn & Chu, 1998; Schmitz & Favara, 1998). In dogs, persistent and recurrent histiocytomas as well as more aggressive Langerhans cell histiocytosis have been identified.

Langerhans cells are the intraepithelial dendritic antigen presenting cells of the skin that are located between keratinocytes (Birbeck et al., 1961). Homotypic binding of E-cadherin keeps the nonactivated Langerhans cells within the epidermis and follicular epithelium (Tang

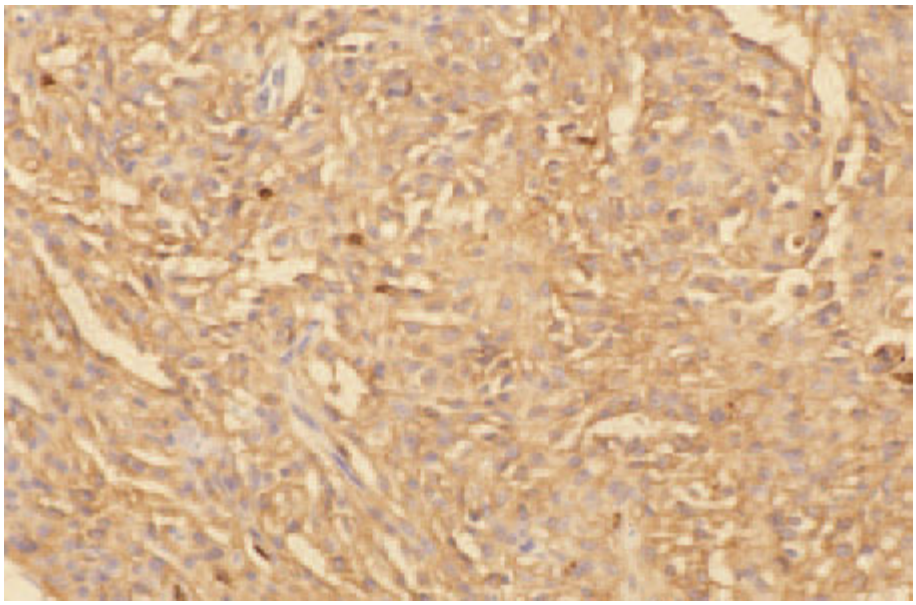


Fig. 35.5 Reactive fibrohistiocytic nodule in a dog. Immunohistochemistry with anti-CD18 confirms the leukocytic origin of the round cells and many of the spindle cells (chromogen diaminobenzidine [DAB]).

et al., 1993). Canine Langerhans cells lack Birbeck granules (Moore et al., 1996), a distinctive ultrastructural marker of Langerhans cells in humans and other species (Chu & Jaffe, 1994). Thus, this morphologic characteristic cannot be used to identify canine histiocytomas (Moore et al., 1996; Affolter & Moore, 2002).

Clinical features

Canine cutaneous histiocytoma is a common, usually benign tumor in dogs. Typically, canine cutaneous histiocytoma presents as rapidly growing, erythematous, dome-shaped nodule or plaque, usually less than 2.5 cm in diameter. These occur as solitary or, occasionally, multiple lesions that develop over a short period of time. Alopecia and ulceration are common. Predilection sites for histiocytomas are the head, ears, neck, and extremities, but they may occur in any location.

Canine cutaneous histiocytoma is seen mostly in younger dogs; the incidence drops drastically after 3 years of age. However, histiocytomas may develop at any age. A higher incidence has previously been reported for certain breeds (Scott et al., 2001). This observation could not be substantiated upon review of 256 cases by one author (V.K.A.); histiocytomas were seen with equal frequency throughout a large number of breeds with the exception of persistent and recurrent histiocytoma (see below). The latter is often observed in Shar Peis and Shar Pei mixed-breed dogs. Sex predilections are not observed.

For the majority of cases, lesions undergo spontaneous regression and, once regression has been initiated, may disappear within days. Lymphadenopathy is probably more common than clinically appreciated (Moore et al., 1996). Histiocytoma cells are Langerhans cells and, as such, are prone to migrate to the draining lymph nodes. Migration of histiocytoma cells to the draining lymph node leads to nonpainful lymphadenopathy and can be seen with both solitary and multiple histiocytomas. The lymphadenopathy usually regresses simultaneously with the skin lesions.

Persistent and recurrent cutaneous histiocytomas

In this form of histiocytoma, numerous lesions may be grouped in one region or, alternatively, are dispersed over the entire body (Moore et al., 1996). New lesions develop as others regress. The lesions may persist over several months. Persistent and recurrent histiocytomas are usually multifocal (Moore et al., 1996; Nagata et al., 2000); occasional solitary histiocytomas are similarly persistent and nonregressive (Moore et al., 1996). Ulcerated nodules are prone to secondary bacterial infection, which may result in septicemia. In some cases, the nodules eventually undergo spontaneous regression. In other cases, however, involution does not occur. Migration of histiocytoma cells to the draining lymph node with lymphadenopathy is relatively common with persistent and recurrent histiocytomas. In rare cases, persistent histiocytomas may result in development of internal lesions (Nagata et al., 2000), a process best referred to as Langerhans cell histiocytosis (see below). Therapy with immunosuppressive drugs is contraindicated for persistent and recurrent cutaneous histiocytomas, as it interferes with the possibility of lymphocyte-induced regression.

Langerhans cell histiocytosis

The syndrome of multiple, persistent and recurrent cutaneous histiocytomas with spread to lymph nodes and ultimate involvement of internal organs is referred to as Langerhans cell histiocytosis as the condition resembles progressive Langerhans cell histiocytosis in humans (Broadbent et al., 1994; Schmitz & Favara, 1998). A minority of dogs with multiple persistent histiocytomas and lymph node involvement develop subsequent internal histiocytic infiltrates in various organ systems, including the lungs, multiple lymph nodes, spleen, heart, kidneys, pancreas, and liver. Subsequent Langerhans cell histiocytosis has occurred in the clinical setting of multiple histiocytomas of the internal surface of the pinna and the external ear canal in several dogs. A case of multiple persistent and recurrent cutaneous histiocytomas with eventual metastasis to lymph node and internal organs has been reported in a Dachshund (Nagata et al., 2000). Langerhans cell histiocytosis has a poor prognosis. Affected dogs are usually euthanized due to rapid deterioration.

Histopathology

Cutaneous histiocytoma (Figures 35.6 through 35.9)

In general, canine cutaneous histiocytomas are circumscribed but nonencapsulated nodules that infiltrate the superficial and deep dermis. They may extend into the subcutis. Histiocytomas have a base-narrow or top-heavy configuration, i.e. their silhouette resembles an inverted trapezoid or wedge. The nodules are composed of a dense proliferation of round and polygonal cells arranged in cords and dense sheets that variably obliterate adnexal structures. In the superficial aspects of the tumor, the cells may form loose cords or rows that stream down from the dermal–epidermal junction. The epidermis may be hyperplastic and rete peg-like extensions may penetrate the neoplasm. Epidermal invasion, characterized by either single cells or aggregates, is present in about 80% of cases and is usually mild; follicular invasion is not a prominent feature (Moore et al., 1996). In some cases, epitheliotropism is pronounced. Early lesions have an intact surface, while ulceration is a common feature of later lesions.

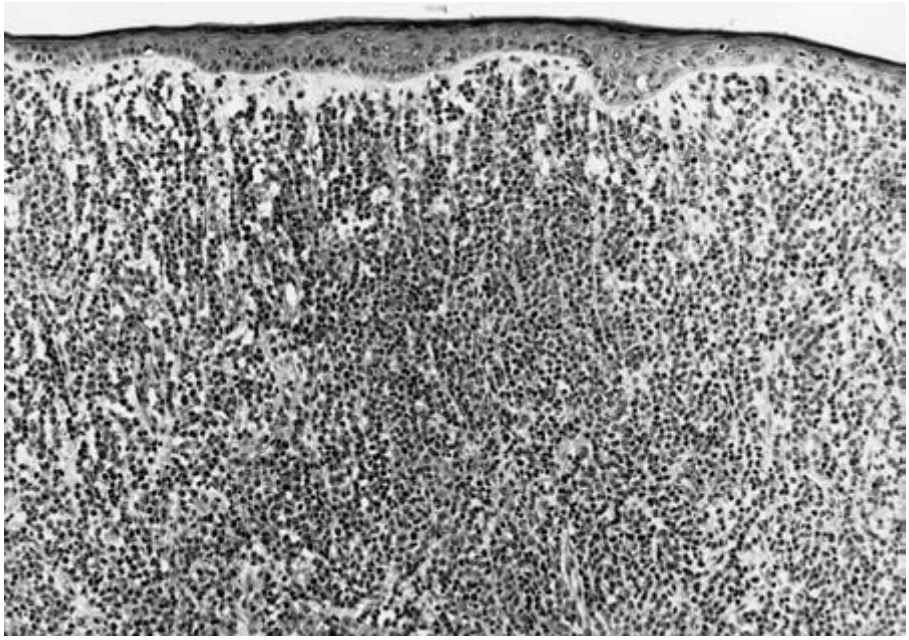


Fig. 35.6 Canine cutaneous histiocytoma. Cords of cells are oriented perpendicularly to the skin surface in the superficial aspect of the tumor, while the dense deep portion is composed of sheets of cells.

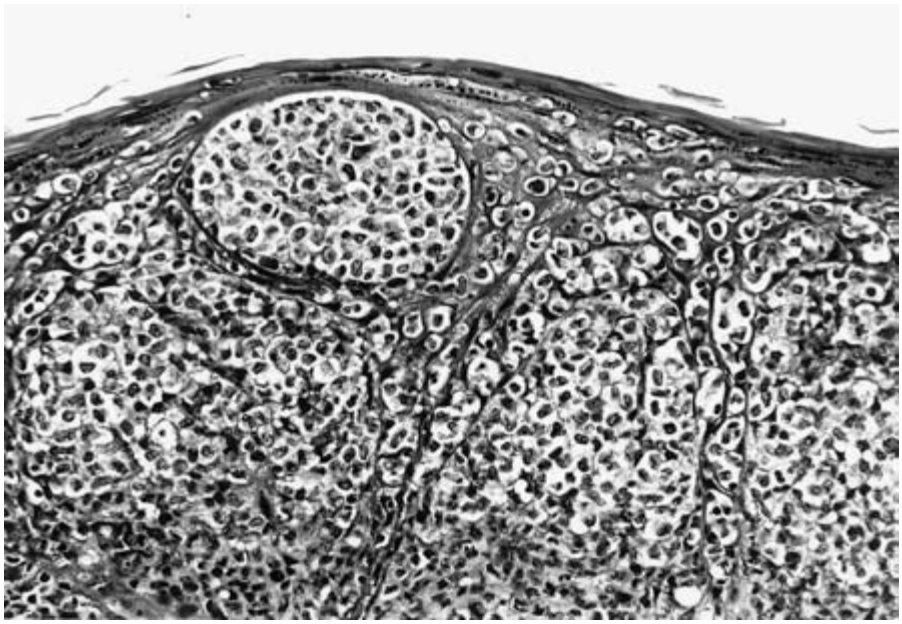


Fig. 35.7 Higher magnification of canine cutaneous histiocytoma, demonstrating unusually marked epitheliotropism of single cells and aggregates.

The tumor cells have discrete cell boundaries and possess moderate to abundant, lightly eosinophilic cytoplasm. Occasionally, the cytoplasm has a pale, clear appearance, a feature that is also referred to as clear cell change. In solid sheet-like areas of proliferation in the deeper dermis, cells have less defined cell borders. The centrally located nuclei are round to oval; indented, C-shaped or folded nuclei are also present, and occasionally they may be slightly paracentral. The nuclei have finely-dispersed or marginated chromatin. Mitotic activity is moderate.

In regressing lesions, the epidermis is often ulcerated, and the tumor nodules have multiple areas of necrosis. There is a dense T cell lymphocytic infiltrate, which first predominates at the base of the tumor nodule and gradually infiltrates the entire tumor mass. In addition, there are variable numbers of larger histiocytic cells admixed with the histiocytoma cells. The former are characterized by a larger amount of amphophilic cytoplasm and indented and slightly twisted nuclei. Giant cells may be evident rarely. These cells represent infiltrating reactive dermal dendritic cells (see immunohistochemistry, below). In some late-

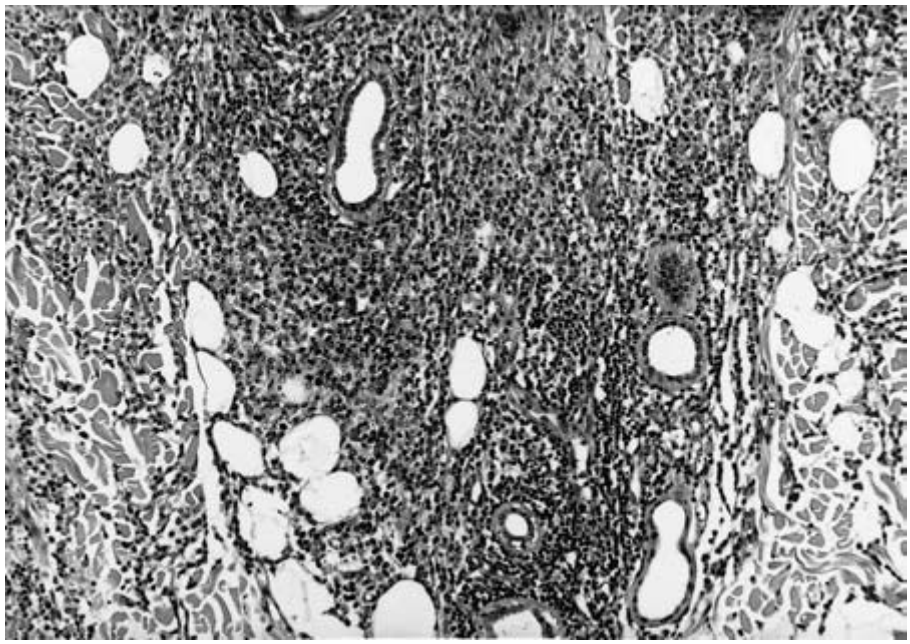


Fig. 35.8 Canine cutaneous histiocytoma. Lymphocytic infiltrates are present at the base of the tumor indicating regression.

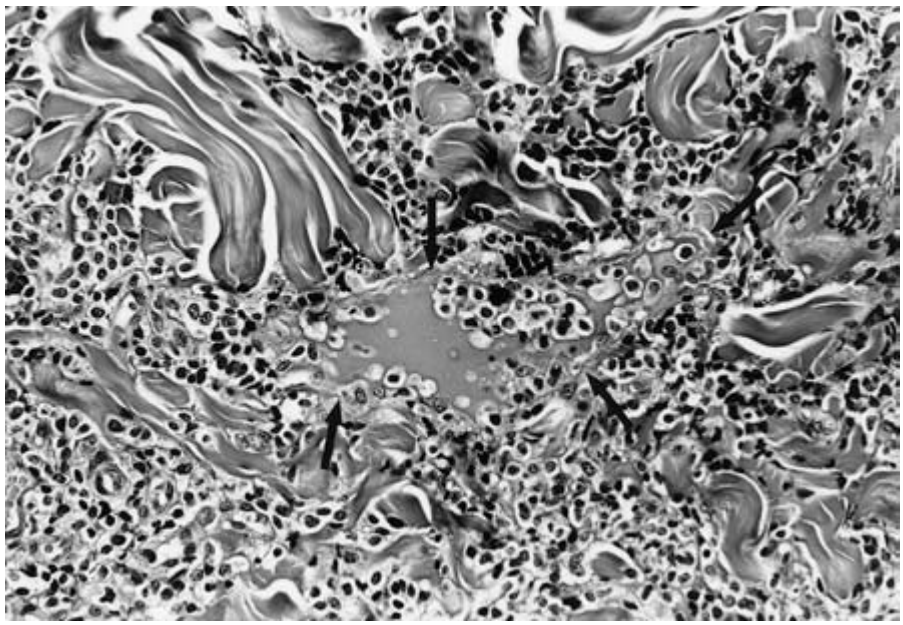


Fig. 35.9 High magnification of canine cutaneous histiocytoma; note neoplastic invasion of a dermal lymphatic (arrows). Note the admixed small reactive lymphocytes.

stage lesions, lymphocytes and reactive histiocytes outnumber the histiocytoma cells, and diagnosis in these cases requires careful search for residual cords or clusters of histiocytoma cells in the superficial dermis. Ulcerated surfaces and areas of necrosis are infiltrated by neutrophils. Occasionally, histiocytomas may contain small numbers of eosinophils.

Lymph node extension may be heralded by the presence of numerous histiocytoma cells in markedly distended dermal lymphatics. Lymph node involvement is characterized by a dense population of histiocytoma cells that obliterates the subcapsular sinusoids and infiltrates paracortical tissue. As a result, there is a variable degree of effacement of the lymph node architecture.

Persistent and recurrent cutaneous histiocytomas

In persistent lesions there is a lack of a reactive T cell infiltrate. Instead there may be aggregates of plasma cells. The neoplastic infiltrate often extends deeper into the subcutaneous tissue. Ulcerations of the epidermis are common, and neutrophils are limited to the ulcerated surface. Mitotic activity is moderate to high, and atypical mitoses

may be present. Infiltration of the draining lymph node tissue with partial effacement of the architecture is common (see above)

Langerhans cell histiocytosis (Figure 35.10)
As in persistent and recurrent cutaneous histiocytomas, the neoplastic cells extend deeply into the subcutaneous tissue. In addition, intralymphatic tumor cell aggregates are common. The neoplastic cells may be more pleomorphic than in routine cutaneous histiocytomas, and anisocytosis and anisokaryosis may be pronounced. The mitotic index is high and atypical mitoses are observed. Reactive T cell infiltrates are not observed, as in typical histiocytoma (see above), but plasma cell aggregates may be present. Metastatic lesions in lymph nodes may largely efface the lymph node architecture and replace the parenchyma by pleomorphic round cells similar to the tumor cell infiltrate in the skin. Distant metastases in internal organs are characterized by nonencapsulated, infiltrative, and obliterative tumor masses. The cellular morphology of these distant metastatic lesions may be similar to the primary skin lesions or, alternatively, display more cellular atypia manifested by larger and more irregular cells with a variable amount of cytoplasm and severe anisokaryosis.

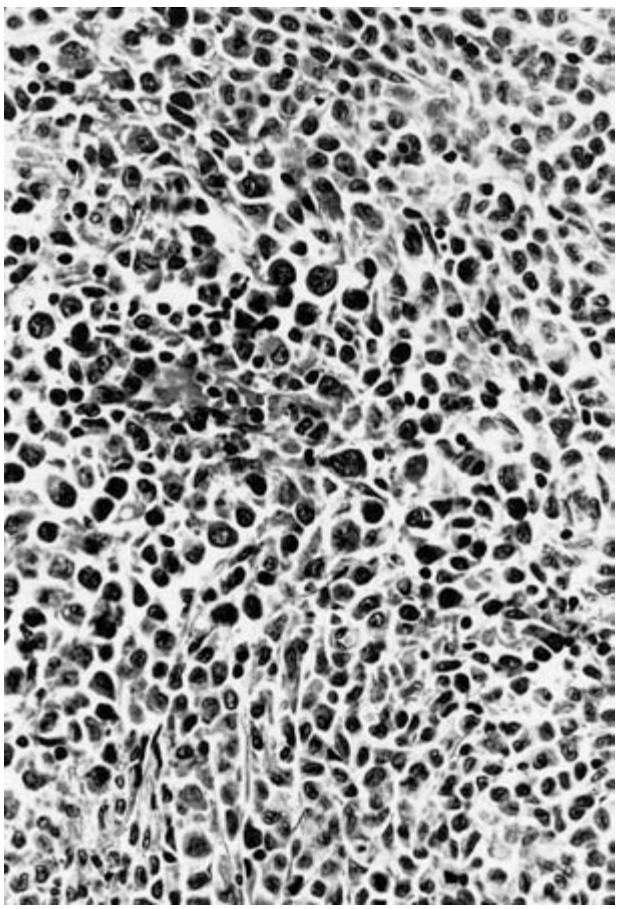


Fig. 35.10 High magnification of Langerhans cell histiocytosis in a dog. The proliferating histiocytoma cells (Langerhans cells) are pleomorphic and have marked anisokaryosis.

In contrast to histiocytomas and Langerhans cell histiocytosis, histiocytic sarcomas involving the skin usually originate in the subcutis and underlying tissues, and secondarily infiltrate the deep dermis. Most histiocytic sarcomas have variable numbers of spindle-shaped tumor cells admixed, a feature not seen with histiocytomas.

Other differential diagnoses for all forms of canine histiocytomas include epitheliotropic lymphoma, as well as amelanotic malignant melanoma with junctional activity, both of which have intraepidermal tumor cell aggregates. In addition, transmissable venereal tumors may rarely feature epidermotropism. Further, plasma cell tumor, nonepitheliotropic lymphoma, poorly granulated mast cell tumor, and Merkel cell tumor should be ruled out. As clinical management of histiocytomas and reactive histiocytosis are very different, it is also crucial to differentiate between these lesions (see Chapter 13). Histiocytoma and cutaneous T-cell lymphoma can mimic each other perfectly, and immunohistochemistry often is required (see below). Most amelanotic melanomas have variable numbers of spindle-shaped tumor cells admixed with the round cell population. Packeting is prominent in melanomas, but not in cutaneous histiocytomas; Fontana–Masson stain may identify small amounts of intracytoplasmic melanin. In contrast to histiocytomas, epidermal involvement is absent in plasmacytomas, mast cell tumors, and most transmissible venereal tumors. Moreover, plasmacytomas are often composed of a fairly pleomorphic cell population arranged in tight packets. Multinucleated tumor cells or cells with multilobular nuclei are common in plasmacytomas, and fairly well-differentiated plasma cells may be observed along the tumor margins. The dense cytoplasmic RNA of plasma cells stains magenta with methyl green pyronine (MGP) stain. Poorly granulated mast cell tumors are separated from histiocytomas by the usual presence of small numbers of intracytoplasmic metachromatic granules, identified with Giemsa or toluidine blue stains. Transmissible venereal tumors can mimic histiocytomas, particularly in the regressing stage, as both tumors have marked lymphocytic infiltrate during regression. However, transmissible venereal tumor cells have fine cytoplasmic vacuoles, a feature much better appreciated in impression smears. Merkel cell tumors are characterized by marked packeting of the tumor cells and a very delicate vascular stroma. In contrast to histiocytomas, Merkel cell tumors lack the presence of indented nuclei. Merkel cells have membrane-bound dense-core granules, desmosomal proteins, and tonofilament-like structures, which can be detected by electron microscopy. Moreover, with Merkel cell tumors, a Grimelius stain highlights argyrophilic cytoplasmic granules in variable numbers of the tumor cells.

Immunohistochemistry

Histiocytomas express the common leukocyte markers CD45, CD18, and are also CD1+, CD11c+, CD90–, CD4–, MHC II+, and ICAM-1+ (Moore et al., 1996). In most cases, the tumor cells also express E-cadherin (Affolter & Moore, 2002). This immunophenotype is characteristic of Langerhans cells (see Table 35.1). The expression of E-cadherin is often maintained in metastatic lesions in the lymph node and other organs; its expression, however, may be weak or limited to a subpopulation of migrating tumor cells. Rarely, cases with lack of E-cadherin expression are observed. The admixed T cell population seen in regressing histiocytomas is composed of cytotoxic CD8+ T cells. The reactive histiocytic infiltration present in regressing histiocytomas is composed of CD1+, CD11c+, MHC II+, CD90+ dermal dendritic cells, which lack expression of E-cadherin.

In contrast to cutaneous histiocytomas, cutaneous lymphomas lack dendritic cell markers. The vast majority of cutaneous lymphomas is composed of CD3+ T cells. Plasma cell tumors are composed of CD45RA+ tumor cells, which may also maintain the expression of CD79a and immunoglobulin. Mast cell tumors are positive for CD45, but detectable expression of CD18 varies. Moreover, canine mast cell tumors express KIT and may be positive for tryptase. Transmissible venereal tumors express CD45, CD45RA, and may express CD49d but lack expression of other lymphocytic or histiocytic markers. Merkel cell tumors and melanocytic tumors lack expression of leukocyte markers and hence, are negative for CD45 and CD18. Melanomas may express melanoma-associated antigen recognized by T cells (MART-1), melanoma-associated antigen (Melan-A), S100, tyrosinase, melanoma isoform of microphthalmia transcription factor (MITF-M), tyrosinase-related protein-2 (TRP-2), or HMB-45/gp100 instead, and Merkel cell tumors are positive for cytokeratin 20 (detected by pan-cytokeratin stains), neuron-specific enolase (NSE), synaptophysin, and chromogranin A.

While histiocytomas are composed of Langerhans cells (E-cadherin+, CD4–, CD90–), reactive histiocytosis is characterized by a proliferation of reactive dermal dendritic cells, which coexpress CD90 and CD4 (Table 35.1) but lack expression of E-cadherin. Histiocytic sarcomas of nonLangerhans cell origin express CD1, CD11c, and MHC II, and may also express CD90; however, they lack expression of E-cadherin.

FELINE PROGRESSIVE DENDRITIC CELL HISTIOCYTOSIS

A small number of cases of a clinically progressive disorder of dendritic cell origin have recently been identified in cats (Affolter & Moore, 2000; Day et al., 2000). Based on the clinical behavior, this entity resembles Langerhans cell histiocytosis in humans (Favara et al., 1997; Arico & Egeler, 1998). Feline progressive dendritic cell histiocytosis can be histologically subdivided into epitheliotropic and nonepitheliotropic forms, both of which are composed of dendritic cells of nonLangerhans cell type (Affolter, V.K. & Moore, P.F., unpublished data, 2002).

Clinical features

The small number of cases recognized to date offers limited clinical information about feline progressive dendritic cell histiocytosis. It is apparently rare, but the exact incidence is not known. Affected cats may initially present with a solitary skin nodule. In most cases lesions are first observed either on the head, neck, or lower extremities. Over time, multiple nonpainful intradermal nodules develop and may occur in any location. Occasionally, the lesions are limited to one extremity. The nodules may measure up to 1.5 cm in diameter. Early lesions have an intact skin surface, while ulceration is a common sequela. The nodules may wax and wane in size, but complete spontaneous regression has not been seen. In general, the nodules progress in size over time, and may coalesce to large plaques.

Based on the limited number of cases seen in cats, there are no sex or breed predilections for this disease. The age in cats observed to date has ranged from 9 to 17 years.

Some cats with progressive histiocytosis develop numerous lesions limited to the skin over a prolonged period of time, without evidence of internal lesions. However, lymph node involvement is common as the disease progresses. Draining lymph nodes are often enlarged but not painful. Progressive dendritic cell histiocytosis may develop morphologic features and clinical behavior of histiocytic sarcoma, as at a terminal stage, one to several internal organs may be affected. Clinical signs vary depending on the organ systems involved.

Histopathology (Figures 35.11 through 35.14)

Feline progressive dendritic cell histiocytosis may be nonepitheliotropic or epitheliotropic. Lesions are characterized by fairly well circumscribed but nonencapsulated nodules that extend from the superficial dermis into the subcutis. Similar to canine cutaneous histiocytomas, the lesions tend to have a base-narrow or top-heavy configuration. Early lesions may appear as multinodular infiltrates that gradually coalesce. The surface of the nodules may be intact, eroded, or ulcerated.

The nodules are composed of a dense proliferation of large round and polygonal histiocytic cells with discrete cell boundaries, and a moderate to abundant amount of lightly eosinophilic cytoplasm. The proliferating cells have centrally located, large, vesicular nuclei. These are oval or reniform and indented, and contain marginated

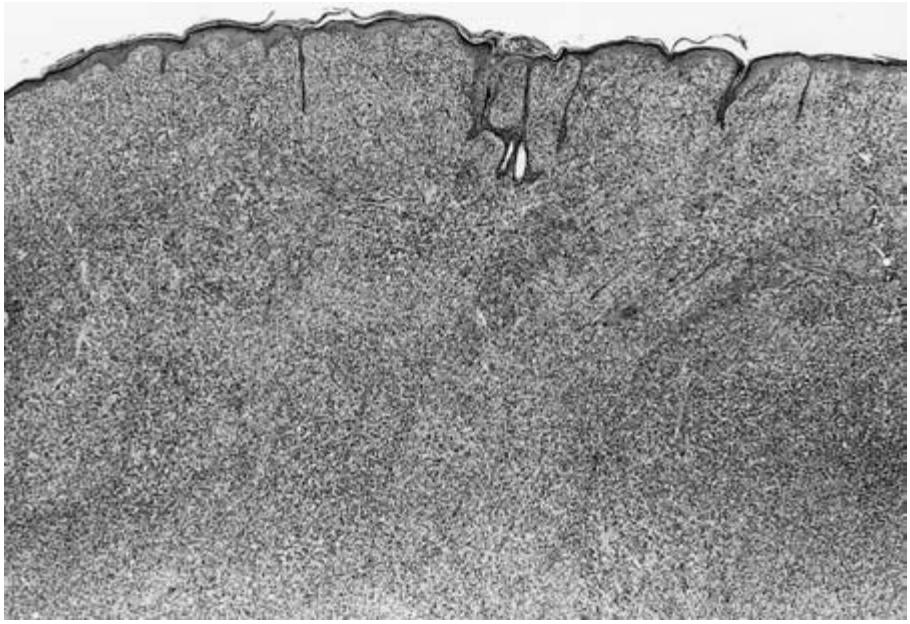


Fig. 35.11 Progressive dendritic cell histiocytosis in a cat demonstrating a diffuse infiltrate of the dermis and subcutis.

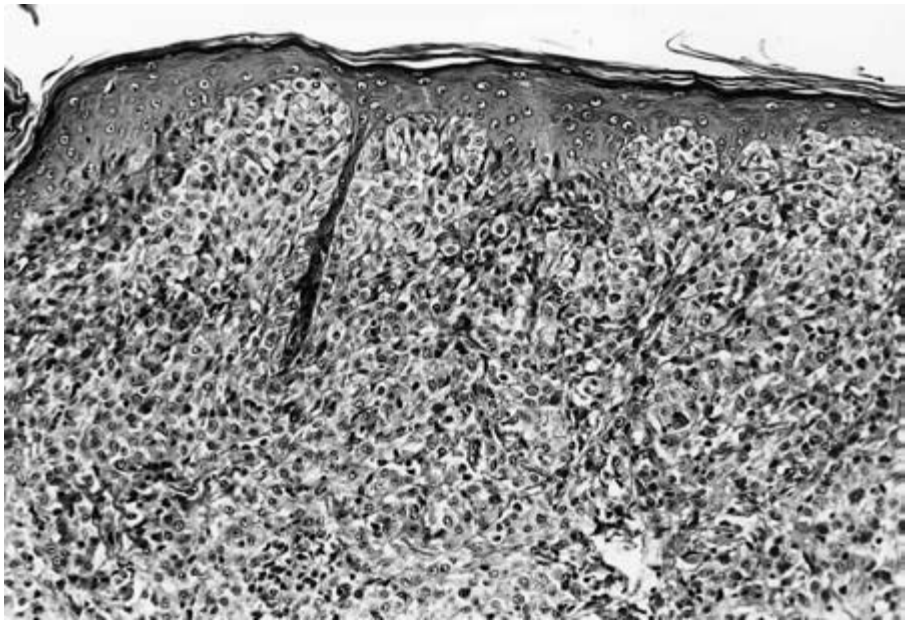


Fig. 35.12 Higher magnification of progressive dendritic cell histiocytosis in a cat. In this nonepitheliotropic form, the large round cells expand to the basement membrane zone but do not infiltrate the overlying epidermis. The centrally located nuclei are surrounded by a moderate to abundant pale cytoplasm.

or finely clumped chromatin. Multinucleated histiocytic cells may be present, and intralymphatic aggregates are occasionally seen. Mitotic activity ranges from moderate to high. Birbeck's granules, characteristic of Langerhans cells, could not be found in a case evaluated by electron microscopy (Madewell, B., personal communication, 2002). Cytoplasmic vacuolation of histiocytic cells occasionally is prominent in older lesions, creating a foamy, xanthomatous appearance; these cells are secondarily infiltrating, circulating macrophages (see immunohistochemistry, below).

In nonepitheliotropic dendritic cell histiocytosis, the infiltrates extend to the superficial dermis and basement membrane, but invasion of the overlying epidermis is not seen. In epitheliotropic dendritic cell histiocytosis, the dermal nodules extend to the basement membrane zone and single cells or aggregates of cells are observed in the overlying epidermis. Involvement of follicular epithelium has not been observed. Reactive inflammation, which is variable in severity, is composed of dispersed lymphocytes and neutrophils.

Primary differential diagnoses for nonepithelio-

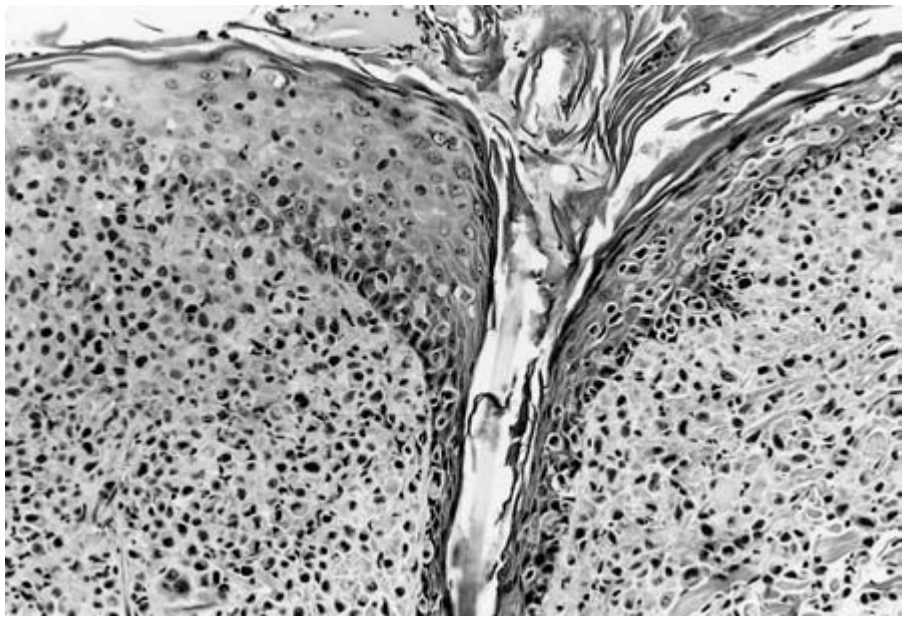


Fig. 35.13 Progressive dendritic cell histiocytosis in a cat, epitheliotropic form. Pale tumor cells are infiltrating the epidermis. Note anisocytosis and anisokaryosis.

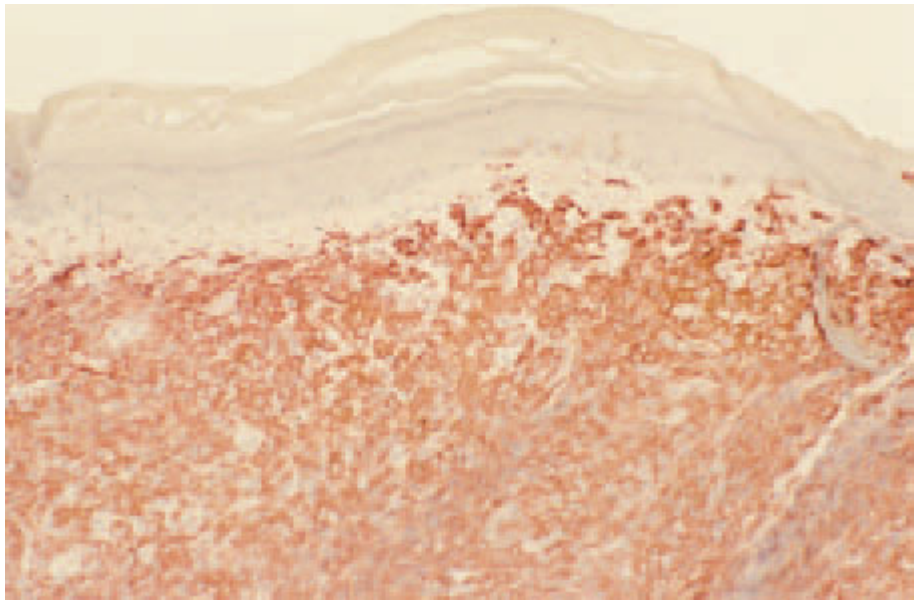


Fig. 35.14 Progressive dendritic cell histiocytosis in a cat. Immunohistochemistry with anti-CD1 confirms the dendritic cell origin of the tumor cells in this frozen section (chromogen aminoethylcarbazole [AEC]).

tropic feline progressive dendritic cell histiocytosis are nonepitheliotropic lymphoma, amelanotic malignant melanoma, cutaneous xanthoma (for vacuolated lesions), Merkel cell tumor, poorly granulated or pleomorphic mast cell tumor, and plasmacytoma. Differential diagnoses for feline progressive dendritic cell histiocytosis with epitheliotropism include epitheliotropic lymphoma and amelanotic melanoma with junctional activity. Lymphoma cells may have a higher nuclear to cytoplasmic ratio when compared to feline progressive dendritic cell histiocytosis, and the tumor cells may have cleaved nuclei with marked margination of chromatin. Amelanotic melanomas may be composed of round cells, which, however, are arranged in packets and accompanied by variable spindle-shaped tumor cells. Small amounts of melanin pigment may be demonstrated by Fontana–Masson staining. Older lesions of progressive feline dendritic cell histiocytosis may be characterized by infiltration of markedly vacuolated macrophages and may be difficult to distinguish from cutaneous xanthomas (see Chapter 13). In cutaneous xanthomas, cholesterol clefts and evidence of phagocytosis may be found in some lesions. Merkel cell tumors are characterized by tight packets of tumor cells surrounded by a delicate fibrovascular stroma. Merkel cells have a smaller

amount of cytoplasm when compared to feline progressive dendritic cell histiocytosis. Moreover, Merkel cell tumors have membrane-bound dense-core granules, desmosomal proteins and tonofilament-like structures, which can be detected by electron microscopy. The demonstration of intracytoplasmic metachromatic granules by Giemsa or toluidine blue stains confirms mast cell origin. Plasmacytomas tend to have a discrete Grenz zone (zone of non-involvement of the superficial-most dermis), while feline dendritic cell histiocytosis usually extends to the basement membrane zone. Moreover, plasmacytomas are composed of round cells arranged in nests and cords. The abundant RNA in plasma cells may be readily demonstrated with methyl green pyronine (MGP) stain, which imparts a magenta hue.

Immunohistochemistry

The proliferating histiocytic cell population in feline progressive dendritic cell histiocytosis consistently expresses CD18, CD1, and MHC II, a phenotype consistent with dendritic cells (Table 35.1). The vast majority of cases of both the epitheliotropic and nonepitheliotropic forms lack expression of E-cadherin, indicating a proliferation of dermal dendritic cells rather than Langerhans cells; however three cases demonstrating expression of E-cadherin have been observed. Thus, the exact sublineage of the proliferating dendritic cells is not yet known. The admixed reactive lymphoid infiltrate is composed of CD8+ cytotoxic T cells.

In contrast to feline progressive dendritic cell histiocytosis, cutaneous xanthomas are composed of CD18+, CD1–, CD11b+ macrophages (Table 35.1). However, older lesions of feline progressive dendritic cell histiocytosis may contain numerous vacuolated macrophages as well. Immunohistochemistry will generally detect the primary proliferating dendritic cells; however, if the infiltration of macrophages is severe, then biopsy of newer lesions may be required for differentiation from cutaneous xanthoma. Feline cutaneous lymphomas evaluated by immunohistochemistry to date have been composed of CD3+ T cells. Mast cells and plasmacytomas lack expression of CD1. Immunostaining for tryptase may permit identification of poorly granulated mast cell tumors. Feline plasmacytomas have not yet been evaluated for expression of CD79a, but presence of cytoplasmic immunoglobulins can be demonstrated. As nonleukocytic cells, melanomas and Merkel cell tumors lack expression of CD45 and CD18. Melanoma isoform of microphthalmia transcription factor (MITF-M) and S100 may identify melanocytic origin, while Merkel cell tumors are positive for cytokeratin 20 (detected by pancytokeratin), neuron-specific enolase (NSE), synaptophysin, and chromogranin A.

HISTIOCYTIC SARCOMA

(Synonym: malignant histiocytosis, localized and disseminated dendritic cell sarcoma)

True histiocytic sarcomas of dendritic cell origin, including localized and disseminated forms, are relatively rare in humans (Bucsky & Egeler, 1998; Gogusev & Nezelof, 1998). Canine histiocytic sarcoma occurs as a localized or disseminated neoplastic proliferation of dendritic cells (Affolter & Moore, 2002). Very few cases of localized histiocytic sarcoma of dendritic cell origin have been identified in cats (Affolter & Moore, 2000). The exact sublineage of the proliferating dendritic cells involved in canine and feline histiocytic sarcomas of different organ systems remains to be determined (see immunohistochemistry, below).

Disseminated histiocytic sarcoma was first reported as 'malignant histiocytosis' in Bernese Mountain Dogs (Moore & Rosin, 1986), but has now been recognized in a variety of breeds. Disseminated histiocytic sarcoma is preferred over 'malignant histiocytosis', because the latter implies a simultaneous development of histiocytic proliferations in different locations. At this point, there is no substantiating evidence that this occurs in dogs (Affolter & Moore, 2002). Disseminated histiocytic sarcoma mostly presents as a malignancy of internal organs with widespread metastasis, but skin and subcutis may occasionally be involved as well (Affolter & Moore, 2002).

Localized histiocytic sarcoma often originates in the subcutaneous tissue; other common primary locations include spleen, tongue, lung, brainstem, nasal cavity, vertebral bone, and epidural space (Affolter & Moore, 2002). Occasionally, numerous multinucleated giant cells are present, which explains why some cases of localized histiocytic sarcoma present with features of anaplastic sarcoma with giant cells, also referred to as 'malignant fibrous histiocytoma' (Gleiser et al., 1979; Kerlin & Hendrick, 1996) (see Chapter 33).

Clinical features

Localized histiocytic sarcomas are fairly common in dogs, but uncommon in cats. The exact incidence of these neoplasms is not known. The tumor masses are firm, may measure up to several centimeters in diameter, and infiltrate the surrounding tissue. In dogs, most tumor masses are located on extremities. Some tumors are located in periarticular regions; these dogs present with lameness and a slowly progressive ill-defined swelling. Skin involvement with disseminated histiocytic sarcoma is occasionally seen and may develop at any site of the body.



Fig. 35.15 Histiocytic sarcoma in a dog demonstrating a coalescing multinodular pattern. There is a small aggregate of reactive small lymphocytes in the upper left corner.

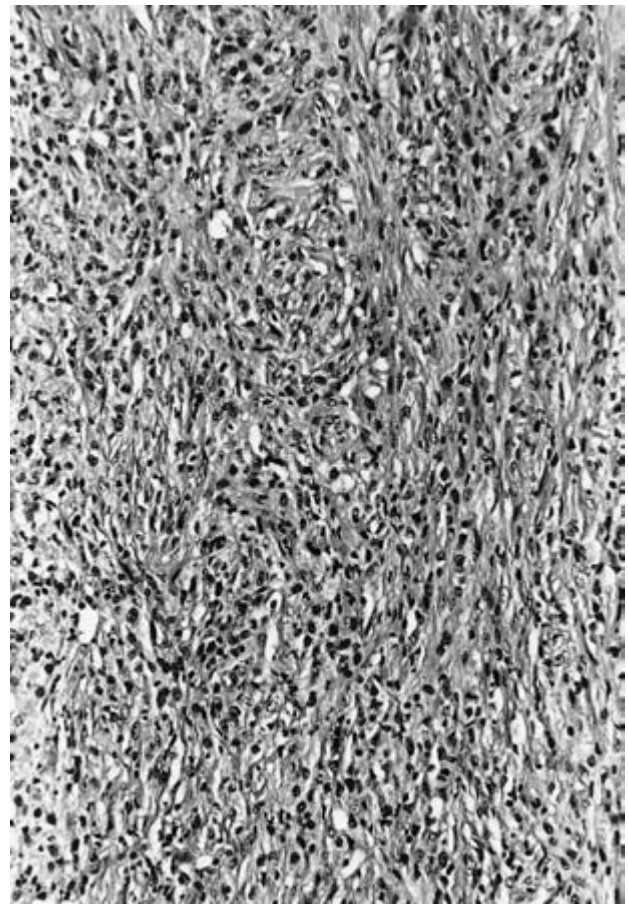


Fig. 35.16 Higher magnification of histiocytic sarcoma in a dog. In this spindle cell predominant example the elongated cells are arranged in irregular bundles.

Histiocytic sarcomas have been recognized in a variety of breeds, but Rottweilers, Bernese Mountain Dogs, and Golden and Labrador Retrievers are over-represented. The age of affected dogs ranges from 2 to 13 years, and a female to male ratio of 1.2:1 has been observed (Affolter & Moore, 2002).

The few cases of feline localized histiocytic sarcomas characterized to date were located on the extremities and abdomen (Affolter & Moore, 2000). Feline histiocytic sarcoma has been diagnosed in cats between 8 and 11 years of age. No breed or sex incidence data are available.

Localized histiocytic sarcomas demonstrate locally invasive growth and metastasize to draining lymph nodes in later stages of the disease. Distant metastases are possible. However, in contrast to disseminated histiocytic sarcoma, localized histiocytic sarcomas of the skin and underlying tissue are detected earlier, which probably reduces the incidence of widespread metastasis. A more favorable outcome is observed with early wide surgical excision of the primary tumor mass, which may involve amputation of the extremity. Prognosis of disseminated histiocytic sarcoma is poor, as the diagnosis is usually made at a stage when surgery is not an option based on widely distributed internal lesions; chemotherapy has been unsuccessful.

Histopathology (Figures 35.15 through 35.18)

Localized histiocytic sarcomas and the cutaneous tumor masses associated with disseminated histiocytic sarcomas have identical histologic features. Histiocytic sarcomas are poorly demarcated, locally invasive neoplasms. These are characterized by a dense pleomorphic cell proliferation that effaces normal tissue architecture. Neoplastic cells may infiltrate diffusely or form multiple coalescing nodules. Multiple areas of necrosis are common.

Morphology and arrangement of the tumor cell population vary among tumors and among different areas of a given tumor. Two major patterns are recognized: round cell predominant and spindle cell predominant. Some

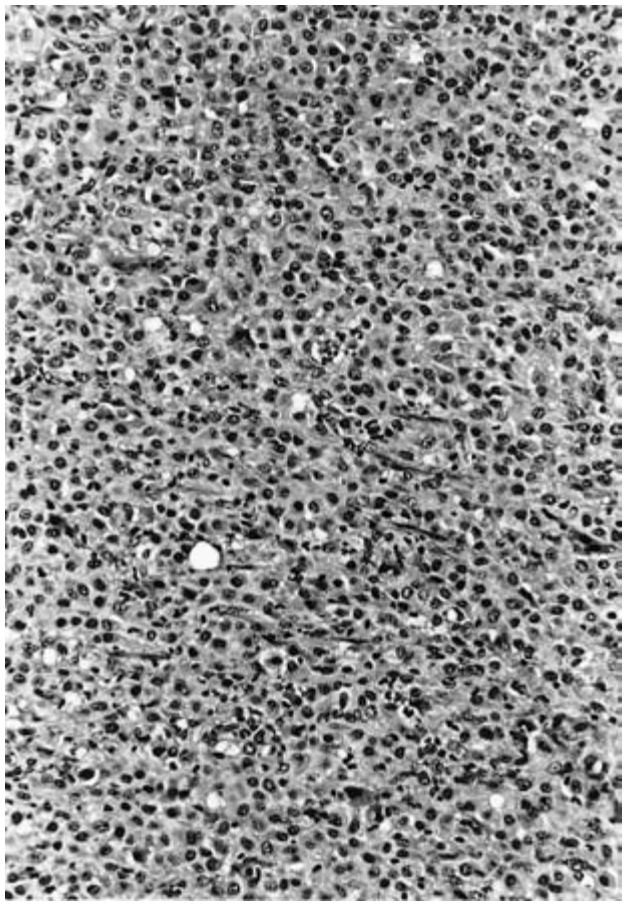


Fig. 35.17 Higher magnification of histiocytic sarcoma in a dog. In this round cell predominant example large neoplastic cells are admixed with neutrophils.

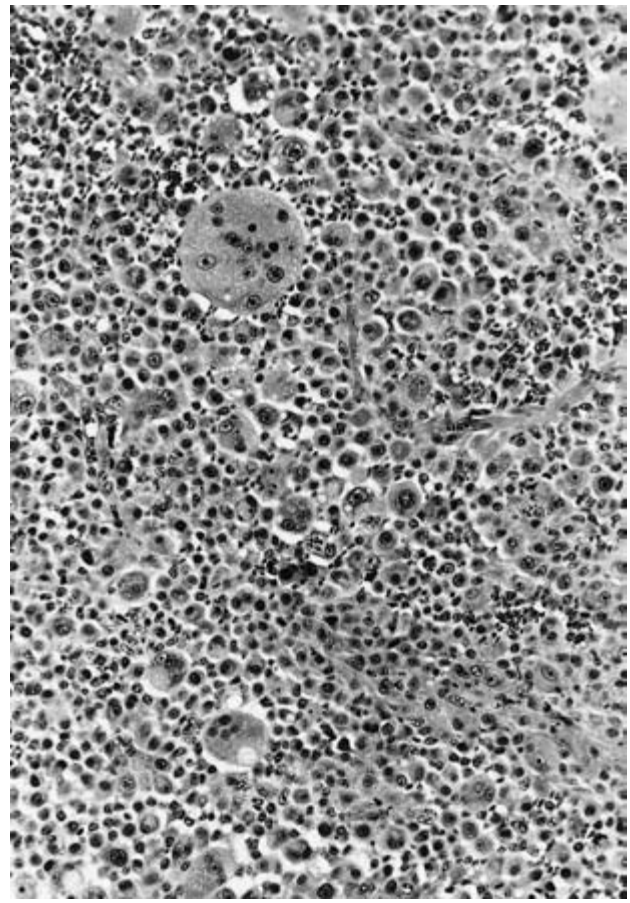


Fig. 35.18 High magnification of histiocytic sarcoma in a cat featuring numerous bizarre multinucleated tumor giant cells.

tumor nodules are predominantly composed of individualized large round cells with abundant amphophilic cytoplasm and occasional cytoplasmic vacuolation. These round cells have large, vesicular, round to oval, or indented and twisted nuclei with one or several nucleoli. A second pattern is characterized by variably dense proliferations of plump spindle cells with long cytoplasmic processes and large, oval, vesicular, and partially twisted nuclei. Occasionally, the nuclei have more condensed, coarse chromatin. Marked anisocytosis and anisokaryosis may be observed. Multinucleated tumor giant cells are common and often bizarre, and present as either large round cells or as stellate cells with long cytoplasmic processes. Up to seven mitotic figures may be present per high power field (40×). Occasional phagocytic vacuoles contain neutrophils or cellular fragments of tumor cells.

Reactive leukocytes range from a few dispersed cells to prominent inflammation. Neutrophils are consistently seen, in particular in conjunction with areas of necrosis. The number of reactive lymphocytes varies; occasional to numerous dispersed lymphocytes or aggregates of lymphocytes can be observed.

Canine spindle cell predominant histiocytic sarcomas can mimic other pleomorphic spindle cell or round cell sarcomas, including poorly-differentiated fibrosarcomas (some of which may be of myofibroblastic origin), malignant peripheral nerve sheath tumors, pleomorphic leiomyosarcomas, pleomorphic liposarcomas, synovial cell sarcomas, and hemangiopericytomas. Some histiocytic sarcomas may have numerous giant cells and thus may require differentiation from anaplastic sarcomas with giant cells of variable origin (see Chapter 33). Fibrosarcomas are usually characterized by a more monomorphic spindle cell population than histiocytic sarcomas, and round tumor cells are uncommon. Also, in contrast to histiocytic sarcomas, poorly-differentiated fibrosarcomas may still produce collagen, which can be demonstrated with Masson's trichrome stain. The presence of palisading tumor cells, occasional arrangement of the tumor cells in Antoni type A or B patterns, and the formation of Verocay bodies separate peripheral nerve

sheath tumors from histiocytic sarcomas. In contrast to histiocytic sarcomas, peripheral nerve sheath tumors are ultrastructurally characterized by a basal lamina around the tumor cells that is often thickened and folded. Leiomyosarcomas arise from either the arrector pili muscles or from dermal vessel walls, and a connection with these structures may be evident. Pleomorphic leiomyosarcomas with giant cells may require differentiation from histiocytic sarcomas by immunohistochemistry (see below). Pleomorphic liposarcomas may be difficult to differentiate from histiocytic sarcomas, particularly if distinctly vacuolated lipoblasts are not evident. Oil red O or Sudan black stains may help to detect neutral lipid. Similar to histiocytic sarcomas, synovial cell tumors may be composed of spindle-shaped and round tumor cells. In most cases, both pleomorphic liposarcomas and synovial cell sarcomas require immunohistochemistry to differentiate them from histiocytic sarcoma. Histiocytic sarcomas lack the perivascular arrangement seen in hemangiopericytomas.

Round cell predominant histiocytic sarcomas should be differentiated from Langerhans cell histiocytosis, poorly granulated grade III mast cell tumors, and amelanotic malignant melanomas. In contrast to histiocytic sarcomas, which originate in the subcutis and may extend into the dermis, Langerhans cell histiocytosis arises in the dermis, infiltrates the epidermis and extends into the subcutis. Poorly granulated mast cell tumors are separated from histiocytomas by the usual presence of small numbers of intracytoplasmic metachromatic granules, identified with Giemsa or toluidine blue stains. Packeting is prominent in melanomas, but not in histiocytic sarcomas; Fontana–Masson stain may identify small amounts of intracytoplasmic melanin; immunohistochemistry may be required in melanin-negative tumors.

Immunohistochemistry

Independent of their morphologic features, the tumor cells of canine histiocytic sarcomas consistently express CD45, CD18, CDI, CD11c, and MHC II, and hence are dendritic antigen-presenting cells (see Table 35.1). These cells lack expression of E-cadherin and are therefore not Langerhans cells. In some cases, a subpopulation of tumor cells expresses CD90. Histiocytic sarcomas of the subcutis and dermis that coexpress CD90 likely arise from dermal dendritic cells. However, in view of the diversity of the dendritic cell populations, histiocytic sarcomas in other visceral locations may arise from other subsets of dendritic cells.

Feline histiocytic sarcomas express CD18, CD1, and MHC II, and lack expression of E-cadherin. The exact subset of dendritic cells in feline histiocytic sarcoma remains to be determined.

Langerhans cell histiocytosis composed of Langerhans cells expresses E-cadherin and consistently lacks expression of CD90, allowing differentiation from histiocytic sarcomas. Anaplastic fibrosarcomas (including myofibroblastic variants), hemangiopericytomas, peripheral nerve sheath tumors, leiomyosarcomas, synovial cell sarcomas, and pleomorphic liposarcomas can be differentiated from histiocytic sarcomas by their lack of expression of common leukocyte markers (CD45, CD18).

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Chapter 36

Mast cell tumors

Mast cell proliferations in humans include solitary or multiple cutaneous mast cell tumors, cutaneous and systemic mastocytosis, and mast cell leukemia (Valent et al., 2001). Solitary and multiple mast cell tumors, and cutaneous and systemic mastocytosis have been recognized in dogs and cats. The highest mast cell density in normal canine and feline skin is found in the perivascular dermis, while few mast cells can be found in the subcutaneous tissue. Compared to other body locations, mast cells are more numerous on the pinnae and the chin in dogs, and the pinnae and feet in cats (Foster, 1994; Auxilia & Hill, 2000). However, there is no increased prevalence of mast cell tumors in these locations.

Mast cell precursors migrate from the bone marrow via blood into peripheral tissues where they differentiate into mature mast cells. Murine mast cells were initially classified into connective tissue (typical) mast cells and mucosal (atypical) mast cells based on the morphology of their granules, tinctorial properties, formaldehyde resistance, and granular components. Canine mast cells, similar to human mast cells, cannot be classified according to the system used in mice (Hill & Martin, 1998; Hill, 2002). Canine mast cells are separated according to their formalin sensitivity and the presence of proteases (Welle, 1997); mast cells contain either chymase (MC_C) or chymase and tryptase (MC_{CT}). In formalin-fixed normal canine skin MC_{CT} predominate, while fixation with Carnoy's fixative reveals a predominance of MC_C (Kube et al., 1998). This variation must be considered when immunohistochemistry for tryptase is used to identify canine mast cells. There is no equivalent characterization of feline cutaneous mast cells available to date.

The importance of the interaction of stem cell factor (SCF) with its specific KIT receptors in regard to mast cell maturation, proliferation, and activation has been documented in a variety of species (Hill & Martin, 1998; Hill, 2002). Human mast cell proliferations have been associated with mutations of the proto-oncogene *c-kit*, which encodes for the KIT protein (CD117), a receptor tyrosine kinase (Longley & Metcalfe, 2000). Constitutive phosphorylation of the KIT protein results in ligand-independent activation of the receptor tyrosine kinase on mast cells and their subsequent proliferation (Longley & Metcalfe, 2000). Similar to humans, canine mast cell tumors have been associated with mutations of the proto-oncogene *c-kit*, characterized by tandem duplications (London et al., 1996, 1999; Zemke et al., 2002). This results in consistent activation of the receptor tyrosine kinase and subsequent mast cell proliferation. Similar mutations of the *c-kit* proto-oncogene were not found in splenic mast cell tumors of cats (London, C.A., personal communication, 2002). In human mast cell tumors, mutations have also been observed in *p53*, a tumor suppressor gene whose encoded protein (p53) serves as a negative regulator for cell proliferation (Levine et al., 1991; Clarke et al., 1993). The aberrant p53 gene product can be detected by immunohistochemistry and its presence correlates with more aggressive behavior of some neoplasias. However, detection of the p53 protein is not useful in characterizing the clinical association between cytologic features and survival time or recurrence in dogs (Jaffe et al., 2000; Ginn et al., 2003).

Mast cells produce and release numerous factors (cytokines, chemokines, prostaglandins, coagulation factors, etc.), which bind to their appropriate ligands to mediate profound physiological effects. These include vascular permeability, smooth muscle contraction, leukocytic chemotaxis (in particular eosinophils), activation of metalloproteinases, and alteration of coagulability (Gordon et al., 1990; Hill & Martin, 1998; Hill, 2002). Thus, a variety of paraneoplastic disorders may occur in conjunction with mast cell proliferations (Rogers, 1996).

CANINE MAST CELL TUMOR

Clinical features

Cutaneous mast cell tumors are common neoplasms in dogs, and represent between 10% and 15% of all skin tumors (Conroy, 1983; Pulley & Stannard, 1990; Goldschmidt & Shofer, 1992). The annual incidence has

been estimated at about 90 mast cell tumors per 100 000 dogs (Rabanal & Ferrer, 2002).

Canine mast cell tumors may be solitary or multicentric in the skin; multiple tumors may be observed synchronously or sequentially. Multiple tumors occur in about 10% to 15% of cases (London & Seguin, 2003). Mast cell tumors are generally alopecic, erythematous, edematous nodules that vary in size from several millimeters to several centimeters. Lesions on distal extremities and lips may present as poorly defined areas of swelling. Ulceration is often present in larger lesions. An increased incidence of mast cell tumors on the proximal rear legs, perineum, and prepuce was reported by Tams and Macy (1981). Rabanal and Ferrer (2002) reported 50% of canine mast cell tumors on the trunk, 40% on the extremities, and 10% on the head. However, mast cell tumors may develop anywhere on the body, and the subcutis as well as dermis may be involved.

The average age of affected dogs is 8 years, but mast cell tumors are occasionally found in dogs as young as 4 months. Breed predilections for Boxers, Boston Terriers, Bull Terriers, Bullmastiffs, Staffordshire Terriers, Fox Terriers, English Bulldogs, Dachshunds, Labrador and Golden Retrievers, Beagles, Pugs, Chinese Shar Peis, Rhodesian Ridgebacks, and Weimaraners have been reported (Goldschmidt & Shofer, 1992; Scott et al., 2001; Rabanal & Ferrer, 2002). Shar Peis often develop mast cell tumors at a younger age (Miller, 1995). It also has been reported that certain predilection sites are associated with a particular breed. Boxers, Boston Terriers, Pugs, English Setters, and American Staffordshire Terriers tend to have hindleg masses; Rhodesian Ridgebacks have a higher incidence of mast cell tumors on the tail; and English Setters often develop lesions on the head (Goldschmidt & Shofer, 1992). Significant sex predilections have not been noted (Goldschmidt & Shofer, 1992).

All canine cutaneous mast cell tumors should be considered potentially malignant. The most commonly utilized grading system (see below) was developed by Patnaik et al. (1984). It classifies the tumors from grades I to III, with grade III being the most aggressive type. A recent review supports this correlation between histopathologic grade and biologic behavior (Bensignor et al., 1998). Using this grading system, the majority of canine mast cell tumors are grades I and II.

The grading system of Patnaik et al. (1984) uses a combination of cytologic features and thickness of the tumor, starting in the superficial dermis and expanding into the subcutis. Hence, it does not account for cytologically well-differentiated mast cell tumors (grade I) that originate in the superficial subcutis. According to the Patnaik system, these tumors are a result of downward extension from the dermis and automatically fall into the grade II category. Also, the Patnaik system does not account for superficial dermal tumors, which, based on their cytologic features, would be considered to be grade II or III. These shortcomings suggest that a revised grading system for canine mast cell disease may be needed.

One early study documents survival times of 51 weeks for well-differentiated tumors, 28 weeks for intermediate-grade tumors, and 18 weeks for poorly-differentiated tumors (Bostock, 1973). Patnaik et al. (1984) reported survival rates at 1500 days of 93% for grade I tumors, 44% for grade II tumors, and 6% for grade III tumors. Bensignor et al. (1998) reported 24 month survival rates after therapy (including surgery, radiotherapy, and chemotherapy) of 54% for dogs with grade II tumors and 6% for dogs with grade III tumors. A more recent study indicates a fair prognosis for grade II mast cell tumors that have been widely excised (3 cm margins) (Seguin et al., 2001). A significant association between tumor-free versus nontumor-free surgical margins and frequency of relapse by 12 to 24 months postoperatively has been documented; however, there were no significant differences in tumor-related death rates between dogs in the tumor-free and nontumor-free margin groups (Michels et al., 2002). Mast cell tumors located in the perineal area, scrotum, prepuce, and digits may have more aggressive behavior (Scott et al., 2001). Another study describes an increased regional metastatic rate of facial mast cell tumors when compared to mast cell tumors of other locations (Gieger et al., 2003). Metastasis occurs first in regional lymph nodes. Any mast cell tumor is capable of metastasis; it is therefore important to evaluate the extent of disease in dogs presenting with cutaneous mast cell neoplasia (London & Seguin, 2003).

Other molecular studies are providing alternative indices for characteristics of mast cell differentiation, and thus prognosis. The proliferation index (based on Ki67 antigen as evaluated by immunohistochemistry with MIB-1 antibody) is significantly higher in grade III tumors (21.17%) than in grade II tumors (13.32%) and grade I tumors (5.95%) (Sakai et al., 2002). Silver stained nucleolar organizing regions (AgNORs) have successfully been used to predict prognosis in canine mast cell tumors, as higher counts are observed in poorly differentiated mast cell tumors when compared with well-differentiated mast cell tumors (Bostock et al., 1989; Kravis et al., 1996). One study comparing the average number of silver-stained nucleolar organizing regions (AoNORs) to the degree of differentiation of subcutaneous canine mast cell tumors reported that 73% of dogs with a high count (greater than 4.9) were lost from tumor-related causes, while none of the dogs with a low count (less than 1.7) was lost (Bostock et al., 1989). Matrix metalloproteinases 2 and 9 (enzymes that break down extracellular matrix) have been suggested to be an important factor in the pathogenesis

of canine mast cell tumors (Leibman et al., 2000). The presence of these gelatinases appears directly related to the degree of malignant behavior of these neoplasms. Additionally, mutations in the proto-oncogene *c-kit* (see introduction, p. 853) were significantly associated with higher grades of mast cell tumors (Zemke et al., 2002). Intensity of expression of KIT increases with increasing grade (Reguera et al., 2000). Increased cytoplasmic staining (but not membrane staining) for the KIT protein was correlated with an increased rate of local recurrence and decreased survival time in a recent study (Kiupel et al., 2004).

Palpation of mast cell tumors or trauma to the tumor masses may result in release of histamine and other vasoactive mediators from the mast cells, causing local edema and inflammation (Darier's sign) (Rabanal & Ferrer, 2002). Due to the ulcerogenic activity of mast cell vasoactive amines, gastric ulcers may be observed. Massive degranulation of neoplastic mast cells may occasionally occur, resulting in generalized edema, altered coagulability, severe hypotension, and/or terminal hemorrhagic gastroenteritis.

Histopathology

In general, canine mast cell tumors are nonencapsulated dermal and/or subcutaneous masses composed of round cells arranged in cords and sheets. The tumors rarely extend to the dermal–epidermal junction, and intraepidermal mast cell aggregates are not seen. The overlying epidermis is usually intact over small lesions and may be ulcerated over larger masses. The collagenous stroma varies from scant to abundant, and may appear edematous or hyalinized. Some tumors show extensive sclerosis and very low cellularity. In some masses, the collagen bundles appear hyalinized and moderately to markedly enlarged, resembling keloidal change of collagen seen with canine keloidal fibroma (see Chapter 27).

Variable numbers of eosinophils are present in almost all lesions. Eosinophils are either dispersed throughout the neoplastic tissue or form aggregates. Marked deposition of mucin and perivascular hyalinization are seen in response to eosinophilic infiltration. Foci of marked eosinophilic degranulation may entrap brightly eosinophilic collagen bundles to form flame figures, previously referred to as collagenolysis.

A recent study reports that nuclear area, nuclear mean diameter, and nuclear perimeter of the tumor cell are statistically different between grades II and III and between grades I and III mast cell tumors (Strefezzi et al., 2003). These results indicate that nuclear morphometry may assist in grading mast cell tumors; however, because there was no significant difference between grades I and II and because there was considerable overlap in the range of values for the grade I to III and II to III comparisons, this technique may not be of practical value.

Grade I mast cell tumor (Figure 36.1)

According to Patnaik's grading system, grade I mast cell tumors are small, fairly well circumscribed but nonencapsulated neoplasms confined to the interfollicular dermis (Patnaik et al., 1984). However, the authors have observed morphologically identical tumors that arise in the superficial subcutis (above the panniculus carnosus), or extend from the dermis into the superficial subcutis, but behave as Patnaik grade I tumors; this is supported by the AgNOR study, which included only subcutaneous mast cell tumors (see above) (Bostock et al., 1989).

Most grade I mast cell tumors have an intact overlying epidermis. Tumor cells are arranged in cords and loose sheets, and resemble normal granulated mast cells. They are characterized by discrete cell borders and cytoplasmic granules that appear gray-blue in color with hematoxylin and eosin stain. Toluidine blue or Giemsa stains are

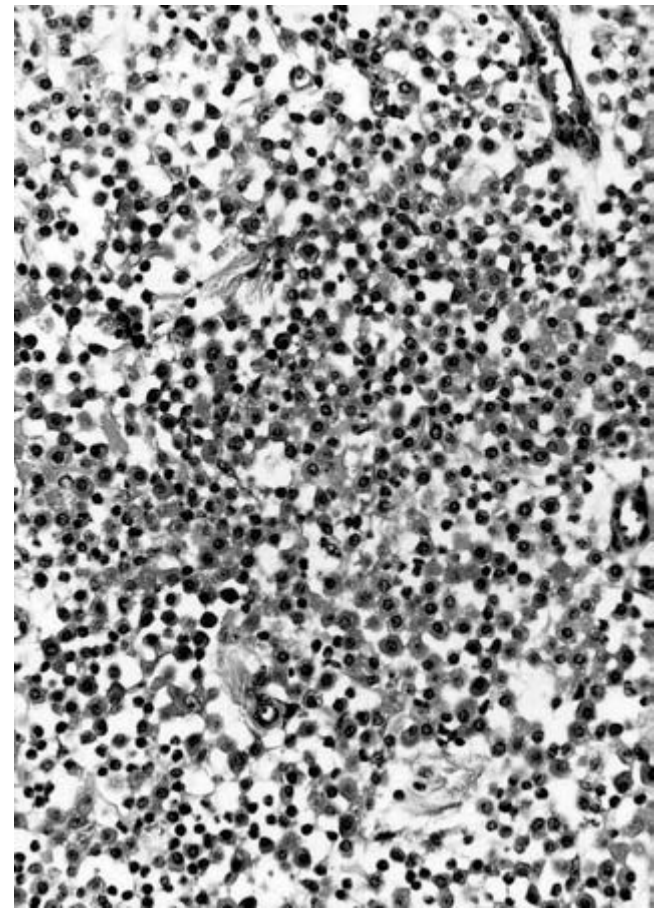


Fig. 36.1 Canine grade I mast cell tumor. Round cells with uniform nuclei and granular cytoplasm are arranged in cords and loose sheets.

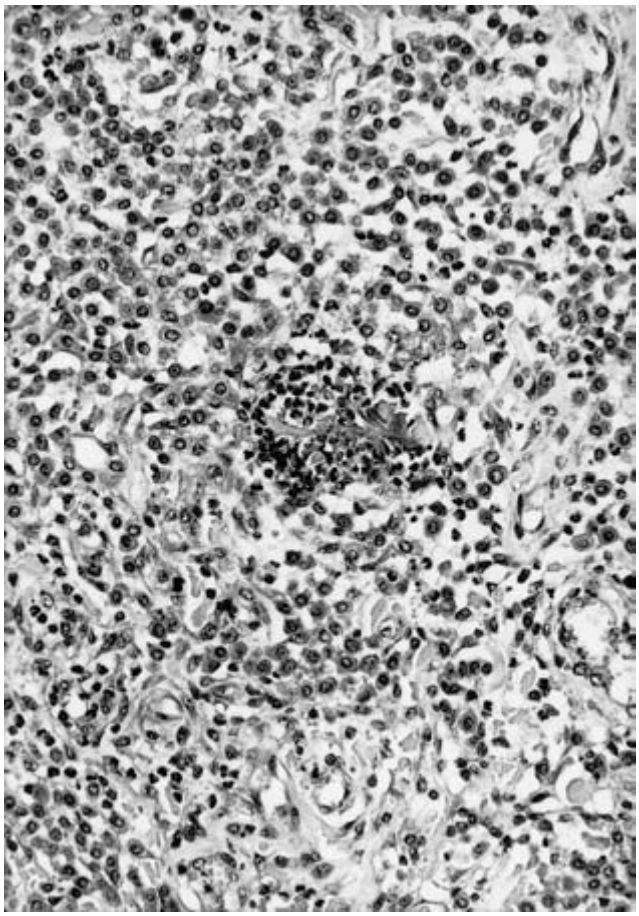


Fig. 36.2 Canine grade II mast cell tumor. Nuclei are larger and slightly more pleomorphic than in Fig. 36.1. Note central focus of eosinophilic degranulation around a collagen bundle (flame figure).

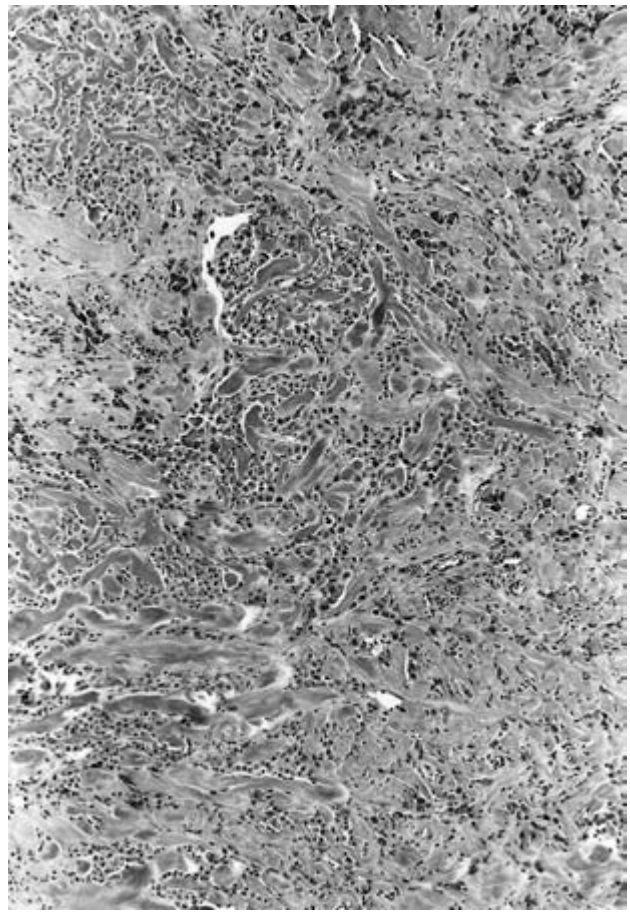


Fig. 36.3 Canine grade II mast cell tumor with keloidal change. Entrapped in the tumor mass are numerous thickened and hyalinized collagen bundles.

usually not necessary to demonstrate cytoplasmic granulation. Nuclei are small, round to oval, and have inconspicuous nucleoli. Mitotic figures are infrequent or absent. Most grade I mast cell tumors have a moderate to large number of eosinophils dispersed throughout the neoplastic tissue, and flame figures are not uncommon. Tumor necrosis is uncommon, but occasional well-differentiated mast cell tumors become extensively infarcted. The diagnosis of grade I mast cell tumors is straightforward, as the vast majority of proliferating mast cells are well differentiated and heavily granulated.

Grade II mast cell tumor (Figures 36.2 and 36.3)
Dermal grade II mast cell tumors are usually larger, deeper, and less well circumscribed than grade I neoplasms. By definition, Patnaik grade II tumors extend into the deep dermis and may involve the subcutis. The authors have observed morphologically well-differentiated tumors that arise in the superficial subcutis or extend from the deep dermis to the subcutis and behave as Patnaik grade I tumors. In the authors' opinion, small well-differentiated tumors should be placed in the lowest category of malignancy (grade I) independent of their location. Moreover, some tumors with grade II cytologic features are confined to superficial dermis. These observations are at odds with the current classification system (Patnaik et al., 1984).

In most grade II mast cell tumors, the neoplastic cells are larger, slightly more pleomorphic, and more sparsely granulated than grade I neoplasms. Nuclei are moderately enlarged, fairly uniform and vesicular, with small but obvious nucleoli. Mitotic activity varies from absent to moderately low. Cytoplasm is moderate and variably granulated. Eosinophils vary from few to numerous. Occasional lesions contain massive numbers of eosinophils and relatively few neoplastic mast cells limited to scattered cords and clusters.

The number of granulated tumor cells in grade II mast cell tumors varies. However, toluidine blue and Giemsa stains usually will identify typical metachromatic purple

intracytoplasmic granules. This will allow differentiation of grade II mast cell tumors from other cutaneous round cell tumors such as cutaneous nonepitheliotropic lymphoma, canine histiocytoma, transmissible veneral tumors, plasmacytomas, and Merkel cell tumors.

Grade III mast cell tumor (Figure 36.4)

Poorly-differentiated canine mast cell tumors are generally large, poorly-circumscribed, and extend deeply into the subcutis. Necrosis and ulceration are common secondary features. The authors have also observed smaller lesions confined to the dermis that have grade III cytologic features; these are not specifically addressed in the original Patnaik system, and their biologic behavior is unknown.

Round to polygonal or highly pleomorphic tumor cells are arranged primarily in solid sheets and nests. Cell margins are often not well defined. Nuclei are large, round to ovoid and vesicular, and have prominent nucleoli. Mitotic activity is moderate to high, and many atypical mitoses are present. The cytoplasm is pale; granulation is sparse to absent.

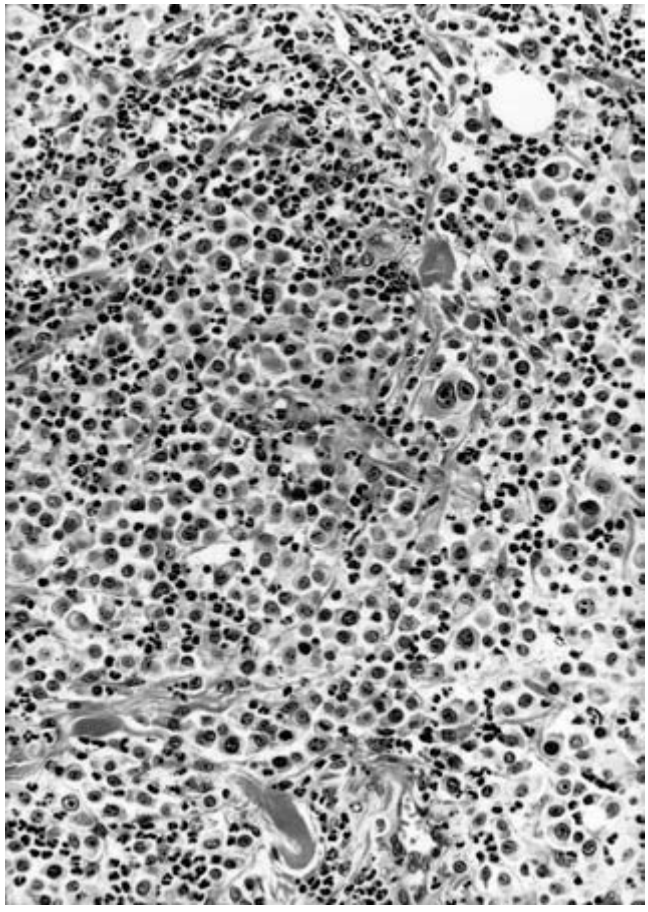


Fig. 36.4 Canine grade III mast cell tumor. Pleomorphic round cells lack obvious cytoplasmic granularity. Anisokaryosis is marked, and nucleoli are often prominent. Note the large population of eosinophils.

The authors also recognize a subset of poorly differentiated mast cell tumors that may mimic lymphoid tumors; these occur mostly at mucocutaneous junctions of the nose and lip. These mast cell tumors are characterized by smaller, uniform cells with minimal cytoplasm, and folded, euchromatic nuclei with small nucleoli; cytoplasmic granules are often indiscernible.

Giemsa and toluidine blue stains often will identify a few cytoplasmic metachromatic granules in at least a small subpopulation of neoplastic cells. The granules may be very small, requiring use of oil immersion for detection. Immunohistochemistry may be required for confirmation of mast cell origin (see below). The eosinophilotactic effects of the mast cells continue to decrease with increasing anaplasia, but eosinophils are still detectable in small numbers in most instances, and may be abundant in rare cases.

Grade III mast cell tumors usually are very poorly granulated, and hence must be differentiated from other cutaneous round cell tumors including nonepitheliotropic lymphomas, plasma cell tumors, canine histiocytomas, transmissible venereal tumors, round cell type histiocytic sarcomas, Merkel cell tumors, and balloon cell malignant melanomas. The presence of eosinophils is not a reliable differential feature of mast cell tumors, as cutaneous lymphomas can have variable numbers of reactive eosinophils. The tumor cells of nonepitheliotropic cutaneous lymphomas usually have less cytoplasm and round, occasionally cleaved nuclei. Plasma cell tumors are usually characterized by packeting of tumor cells, moderate pleomorphism, and the presence of binucleated and multinucleated tumor cells. The dense cytoplasmic RNA in plasma cells stains magenta with methyl green pyronine (MGP) stain; also, well-differentiated plasma cells are often present along the margin of the tumor mass. Canine histiocytomas have intraepithelial tumor aggregates, a feature not observed with mast cell tumors. Canine histiocytomas also have a top-heavy configuration and are composed of a relatively monomorphic cell population of round cells with round or indented nuclei. Transmissible venereal tumors have cytoplasmic vacuoles that can be easily appreciated in imprint preparations or aspirates. Moreover, eosinophils are not common in transmissible venereal tumors. Both regressing histiocytomas and transmissible venereal tumors are characterized by lymphoid infiltrates, a feature not usually seen in mast cell tumors. Histiocytic sarcomas primarily composed of round cells may mimic grade III mast cell tumors perfectly and immunohistochemistry may be required. The majority of histiocytic tumors, however, have at least a small subpopulation of tumor cells that are spindled. In

contrast to mast cell tumors, Merkel cell tumors are composed of tight packets of round cells separated by a delicate fibrovascular stroma. The argyrophilic cytoplasmic granules in Merkel cells are highlighted with Grimelius stain. Moreover, Merkel cell tumors have membrane bound dense core granules and tonofilament-like structures that are identified with electron microscopy. Fontana–Masson stain should reveal small amounts of melanin pigment in balloon cell melanomas.

Immunohistochemistry

Based on limited data, mast cells tumors are positive for the common leukocyte marker CD45 and variably retain their expression of the leukocyte antigens CD45RA and CD18 (Moore, P.F. & Affolter, V.K., unpublished data, 2003). Immunohistochemistry with antitryptase and antichymase antibodies may assist identification of mast cell origin (Fernandez et al., 2003). However, based on the experience of one author (V.K.A.), immunohistochemistry with antitryptase antibodies is often associated with background staining and occasional spurious staining of histiocytes.

Canine mast cell tumors express KIT (Reguera et al., 2000), and there is a direct correlation between advancing grade and the intensity of expression of this protein (see above). Thus the immunohistochemical detection of KIT is useful both for the identification of mast cell tumors as well as for prognostication. The proliferation index based on Ki67, also of prognostic value (see above), can be assessed by immunohistochemistry utilizing MIB-1 antibody.

Similar to mast cell tumors, lymphomas, plasma cell tumors, cutaneous histiocytomas, histiocytic sarcomas, and transmissible venereal tumors all express the common leukocyte antigen CD45. The vast majority of canine cutaneous lymphomas are composed of CD3+ T cells. Plasma cell tumors express CD45RA, immunoglobulins or immunoglobulin light chains, and may retain the expression of CD79a. Histiocytomas and histiocytic sarcomas are composed of CD18+, CD1+, CD11c+, MHC I+ dendritic cells; histiocytomas co-express E-cadherin. Transmissible venereal tumors coexpress CD45RA and may be positive for the adhesion molecule CD49d. Both melanocytic tumors and Merkel cell tumors lack expression of leukocytic proteins such as CD45 and CD18. Melanocytic tumors may be positive for S100, melanoma-associated antigen (Melan-A), melanoma-associated antigen recognized by T cells (MART-1), tyrosinase-related protein-2 (TRP-2), E-cadherin, tyrosinase, HMB45/gp100, and melanoma isoform of microphthalmia transcription factor (MITF-M). Merkel cell tumors are positive for pancytokeratins, neuron-specific enolase (NSE), synaptophysin, and chromogranin A.

FELINE MAST CELL TUMOR

Feline mast cell tumors include well-differentiated mast cell tumors, atypical poorly granulated mast cell tumors, also referred to as 'histiocytic mast cell tumors' (Wilcock et al., 1986), and pleomorphic mast cell tumors (Johnson et al., 2002). The authors choose to use the term 'atypical poorly-granulated mast cell tumor' instead of 'histiocytic mast cell tumor' (Wilcock et al., 1986), as the latter term may lead to confusion with true histiocytic proliferations. Histopathologic grading using the system of Patnaik et al. (1984) does not appear to have reliable prognostic significance in cats (Molander-McCrary et al., 1998). The presence of *c-kit* mutations similar to those in mast cell proliferations in humans and dogs was not documented in splenic mast cell tumors in cats (London, C.A., personal communication, 2002). Thus, the use of anti-KIT antibodies for diagnosis of cutaneous mast cell tumors in cats may not be of value, but has not been specifically investigated.

Clinical features

The incidence of feline mast cell tumors documented in most reports varies between about 8% and 15% of skin tumors (Macy & Reynolds, 1981; Buerger & Scott, 1987; Goldschmidt & Shofer, 1992). Another survey reported an incidence of 21% (Miller et al., 1991). Feline mast cell tumors present as discrete, firm, tan, alopecic papules and nodules, ranging from a few millimeters to 2 cm in diameter. Solitary or multiple nodules may develop. Larger lesions are often focally ulcerated. The head and legs are more often affected (Buerger & Scott, 1987; Goldschmidt & Shofer, 1992); the head, upper thigh, and dorsal tail were favored in another report (Macy & Reynolds, 1981). Atypical poorly granulated mast cell tumors, first documented as 'histiocytic mast cell tumors' (Wilcock et al., 1986), occur as grouped papular or nodular lesions, usually on the head.

Typical mast cell tumors are rarely observed in cats under 4 years of age. The average age of affected animals in all surveys is about 9 to 11 years. Atypical poorly-granulated mast cell tumors have been observed in 6-week-old to 4-year-old cats (Wilcock et al., 1986). Siamese cats are predisposed to develop mast cell tumors, including the atypical poorly-granulated mast cell tumors (Wilcock et al., 1986; Goldschmidt & Shofer, 1992). There is no apparent sex predilection. An association between feline immunodeficiency virus (FIV) infection and the development of multiple cutaneous mast cell tumors has been reported (Goldschmidt & Shofer, 1992).

Most reviews consider the majority of feline mast cell tumors to be largely benign neoplasms with low local recurrence rates (Wilcock et al., 1986; Buerger & Scott,

1987; Molander-McCrary et al., 1998; Johnson et al., 2002). Development of additional primary tumors at other cutaneous sites has been reported in 35% of affected cats in one survey; distant metastasis was not observed (Buerger & Scott, 1987). Atypical poorly-granulated mast cell tumors sometimes recur as multiple crops of miliary nodules, which eventually regress spontaneously (Wilcock et al., 1986). This behavior suggests a reactive hyperplasia rather than neoplasia. Most studies indicate that morphologic features usually associated with malignancy, such as pleomorphism and infiltrative growth, do not correlate with malignant behavior (Buerger & Scott, 1987; Molander-McCrary et al., 1998; Johnson et al., 2002), although high mitotic activity may be an exception (Johnson et al., 2002). It is thus apparent that feline cutaneous mast cell tumors, regardless of morphology, generally have a favorable prognosis despite their tendency to occur at additional skin sites. However, the authors have observed nodal mast cell infiltrates in rare cats with a history of cutaneous mast cell neoplasia. Rarely, numerous and widespread papular to small nodular cutaneous mast cell tumors may result from cutaneous spread of primary visceral mast cell neoplasia.

Histopathology

Well-differentiated mast cell tumor (Figure 36.5)

In general, feline mast cell tumors, as typified by the well-differentiated subtype, present as variably demarcated but unencapsulated dermal masses that may occasionally extend into the subcutaneous tissue. Usually, there is a narrow band of uninvolved superficial dermis (Grenz zone). Occasionally, tumor cells extend to the dermal–epidermal junction (Buerger & Scott, 1987). Single tumor cells may rarely be seen within the epidermis, but intraepithelial tumor aggregates are not observed (Buerger & Scott, 1987). Larger masses may be ulcerated. There is a delicate collagenous stroma. The number of admixed eosinophils varies, but is usually small. Nodular aggregates of lymphocytes may be observed.

The tumors are composed of solid sheets and cords of uniform round cells with discrete cytoplasmic margins. The cytoplasm is variably granular and may appear eosinophilic, grayish, or muddy. The granules, although often very fine, can usually be recognized without special stains. They are metachromatically purple with toluidine blue or Giemsa stains. The centrally or slightly paracentrally located nuclei are round and have moderately stippled chromatin. Nuclear pleomorphism is absent to minimal. Nucleoli are inconspicuous, and mitotic figures are rarely observed. Feline well-differentiated mast cell tumors are fairly characteristic, and differentiation from other round cell tumors is not problematic.

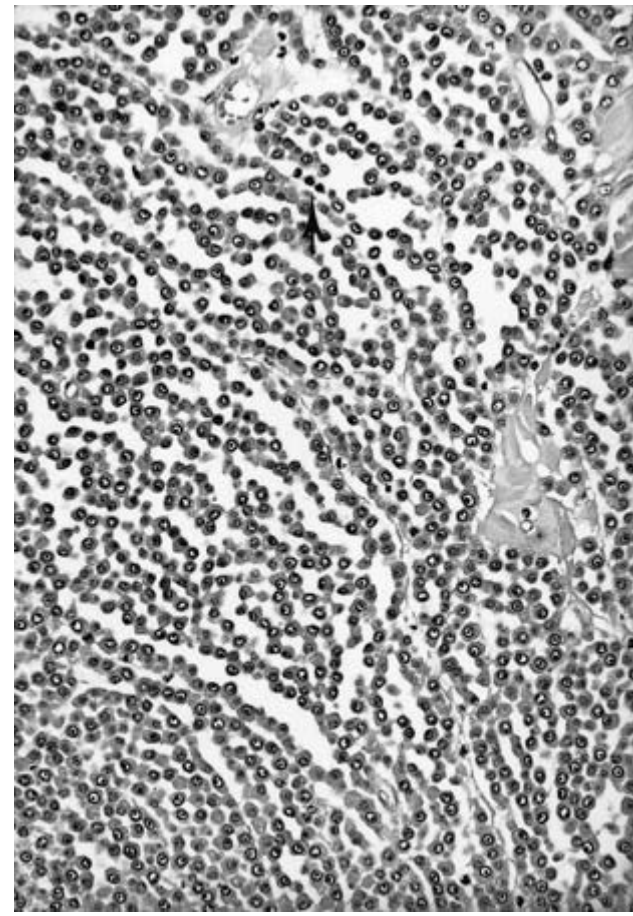


Fig. 36.5 Well-differentiated mast cell tumor in a cat. Uniform round cells with centrally-located nuclei and granular cytoplasm are arranged in cords and sheets. Note scattered eosinophils (arrow).

Atypical, poorly granulated ('histiocytic') mast cell tumor (Figure 36.6)

These mast cell proliferations are small, nonencapsulated, deep dermal and subcutaneous nodules comprising solid sheets of a mixture of large polygonal cells and slightly spindle-shaped cells, which may resemble histiocytes. The nuclei are large, vesicular and may be slightly indented. Nucleoli are small, and mitotic activity is low. The tumor cells have ample, pale eosinophilic cytoplasm, which may be vacuolated. There is equivocal cytoplasmic granularity when evaluated by hematoxylin and eosin (HE) stains. Most cells have orthochromatic (blue) granules when stained with Giemsa or toluidine blue stains. Some tumor cells have faint metachromatic purple granulation, indicating mastocytic origin. Moreover, these granules have features typical of feline mast cells when evaluated by electron microscopy (Wilcock et al., 1986). Eosinophils tend to be more numerous than in typical feline mast cell tumors.

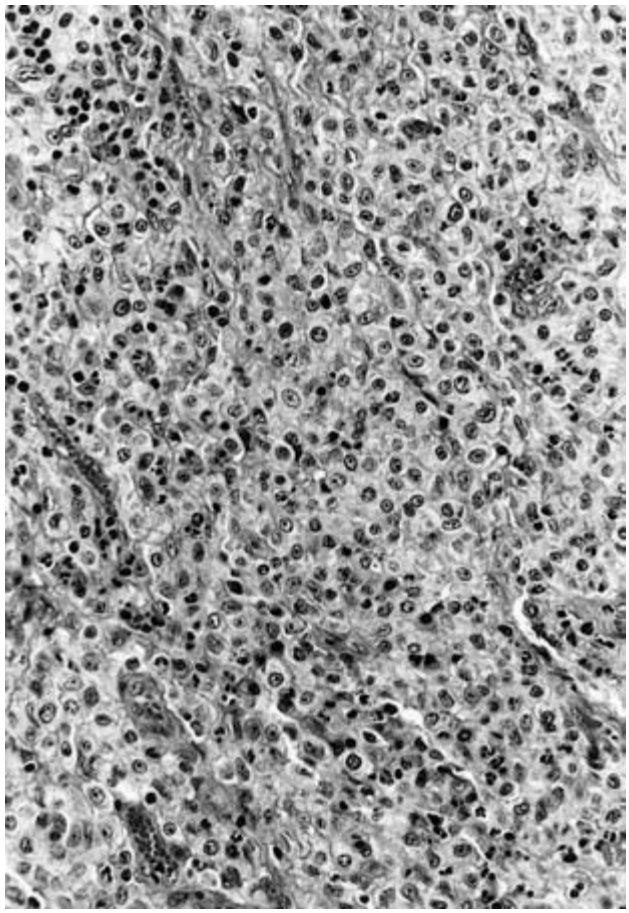


Fig. 36.6 Atypical, poorly granulated mast cell tumor in a cat. There are well-defined, large round tumor cells with vesicular, round to oval nuclei and amphophilic finely vacuolated cytoplasm with lack of cytoplasmic granules. Note resemblance to histiocytes.

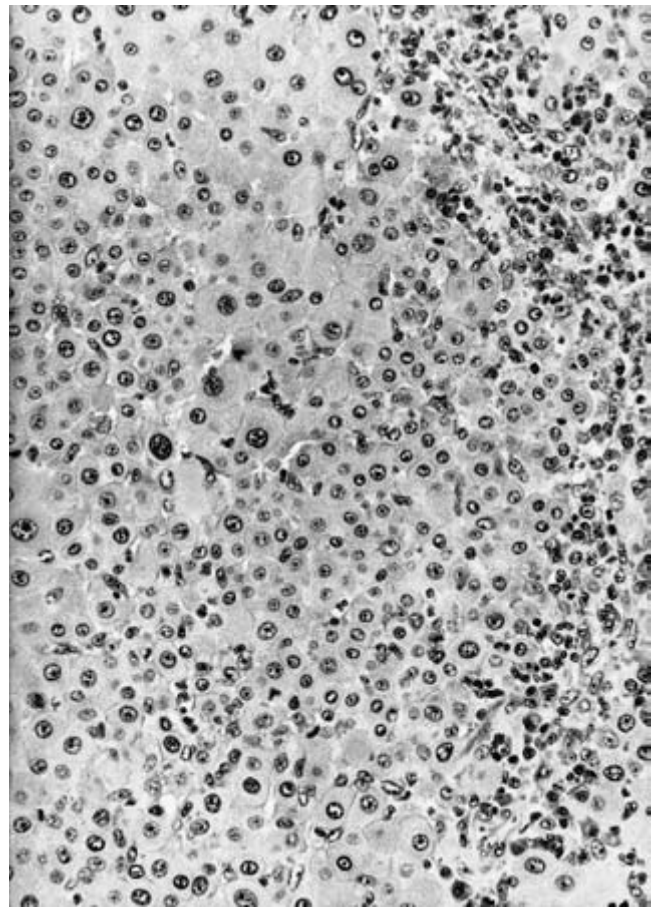


Fig. 36.7 Pleomorphic mast cell tumor in a cat. This tumor is composed of large pleomorphic cells which have slightly granular cytoplasm and moderate anisokaryosis. Note the infiltrate of eosinophils and lymphocytes at right edge.

Atypical, poorly-granulated mast cell tumors in cats must be differentiated from histiocytic lesions, in particular, feline progressive dendritic cell histiocytosis and cutaneous xanthomas. The presence of metachromatic granules, visualized by toluidine blue or Giemsa stains, confirms mast cell origin. Moreover, progressive histiocytosis generally lacks eosinophils, which are usually present in moderate numbers in atypical poorly-granulated mast cell tumors. Xanthomas may contain eosinophils as well, but they are usually associated with admixed lymphocytes and neutrophils. In contrast to atypical poorly-granulated mast cell tumors, cutaneous xanthomas are composed of macrophages that contain numerous, delicate, lipid vacuoles. Immunohistochemistry may be necessary to differentiate between histiocytic proliferations and atypical poorly-granulated mast cell tumors (see below).

Pleomorphic mast cell tumor (Figure 36.7)
A small percentage of feline mast cell tumors exhibit marked pleomorphism. These poorly-differentiated neoplasms are usually larger, less discrete, and infiltrate more deeply into the underlying tissue. Partial or total loss of cytoplasmic granulation is evident with routine HE stains as well as with toluidine blue and Giemsa stains. The few metachromatic granules that may be present are very delicate, and oil immersion may be required for their detection. The nuclei are large and often eccentric in location, and they have variable chromatin patterns. Nucleoli are single and vary from inconspicuous to prominent. Mitotic activity may be moderate to high. Tumor giant cells with single multilobulated nuclei or occasional multiple nuclei may be seen.

Pleomorphic feline mast cell tumors should be differentiated from other cutaneous round cell tumors, includ-

ing nonepitheliotropic lymphomas, plasma cell tumors, some amelanotic melanomas, and feline progressive dendritic cell histiocytosis. In the majority of cases, Giemsa or toluidine blue stain reveals metachromatic granulation in at least a small subpopulation of tumor cells. Nonepitheliotropic lymphoma is mostly composed of round cells with a high nuclear to cytoplasmic ratio, and nuclear cleavage may be seen. Plasma cell tumors have less abundant, glassier cytoplasm; the high concentration of cytoplasmic RNA stains magenta with methyl green pyronine (MGP) stain. Small numbers of well-differentiated plasma cells can usually be identified, and amyloid may be present. Occasional amelanotic melanomas in cats have abundant, eosinophilic cytoplasm and eccentric, pleomorphic nuclei, but a few melanin granules can usually be demonstrated by Fontana–Masson staining. Feline progressive dendritic cell histiocytosis is characterized by proliferations of large cells with abundant, pale eosinophilic cytoplasm, and often indented nuclei.

Immunohistochemistry

The use of anti-KIT antibodies for feline cutaneous mast cell tumors has not been specifically investigated but may not be of value, as *c-kit* mutations were not found in splenic mast cell tumors in cats (London, C.A., personal communication, 2002). Moreover, the protease content of feline cutaneous mast cells has not been evaluated, so the value of immunohistochemistry for tryptase and chymase in identifying poorly differentiated mast cell proliferations in cats is still undetermined.

Pleomorphic feline mast cell tumors can be identified by using immunohistochemistry to rule out other round cell tumors. Feline cutaneous lymphomas evaluated to date are composed of CD3+ T cells. Feline plasmacytomas have not been completely evaluated for expression of leukocyte antigens such as CD45RA and CD79a, but the presence of intracytoplasmic immunoglobulins can be identified. Feline progressive histiocytosis is composed of CD18+, CD1+, MHC II+ cells, a phenotype consistent with dendritic antigen-presenting cells. Dermal amelanotic melanocytic tumors lack expression of the common leukocyte antigens (CD45, CD18) and are usually positive for S100. Melanoma isoform of microphthalmia transcription factor (MITF-M) appears to be strongly expressed in feline melanomas.

CUTANEOUS MASTOCYTOSIS

Based on the age of onset, mastocytosis in humans is usually divided into pediatric and adult forms (Longley & Metcalfe, 2000; Valent et al., 2001; Wolff et al., 2001). Cutaneous mastocytosis in humans ranges from benign self-limiting mast cell hyperplasia to progressive, malignant disease. Most pediatric cases of cutaneous mastocytosis do not include systemic involvement and, in general, have a higher incidence of spontaneous regression. Some forms of cutaneous mastocytosis in humans are associated with mutations of the *c-kit* oncogene (Longley & Metcalfe, 2000).

In humans, cutaneous mastocytosis presents as either urticaria pigmentosa (also referred to as maculopapular cutaneous mastocytosis) or as diffuse cutaneous mastocytosis (Valent et al., 2001). Urticaria pigmentosa is characterized by nodules or plaques, and may be associated with telangiectasia. Diffuse mastocytosis is associated with diffusely thickened skin, which may have a smooth surface.

Although involvement of the skin may occur, most case reports of mastocytosis in dogs and cats describe systemic mastocytosis affecting several internal organs with or without mastocytemia (Orkin, 1967; Confer et al., 1978; Weller, 1978; O'Keefe et al., 1987). A few cases of primary papular cutaneous mastocytosis resembling urticaria pigmentosa in humans have been described in dogs and cats (Davis et al., 1992; Vitale et al., 1996). Clark also described a case of urticaria pigmentosa in a dog (Gross & Schick, 1992). One case of cutaneous mastocytosis reported in a cat is more consistent with diffuse mastocytosis as described in humans (Brown & Chalmers, 1990).

Clinical features

Urticaria pigmentosa/papular mastocytosis

(Figure 36.8 through 36.10)

Urticaria pigmentosa is a rare disease in dogs and cats (Davis et al., 1992; Gross & Schick, 1992; Vitale et al., 1996). The dogs present with partially erythematous small papules; some papules progress to plaques. There may be occasional wheals. Rarely, hemorrhagic bullae develop. The lesions are observed on the head, neck, trunk, perineum, and legs. Lymphadenopathy may be present. Dermatographism occurs, as manipulation induces erythema, edema, and subsequent induration (Darier's sign).

Urticaria pigmentosa has been described in a Newfoundland, Cocker Spaniel, Labrador Retrievers, and a Jack Russell Terrier (Davis et al., 1992; Gross & Schick, 1992; Vitale et al., 1996), but the authors have observed it in other breeds, including Chinese Shar Peis. Affected dogs are mostly under 1 year of age.

Feline urticaria pigmentosa has been reported in three related Sphinx cats (Vitale et al., 1996). Partially symmetrical, coalescing, dark brown macules with erythema and miliary, crusted papules were noted on the ventrum,

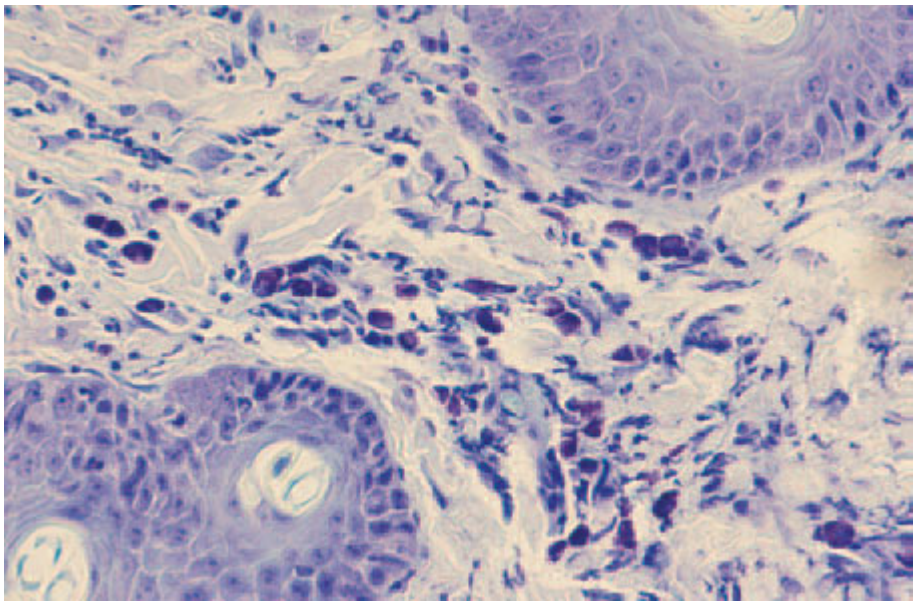


Fig. 36.8 Early urticaria pigmentosa in a cat. A Giemsa stain shows metachromatic granules in the cytoplasm of the well-differentiated mast cells.

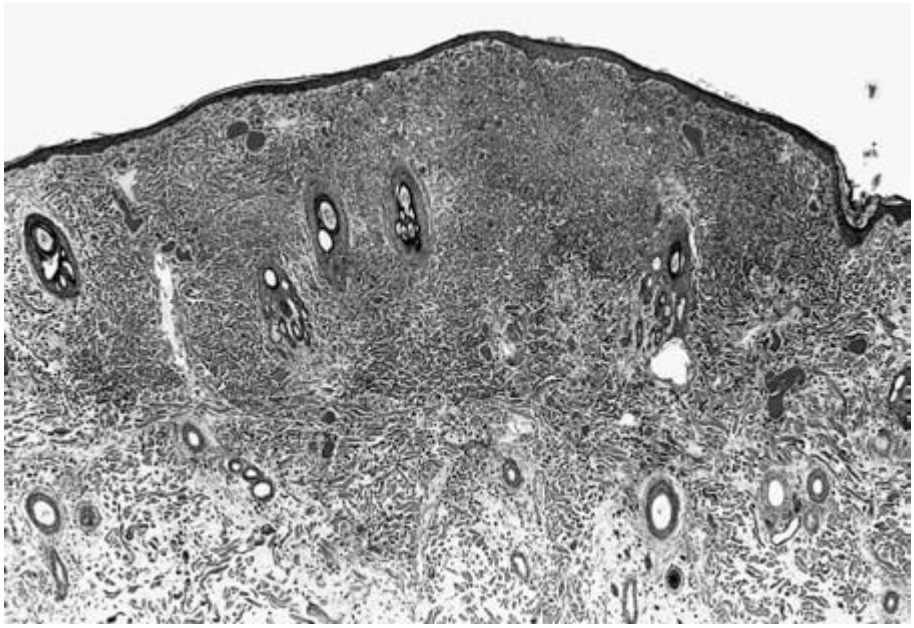


Fig. 36.9 Urticaria pigmentosa/papular mastocytosis in a puppy. The small dermal nodule is composed of densely packed mast cells.

chest, neck, and extremities. The lesions were arranged in a strikingly linear fashion and the skin was thickened and lichenified. Dermatographism was not present. Generalized pruritus was observed as well as moderate lymphadenopathy. The age of the three Sphinx cats ranged from 8 months to 2.5 years. The fact that all three cats had the same grandsire may indicate a hereditary component to feline urticaria pigmentosa.

Similar to urticaria pigmentosa in infants, early onset urticaria pigmentosa in dogs may regress spontaneously leaving hyperpigmented macules. Other cases require continuous antihistamine therapy. However, progression from urticaria pigmentosa to systemic mastocytosis may occur and has been observed in a Labrador Retriever by one author (T.L.G.) (Gross & Schick, 1992). The lesions in the Sphinx cats regressed completely with antihistamine therapy. Progression to systemic lesions was not observed.

Diffuse cutaneous mastocytosis

A single case was reported in a 1-year-old domestic shorthaired cat (Brown & Chalmers, 1990). Generalized, miliary, crusted papules with alopecia and erosions were seen. The skin was diffusely lichenified and thick skinfolds were noted. The lesions were pruritic. There was moder-

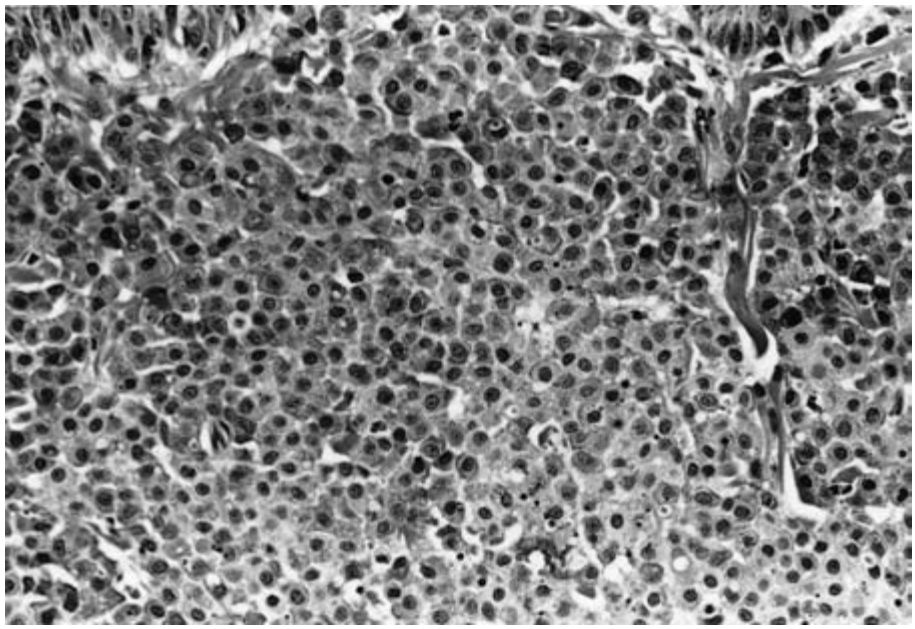


Fig. 36.10 Higher magnification of urticaria pigmentosa/papular mastocytosis of Fig. 36.9 showing well differentiated mast cells with heavily granulated cytoplasm.

ate generalized peripheral lymphadenopathy. Mast cells were seen in the buffy coat, but involvement of internal organs could not be found at the time of evaluation. Euthanasia precluded determination of the natural clinical course.

Histopathology

Urticaria pigmentosa/papular mastocytosis

The lesions of urticaria pigmentosa are characterized by a moderate to severe, perivascular to diffuse infiltrate of fairly monomorphic, well-differentiated mast cells that may extend from the superficial to the deep dermis. The infiltration is poorly demarcated and may extend into the subcutis. A perivascular arrangement of mast cells may be seen at the margins of the lesions. The lesional mast cells are characterized by a central nucleus and granular cytoplasm. Toluidine blue and Giemsa stains demonstrate the typical metachromatic character of the cytoplasmic granules. Mitotic figures are rare. Small numbers of eosinophils and neutrophils are admixed, and lymphoid aggregates may be present.

With lymph node involvement, numerous mast cells are detected in the subcapsular sinusoids and the paracortex. The migrating mast cells are well differentiated and have obvious granulated cytoplasm.

Urticaria pigmentosa is characterized by well-differentiated mast cells and definitive diagnosis is usually not problematic. Clinical characteristics should permit differentiation of urticaria pigmentosa in dogs from small dermal grade I mast cell tumors. Mild early changes, characterized by predominantly perivascular mast cell aggregates, should be differentiated from a hypersensitivity reaction, which may contain numerous mast cells as well, particularly in cats.

Diffuse cutaneous mastocytosis

The case reported in a domestic shorthaired cat was described as a diffuse dermal or superficial band-like infiltration of moderately pleomorphic polygonal cells with large vesicular nuclei (Brown & Chalmers, 1990). The cells had abundant eosinophilic cytoplasm, which contained metachromatic purple granules with toluidine blue and Giemsa staining. Binucleated and multinucleated mast cells were common, and occasional mitotic figures were seen. The surrounding dermal and subcutaneous tissue was edematous. Lymph node involvement was characterized by subcapsular, paracortical, and medullary infiltration of similar moderately pleomorphic mast cells. Diffuse cutaneous mastocytosis is differentiated from urticaria pigmentosa by a pleomorphic cell type, in contrast to the well-differentiated infiltrate of the latter.

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Chapter 37

Lymphocytic tumors

Skin tumors of lymphocytic origin in humans include neoplastic and reactive lesions that are composed of skin-seeking lymphocytes (Le Boit & McCalmont, 1997). These cells are an essential component of the skin-associated lymphoid tissue (SALT) (Bos & Kapsenberg, 1990). They express the cutaneous lymphocyte antigen (CLA), a glycoprotein that facilitates the binding of lymphocytes to E-selectin on high endothelial venules in the skin (Picker et al., 1990, 1991). Cutaneous lymphocytic proliferations in humans have been categorized as: (1) epitheliotropic lymphoma, also referred to as mycosis fungoides; (2) Sézary syndrome, which is a leukemic variant of epitheliotropic lymphoma; (3) nonepitheliotropic lymphoma, which also includes vasotropic lymphoma (also referred to as lymphomatoid granulomatosis) and intravascular large B cell lymphoma; (4) cutaneous lymphocytosis (also referred to as lymphocytoma cutis, cutaneous lymphocytic hyperplasia, and pseudolymphoma); and (5) cutaneous (extramedullary) plasmacytoma or plasma cell tumor (Le Boit & McCalmont, 1997).

Histologic differences between reactive and neoplastic lymphocytic proliferations are not always evident. Evaluation of lesions for expansion of clonal lymphocytic populations can be achieved by amplification of variable regions of immunoglobulin heavy chain (IgH) for B cells and of T cell receptors for T cells using polymerase chain reaction (PCR) or Southern blotting (Bakels et al., 1997; Wood, 2001; Holm et al., 2002). The presence of a clonal lymphocytic population is supportive of a neoplastic proliferation (Bakels et al., 1997; Wood, 2001), while reactive lymphocytic infiltrates are usually composed of polyclonal lymphocytic populations. However, clonal lesions with subsequent spontaneous regression have been reported to occur in humans within the context of a reactive process such as drug reaction or lichen planus (Bakels et al., 1997; Ceballos et al., 2002; Holm et al., 2002).

As reviewed by Moore and Olivry (1994), cutaneous lymphocytic proliferations represent about 3% to 8% of all canine lymphomas and about 0.2% to 1.7% of feline lymphomas, with the overall incidence of lymphoma in cats, irrespective of location, being about twice as high as in dogs. The role of feline leukemia virus (FeLV) in feline leukemia and lymphoma has been well established. The presence of FeLV was demonstrated in a cat with epitheliotropic lymphoma (Tobey et al., 1994). A canine retrovirus has been isolated from a leukemic dog (Safran et al., 1992), but there is no clear indication of retroviral involvement in canine cutaneous lymphoma (Moore & Olivry, 1994).

The majority of feline and canine lymphocytic proliferations in the skin are composed of T cells. B cell lymphomas are extremely rare. Most cutaneous B cell proliferations present as plasma cell tumors. Lymphocyte subpopulations express different cell surface antigens (Table 37.1), and hence can be identified by their immunophenotype using immunohistochemistry (Moore et al., 1998). A limited panel of antibodies is currently available to identify and characterize lymphocytes and plasma cells in formalin-fixed, paraffin-embedded tissues (Table 37.1). Immunohistochemical evaluation of fresh, snap-frozen tissue allows use of a more extensive panel of antibodies, as epitopes are not denatured by the process of fixation. Clonality testing of T cell and B cell populations by PCR is becoming more accessible in veterinary medicine, which should continue to provide more in depth assessment of lymphocytic proliferations of dogs and cats (Dreitz et al., 1999; Vernau & Moore, 1999).

CUTANEOUS PLASMACYTOMA

(Synonym: plasma cell tumor)

Extramedullary plasma cell tumors in humans may develop in various organs, including the skin and subcutis (Grogan et al., 2001). Cutaneous plasmacytomas have been recognized in dogs and cats (Carothers et al., 1989; Schrenzel et al., 1998; Majzoub et al., 2003). The etiology of plasmacytomas is unknown. In murine plasmacytoma models, a direct relationship between chronic persistent antigen-induced inflammation or administra-

Cell type	Phenotype in	
	Fresh-frozen tissue	Formalin-fixed tissue
T cells	CD45 [CD45RA]* CD18 CD3 CD5 CD4 (helper cells) CD8 (cytotoxic cells); αα or αβ T cell receptor (TCRαβ or TCRγδ)	CD45 [CD45RA]* CD18 CD3ε
B cells	CD45 CD18 CD79a [CD45RA]* CD21	CD45 CD18 CD79a [CD45RA]*
Plasma cells	CD45 [CD18]* CD45RA* Immunoglobulin (IgG, IgA, IgM) [CD79a]*	CD45 [CD18]* CD45RA* Immunoglobulin (IgG, IgA, IgM) [CD79a]*

Table 37.1 Phenotypic characteristics of T cells, B cells, and plasma cells.

*[Incidence of expression varies]

tion of immunomodulatory drugs and tumorigenesis has been documented (Potter et al., 1994). Canine plasmacytomas were reported to occur in the context of otitis and periodontal disease in dogs (Schrenzel et al., 1998).

Clinical features

Canine cutaneous plasmacytomas have been reported with increasing frequency, and are considered to represent a significant portion of canine cutaneous round cell tumors (Schrenzel et al., 1998). The incidence of plasmacytomas is reported to be 1.5% of all canine skin tumors (Goldschmidt & Shofer, 1992). Cutaneous plasmacytomas are rare in cats.

In most instances, canine cutaneous plasmacytomas develop as solitary lesions, but multiple masses may occur, and may be numerous in some cases (Rakich et al., 1989). Plasmacytomas are sessile, firm, raised dermal masses measuring less than 2 cm in diameter. There is rare extension to the subcutis. The surface is either sparsely haired or alopecic, but rarely ulcerated. Mucosal plasmacytomas have an intact surface epithelium and are either pedunculated or have a broad base. Common locations are the pinnae, lips, digits, chin, and oral cavity. In one study of canine plasmacytomas, the legs and trunk were common sites (Cangul et al., 2002), while in another, the paws and oral mucosa were affected most often (Platz et al., 1999). Masses of the pinna may be observed in dogs with chronic otitis, and oral masses mainly involve the maxillary gingiva, particularly in dogs with chronic periodontal disease (Schrenzel et al., 1998).

A case resembling human systemic plasmacytosis was described in a Keeshond with edematous, alopecic, erythematous, and crusting lesions of the rear legs, groin, scrotum, and chest (Gookin et al., 1998). Regional lymphadenopathy and polyclonal gammopathy were observed; Bence–Jones proteins and osteolysis (as seen in multiple myeloma) were not discovered.

In cats, solitary or multiple cutaneous or subcutaneous plasmacytomas have been documented on the paws, thorax, neck, shoulder, tail, metatarsus, and nose (Majzoub et al., 2003), but may also develop on the face, in particular lip and chin, as well as in the oral cavity. One reported case of feline extramedullary plasmacytoma included multiple masses in the subcutis; subsequently internal lesions developed (Carothers et al., 1989).

Plasmacytomas have been seen in dogs between 4 and 13 years of age, with an average age of approximately 10 years. Some surveys did not observe an apparent breed predilection (Rowland et al., 1991; Schrenzel et al., 1998). However, others report Cocker Spaniels, Airedale Terriers, Kerry Blue Terriers, Scottish Terriers, and Standard Poodles to be predisposed (Rakich et al., 1989; Goldschmidt & Shofer, 1992; Platz et al., 1999). Some studies report a predisposition for males (Breuer et al., 1993; Platz et al., 1999; Cangul et al., 2002), while

another source does not indicate any sex predisposition (Goldschmidt & Shofer, 1992).

Feline plasmacytomas are usually seen in older cats, and have been reported in cats between 6 and 20 years of age (Majzoub et al., 2003). There is no breed predilection based on the small number of cases described (Breuer et al., 1993; Majzoub et al., 2003). Some studies report that male cats appear to be affected more often than female cats (Lucke, 1987; Breuer et al., 1993; Day, 1995). However, others do not report a sex predilection (Goldschmidt & Shofer, 1992; Majzoub et al., 2003).

Most cutaneous plasmacytomas are benign lesions, and surgical excision is usually curative. The authors suspect that digital plasmacytomas, as well as plasmacytomas of the oral cavity or subcutis may be more behaviorally aggressive; this has not been documented in the literature, however. Occasionally, solitary or multiple cutaneous plasmacytomas exhibit malignant behavior and may metastasize to internal organs.

Recent studies describe six histologic subtypes of plasmacytomas in dogs (Platz et al., 1999; Cangul et al., 2002) and four histologic subtypes in cats (see below) (Majzoub et al., 2003). There was no reported correlation in dogs between cell type of plasmacytoma and prognosis in one study (Cangul et al, 2002). In a second study, three of 14 polymorphous-blastic type tumors demonstrated metastasis to regional lymph nodes (Platz et al., 1999).

Recent studies have assessed the proliferative rates of canine plasmacytomas, considered of prognostic relevance in human tumor studies, by immunohistochemistry for the nonhistone nuclear antigen Ki67 (Platz et al., 1999) and the proto-oncogene cyclin D1 (Cangul et al., 2002). There was no statistical correlation between cell type and the presence of the cell proliferation marker Ki67 assessed by MIB1 monoclonal antibody (Platz et al., 1999). Staining for cyclin D1 was sparse to negative in all but one tumor in another study; in contrast, three of six cases of multiple myeloma were positive (Cangul et al., 2002). Similar feline studies have not been performed.

An association with systemic plasma cell dyscrasia is considered to be uncommon in dogs (Rakich et al., 1989); two out of 75 dogs in that study had multiple myeloma; monoclonal gammopathy was not investigated. Similar to multiple myeloma in humans (Grogan et al., 2001), a reported feline extramedullary plasmacytoma with subsequent internal metastasis was associated with a monoclonal gammopathy (Carothers et al., 1989); an additional cat reported separately had a solitary cutaneous plasmacytoma that progressed to multiple myeloma (Patel et al., 2003). Conversely, dissemination of multiple myeloma to multiple extraosseous cutaneous sites also has been reported in a cat (Patel et al., 2003).

Histopathology (Figures 37.1 through 37.6)

Canine cutaneous plasmacytomas are usually circumscribed but nonencapsulated uni- or multinodular masses that are mostly confined to the dermis; some lesions have poorly defined margins, and some extend into the subcutis. There is usually a narrow but distinct zone of uninvolved superficial dermis (Grenz zone), but tumor cells will occasionally extend to the epidermis. The neoplasms are composed predominantly of round to polygonal cells arranged in sheets and tightly packed nests. Occasionally, there is a pseudoglandular arrangement of cells with erythrocytes in the center. At the periphery of the neoplasm the plasmacytic character of the tumor cells is more apparent, and the cells are smaller, less cohesive, and are arranged in rows. The tumor nests are separated by a delicate, interlaced fibrovascular stroma. Reticulin fibers, which can be demonstrated with Gomori's or Wilder's silver stains, incompletely surround the plasma cell aggregates.

Marked variation in tumor cell differentiation is common, and anisocytosis and anisokaryosis are usually

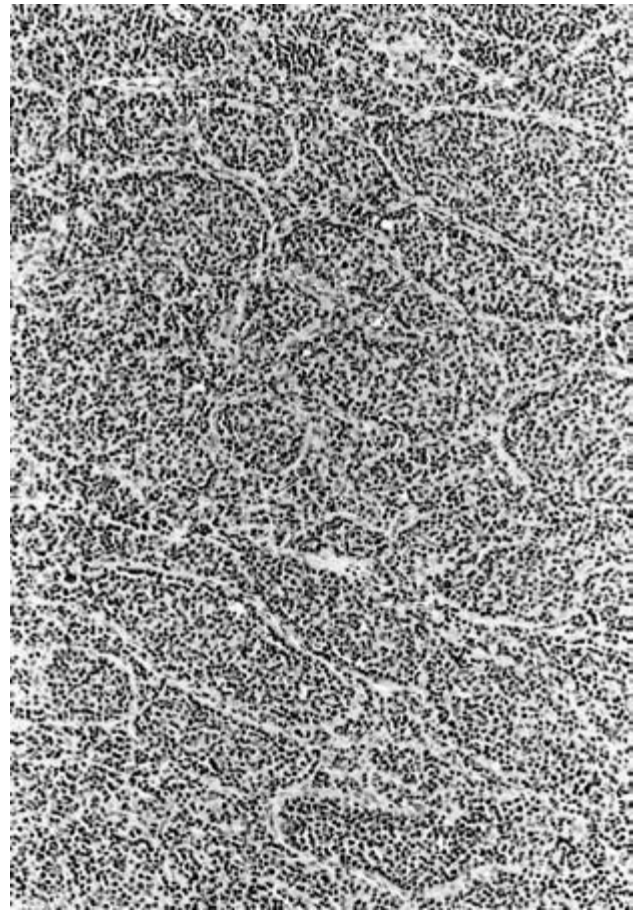


Fig. 37.1 Plasmacytoma in a dog featuring tumor cells arranged in packets and separated by a fibrovascular stroma.

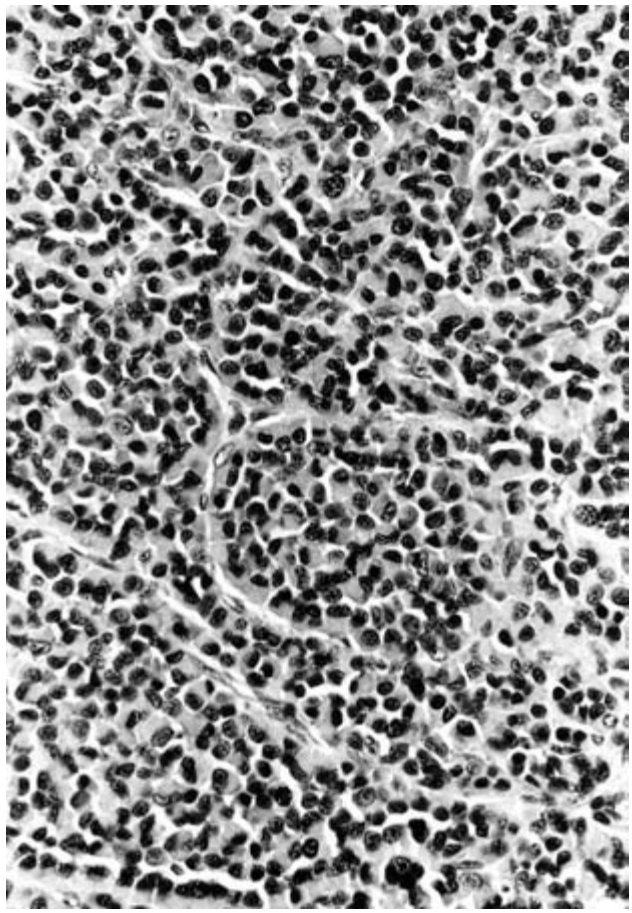


Fig. 37.2 Higher magnification of plasmacytoma in a dog composed of fairly well differentiated plasma cells characterized by eccentric nuclei and glassy pale cytoplasm.

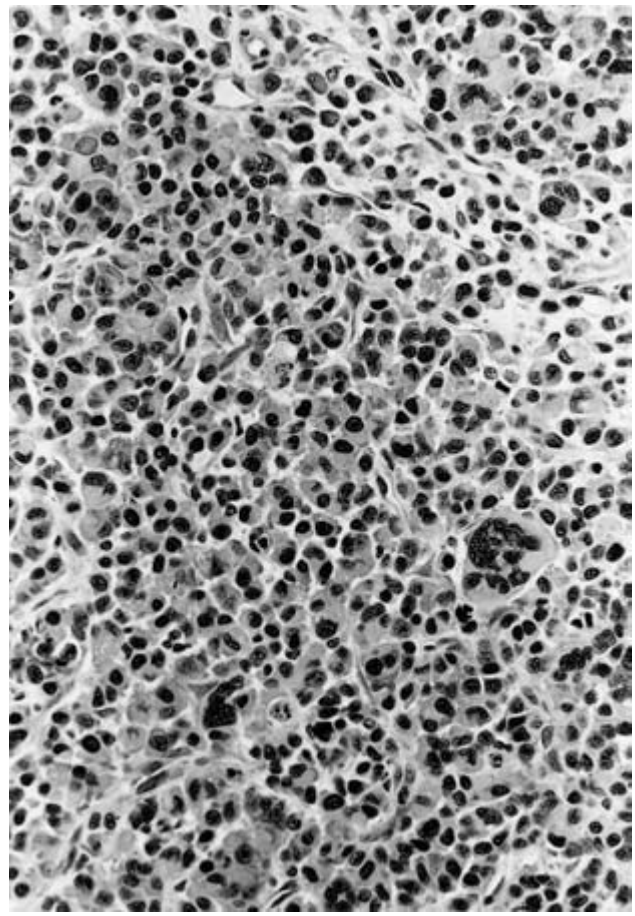


Fig. 37.3 Plasmacytoma in a dog demonstrating anisokaryosis, including large, often lobulated hyperchromatic nuclei and several multinucleated tumor cells.

noted. The majority of the tumor cells are round with discrete borders. The cells are further characterized by moderate to abundant cytoplasm, which has a glassy, eosinophilic or amphophilic appearance. Occasionally, the cytoplasm has a granular quality. The nuclei are situated centrally or paracentrally. They may be round, crescentic or irregular, and may have single or multiple nucleoli; vesicular or stippled, dense chromatin is observed. Mitotic activity ranges from one to nine mitotic figures per 10 high power fields (40×). Multinucleated cells, or cells with enlarged, lobulated, often hyperchromatic nuclei, usually are seen and are more abundant in poorly differentiated lesions.

The smaller peripheral cells often exhibit typical plasmacytic differentiation, characterized by a moderate amount of pale or muddy purple cytoplasm and eccentric nuclei with peripherally clustered chromatin. Perinuclear halos are evident frequently. Karyorrhexis and pyknosis are more common in areas with well-differentiated tumor cells. The high density of RNA in plasma cells can be readily demonstrated in most plasmacytomas with methyl green pyronine (MGP) stain, particularly within the peripheral well-differentiated population. The positive reaction creates magenta staining of the cytoplasm, in particular around the perinuclear halo. In rare neoplasms there may be partial clear cell change characterized by swollen, pale cytoplasm; this alteration may represent a degenerative process. Reactive infiltrates of histiocytes and lymphocytes usually are more prominent in poorly differentiated plasmacytomas. Occasionally, a few eosinophils can be seen.

Two recent studies present subclassifications of canine plasmacytomas based on the variable morphologic features described above (Platz et al., 1999; Cangul et al., 2002). Plasmacytomas are described as hyaline type, mature type, cleaved type, asynchronous type, and polymorphous-blastic type (Platz et al., 1999; Cangul et al., 2002). Features of different subtypes can be found within a particular tumor mass. The hyaline type is characterized by tumor cells with somewhat pale eosinophilic cyto-

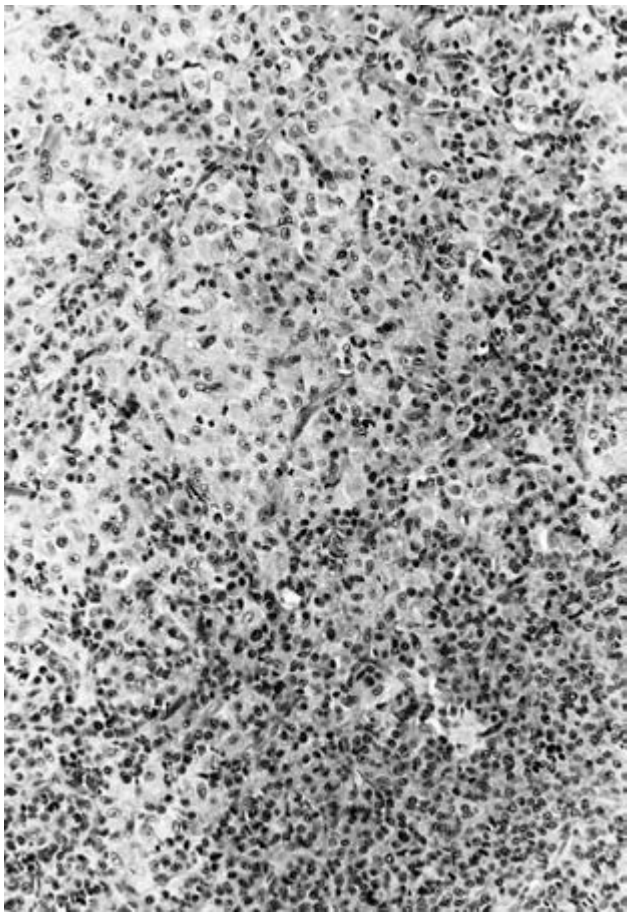


Fig. 37.4 Plasmacytoma in a dog. The upper aspect features clear cell change of the tumor cells, characterized by pale cytoplasm.

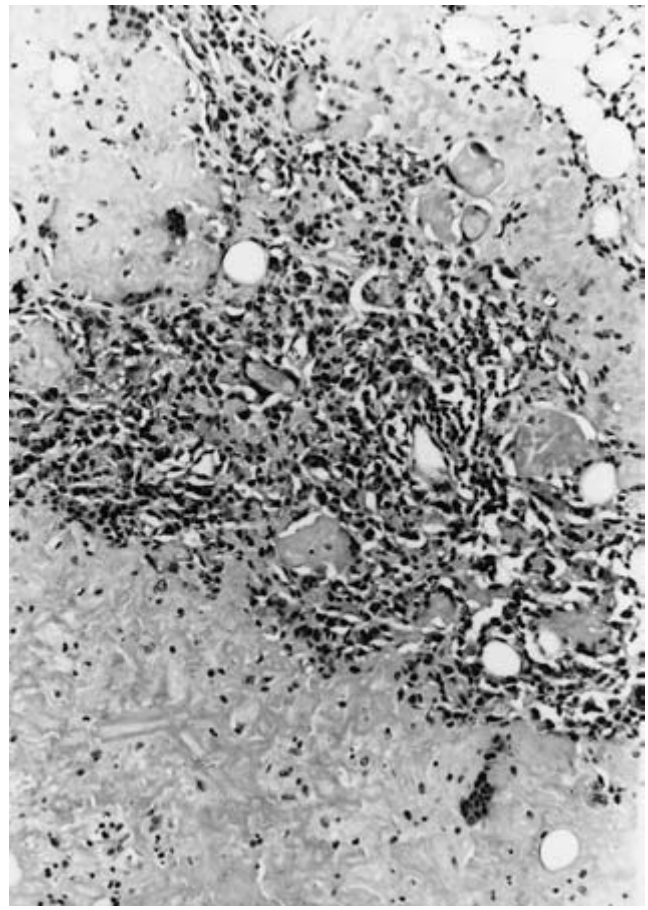


Fig. 37.5 Plasmacytoma in a dog. Well-differentiated plasma cells are surrounded by large deposits of amyloid. Note large foreign body-type giant cells.

plasm, sometimes featuring sickle-shaped nuclei; the mature type is composed of cells resembling mature plasma cells with darker cytoplasm (Platz et al., 1999; Cangul et al., 2002). Both of these types have low numbers of multinucleated tumor cells. The cleaved type is characterized by cells with convoluted nuclei, slightly granular cytoplasm, and a moderate number of multinucleated tumor cells. The asynchronous type describes tumor cells that have a nuclear to cytoplasmic asynchrony in maturation, but retain the perinuclear halo; the nuclei are blastic. The polymorphous-blastic type is characterized by marked cellular pleomorphism, lack of a perinuclear halo, and a high mitotic rate. The number and size of giant cells increase as tumor types become more pleomorphic. Oral plasmacytomas may reveal an additional type referred to as monomorphous-blastic type; the cells are large with euchromatic nuclei and small, centrally located nucleoli (Cangul et al., 2002).

The single case of canine systemic plasmacytosis with polyclonal gammopathy was characterized by severe perivascular infiltration of the skin by mature plasma cells. Plasmacytosis of the affected lymph nodes was found (Gookin et al., 1998).

Feline cutaneous plasmacytomas present with histologic features similar to plasmacytomas in dogs. Similar to dogs, a recent review categorizes feline plasmacytomas based on the degree of differentiation, as mature plasmacytomas, cleaved plasmacytomas, asynchronous plasmacytomas, and polymorphous plasmacytomas (see above) (Majzoub et al., 2003).

Approximately 10% of canine cutaneous plasmacytomas show varying degrees of amyloid production (see Chapter 15). Amyloidosis appears to occur more frequently in association with feline plasmacytomas (Majzoub et al., 2003). Primary or immunoglobulin-associated (AL) amyloid is derived from immunoglobulin light chains (Rowland & Linke, 1994; Platz et al., 1997; Majzoub et al., 2003). Plasmacytomas with amyloid are invariably composed of well-differentiated tumor cells. Occasional tumors are overwhelmed by amyloid and contain only scattered islands of residual tumor cells.

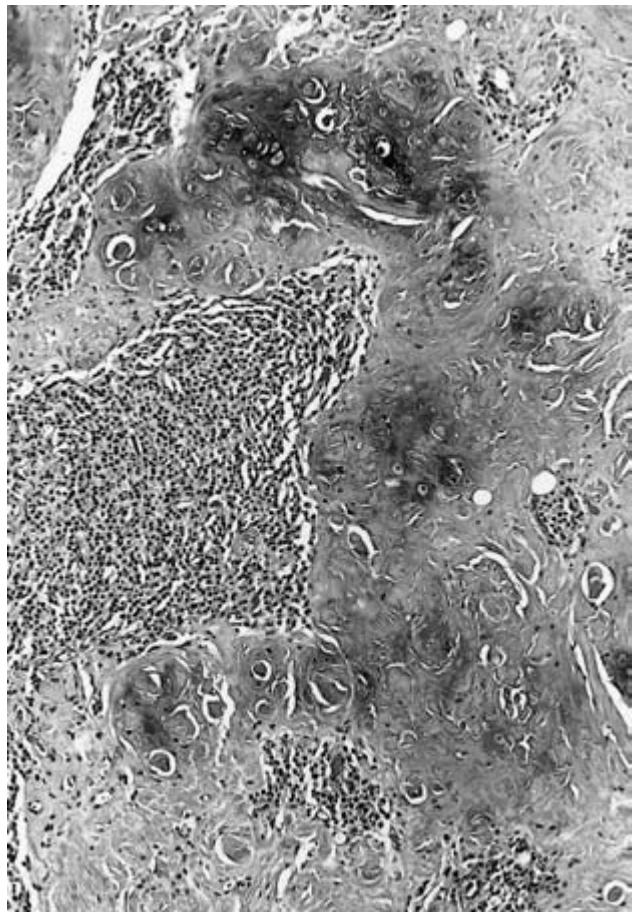


Fig. 37.6 Plasmacytoma in a dog. Most of the accumulated amyloid has undergone cartilaginous metaplasia.

Amyloid usually is accompanied by a granulomatous inflammatory reaction, which includes foreign body-type multinucleated giant cells. Multifocal chondroid metaplasia can develop in the deposited amyloid.

Differential diagnoses for cutaneous plasmacytomas are other cutaneous round cell tumors, including histiocytomas, nonepitheliotropic lymphomas, poorly granulated mast cell tumors, amelanotic dermal malignant melanomas of round cell type, transmissible venereal tumors, Merkel cell tumors, glomus tumors, and round cell type histiocytic sarcomas. Tumor cells with large, multilobular nuclei, multinucleated tumor cells as well as marginal well-differentiated plasma cells are the primary distinguishing features of plasmacytomas. Also, dense cytoplasmic RNA is demonstrable with MGP stain in plasma cells. Histiocytomas usually contain small intraepithelial tumor cell aggregates, a feature not observed in plasmacytomas. Nonepitheliotropic lymphomas tend to be composed of more homogeneous round cells characterized by a high nuclear to cytoplasmic ratio. Small numbers of intracytoplasmic metachromatic granules can be identified with Giemsa or toluidine blue stains in poorly granulated mast cell tumors. Moreover, mast cell tumors have more stromal collagen and are often accompanied by a reactive eosinophilic infiltrate. Most amelanotic dermal melanomas have some admixed spindle-shaped tumor cells. Fontana–Masson stain may reveal small amounts of intracytoplasmic melanin. Transmissible venereal tumors lack the nesting or packeting of plasmacytomas, and the cells have fine cytoplasmic vacuoles, a feature much better appreciated in fresh imprints and smears. Merkel cell tumors are characterized by marked packeting, and hence can mimic plasmacytomas. However, in contrast to plasmacytomas, Merkel cell tumors are composed of a more monomorphic round cell population, and have argyrophilic cytoplasmic granules demonstrable with Grimelius stain. Ultrastructurally, they have membrane-bound dense-core granules, desmosomal proteins, and tonofilament-like structures. Glomus tumors are usually very well circumscribed and encapsulated, and there are numerous vascular structures and nerves associated with the tumor mass. Most cutaneous histiocytic sarcomas represent extensions from tumor masses arising in the subcutis and underlying tissues. Round cells of histiocytic sarcomas are larger and are characterized by large round to oval and indented vesicular nuclei, and a large amount of amphophilic cytoplasm; most histiocytic sarcomas also have admixed plump spindle cells.

Immunohistochemistry

Antigens used to characterize lymphoid proliferations immunophenotypically are listed in Table 37.1. Canine plasmacytomas consistently express the common leukocyte marker CD45, but are often negative for CD18 (Table 37.1). The expression of the restricted isoform CD45RA varies; CD45RA may be expressed diffusely or by a subpopulation of tumor cells only. In about 80% of canine plasmacytomas, the tumor cells express CD79a (MB-1), the signaling molecule associated with the B cell receptor (Schrenzel et al., 1998). There is no information available regarding expression of these glycoproteins by feline plasmacytomas. Documentation of cytoplasmic immunoglobulins by immunohistochemistry has been made in both canine and feline tumors (Baer et al., 1989; Rakich et al., 1989; Platz et al., 1999; Cangul et al., 2002; Majzoub et al., 2003). Moreover, lambda light chain reactivity was found in all nine cats evaluated in one study (Majzoub et al., 2003) and in the vast majority of dogs in two large studies (Platz et al., 1999; Cangul et al., 2002). This is not surprising, as normal feline and canine plasma cells preferentially express lambda light chains as well (Arun et al., 1996).

The vast majority of cutaneous lymphomas express CD3 (T cell origin). Cutaneous B cell lymphomas, expressing CD21 and CD79a, are extremely rare in dogs and cats. Mast cell tumors are CD45+ and variably express CD45RA and CD18, but lack expression of CD79a. Immunohistochemistry for tryptase and KIT may identify poorly differentiated mast cell tumors. Histiocytomas are composed of CD18+, CD1+, CD11c+, MHC II+, E-cadherin+ Langerhans cells. Transmissible venereal tumors consistently express CD45 and may be positive for CD45RA and CD49d, but lack expression of CD79a. Merkel cell tumors, melanomas and glomus tumors lack expression of the leukocyte markers CD45 and CD18; instead, Merkel cell tumors are positive for pancytokeratins, neuron-specific enolase (NSE), synaptophysin and chromogranin A. Melanomas may express melanoma-associated antigen recognized by T cells (MART-1), melanoma-associated antigen (Melan-A), S100, melanoma isoform of microphthalmia transcription factor (MITF-M), tyrosinase-related protein-2 (TRP-2) tyrosinase, or HMB45/gp100. Glomus tumors are positive for α-smooth-muscle actin and the cells are surrounded by a laminin-positive and collagen IV-positive basement membrane; some tumors express desmin as well.

CUTANEOUS LYMPHOCYTOSIS

(Synonyms: cutaneous lymphocytoma, cutaneous lymphocytic hyperplasia, pseudolymphoma)

Cutaneous lymphocytosis, cutaneous lymphocytoma, cutaneous lymphoid hyperplasia, pseudolymphoma, and lymphadenosis benigna cutis are all terms that have been introduced to describe a heterogeneous group of lymphocytic proliferations in humans (Rijlaarsam & Willemze, 1994; Le Boit & McCalmont, 1997; Ploysangam et al., 1998). In contrast to cutaneous lymphoma, these lesions exhibit a mostly benign, self-limiting behavior characterized by slow progression, lack of metastasis, and potential regression. Cutaneous lymphocytosis is considered to be the result of a persistent antigenic stimulus, and may be associated with a variety of antigens such as drug reactions, arthropod bites, contactants, borreliosis, and herpesvirus infections. In humans these lesions may involve either B cell or T cell expansion (Ploysangam et al., 1998; Wood, 2003).

Studies in humans have shown that histologic and immunophenotypic evaluations do not reliably permit differentiation of cutaneous lymphocytosis from cutaneous lymphoma. In contrast to lymphoma, which represents a clonal lymphocytic population, lymphocytosis was thought to be composed of a polyclonal reactive lymphocytic infiltrate; spontaneous regression is not uncommon (Bakels et al., 1997). However, a clonal subpopulation may evolve from a polyclonal reactive lymphocytic infiltrate with transformation to cutaneous lymphoma (Winkelmann & Dabski, 1987). Recently, with the use of more sensitive polymerase chain reaction (PCR) based techniques, 27 of 44 human patients with cutaneous lymphocytosis were found to have clonality of B and T cells; however, only one patient developed overt lymphoma within a few years of onset (Nihal et al., 2003). Lesions with clonal lymphocyte expansion can undergo spontaneous regression (Ceballos et al., 2002), and clonal T cell receptor arrangement has been documented in a few cases of transient cutaneous drug-induced lymphocytosis in humans (Brady et al., 1999).

Lesions resembling cutaneous lymphocytosis have been documented in cats (Gilbert et al., 2004a) and a few cases have been seen in dogs by the authors. In contrast to lymphocytosis in humans, the feline and canine lesions are predominated by T cells. Although the histological presentation is of a banal, well-differentiated lymphocytic infiltrate, as in humans, differentiation from indolent lymphoma relies mostly on clinical follow-up documenting long-term survival and benign clinical behavior. Currently, the exact nature of this lymphocytic proliferation remains uncertain. Some reported cases of cutaneous lymphoma in the cat may, in fact, represent lymphocytosis, as clinical follow-up showed a prolonged survival time and no progression of the lymphocytic proliferation (Baker & Scott, 1989). Drugs and vaccines have been suggested as possible antigenic triggers of cutaneous lymphocytosis in cats (Gilbert et al., 2004a).

Clonality testing for rearrangement of the T cell receptor genes in lesions of feline lymphocytosis has shown that clonal rearrangement is more often observed than polyclonal rearrangement (Gilbert et al., 2004b). Hence, feline clonal cutaneous lymphocytosis may represent low-grade, indolent lymphoma, or as recently defined in humans, an intermediate state ('clonal lymphocytosis') with potential for developing into overt lymphoma (Nihal et al., 2003). Preliminary studies in the dogs with lymphocytosis indicate a clonal rearrangement of the T cell receptor as well (Moore P.F. & Affolter V.K., unpublished data, 2003). As in humans, while clonal rearrangement suggests a potential neoplastic process, difficulties in strict interpretation of clonality studies exist; clonal lesions may regress, and transient inflammatory lesions may occasionally be clonal.

Clinical features

The exact incidence of cutaneous lymphocytosis in cats and dogs is not known. Many cats present with solitary lesions, but multiple lesions may occur. The majority of cats exhibit alopecia, erythema, and scaling, which may be accompanied by crusting. Other lesions observed are

alopecic and erythematous plaques, and, less commonly, nodules or miliary papules. The principal predilection site is the thorax, but lesions may develop anywhere on the body and are common on the legs, pinnae, flank, and neck (Gilbert et al., 2004a). Pruritus is common.

The small number of cases observed in dogs offers limited information about cutaneous lymphocytosis in this species. Similar to cats, dogs present with patches of erythroderma several centimeters in diameter, or have erythematous and scaly plaques. Nodules have not been observed. One unique case of epitheliotropic lymphocytosis presented with progressive leukotrichia only (Rosenkrantz & Gross, 2001). This case was not available for clonality testing. Canine lymphocytosis lesions have been observed in the axillae, the dorsal head, the ears, on the neck and thorax, in the inguinal region, and on the cranial thighs.

The average age of affected cats is 12 years with a range of 6 to 15 years (Gilbert et al., 2004a). Breed or sex predilections have not been observed. Canine cutaneous lymphocytosis has been seen in a Golden Retriever, a Shetland Sheepdog, a Chinese Crested, a Welsh Corgi, and a mixed breed dog. The case of epitheliotropic lymphocytosis was in a Boxer. Except for the Boxer, all dogs were intact or spayed females, and the ages ranged from 8 to 14 years.

Most data for the clinical behavior of cutaneous lymphocytosis have been collected from feline cases. Cutaneous lymphocytosis in cats currently is best considered a relatively benign disease with a prolonged clinical course in most cases. Skin lesions develop to a certain size and then remain stable for an extended period of time, sometimes for up to 2 years (Gilbert et al., 2004a). The lesions may wax and wane, but in contrast to lymphocytosis in humans, spontaneous regression has not been reported (Gilbert et al., 2004a). Most cats have no systemic signs and no evidence of internal lesions; however, investigation for potential internal involvement has not been performed in clinically healthy cats. Spread to internal organs was associated with systemic signs of weight loss, anorexia, pulmonary edema, diabetes mellitus, and kidney failure in six of 12 euthanized cats (Gilbert et al., 2004a). It is not known whether skin lesions preceded the internal lesions, or if they arose concurrently in these cats.

The single case of epitheliotropic lymphocytosis observed in the Boxer with leukotrichia remained stable over a follow-up period of 2 years after progression to nearly diffuse loss of pigment from the haircoat; progression to cutaneous lymphoma was not seen (Rosenkrantz & Gross, 2001). One dog observed by the authors with a 3 year history of cutaneous lymphocytosis developed subsequent multicentric lymphoma; follow-up was not available in the other canine cases.

Histopathology (Figures 37.7 through 37.11)

Cutaneous lymphocytosis is usually characterized by perivascular to diffuse infiltration of small lymphocytes. In cats, early lesions may involve the superficial dermis primarily, but the infiltrate usually extends into the deep dermis. In dogs, the lymphocytic infiltrate is predominantly seen in the superficial dermis; a zone of acellularity in the superficial dermis (Grenz zone) is present. The

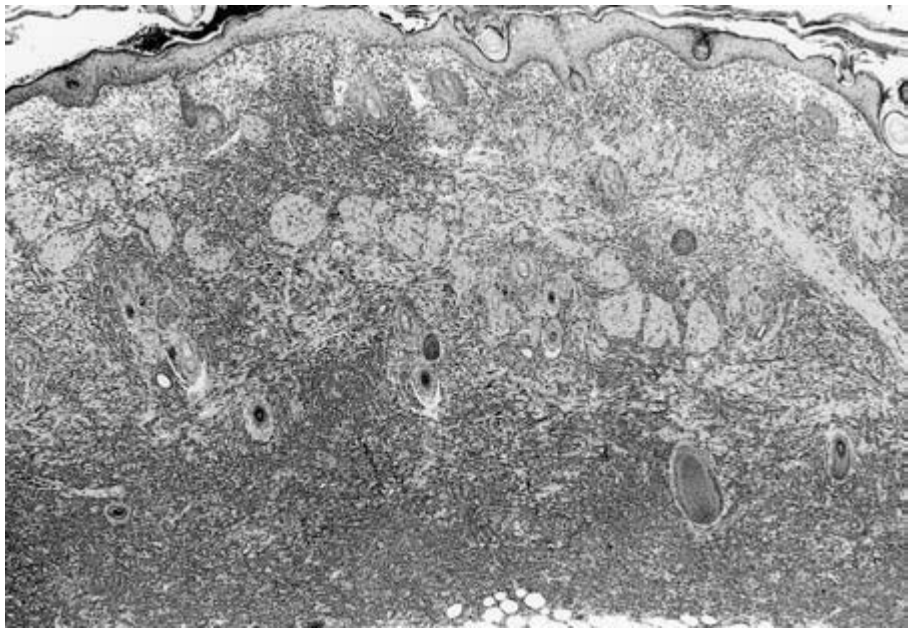


Fig. 37.7 Lymphocytosis in a cat. There is a diffuse dermal infiltrate of small lymphocytes. Epitheliotropism is not observed.

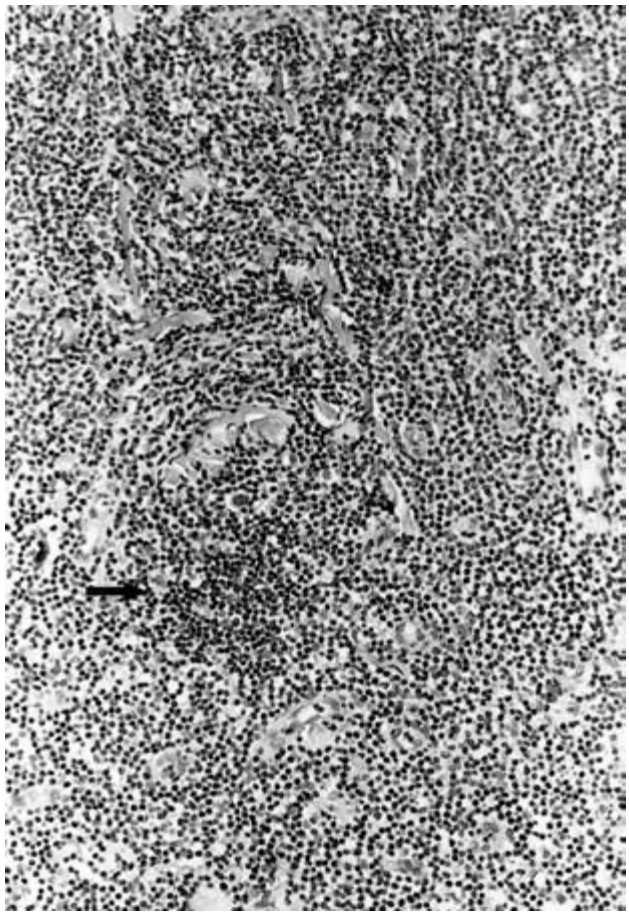


Fig. 37.8 Higher magnification of lymphocytosis in a cat. Admixed with the diffuse dermal lymphocyte infiltrate (T cells) there is an aggregate of small lymphocytes (B cells) (arrow).

lymphocytic infiltrate may spare the epithelial structures completely in dogs; foci of dispersed intraepidermal and intrafollicular lymphocytes are seen in approximately half of the feline cases (Gilbert et al., 2004a). In contrast to the other dogs observed to date, the Boxer with leukotrichia had an epitheliotropic mature lymphocytic infiltrate primarily affecting the follicular epithelium (Rosenkrantz & Gross 2001).

The primary population of lymphocytes is characterized by small, dark nuclei and a small or moderate amount of very pale cytoplasm. Mitotic figures are extremely rare or absent. Small, tightly packed aggregates of smaller lymphocytes with minimal cytoplasm may be embedded within the diffuse infiltrate in cats; these correlate with B cell populations (see immunohistochemistry, below). B cell aggregates have not been seen in the canine cases. Dispersed throughout the lesion there is a mild to moderate reactive infiltrate of histiocytes, mast cells, and eosinophils. The overlying epidermis is moderately hyperplastic. Erosion or ulceration is occasionally seen.

Cutaneous lymphocytosis is unique histologically. Polymerase chain reaction (PCR) amplification for T cell receptor and immunoglobulin heavy chain (IgH) rearrangement, although currently of limited availability, is useful to distinguish monoclonal from polyclonal T cell or B cell populations. Some cases of clonal lymphocytosis may eventually progress to lymphoma. Cutaneous lymphocytosis also should be differentiated from lymphocytic leukemia with cutaneous involvement. With the latter, the neoplastic lymphocytes are tightly packed around dermal vessels, while in lymphocytosis the cells

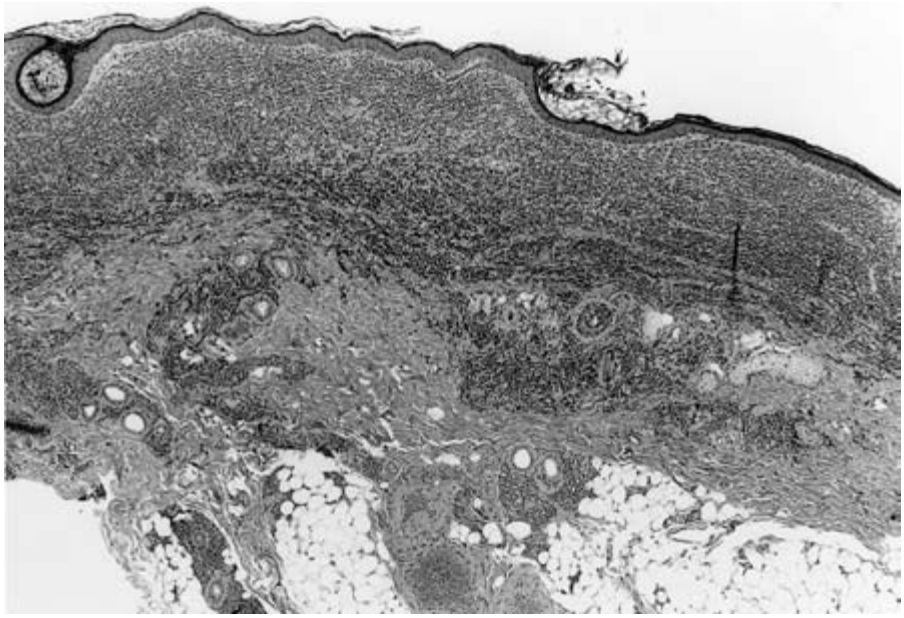


Fig. 37.9 Lymphocytosis in a dog. There is a superficial and mid-dermal dense infiltrate with multifocal extension into the deep dermis and subcutis.

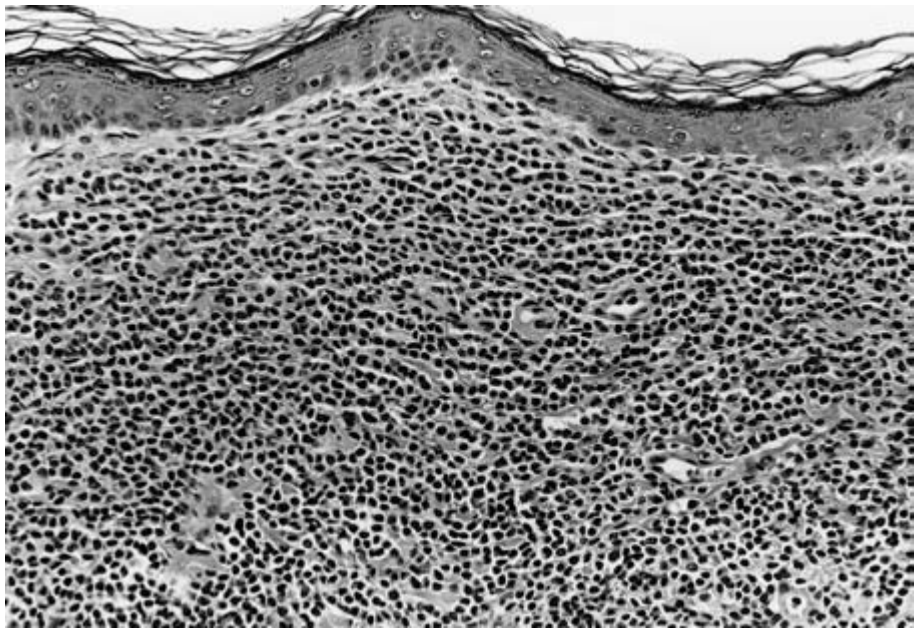


Fig. 37.10 Lymphocytosis in a dog. The diffuse infiltrate is composed of small well-differentiated lymphocytes.

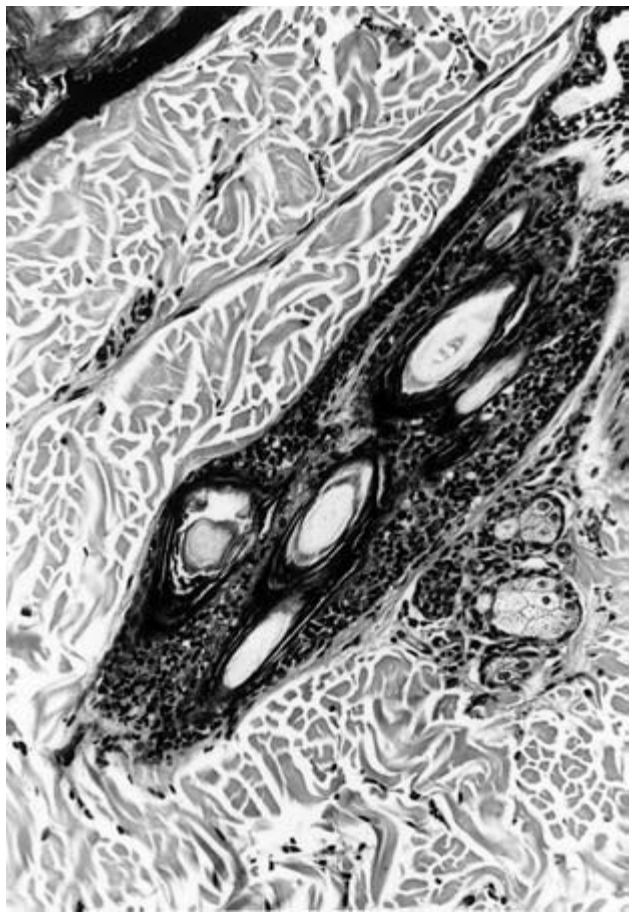


Fig. 37.11 Follicular mural lymphocytosis in a dog demonstrating diffuse intramural infiltrates of mature lymphocytes. (Case material courtesy W.S. Rosenkrantz.)

are more loosely arranged and present as an interstitial to diffuse lymphoid infiltrate. Some cases of feline lymphocytosis may mimic feline mast cell tumor because the lymphoid infiltrate is characterized by a larger amount of clear cytoplasm; however, Giemsa or toluidine blue stains are uniformly negative for mast cell granules.

Immunohistochemistry

Antigens used to characterize lymphocytic proliferations immunophenotypically are listed in Table 37.1. In cats, the diffuse lymphocytic infiltrate of cutaneous lymphocytosis is composed of CD3+, CD5+ T cells. The small lymphocytic aggregates comprise CD79a+, CD21+ small B cells (Gilbert et al., 2004a). Occasionally, there are a few dispersed CD79a+ B cells admixed with the CD3+ T cells. The T cell population is either a mixed population of CD4+ and CD8+ T cells or is of uniformly double-negative (CD4–, CD8–) T cells (Gilbert et al., unpublished data, 2003). The latter phenotype usually is not seen in reactive lymphocytic infiltrates, and suggests the presence of a neoplastic cell population.

Canine lymphocytosis is composed of CD3+ T cells; B cells are not seen. The immunophenotype of the T cell population varies among cases: double-negative (CD4–, CD8–) αβ T cell receptor (TCRαβ)+ T cells, CD8+, TCRαβ+ T cells, or CD8+, TCRγδ+ T cells have been observed. Immunophenotypic features fail to reliably differentiate cutaneous lymphocytosis from malignant lymphoma and chronic leukemia with cutaneous lesions, as all these lesions are composed of T cells (see Table 37.1).

EPITHELIOTROPIC LYMPHOMA

(Synonyms: mycosis fungoides; epitheliotropic T cell lymphoma)

Cutaneous epitheliotropic lymphoma or 'mycosis fungoides' (MF) is an uncommon, unrelentingly progressive disease characterized by neoplastic infiltration of the epidermis and adnexal structures. The archaic misnomer 'mycosis fungoides' is well-accepted in the human and veterinary literature (Moore et al., 1994; Le Boit & McCalmont, 1997; Ralfkiaer & Jaffe, 2001). The classification of epitheliotropic lymphoma is well-entrenched in the human literature, but controversial in veterinary medicine. The classification scheme commonly used in human medicine is perhaps most useful histopathologically rather than clinically in dogs and cats.

Epitheliotropic lymphoma in humans is subclassified as: (1) pagetoid reticulosis, also referred to as 'Woringer–Kolopp disease' (localized) and 'Ketron–Goodman disease' (generalized); (2) 'classical' mycosis fungoides; (3) d'emblée form; and (4) Sézary syndrome (Le Boit & McCalmont, 1997; Ralfkiaer & Jaffe, 2001). The vast majority of epitheliotropic lymphomas in humans are composed of CD4+ helper T cells expressing the αβ T cell receptor (TCRαβ+), while cytotoxic CD8+ and TCRγδ+ epitheliotropic lymphomas are uncommon (Knowles, 1989; Berti et al., 1991, 1999; Ralfkiaer, 1991; Lu et al., 2002). In contrast, the proliferating T cells in canine epitheliotropic lymphoma express CD8 in the majority of cases and are double negative (CD4–, CD8–) in the minority (Moore et al., 1994). A small number of fully phenotyped cases of feline epitheliotropic lymphoma were composed of CD3+, double negative (CD4–, CD8–) T lymphocytes as observed by one author (V.K.A.).

The etiology of mycosis fungoides is largely unknown. Truncated sequences of human T-lymphotropic virus (HTLV-1) have been identified in some cutaneous epitheliotropic lymphomas in humans (Ghosh et al., 1994; Pancake et al., 1995). Cats with epitheliotropic cutaneous lymphoma are negative for feline leukemia virus (FeLV) using immunofluorescence and enzyme-linked immunosorbent assay (ELISA) on blood (Caciolo et al, 1984; Tobey et al., 1994). However, the presence of FeLV DNA was identified in one case of feline epitheliotropic lymphoma using amplification by polymerase chain reaction (PCR) (Tobey et al., 1994). A canine retrovirus has been isolated from a leukemic dog, but no clear relationship to leukemia and lymphoma has been established (Safran et al., 1992).

Persistent environmental antigens and/or Langerhans cell abnormalities act as a stimulus for chronic T-cell activation and proliferation; progression to a clonal expansion has been suggested as a possible cause of cutaneous epitheliotropic lymphomas in humans (Burg et al., 2001). Both human and canine cutaneous epitheliotropic lymphoma are composed of memory T cells (see below). Moreover, canine cutaneous epitheliotropic lymphoma predominantly develops in areas commonly affected with allergic conditions such as atopic dermatitis (Duclos & Hargis, 1996). Some dogs with cutaneous epitheliotropic lymphoma have a previous history of chronic allergic skin disease. These observations support the hypothesis that chronic antigen stimulation may be an initiator of a clonal neoplastic T cell population in the skin.

Clinical features

Cutaneous lymphoma is reported to represent 1% of all canine skin tumors and 2.8% of all feline skin tumors, but these data include both epitheliotropic and non-epitheliotropic types (Goldschmidt & Shofer, 1992). Cutaneous epitheliotropic lymphoma is less common in cats than in dogs (Moore & Olivry, 1994). Epitheliotropic lymphoma presents with a wide range of skin lesions and can mimic virtually any inflammatory disease of the skin.

'Classical' MF is the most common form of epitheliotropic lymphoma seen in the dog (Moore & Olivry, 1994). Three clinical stages are often referred to as patch, plaque, and tumor stage in humans. However, there is often considerable overlap of these stages, particularly in dogs. Patch and plaque stages usually are present simultaneously. Progression from the patch or plaque stage to tumor stage is more rapid in dogs, when compared to human epitheliotropic lymphoma (Moore & Olivry, 1994). This rapidity of progression may explain the high incidence of tumor formation with epitheliotropic lymphoma in dogs. Spread to lymph nodes and other organs may be observed with the tumor stage in dogs (Beale & Bolon, 1993; Moore et al., 1994). Patch and plaque lesions are common in cats; the tumor stage appears less prevalent. The d'emblée form of MF is characterized by tumor formation without previous patch and plaque stage, and is more common in dogs than in humans (Moore & Olivry, 1994).

Canine pagetoid reticulosis is characterized by exfoliative erythroderma with scaling, alopecia, erosions or ulcerations, but without palpable masses. The pagetoid form often favors mucocutaneous junctions and pawpads in dogs, but lesions may occur anywhere. In cats, the mucocutaneous junctions and oral cavity are less commonly affected. Most canine and feline cases involve multiple areas of the body, which resembles the clinical presentation of disseminated pagetoid reticulosis in humans, also referred to as the Ketron–Goodman variant (Le Boit & McCalmont, 1997).

Sézary syndrome is characterized by the simultaneous presence of cutaneous epitheliotropic lymphoma, periph-

eral lymphadenopathy, and circulating tumor cells in the peripheral blood (Ralfkiaer & Jaffe, 2001). Sézary syndrome is rare in dogs and cats (Moore & Olivry, 1994). Typical clinical signs include extensive erythematous scaling and patchy alopecia, accompanied by marked pruritus (Thrall et al., 1984; DeBoer et al., 1990). This syndrome rarely may also be observed in conjunction with tumor formation. Other clinical signs are lymphadenopathy and leukemia. Often other organs are affected; one dog presented with additional lesions in lymph nodes, spleen, liver, heart, lung, and kidneys (Thrall et al., 1984). Visceral involvement was not observed in the case reported in a cat (Schick et al., 1993).

The clinical presentation of epitheliotropic lymphoma in both the dog and the cat is highly pleomorphic. Thus, it may be most useful clinically to subdivide epitheliotropic lymphoma into four principal categories of clinical presentation (Scott et al., 2001: (1) exfoliative erythroderma; (2) mucocutaneous localization; (3) solitary or multiple plaques or nodules; and (4) ulcerative disease of the oral mucosa. Mucocutaneous and cutaneous forms merge with chronicity and disease progression.

The clinical features of category 1, 'exfoliative erythroderma', include generalized erythema, scaling, loss of pigmentation, and alopecia. This category is most challenging clinically as it closely mimics other inflammatory, exfoliative skin diseases. Over time, patches, plaques, and nodules commonly develop (category 3; see below). Hemorrhage into the skin may mimic hyperpigmentation. The trunk and head commonly are affected, but lesions may begin or develop in any location. Lesions affecting the face tend to be partially bilaterally symmetric. Lymphadenopathy can occur. However, frequently, it is not determined if this reflects reactive inflammation or neoplastic invasion. Pruritus is variable and, if present, can vary between mild and severe.

Animals with category 2, 'mucocutaneous localization', are characterized by erythema, depigmentation, alopecia, irregular infiltration, erosion, and ulceration. Depigmentation is a common and clinically striking feature. The facial mucocutaneous junctions of the mouth, planum nasale, and eyelids are affected most frequently. Localized involvement restricted to the lips is a common feature. Marked bilateral symmetry can be noted on the lips and philtrum. The planum nasale also may be affected, as may the anorectal junction, vulva, and prepuce.

Category 3 is characterized by 'solitary or multiple plaques or nodules' that usually are erythematous and scaly or crusted. Larger lesions erode and ulcerate. Grouped lesions gradually coalesce. In rare cases, individual lesions may regress as other lesions develop and expand. Neoplastic lymphadenopathy is noted in more advanced disease.

Category 4, 'ulcerative disease of the oral mucosa', is a striking subgroup. Ulceration can occur in palpably infiltrated areas or seemingly occurs in normal-appearing mucosa. The gingiva, palate, or tongue may be involved.

Biopsy specimens from a single case of canine mycosis fungoides were observed by the authors in which skin lesions were clinically described as 'scalded', accompanied by nearly diffuse alopecia. Although blisters were not described clinically, there was subepidermal blister formation evident histopathologically (see below), comparable to bullous mycosis fungoides of humans (Bowman et al., 2001).

Although feline MF is less common than canine MF, all four of the clinical categories of epitheliotropic lymphoma also are seen in cats. Feline lesions most frequently affect the face, eyelids, mucocutaneous junctions, elbow, and trunk (Affolter & Moore, 2000; Scott et al., 2001).

The melding of clinical and histopathologic classifications is not always clear-cut. Animals diagnosed as having 'pagetoid reticulosis', for example, usually present clinically with exfoliative erythroderma (category 1) or mucocutaneous localization (category 2). The term 'd'emblée form' refers to tumor formation in the absence of previous patches or plaques and can be placed in category 3. Sézary syndrome can occur with any cutaneous clinical presentation; circulating tumor cells are required for this diagnosis.

Cutaneous epitheliotropic lymphoma is a disease of older cats and dogs. The ages in one study ranged from 6 to 14 years with a mean age of 11 years in dogs (Moore et al., 1994). Feline cases have been seen in cats between 12 and 17 years old (Baker & Scott, 1989; Schick et al., 1993; Affolter, V.K., & Moore, P.F., unpublished data, 2000). There are no apparent breed or sex predilections.

Cutaneous epitheliotropic lymphoma is a progressive disease. None of the known protocols of chemotherapy appears to affect the long-term clinical course. In dogs, the course of the disease varies from a few months up to 2 years (Moore et al., 1994). Eventually, the lesions may extend to lymph nodes and other organs as well (Moore et al., 1994). The small number of feline cases observed restricts any reliable conclusions regarding clinical behavior.

Clinical differential diagnoses vary considerably contingent on clinical classification, and are numerous due to the clinical pleomorphism of MF. The 'exfoliative erythroderma' group must be differentiated from sarcoptic acariasis, atopic dermatitis, food allergy, vasculitis, and diseases of abnormal cornification. Lack of blanching with diascopy may suggest vasculitis. Animals with 'mucocutaneous localization' must be differentiated from ulcerative autoimmune disease or erythema multiforme. 'Solitary or multiple plaques or nodules' caused by epitheliotropic lymphoma are not visually distinctive and must be differentiated from other neoplasms as well as inflam-

matory diseases causing plaques or nodules. Epitheliotropic lymphoma presenting as 'ulcerative disease of the oral mucosa' must be differentiated from chronic stomatitis of any etiology, including oral autoimmune skin disease.

Histopathology

The key diagnostic feature of epitheliotropic lymphoma is the tropism of the neoplastic cells for the epidermal or mucosal epithelium and the adnexal structures, in particular the follicular wall. The intraepithelial neoplastic lymphocytes are either diffusely distributed within the epithelium or form discrete aggregates, referred to as 'Pautrier's microaggregates' or 'microabscesses'. Diffuse infiltrates tend to remain in the lower levels of the epidermis. Tropism to adnexal structures may be more prominent than invasion into the epidermis, and complete obliteration of the hair follicles and adnexal glands may occur. Infiltration of apocrine sweat glands may be striking in some cases, and is highly diagnostic for epitheliotropic lymphoma, as inflammatory infiltrates generally do not occur in this location.

The epidermis may be moderately acanthotic, but marked epidermal hyperplasia is not a feature of epitheliotropic lymphoma. Hyperkeratosis may be mild to moderate. Spongiosis is absent or mild. Severe lesions may be ulcerated and exudative, in which case there is an inflammatory infiltrate admixed with the neoplastic lymphocytes. Occasionally, accompanying mucinosis of the invaded follicular epithelium is observed. The degree of dermal involvement and cytologic features vary amongst the different forms (see below). Autoregression of lesions is associated with dermal fibrosis and scant reactive lymphocytic infiltrates.

'Classical' mycosis fungoides and d'emblée form

(Figures 37.12 through 37.15)

Typically, neoplastic infiltrates are present in the epidermis and adnexa as well as the underlying dermis. The dermal–epidermal junction often is obliterated and blurred by the dense tumor cell infiltrate. With patch and plaque lesions, the dermal infiltrate is limited to the superficial dermis. The tumor stage and d'emblée forms are characterized by diffuse infiltration of tumor cells in the deep dermis and subcutis, but in contrast to the tumor stage and d'emblée form in humans, intraepithelial involvement is usually still present and the adnexal structures are obliterated. Residual follicles and sweat glands show marked epitheliotropic infiltration by tumor lymphocytes, and are often demarcated only by an intact glassy or basement membrane. The infiltrate usually affects the entire length of the hair follicle; however, in some cases the infiltrate is focused in the region of the isthmus, creating a nodular effect on low power examination. Occasionally the tumor cell infiltrate may spare the overlying epidermis while markedly invading follicles and adnexal glands. Accompanying the epitheliotropic cells there may be mild to occasionally striking apoptosis of keratinocytes, characterized by shrinkage and intense eosinophilia, sometimes leading to confluent necrosis and ulceration. The dermal component of patch and plaque stage lesions may include reactive small lymphocytes, plasma cells, eosinophils, and neutrophils.

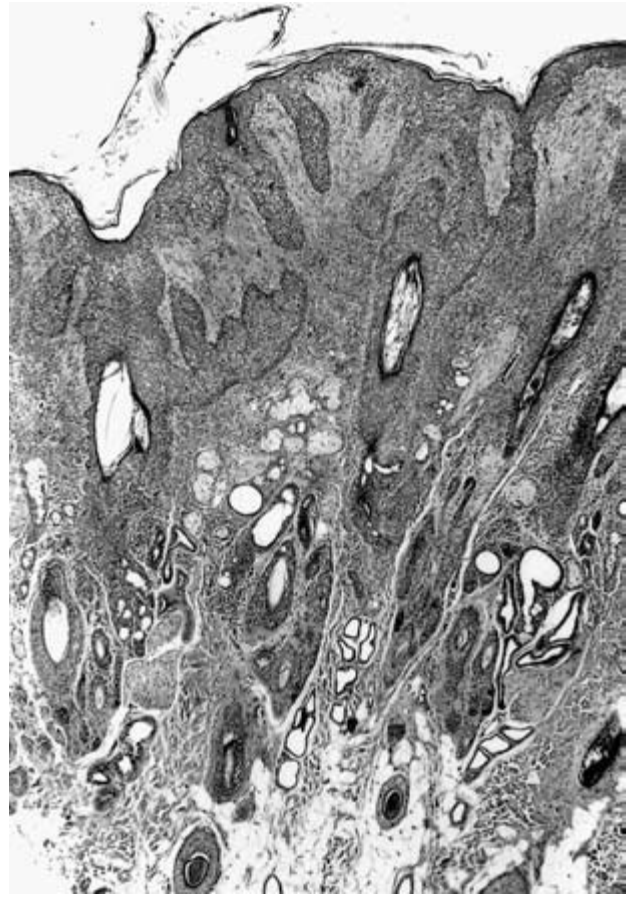


Fig. 37.12 Mycosis fungoides in a dog, plaque stage. This low power magnification demonstrates proliferating neoplastic lymphocytes predominantly in the epidermis and superficial follicles; these also infiltrate the superficial dermis.

Cytologic features may be quite diverse. With patch and plaque lesions, the tumor cells are often small, resembling mature lymphocytes, or are medium-sized. They have euchromatic or hyperchromatic nuclei with a variably irregular contour and a small to moderate amount of cytoplasm. The intraepithelial lymphocytes often appear slightly larger than their intradermal counterparts. With tumor-stage lesions, all of the neoplastic cells are larger. They have more cytoplasm, which often is pale and eosinophilic, or clear; the former cytoplasmic appearance

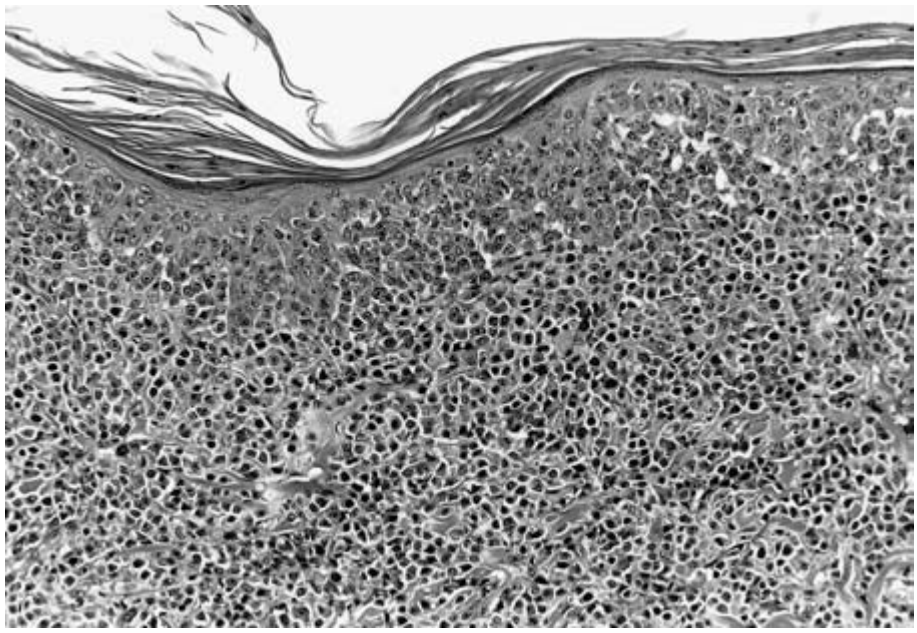


Fig. 37.13 Mycosis fungoides in a dog, tumor stage. The dermal–epidermal junction is blurred by intra-epidermal neoplastic lymphocytes that coalesce with the dermal infiltrate.

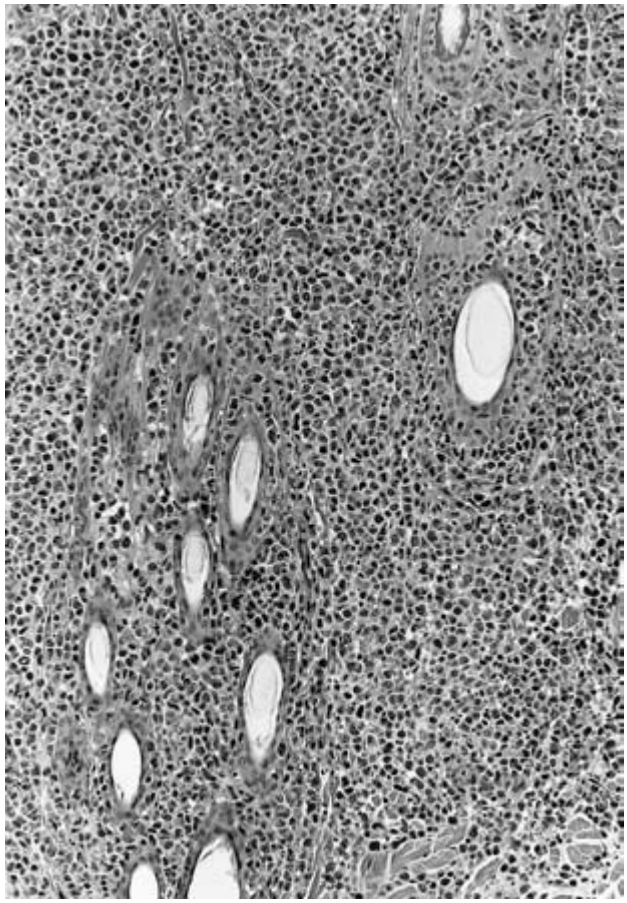


Fig. 37.14 Mycosis fungoides in a dog, tumor stage. The diffuse neoplastic infiltrate is invading the epithelium of multiple hair follicles.

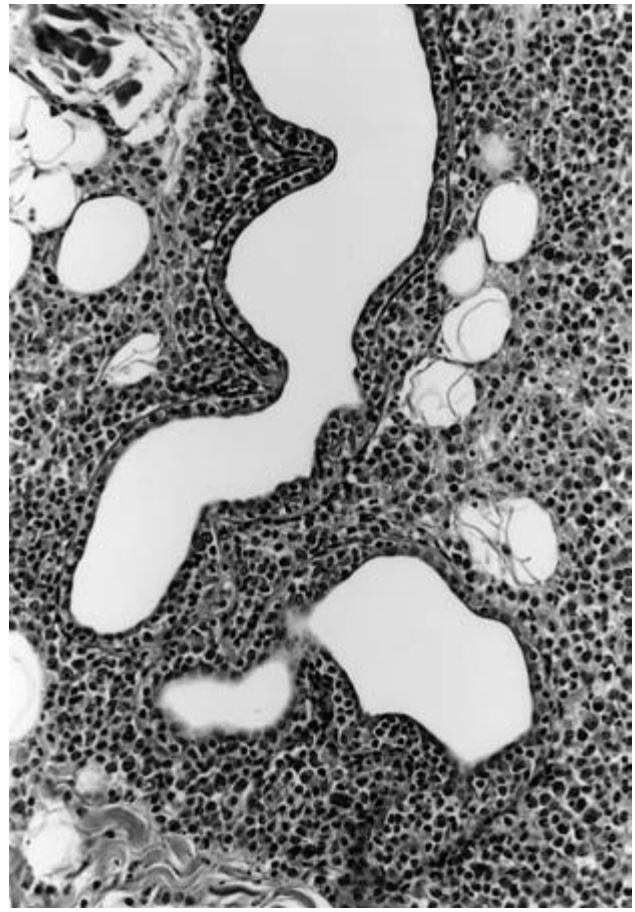


Fig. 37.15 Mycosis fungoides in a dog, tumor stage. The apocrine sweat glands are invaded by neoplastic lymphocytes.

resembles histiocytes. The nuclei are large and often folded or cleaved, with margination of the chromatin. In the small or medium-sized lymphocytes, the nucleoli are inconspicuous and mitotic activity is low. In the large lymphocytes of tumor-stage MF, nucleoli are also larger and mitotic figures may be more numerous.

In the single case of MF with bullous lesions, tumor cells infiltrated the follicular epithelium and superficial dermis predominantly; epidermal infiltration was surprisingly sparse. There was also superficial mixed dermal inflammation in which mature lymphocytes and plasma cells predominated; a few neurophils and occasional eosinophils were found. The epidermis was separated along the dermal–epidermal junction to form bullae which were generally devoid of content, or contained a few degenerated cells. The epidermis of the bullae was often diffusely devitalized, morphologically resembling toxic epidermal necrolysis (see Chapter 4). This appearance suggests a toxic effect, perhaps mediated by the neoplastic infiltrate.

Very early patch and plaque stage lesions mimic inflammatory interface dermatitis, and differentiation requires clinical follow-up and evaluation of biopsies at a later stage. Early stages of patch and plaque stage epitheliotropic lymphoma need to be differentiated from reactive lymphocytic inflammation with marked exocytosis, as seen in hypersensitivity reactions (see Chapter 9), as well as erythema multiforme (see Chapter 4). Reactive inflammatory lesions often are associated with more severe spongiosis, and epidermal hyperplasia tends to be more pronounced when compared to epitheliotropic lymphoma. Moreover, intraepidermal inflammatory lymphocytes tend to migrate through the entire thickness of the epidermis, while intraepidermal neoplastic aggregates tend to accumulate in the lower half of the epidermis.

In contrast to epitheliotropic lymphoma, intraepithelial lymphocytes tend to be less numerous in erythema multiforme and are mostly associated with the apoptotic keratinocytes (satellitosis). Lymphocytic infiltration of apocrine sweat glands is much more characteristic of epitheliotropic lymphoma than erythema multiforme. The authors have seen cases of erythema multiforme featuring large histiocytic round cells (putative Langerhans cells) in clusters. These lesions strongly mimic epitheliotropic lymphoma with apoptosis; clinical as well as immunohistological differentiation may be required for these problematic cases. The presence of intraepithelial aggregates of Langerhans cells has been referred to as 'pseudo-Pautrier abscesses' (Candiago et al., 2000; Burkert et al., 2002).

Mycosis fungoides with bullous lesions should be differentiated from subepidermal bullous diseases such as bullous pemphigoid and epidermolysis bullosa acquisita (see Chapter 2). Diffuse devitalization of the epidermis is also similar to toxic epidermal necrolysis. Identification of epitheliotropic neoplastic lymphocytes is key to differentiation.

The tumor stage of classical MF should be differentiated from other round cell tumors of the skin featuring epitheliotropism particularly canine cutaneous histiocytomas and Merkel cell tumors. Rare transmissable venereal tumors also may exhibit mild intraepidermal accumulations of tumor cells. Dermal amelanotic melanomas of round cell type, plasmacytomas, and mast

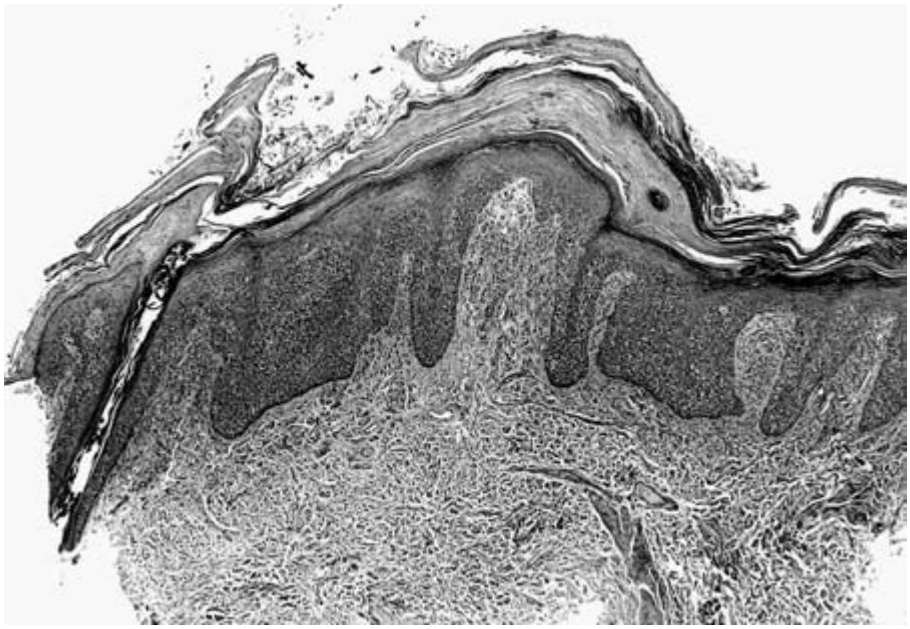


Fig. 37.16 Pagetoid reticulosis at the mucocutaneous junction of a dog. The neoplastic cell population is confined to the hyperplastic epithelium. In the underlying dermis there is a mild reactive infiltrate only.

cell tumors can usually be ruled out as they do not exhibit epitheliotropism. Histiocytomas and cutaneous lymphomas can mimic each other perfectly. In contrast to epitheliotropic lymphoma, histiocytomas rarely exhibit epitheliotropism to adnexal structures. In contrast to lymphomas, Merkel cell tumors are characterized by prominent nesting or packeting of tumor cells, separated by a delicate fibrovascular stroma.

Pagetoid reticulosis (Figures 37.16 through 37.18)
In this form of epitheliotropic lymphoma, the lymphocytic infiltrate is confined essentially to the epidermis and the adnexal structures, in particular the follicular epithelium and sweat glands. Variable numbers of apoptotic keratinocytes may be observed in conjunction with the lymphocytic infiltrate. The neoplastic cells are often small lymphocytes with hyperchromatic nuclei, resembling those of early patch stage (see above), or may be larger with more cytoplasm. The infiltrate may be severe enough to replace all of the keratinocytes in some areas. The superficial dermis may contain a mild to moderate pleocellular infiltrate composed of reactive lymphocytes, plasma cells, histiocytes, and occasional granulocytes. As the disease progresses the dermis is infiltrated by neoplastic lymphocytes; at that point it may be indistinguishable from tumor stage (see above). Systemic spread may be observed.

Pagetoid reticulosis has characteristic histologic features, and differential diagnosis is not problematic in well-developed lesions. Early stages may be difficult to differentiate from reactive lymphocytic dermatitis with severe exocytosis, as seen in some hypersensitivity reactions, as well as erythema multiforme. Inflammatory

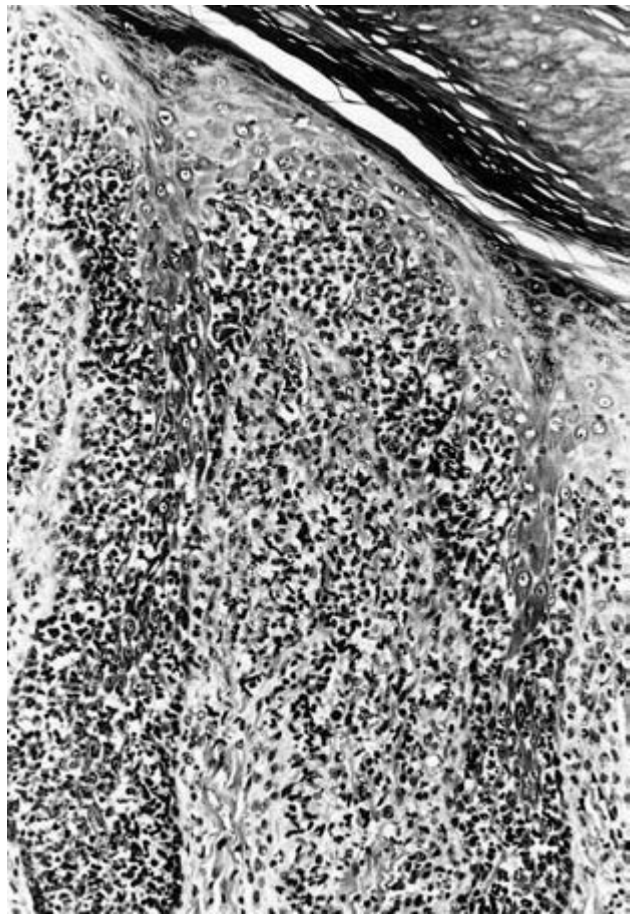


Fig. 37.17 Higher magnification of pagetoid reticulosis of Fig. 37.16. The architecture of the lower half of the epidermis is disrupted by a coalescing infiltration of neoplastic lymphocytes. The dermal infiltrate is pleocellular and reactive.

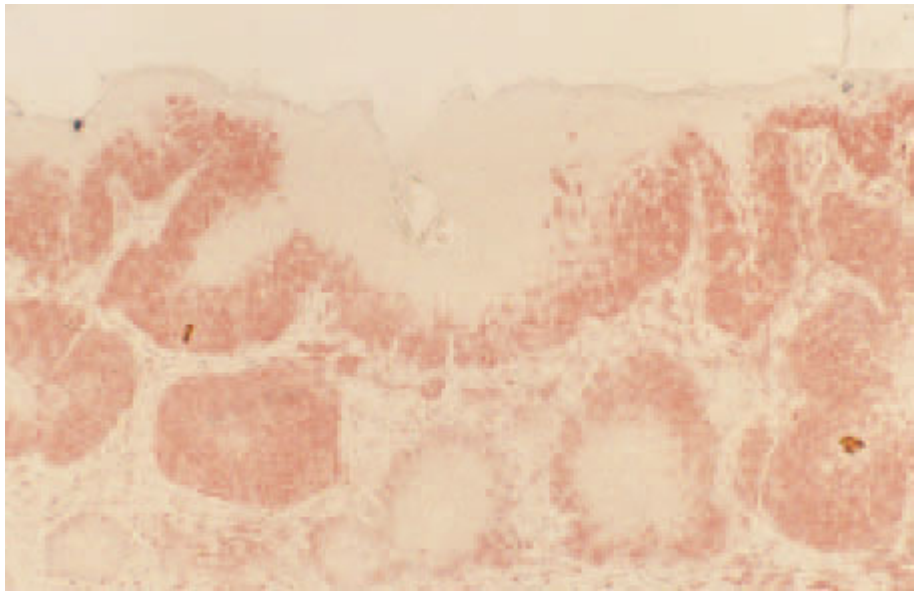


Fig. 37.18 Pagetoid reticulosis in a dog. Immunohistochemistry on a frozen section with anti-γδ-TCR (T cell receptor) antibody demonstrates diffusely positive neoplastic γδ-T cells in the epidermis; the dermal infiltrate is largely negative (chromogen, aminoethylcarbazole [AEC]).

lesions, however, usually exhibit features of exudative dermatitis, including patchy or diffuse spongiosis, as well as more pronounced epidermal hyperplasia. In contrast to pagetoid reticulosis, intraepithelial lymphocytes tend to be less numerous in erythema multiforme and are often closely associated with the apoptotic keratinocytes (satellitosis). Lymphocytic infiltration of apocrine sweat glands is much more characteristic of epitheliotropic lymphoma than erythema multiforme.

Sézary syndrome

Cutaneous lesions exhibit features of classical MF (see above). Neoplastic lymphocytes are also present in the lymph nodes and the peripheral blood. About 50% of the neoplastic lymphocytes in the peripheral blood may have hyperchromatic, folded, and grooved nuclei (Thrall et al., 1984), referred to as Sézary cells. Sézary syndrome should be differentiated from lymphocytic leukemia with secondary involvement of the skin (see p. 888). The latter is characterized by dermal perivascular accumulations of neoplastic lymphocytes and lacks epitheliotropism of the neoplastic lymphocytic population.

Immunohistochemistry

Antigens used to characterize lymphomas immunophenotypically are listed in Table 37.1. Epitheliotropic lymphoma in cats and dogs is composed of CD3+ T cells (Moore et al., 1998; Affolter & Moore, 2000). The majority of canine epitheliotropic lymphomas are composed of memory T cells, which lack expression of CD45RA, but express high levels of adhesion molecules (β1 integrin VLA-4). The presence of memory cells supports the hypothesis of previous antigen stimulation. In contrast to humans, the proliferating T cells in canine epitheliotropic lymphoma express CD8 in approximately 80% of the cases and are double negative (CD4–, CD8–) in the remaining 20% (Moore et al., 1994). Canine pagetoid reticulosis is a proliferation of CD3+, γδ T cell receptor (TCRγδ)+ T cells (Moore et al., 1998). The reactive dermal lymphocytic infiltrate in the superficial dermis is composed of TCRαβ+ T cells. 'Classic' MF in dogs is either composed of TCRαβ+ T cells, or TCRγδ+ T cells (Moore et al., 1998). The tumor cell population may no longer express other surface proteins that are expected to be found on normal T cells (Ralfkiaer & Jaffe, 2001). For example, a loss of expression of CD5 was seen in 64% of the canine cases in one study and was more common in TCRγδ+ T cell (73%) than in TCRαβ+ T cell (29%) lymphoma (Moore et al., 1998). The lack of CD5 expression may be useful as a prognosticator in the TCRαβ immunophenotype as it occurred only in tumor stage lesions (Moore et al., 1998).

Two feline cases evaluated by one author (V.K.A.) expressed a double negative (CD8–, CD4–) immunophenotype. Monoclonal antibodies to evaluate T cell receptors of the lesional T cells in feline epitheliotropic lymphomas are currently not available. The exact immunophenotype of the Sézary syndrome cases reported in dogs and cats is unknown.

In differentiation, other round cell tumors (except nonepitheliotropic T cell lymphoma) lack T cell surface molecules. Histiocytomas strongly express CD1, CD11c, MHC II, and E-cadherin instead. Merkel cell tumors lack expression of leukocyte antigens CD45 and CD18, but are positive for cytokeratin 20 (detected by pancytokeratin), neuron-specific enolase (NSE), synaptophysin, and chromogranin A.

Immunohistochemistry for the proliferating cell nuclear antigen (PCNA) is not reliable in the differentiation of early epitheliotropic lymphoma from reactive lymphocytic processes (Murphy & Olivry, 2000). Moreover, reactive lymphoid infiltrates are mostly composed of a mixture of CD4+ T cells and CD8+ T cells, with both T cell populations continuing to express CD5. The intraepithelial Langerhans cell aggregates seen in association with erythema multiforme are positive for CD1, CD11c, MHC II, and E-cadherin, but lack expression of T cell markers.

NONEPITHELIOTROPIC LYMPHOMA

Cutaneous nonepitheliotropic lymphoma may be primary or may occur in conjunction with disseminated lymphoma (Ralfkiaer et al., 2001a,b). In humans, extensive histologic subtyping of lymphomas based on their cellular morphology has resulted in somewhat controversial classification systems, including the Rappaport nomenclature, the National Cancer Institute Working Formulation, and the Kiel classification (Greenlee et al. 1990). In humans, cutaneous nonepitheliotropic lymphoma may be of T cell or B cell origin (Harris, 2001; Ralfkiaer et al., 2001a,b).

Cutaneous nonepitheliotropic lymphoma has been recognized in dogs and cats (Moore et al., 1998). Unfortunately, the elaborate classification systems of lymphomas in humans are of limited value for predicting the behavior and prognosis of primary cutaneous nonepitheliotropic lymphoma in dogs and cats (Valli et al., 2002). In addition to the classical form, nonepitheliotropic lymphomas in dogs and cats also include vasotropic and vasoinvasive lymphoma, also referred to as lymphomatoid granulomatosis (Walder & Barr, 1986; Smith et al., 1996), and intravascular lymphoma, also referred to as malignant angioendotheliomatosis (Vangessel et al., 2000). The vast majority of cutaneous canine and feline

nonepitheliotropic lymphomas are of T cell origin (Moore et al., 1998; Affolter & Moore, 2000). B cell lymphomas are extremely rare (Day, 1995), and were not found in one study of 24 dogs (Moore et al., 1998).

The etiology of canine and feline nonepitheliotropic lymphoma is unknown. The presence of feline leukemia virus (FeLV) could not be shown by immunofluorescence on blood samples of affected cats (Caciolo et al., 1984). Nevertheless, a retroviral etiology should be considered, as FeLV virus was demonstrated in feline cutaneous epitheliotropic lymphoma using amplification by polymerase chain reaction (PCR) (Tobey et al., 1994). Although canine retrovirus has been isolated from a leukemic dog, a clear relationship to leukemia and lymphoma has not been established (Safran et al., 1992).

Clinical features

Nonepitheliotropic lymphoma is the most common form of cutaneous lymphoma in cats, while it is less common in dogs (Caciolo et al., 1984; Beale & Bolon, 1993; Moore & Olivry, 1994). Cutaneous lymphoma is reported to represent 1% of all canine skin tumors and 2.8% of all feline skin tumors, but these data include both epitheliotropic and nonepitheliotropic types (Goldschmidt & Shofer, 1992). Solitary or multiple, discrete dermal and subcutaneous nodules or infiltrative plaques may develop at any site of the body (Beale & Bolon, 1993). The oral cavity is less commonly affected. Ulcers and regional lymphadenopathy are common.

Sex predilections are not reported. Weimaraners, Boxers, Saint Bernards, Basset Hounds, Irish Setters, Cocker Spaniels, German Shepherd Dogs, Golden Retrievers, and Scottish Terriers have been reported to be predisposed (Beale & Bolon, 1993; Scott et al., 2001). The cutaneous intravascular lymphoma was reported in a 9-year-old, female spayed Boxer (Vangessel et al., 2000).

Surgical excision of solitary tumors in dogs has been reported as curative in a few cases of cutaneous nonepitheliotropic lymphomas (Brown et al., 1980; McKeever et al., 1982). However, the vast majority of canine and feline nonepitheliotropic lymphomas exhibit rapid progression and metastasis to draining lymph nodes; subsequent systemic involvement is common (Moore et al., 1998).

Vasotropic and vasoinvasive nonepitheliotropic lymphoma (lymphomatoid granulomatosis)

This form of cutaneous lymphoma is characterized by recurrent dermal and subcutaneous nodules or black fluctuant plaques. These progress to punctate or crateriform ulcers with massive exudation and crusting (Walder & Barr, 1986; Smith et al., 1996; Wood et al., 2001). The lesions involve the face, eyelids, mucocutaneous junctions, and trunk. Affected dogs also develop respiratory distress due to pulmonary involvement (Postorino, 1987; Moore et al., 1998). Although pulmonary lymphomatoid granulomatosis has been reported in the cat (Valentine et al., 2000), cutaneous involvement has not been seen in that species.

Cutaneous intravascular lymphoma (malignant angioendotheliomatosis)

This form of lymphoma has been reported in the skin of one dog (Vangessel et al., 2000). The animal presented with hyperpigmented, dark red, alopecic plaques and nodules on the head, neck, and trunk. Upon necropsy, additional tumor infiltrates were identified in the frontal lobe of the brain. Intravascular lymphoma has previously been reported in the brain and other organs in dogs and cats (Summers & Lahunta, 1985; Lapointe et al., 1997). Cutaneous intravascular lymphoma has not been described in cats.

Histopathology

Nonepitheliotropic lymphoma

(Figures 37.19 through 37.22)

Classical nonepitheliotropic lymphoma is characterized by predominantly deep dermal and subcutaneous nonencapsulated masses composed of sheets or nodular perivascular aggregates of relatively monomorphic cells. The neoplastic infiltrates have a bottom-heavy or base-wide configuration and efface cutaneous structures. With superficial dermal involvement, an area of uninvolved superficial dermis (Grenz zone) is usually seen, and adnexal structures are not invaded. However, occasional intraepidermal tumor cells may be present. The epidermis overlying the tumor may be ulcerated. Dispersed reactive eosinophils are common (Moore & Olivry, 1994), which is likely due to release of eosinophilic chemotactic factor IL-5 by the neoplastic lymphocytes.

The cellular morphology of cutaneous nonepitheliotropic lymphoma is highly variable, and can be subclassified as small cell, large cell, or immunoblastic type. The large cell phenotype is most common. Small cells are characterized by round nuclei with condensed chromatin and scant cytoplasm. Large cells have large, oval, folded, vesicular nuclei and abundant clear cytoplasm, and hence may mimic the appearance of histiocytes. Large cell lymphomas also have been referred to as ‘clear cell’ lymphomas or, inaccurately, ‘histiocytic’ lymphomas. Occasionally, the neoplastic lymphocytes resemble immunoblasts and contain large vesicular nuclei, one central large nucleolus, and scant cytoplasm.



Fig. 37.19 Nonepitheliotropic lymphoma in a dog. The tumor cells have vesicular nuclei with irregular or folded profiles. Mitotic activity is fairly high.

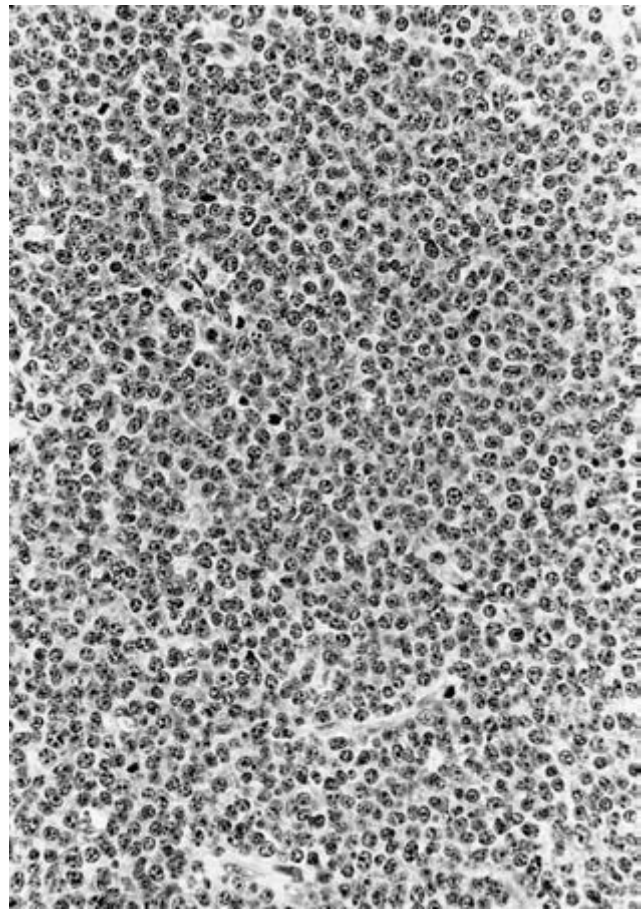


Fig. 37.20 Nonepitheliotropic lymphoma in a dog. Large, vesicular nuclei contain multiple nucleoli, which tend to have a peripheral distribution. Note fairly high mitotic activity.

Anisokaryosis may be prominent and cleavage of the nuclei may be seen. Mitotic activity is highly variable and corresponds to cell type and/or tumor grade. Small cell lymphomas have a low mitotic activity, while most large cell and immunoblastic lymphomas have a moderate to high mitotic rate.

The authors have observed a small number of nonepitheliotropic lymphomas in dogs in which early stages were associated with severe pleocellular inflammation. In some cases, the dermatitis features numerous eosinophils, and eosinophilic furunculosis may be present. Admixed with the reactive infiltrate are large, poorly differentiated, rounded, pleomorphic tumor cells with large, round and cleaved, hyperchromatic nuclei and a high nuclear to cytoplasmic ratio. With disease progression, the neoplastic cells become more numerous and accumulate in sheets.

Occasionally, reactive lymphoid infiltrates cannot be differentiated from neoplastic cell populations based on morphologic features and immunohistochemistry. One author (V.K.A.) has observed cutaneous pleomorphic T cell or B cell lesions suggestive of cutaneous lymphoma. Clinical follow-up, however, indicated a reactive process, as the T cell lesions regressed spontaneously and the B cell lesions regressed while on treatment with antibiotics. Evaluation of clonality for B cells (clonal rearrangement of immunoglobulin heavy chain [IgH] and for T cells (clonal rearrangement of T cell receptors [TCRs]) assists in identifying a clonal lymphocyte population, which supports the presence of a neoplastic process. Reactive B cell or T cell infiltrates are usually polyclonal.

Immunohistochemistry (see below) often is required to differentiate nonepitheliotropic lymphoma from other cutaneous round cell tumors, such as histiocytomas, plasmacytomas, mast cell tumors, transmissible venereal tumors, Merkel cell tumors, and amelanotic melanomas with predominantly round cells. Moreover, early lymphomas associated with massive reactive pleocellular infiltrates often cannot be differentiated from purely inflammatory processes. Identification of T cell origin of the interspersed atypical tumor cells requires immunohis-

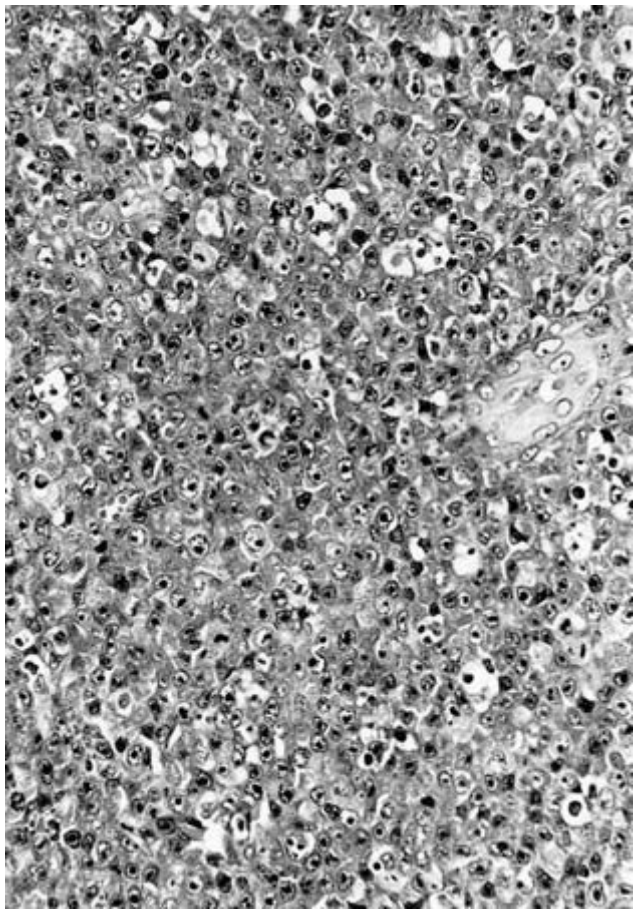


Fig. 37.21 Nonepitheliotropic lymphoma in a dog. The tumor cells resemble immunoblasts: they have a moderate amount of amphophilic cytoplasm, large vesicular nuclei, and prominent centrally-located nucleoli. Note numerous mitotic figures.

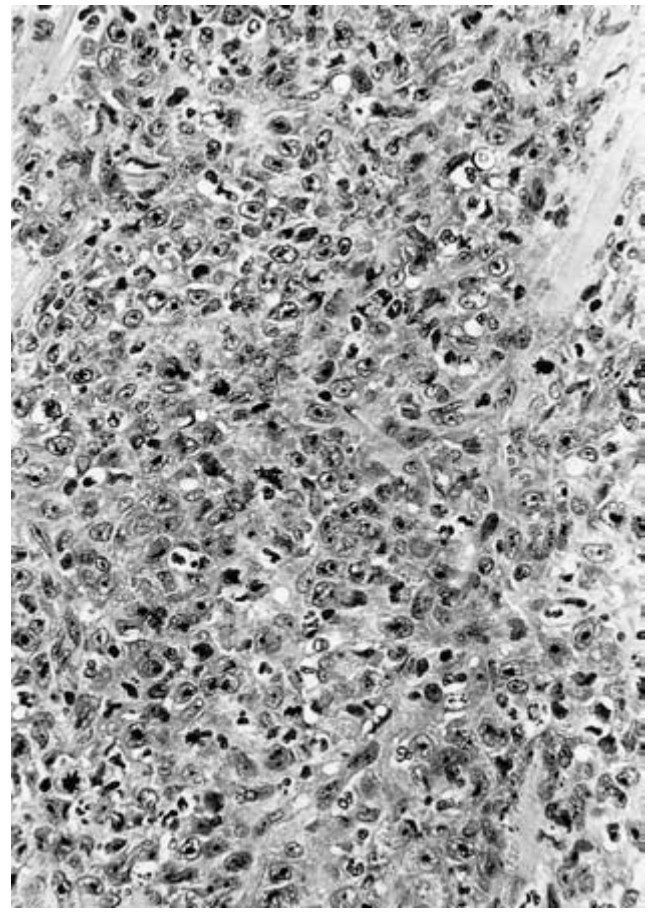


Fig. 37.22 Nonepitheliotropic lymphoma in a cat. The highly mitotic cells have abundant poorly-defined cytoplasm, large pleomorphic nuclei, and prominent nucleoli; note resemblance to histiocytes.

tochemistry. In contrast to nonepitheliotropic lymphomas, histiocytomas have a 'top-heavy' configuration and intraepidermal tumor cells can usually be found. The cytologic features, however, may be indistinguishable between these two tumors, requiring immunohistochemistry. Plasmacytomas often display marked anisocytosis, and anisokaryosis, and binucleated and multinucleated cells are common. Moreover, the proliferating plasma cells are arranged in tight packets, and well-differentiated plasma cells can usually be identified along the tumor margins; eosinophils, however, are not present. Dense cytoplasmic RNA of plasma cells stains magenta with methyl green pyronine (MGP) stain. Both mast cell tumors and lymphomas may have many intralesional eosinophils. Toluidine blue and Giemsa stains will usually identify the metachromatic granules of poorly granulated mast cell tumors. Transmissible venereal tumors comprise round cells with fine cytoplasmic vacuoles, which are best identified by aspirates and imprints from fresh specimens. Merkel cell tumors are characterized by marked packeting or nesting of the tumor cells, and a fine vascular stroma is noted. Round cell amelanotic melanomas may be characterized by cells with a larger amount of cytoplasm when compared to lymphomas, and there may be few admixed spindle tumor cells. Fontana–Masson stain may assist in detecting small amounts of melanin within the tumor cells.

Vasotropic and vasoinvasive nonepitheliotropic lymphoma (lymphomatoid granulomatosis)

(Figures 37.23 and 37.24)

Similar to lesions in humans, abrupt full-thickness epidermal ulceration overlying wedge-shaped zones of ischemic dermal necrosis are present. Angiocentric, multinodular tumor cell aggregates, which may coalesce to a diffuse tumor cell infiltrate, are noted in the surrounding intact deep dermis and subcutis. In many cases of vasotropic lymphoma, a monomorphic population is

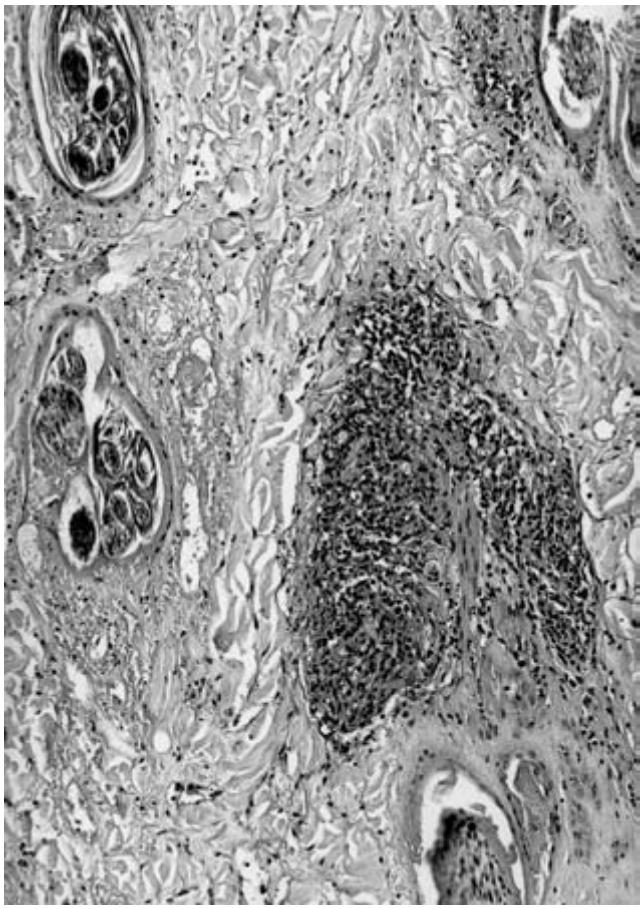


Fig. 37.23 Vasotropic and vasoinvasive, nonepitheliotropic lymphoma in a dog. The pleomorphic neoplastic infiltrate obliterates blood vessels at right. Note granular degeneration of dermal collagen and necrosis of adnexal epithelium within the margin of a dermal infarct at left.

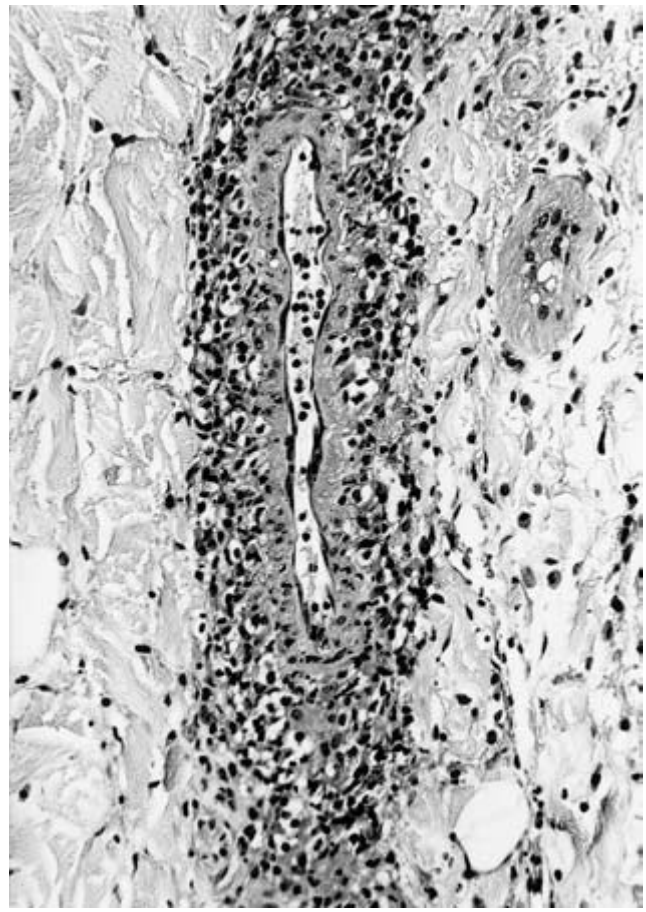


Fig. 37.24 Higher magnification of vasotropic and vasoinvasive, nonepitheliotropic lymphoma in a dog. The wall of a deep dermal arteriole is infiltrated by pleomorphic tumor cells.

present within and around blood vessel walls. Early lesions of lymphomatoid granulomatosis are more pleocellular and may have features of a granulomatous angiocentric inflammatory response. Over time, the number of pleomorphic large round cells increases, an increase in mitotic figures is noted, and vasoinvasion is observed. Vascular invasion may be associated with fibrinoid necrosis of the vascular wall (Smith et al., 1996).

The large neoplastic cells have pale cytoplasm and vesicular nuclei, which are slightly elongated and twisted or irregular in profile, and hence resemble histiocytes. However, their immunophenotype indicates T cell origin.

Cutaneous lymphomatoid granulomatosis may be overlooked primarily because of its rarity, and because it can mimic pleocellular, angiocentric reactive processes, such as reactive histiocytosis (see Chapter 13). The lesional histiocytes in reactive histiocytosis are fairly monomorphic and rarely exhibit mitotic activity, while progressive lesions of vasoinvasive lymphoma are characterized by pleomorphic large round cells with moderate to marked mitotic activity. Immunohistochemistry may be necessary to differentiate the two diseases (see below).

Intravascular lymphoma (malignant angioendotheliomatosis) (Figures 37.25 and 37.26)

Intravascular lymphoma is characterized by intravascular proliferations of neoplastic lymphocytes in the absence of a solid primary tumor (Valli et al., 2002). The reported canine cutaneous case was characterized by multinodular dermal masses that invaded the subcutaneous tissue, and was accompanied by vascular proliferation as occasionally seen in humans (Vangessel et al., 2000). The mass was composed of thin-walled vascular channels lined by plump fusiform cells. Multiple foci of hemorrhage and necrosis were noted. The vascular channels were packed with small to medium-sized, fairly monomorphous round cells with sparse cytoplasm and round to oval indented nuclei with one or two nucleoli. Histologic features of intravascular lymphoma are unique and characteristic,

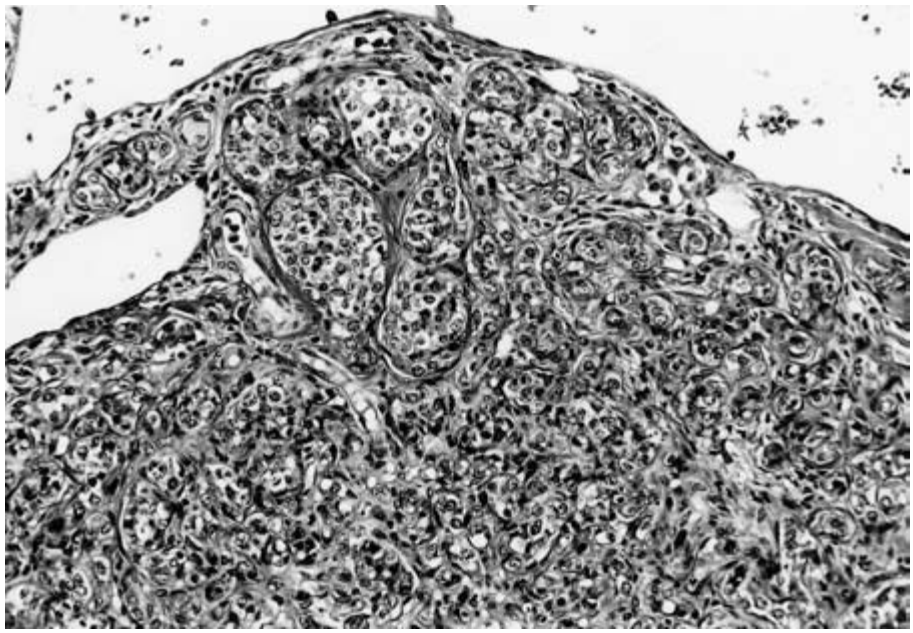


Fig. 37.25 Intravascular lymphoma in a dog. Proliferating small vessels are filled with neoplastic lymphocytes (Case material courtesy S.P. McDonough.)

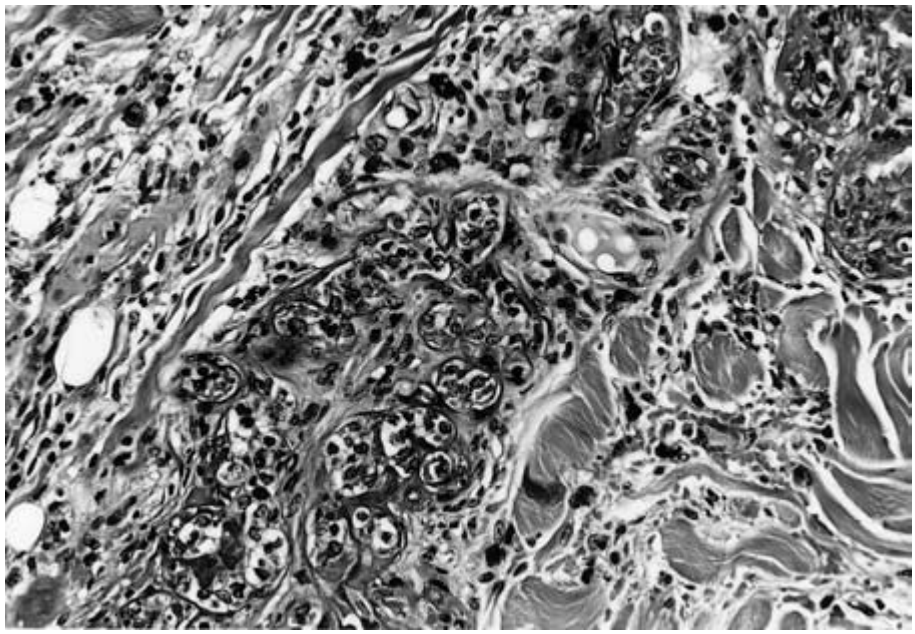


Fig. 37.26 Higher magnification of intravascular lymphoma of Fig. 37.25. Thin-walled vascular structures are filled with neoplastic lymphocytes.

and allow differentiation from other cutaneous round cell tumors.

Immunohistochemistry (see Table 37.1)

Classical canine and feline nonepitheliotropic lymphomas are predominantly composed of CD3+ T cells (Moore & Olivry, 1994; Moore et al., 1998). The few cases of reported B cell lymphomas have been identified by their expression of immunoglobulin G (IgG) (Day, 1995). Occasional cases of CD3–, CD79a– non-B, non-T cell proliferations have been observed in dogs (Moore et al., 1998). Canine nonepitheliotropic CD3+ T cell lymphomas comprise either CD8+ or double negative (CD4–, CD8–) lymphocytes; one CD4+ case was observed in a single study of 16 cases (Moore et al., 1998). The canine tumor cell population may express either αβ T cell receptor (TCRαβ) or TCRγδ; double negative cases can be observed with both TCRαβ or TCRγδ lymphomas. The T cells usually express CD45RA, in contrast to epitheliotropic lymphomas, and CD5 is expressed by about 60% of the cases (Moore et al., 1998). T cell receptor-silent cases have been seen in dogs as well, indicative of the loss of TCR expression by the tumor cells (Moore et al., 1998). Alternatively, these cases

could also represent CD3ε+ natural killer (NK) cell lymphomas (Yamaguchi et al., 1993). The tumor population may contain admixed numerous reactive CD1+, CD11c+, MHC II+ dendritic cells as well as reactive, well differentiated, small CD3+, CD8+ T cells.

In cats the immunophenotype has varied in the few cases evaluated to date. Neoplastic T cells are consistently CD3+ and CD5+, but CD4 and CD8 expression is variable. Further studies are needed.

In contrast to vasoinvasive lymphoma in humans, which is a clonal expansion of B cells (Gogstetter et al., 2000), canine vasoinvasive lymphomas (lymphomatoid granulomatosis) are composed of T cells (Smith, et al., 1996; Moore et al., 1998). The exact phenotype of the CD3+ cells has not been characterized to date. The intravascular lymphoma (malignant angioendotheliomatosis) reported in the dog was composed of CD45+, CD3+, CD8+, TCRαβ+ T cells entrapped in proliferative blood vessels (Vangessel et al., 2000).

In contrast to cutaneous nonepitheliotropic lymphoma, other round cell tumors lack T cell surface molecules. Instead, histiocytomas are positive for CD1, CD11c, MHC II, and E-cadherin. Transmissible venereal tumors consistently express CD45, and may be positive for CD45RA and CD49d. In contrast to lymphomas, poorly granulated mast cell tumors are positive for KIT and may also be positive for tryptase. Amelanotic melanomas and Merkel cell tumors both lack expression of leukocyte antigens CD45 and CD18. Merkel cell tumors are positive for cytokeratin 20 (detected by pancytokeratin stains), neuron-specific enolase (NSE), synaptophysin, and chromogranin A, while melanomas may express melanoma-associated antigen recognized by T cells (MART-1), melanoma-associated antigen (Melan-A), S100, tyrosinase-related protein-2 (TRP-2) tyrosinase, the melanoma isoform of microphthalmia transcription factor (MITF-M) or HMB45/gp100 instead.

Differentiation of neoplastic versus reactive T cell proliferations cannot be reliably achieved by evaluating the expression of proliferating cell nuclear antigen (PCNA), as both conditions may be characterized by an increase of PCNA (Murphy & Olivry, 2000). Evaluation of the lesions for clonal T cell receptor arrangement of the lesional T cell population may identify a neoplastic lymphoid population within a reactive cellular infiltrate.

CHRONIC LYMPHOCYTIC LEUKEMIA WITH CUTANEOUS LESIONS

(Synonym: leukemia cutis)

In contrast to acute lymphocytic leukemia, a process characterized by a very rapid deterioration, chronic lymphocytic leukemia presents with a slowly progressive clinical course during which cutaneous lesions may develop. Lymphocytic leukemia associated with neoplastic infiltrates in the skin is also referred to as leukemia cutis (McLean & Haynes, 2003). In humans, these lesions are usually characterized by nodules, plaques, and ulcers, or diffuse erythroderma (Head & Edelson, 1993; McLean & Haynes, 2003). Chronic T cell lymphocytic leukemia with cutaneous lesions has been recognized in two dogs (Moore, P.F. & Vernau, W. personal communication, 2003), and a cat (Affolter & Moore, 2000). The morphologic and immunophenotypic characteristics of the tumor cells in the skin are similar to the cells in the peripheral blood.

Clinical features

Both dogs and the cat had been diagnosed with chronic T cell leukemia prior to the development of skin lesions. Leukemia had been confirmed by complete blood count (CBC), flow cytometry, and immunohistochemistry on cytospin preparations from peripheral blood.

All three animals were middle-aged. The domestic shorthaired cat had CD3+, CD5+, CD4+ leukemia (Affolter & Moore, 2000). One dog, a male, had CD3+, CD8+, TCRγδ+ T cell leukemia, and cytology was suggestive of a proliferation of large granular lymphocytes (Moore, P.F. & Vernau, W., personal communication, 1999). The second dog, an 8-year-old, neutered male Labrador Retriever, was diagnosed with a CD3+, CD8+, TCRαβ+ T cell leukemia (Moore, P.F. & Affolter, V.K., unpublished data, 2003).

Numerous small skin papules and nodules were observed in all three animals. In the first dog, the skin lesions developed while receiving chemotherapy. Small papules and nodules were present on the head, trunk, and extremities, and were arranged in a symmetrical distribution. A linear arrangement of nodules along the ear margins and the eyelids was seen in the cat; this linear configuration suggested an association with vessels or lymphatics (Affolter & Moore, 2000). In both dogs and the cat, the nodules were not pruritic and not painful. Some nodules were ulcerated.

Histopathology (Figures 37.27 and 37.28)

Skin biopsies reveal a dense nodular, monomorphic lymphocytic infiltrate closely associated with dermal blood vessels, forming perivascular cuffs. The dermal infiltrate may become more diffuse and extend to the basal lamina. However, epitheliotropism is not noted. The samples from the cat revealed superficial and deep dermal involvement. The first dog had primarily deep dermal infiltrates (Moore, P.F. & Vernau, W., personal communication, 2003), while the second dog had mid-dermal to superficial perivascular infiltrates.

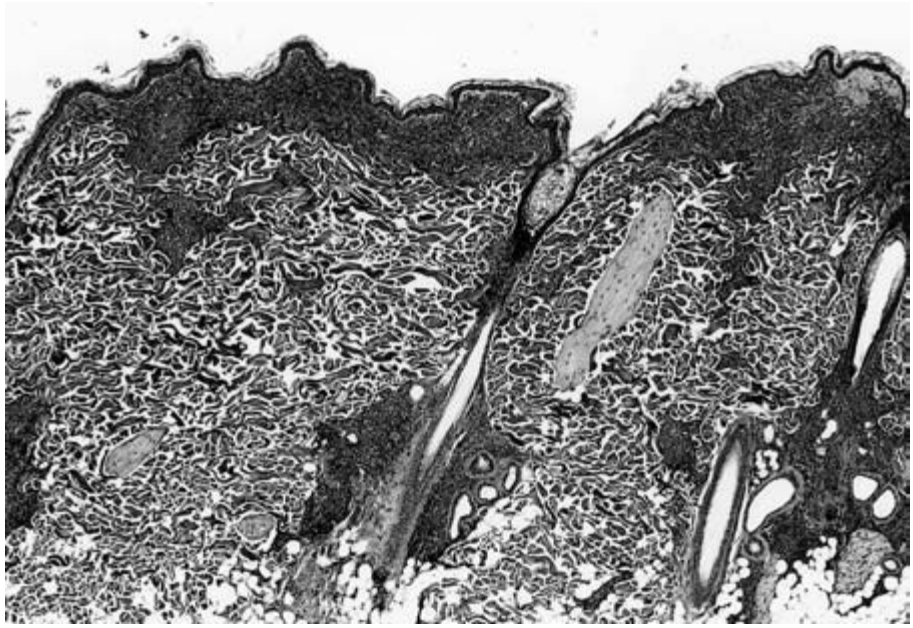


Fig. 37.27 Chronic lymphocytic leukemia with cutaneous lesions in a cat. Small lymphocytes are accumulating perivascularly; these have coalesced superficially and around adnexa.



Fig. 37.28 Higher magnification of chronic lymphocytic leukemia with cutaneous lesions of Fig. 37.27 demonstrating uniformly small neoplastic lymphocytes.

Some vessels may be dilated and obliterated by neoplastic cells that are morphologically identical to the infiltrate in the dermis. Tissue necrosis subsequent to vascular obstruction may be present. Neoplastic cells have a relatively well-differentiated morphology, with small or slightly enlarged nuclei, dense or finely stippled chromatin, and a scant or moderate amount of cytoplasm. Mitotic figures were not seen in the three observed cases.

Chronic lymphocytic leukemia with cutaneous involvement should be differentiated principally from primary cutaneous nonepitheliotropic T cell lymphoma, including intravascular lymphoma (malignant angioendotheliomatosis), as well as cutaneous lymphocytosis (if the infiltrating population is well differentiated). Intravascular lymphoma is composed of tumor cells confined to the vascular structures, and a dermal infiltrate is not present. In chronic lymphocytic leukemia with cutaneous involvement, the close association of the tumor cell population with the dermal vasculature and the presence of intravascular tumor cells are in contrast to primary cutaneous nonepitheliotropic lymphoma, which is characterized by a more diffuse neoplastic lymphocytic infiltrate with

variable numbers of tumor cells in lymphatics. In contrast to leukemia with cutaneous lesions, cutaneous lymphocytosis is not as tightly related to the vasculature, and generally presents as a diffuse dermal infiltrate of well differentiated lymphocytes.

Immunohistochemistry (see Table 37.1)

The cutaneous T lymphocytic infiltrates exhibit an immunophenotype identical to the neoplastic lymphocytic infiltrate in the peripheral blood. The tumor cells in the cat were positive for CD3, CD5, and CD4 (Affolter & Moore, 2000). The intravascular and perivascular tumor cells in the first dog were CD3+, CD8+, TCRγδ+ (Moore, P.F. & Vernau,W., personal communication, 2003) and in the second dog were CD3+, CD8+, TCRαβ+ (Moore, P.F. & Affolter, V.K., unpublished data, 2003).

Immunophenotyping of the lesional lymphocytic infiltrate does allow differentiation between leukemia with cutaneous involvement and primary cutaneous lymphoma with secondary systemic involvement. However, similar to nonepitheliotropic lymphoma (see p. 882), immunohistochemistry will help to rule out other round cell tumors because they lack expression of T cell markers.

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Thelma Lee Gross, Peter J. Ihrke, Emily J. Walder, Verena K. Affolter
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