lymphocytic satellitosis, and this may be individual cells or progress to confluent areas of the epidermis, leading to ulceration.[469,470] There is usually an interface dermatitis. Rare cases have been reported with predominantly hair follicle involvement.[469]

A trigger for the disease should be pursued with a thorough history of a possible drug exposure, infections, or neoplasia. Polymerase chain reaction (PCR) testing for the presence of virus in the skin, particularly herpes and parvovirus, is indicated; recognition of such a triggering disease may lead to additional treatment options. Idiopathic cases occur and may be more common in old dog erythema multiforme. Diet trials should also be attempted prior to making such a diagnosis, since food has been a reported trigger.[47]

Direct immunofluorescence testing usually yields negative results but may demonstrate IgG, IgM, or C3 between epidermal keratinocytes, around globoid bodies in the superficial dermis, or in association with dermal blood vessel walls.[47,411]

CLINICAL MANAGEMENT

Erythema multiforme may run a mild course, spontaneously regressing within a few weeks. An underlying cause should be sought and corrected whenever possible, an intervention that may result in spontaneous resolution.[47] Severe vesiculobullous cases of erythema multiforme require supportive care and an exhaustive search for underlying causes. When trigger factors can be identified and eliminated, the erythema multiforme usually resolves within 3 weeks.[47] Immunosuppressive drugs such as glucocorticoids, azathioprine, and cyclosporine have been used for treating some cases. IVIG, an expensive treatment useful for a variety of immune-mediated diseases, has been effective in some life-threatening cases.[460,471] Pentoxifylline has anecdotal reports of benefit.

TOXIC EPIDERMAL NECROLYSIS

TEN is a rare, life-threatening, extensive vesiculobullous and ulcerative disorder of skin and oral mucosa in dogs, cats, and human beings. As noted earlier, TEN and Stevens-Johnson syndrome in humans are now believed to be the same disease, with the latter less extensive and severe. These are separate from erythema multiforme.[472,473]

CAUSE AND PATHOGENESIS

In humans, TEN is usually considered an adverse drug reaction, but a small number of cases have been associated with other causes, including vaccine reactions, neoplasia, infections, and pregnancy.[472-475] This appears to be true in dogs and cats as well. Genetics also plays a role in humans, where it has been shown the reaction to the drug carbamazepine is associated with HLA-B1502.[476] Over 200 drugs have been associated with TEN in humans, though most cases are related to a group of 14 high-risk drugs.[472,474] A variety of drugs and causes have been associated with TEN in dogs, most notable are the antibiotics trimethoprin sulfa, cephalosporins and penicillins (Box 9-2).[25,133,430,477-480] Flea dips were implicated in both a dog and cat that experienced TEN.[481] Some cases have been associated with other disease such as pseudomonas otitis and anal sacculitis. The definitive association with the disease has not been made. Some of these had been treated with drugs and since even topicals may induce the disease the exact cause is uncertain. Some cases are idiopathic.

The pathomechanism of TEN is not exactly known but is believed to be a cellular immunologic reaction involving primarily keratinocytes; however, T cells and macrophages may play some part. In humans, massive keratinocyte apoptosis is the key event.[472] *Apoptosis* is a form of programmed cell death that results in cell shrinkage, nuclear pyknosis, then karyorrhexis and formation of plasma membrane–bound apoptotic bodies.[482] The massive apoptosis appears to be triggered by two pathways. The perforin-granzyme pathway involves formation of perforin channels in the cell membrane that allow granzyme to enter the cell and activate the intracellular caspase enzyme system. Activation of cell surface death receptors also occurs by binding of cytokines from the TNF family, most notably TNF-α and Fas-ligand.[474,483,484] Activation of the death receptors results in activation of the intracellular caspase system that triggers apoptosis.[473,482]

There are elevations in multiple other cytokines; in TEN, IL-13 is elevated but is not elevated in erythema multiforme.[483,485] Increased levels of glutathione-S-transferase in keratinocytes early in lesion development has led to the hypothesis that drug interactions lead to production of intracellular reactive oxygen species and subsequent keratinocyte damage.[473] In dogs, a study evaluating a histopathologic marker for apoptosis did not find it in any of seven cases diagnosed as TEN, though apoptotic cells were found in other diseases including erythema multiforme.[292] This discrepancy has yet to be explained and raises the question of whether the mechanism in dogs is similar to humans. Certainly it is still unknown in dogs.

Box 9-2 Causes of TEN/EM Reactions in the Dog

Antibiotics
Amoxicillin
Amoxicillin clavulanate
Cephalexin
Chloramphenicol
Enrofloxacin
Erythromycin
Gentamicin
Lincomycin metonidazole
Ormetoprim-sulfadimethoxine
Penicillin
Tetracycline
Trimethoprim-sulfadiazine
Trimethoprim-sulfamethoxazole
Infections
Pseudomonal otitis externa
Staphylococcal dermatitis
Anal sacculitis
Miscellaneous
Anesthetic agents
Aurothioglucose
Chlorpyrifos
Beef and/or soy (in diet and chewable heartworm preventive)
Diethylcarbamazine
D-limonene
Dinotefuran/permethrin
Idiopathic
Ivermectin
Levamisole
L-Thyroxine
Moxidectin
Otic drops
Phenobarbital

CLINICAL FEATURES

There are no apparent age, breed, or sex predilections. Clinically, TEN is usually characterized by an acute onset of constitutional signs (pyrexia, anorexia, lethargy, depression) and multifocal to generalized erythematous macules or patches usually involving the body and multiple mucosal surfaces.[430,444,469,480] It has been proposed that the percentage of body affected with ulcerations or epidermal detachment be used to separate Stevens-Johnson syndrome (<10%), overlap

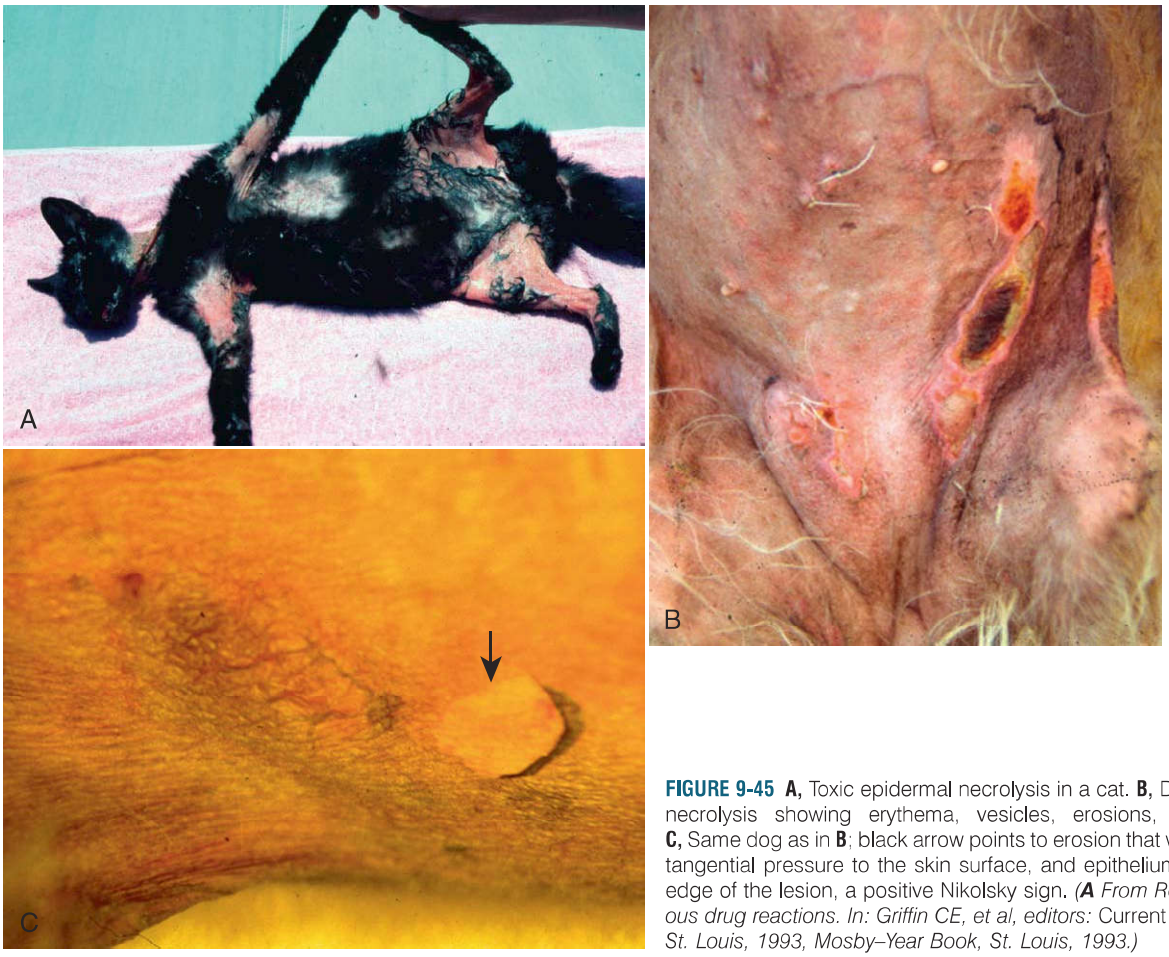


FIGURE 9-45 **A,** Toxic epidermal necrolysis in a cat. **B,** Dog with toxic epidermal necrolysis showing erythema, vesicles, erosions, ulcers, and necrosis. **C,** Same dog as in **B**; black arrow points to erosion that was created by applying tangential pressure to the skin surface, and epithelium sloughing to the right edge of the lesion, a positive Nikolsky sign. *(**A** From Rosenkrantz WS: Cutaneous drug reactions. In: Griffin CE, et al, editors:* Current veterinary dermatology, *St. Louis, 1993, Mosby–Year Book, St. Louis, 1993.)*

syndrome (10%-30%), and TEN (>30%).[444] Classic target lesions have not been described in dogs and are also not present in humans, though flat atypical target lesions may be seen in humans. This specific lesion distinction, of atypical target lesions, has not been evaluated in dogs and cats. Some lesions rapidly progress to vesiculobullous, necrotic, then ulcerative lesions (Fig. 9-45, *A* and *B*). Nikolsky sign is often positive, and even routine touching or handling of skin may result in epidermal sloughing (Fig. 9-45, *C*). Anywhere on the body may be involved, but oral mucosa and pads are commonly affected. Other mucosa that may be involved include rectal, esophageal, conjunctival, and tracheal mucosa. Hemorrhagic diarrhea has also been described, suggesting greater involvement of the intestinal mucosa.[469] Cutaneous pain is usually moderate to marked.

DIAGNOSIS

The differential diagnosis is relatively limited in severe cases with constitutional signs and acute history and rapid progression. In this clinical setting, burns, severe erythema multiforme without target lesions, superficial suppurative necrolytic dermatitis, toxic shock syndrome, and vasculitis would be the major differentials. Definitive diagnosis is based on acute progressive history, physical examination, and skin biopsy. The key histopathologic findings in TEN are full-thickness devitalization of the epidermis, evidenced by hypereosinophilic cytoplasm and pale or hyperchromatic nuclei, and minimal dermal inflammation.[469,470] The relative lack of dermal inflammation is in contrast with the cell-rich inflammation that occurs in erythema multiforme. In humans, early lesions have some T lymphocytes present, and later lesions, though still cell-poor, have more macrophages and dermal dendrocytes—again, a feature different from the cell-rich T-lymphocyte infiltrate found in erythema multiforme. The infundibular region of hair follicle outer root sheath epithelium may be similarly affected. Following epidermal death, dermo-epidermal separation results in subepidermal vesicles or bullae. The periodic acid–Schiff (PAS)-positive BMZ, when present, is usually located at the floor of the vesicles. Because this disease in humans and dogs is not characterized by antibody-mediated disease, direct and indirect immunofluorescence testing is not warranted, and if done when other ulcerative bullous diseases are suspected will be negative.

TEN is a life-threatening disease with significant mortality in all species. The diagnosis is associated with a mortality rate of 30% to 50%. In hospitalized human patients with TEN, a specific scoring system was developed with a linear regression analysis of 162 patients, and then the system was validated in 75 patients.[486] This system evaluates seven patient features, giving a score of 1 for every positive response, and total score correlates with mortality rate. A score of 0 to 1 has only 3.2% mortality, but a score over 5 has 90% mortality. Therefore a diagnosis is one step, but scoring patients is important to determine the real prognosis. Some features evaluated such as tachycardia and serum urea, glucose, and bicarbonate levels have not been analyzed in dogs and cats in a similar way. In dogs and cats, the more extensively the lesions cover the body,

the poorer the prognosis. In humans, sepsis is the leading cause of death.

CLINICAL MANAGEMENT

The prognosis for TEN in dogs and cats is guarded to poor, but no mortality rate has been published, and the overlap with what has been called "severe erythema multiforme" would likely affect the results of a review of veterinary cases. Mortality is greatest in idiopathic cases, wherein a precipitating factor cannot be recognized and specifically corrected.[487] The sequelae and prognosis are similar to those of a massive second-degree burn, owing to fluid, electrolyte, and colloid losses and to secondary infections and sepsis that compound the loss of epidermal barrier function. Mortality rates are lower when therapy in humans is conducted in specialty treatment centers for burn patients.[488,489]

Initially, treatment should consist of (1) stopping any suspected drug or correction of the underlying cause, (2) fluid and electrolyte replacement, and (3) ulcer wound management to prevent infections and sepsis. In addition, treatments directed at stopping or counteracting the immune mechanism have been used in both humans and animals, but unfortunately there are no controlled or prospective studies documenting the efficacy of any specific treatment. The use of systemic glucocorticoids is controversial, some investigators thinking that these drugs are at best not helpful and at worst detrimental, though a large retrospective study did not show a detrimental effect.[472,474,490] Overall they are not considered valuable as primary immunosuppressive treatment, partly because they increase the risk of sepsis.[474] Cyclosporine, because of its effects on T lymphocytes and apoptotic pathway, has also been recommended and reported as effective.[474,491] Though reports are limited in dogs and cats, cyclosporine 5 to 7 mg/kg every 24 hours has been used as an initial immunosuppressive treatment. Plasmapheresis has been reported beneficial in humans but is again controversial because of the risk it poses for sepsis.[472,474] IVIG has been used with reported success in humans, dogs, and cats.[399,471,490,492,493] IVIG therapy may be effective presumably via Fas (CD95) blockade.[494] Anti-TNF antibodies are also being used to treat some humans with TEN. It is suggested that these treatments should be used very cautiously because one anti-TNF drug, thalidomide, had a trial stopped owing to a higher mortality rate in the treatment group.[474] No sole therapy has proven effective, so a variety of combinations have been proposed. Plasmapheresis combined with IVIG, as well as anti–TNF-α antibodies and *N*-acetylcysteine to counteract drug-induced reactive oxygen species have been combinations recently recommended.[473,474] Recovery (depending on identification and correction of the underlying cause) usually occurs in 2 to 3 weeks.

VASCULAR DISEASES

A variety of diseases affecting dogs and cats are related to abnormalities of cutaneous blood vessels and result in skin lesions, some of which are characteristic. *Cutaneous vasculitis* is the term used to describe diseases where blood vessel walls appear to be the target of an inflammatory response. Confirming a diagnosis requires histopathologic analysis showing inflammation targeting blood vessel walls. However, the criteria for making the histopathologic diagnosis are associated with several problems:

1. Histopathologic evaluation is performed on biopsy samples selected by the clinician. Site selection and stage of the disease being biopsied may impact the ability to "confirm" the diagnosis even though it might have been confirmed if a different lesion had been sampled.
2. The pathologist has to recognize sufficient changes to reach the diagnosis. This problem is compounded by determining that the changes seen in vessels truly represent inflammation of the vessel, and not inflammatory cells leaving the vessels on the way to another primary skin site.[470] This has been shown to be a significant problem in cats with eosinophils in vessel walls.[495]
3. Cell-poor vasculitic diseases are now recognized that have very subtle vessel changes, such as thickened indistinct walls, loss of endothelial cells, and hyaline mural changes, though lesions may be more obvious (e.g., thrombosis).[359,470]

Vascular diseases are also recognized by other dermal changes, such as pale-staining collagen, atrophy of hair follicles, and cell-poor interface dermatitis, and therefore the diagnosis is now sometimes made even without true confirmation of the vessel wall being abnormal or the target of an inflammatory response.

Normally with dermal inflammation, the inflammatory cells migrate out of the vascular system in the postcapillary venules.[470,496] This makes the presence of inflammatory cells in other vessels, especially large vessels or arterial vessels, more likely to be indicative of vascular targeting. Determining that the postcapillary venule is the target of an inflammatory response requires that other histopathologic criteria be recognized, such as leukocytoclasia in the vessel wall and disproportionately more cells in the vessel wall than adjacent dermis.[470] The postcapillary venules have specialized endothelial cells that contain a variety of specific molecular markers including Toll-like receptors, which may initiate an inflammatory response (see Chap. 1).[496] In dogs and cats, the main vessels affected are the small vessels.[359]

The term *vasculitis* is used by some as a diagnosis, but it is not a definitive diagnosis but a cutaneous reaction pattern that is associated with multiple causes. This chapter also deals with other diseases associated with vascular lesions, such as proliferation or thrombosis and ischemic dermatopathy, that do not show actual vasculitis. Dermatomyositis is believed to be a vascular disease and has a strong breed association in shelties and collies (see Chap. 12). The vascular diseases or syndromes generally share a group of clinical lesions that should make the clinician suspicious they are dealing with a vascular problem. Table 9-8 lists most vascular syndromes/diseases described in dogs and cats, with key features. As a group, vascular diseases are uncommon in dogs and rare in cats.

CAUSE AND PATHOGENESIS

Since the vascular diseases comprise a variety of diseases or syndromes, it is only natural that the causes may vary. In general, it is believed that most of the syndromes are associated with an immunologic response that ends up damaging the vascular components of the dermis or subcutaneous tissue. Cutaneous vasculitis may be associated with coexisting disease, such as food hypersensitivity, insect bites, malignancies, and connective tissue disorders such as lupus erythematosus.[290,359,426,497] Many drugs have also been implicated as a cause of vasculitis.[133,358,359,399,404-406,410,413,426,430,497-502] Rosser and Merchant even reported dexamethasone and prednisone causing drug-induced vasculitis.[358] Drug dose may be important in some reactions; 7.5% of dogs with blastomycosis treated with itraconazole at 10 mg/kg/day experience cutaneous vasculitis (lymphedema and/or necrotizing lesions on one or more limbs), whereas dogs treated with 5 mg/kg/day do not experience this reaction.[503] Vaccines are also responsible for many cases of vasculitis, and there are two syndromes associated predominantly with vaccines. A variety of infections

Table 9-8 Vascular Syndromes

Syndrome Name	Key Feature
Lupus vasculitis	A form of lupus usually associated with systemic or cutaneous lupus erythematosus
Cryoglobulinemia/ cryofibrinogenemia	Associated with precipitation of cold-reactive immunoglobulins or immune complexes
Vaccine-associated vasculitis	Lesions develop following a vaccination, often with a lesion near the site of the vaccination; pinna apex is a common noninjected lesional site.
Septic vasculitis	Follows a severe bacterial infection and can be seen in deep pyoderma or secondary to severe generalized *Demodex* with cellulitis
Neutrophilic vasculitis	Characterized by neutrophilic vessel wall infiltration and may be leukocytoclastic
Eosinophilic vasculitis	Associated with arthropod reactions, adverse food reactions, or canine eosinophilic dermatitis
Granulomatous vasculitis	Characterized by granuloma formation with vasculitis and tending to involve panniculus or (one case) gingiva
Familial cutaneous vasculopathy of German shepherd dogs	Primarily affects paw pads and German shepherd dogs
Vasculopathy of greyhounds	Usually has concomitant renal disease
Solar vasculopathy	Develop in areas with little or no pigment or hair, most often nose or face
Proliferative arteritis of the nasal philtrum	Ulcerative lesion of the nasal philtrum initially reported in Saint Bernards
Proliferative thrombovascular necrosis of the pinnae	Wedge-shaped lesions typically involving the pinna apex only
Ischemic dermatopathy	Lesions not typically very inflammatory and characterized by alopecia, scale, and scarring

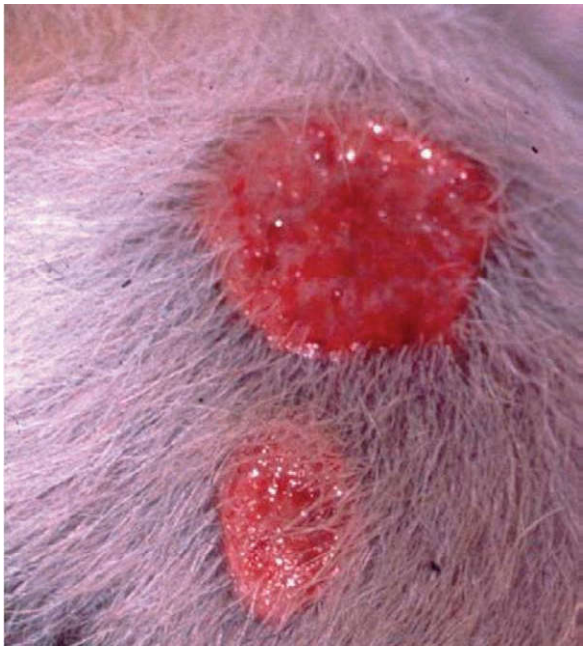


FIGURE 9-46 A case of eosinophilic dermatitis and vasculitis with two granulating crateriform ulcerative lesions.

including bacteria, protozoa, and viruses have also been associated with vasculitis.[359,497,504-507] Similar to the situation in humans, many dogs and cats with vasculitis do not have an underlying cause determined, and the disease is idiopathic. Eosinophilic vasculitis has been associated with arthropod reactions, canine eosinophilic dermatitis, food hypersensitivity, and mast cell tumors.[416,426,470] Some have suggested that eosinophils in vessels with feline eosinophilic granuloma and canine eosinophilic dermatitis are not a primary eosinophilic vasculitis.[417,495] Typical necrotic vascular-type lesions may be seen in cases of severe eosinophilic dermatitis and vasculitis (Fig. 9-46). Granulomatous vasculitis has been associated with septal panniculitis, Wegener granulomatosis that presented as gingivitis in a dog, and a case report of periocular edema and alopecia from cyclosporine.[470,508,509]

Vasculitis can occur via nonimmune mechanisms such as burns and trauma.[417,510] As a cause of cutaneous disease, however, it is thought to usually be immunologically mediated and most often the result of a drug reaction or infection.[349] The pathomechanism of most cutaneous vasculitides is assumed to involve type III hypersensitivity reactions.[349,358,499] Immune complexes formed during antigen excess are deposited in vessel walls. However, it certainly is more complex, and multiple mechanisms appear to play a role. There is evidence that alterations in blood flow (increased turbulence), alterations in vessel permeability, activation of immune receptors on endothelial cells in venules, defects in immune complex clearance, and autoantibodies may also be involved in many cases.[496,511-513] Even other cells in the skin, such as mast cells and nerves, via production and release of neuropeptides may be involved in the development of cutaneous necrotizing venulitis.[513] Genetics may also contribute; HLA-A11, Bw35, and genetic association with connective-tissue diseases have been shown in humans.[513] In dogs, breed predispositions and breed-related syndromes such as seen in the Chinese Shar-Pei, German shepherd dogs, greyhounds, Parson (Jack) Russell terriers, Scottish terriers, and Saint Bernards suggests this may be true in dogs as well.[514-519] It has also been suggested vaccine reactions are more commonly recognized in poodles, silky terriers, Yorkshire terriers, Pekingese, and Maltese, which may reflect breed predilection, small body size, and vaccine dose relationship, or the long period of anagen hair growth and "fuzzy" haircoat phenotype in these breeds.[358,394,504]

CLINICAL FEATURES

In dogs and cats, skin is often the only organ system involved, but other organ systems may be affected, such as the frequent association with renal involvement in greyhounds.[514] In these cases, skin lesions may represent the initial sign of a systemic disease or even precede development of other organ disease. Skin lesions typically occur in dependent areas of the body, in skin over areas of pressure and normal "wear and tear," and in skin covering extremities (pinnae, tip of tail, pads, elbows). Why there is a predilection for these sites has not been determined, but increased trauma, more susceptibility to cold temperatures, and sparse collateral vascular or supply in these regions are possible.

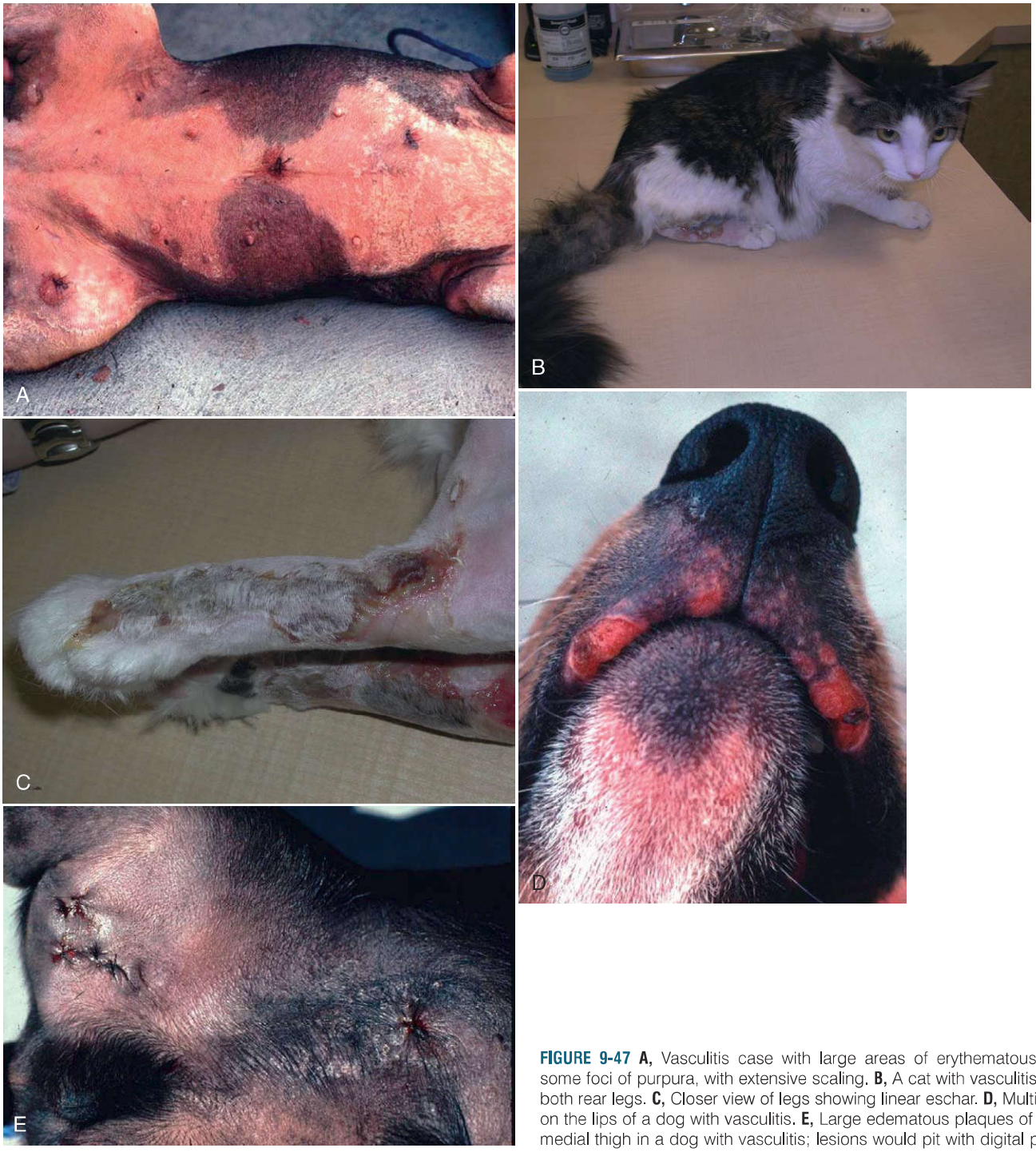


FIGURE 9-47 A, Vasculitis case with large areas of erythematous plaques, some foci of purpura, with extensive scaling. **B,** A cat with vasculitis mainly of both rear legs. **C,** Closer view of legs showing linear eschar. **D,** Multiple ulcers on the lips of a dog with vasculitis. **E,** Large edematous plaques of groin and medial thigh in a dog with vasculitis; lesions would pit with digital pressure.

Cutaneous signs of relatively acute or severe vasculitis usually include palpable purpura, erythematous to purpuric plaques, hemorrhagic bullae, eschar, crateriform ulcers, pitting edematous areas, and occasionally acrocyanosis (Fig. 9-47). Other lesions that may be seen include erythematous urticaria, plaques, papules, pustules, and lesions associated with ischemic dermatopathy (discussed later in this chapter under "Vascular Diseases"). Lesions typically involve the extremities (paws, lower legs, pads, claws), pinnae, lips, tail, scrotum, and oral mucosa (Fig. 9-47, *B* through *D*; Fig. 9-48). Lesions can follow vascular pathways and will then have a linear pattern (see Fig. 9-47, *B* and *C*; Fig. 9-48, *A* and *B*; Figs. 9-49 and 9-50).

Pinnal lesions are often more prevalent on the apex and concave surface (Fig. 9-51; see Fig. 9-49). Claws may be affected and show petechiae within the claw, onychodystrophy, onychomadesis, or exudate within the claw (Fig. 9-52; see Fig. 9-48, *C*). Pads may develop ulcers, depressed scarred or crusted hyperkeratotic plaques, leukoderma, thinning, and smoothness of pad surface (Fig. 9-53). Often, multiple pads are affected, and in some cases lesions will be confined to digital or metacarpal metatarsal pads. Pad lesions may affect pad margins, the center of the pad, or a combination. Generalized urticaria may occur and, in our experience as well as in the results of one study, this is more common with food hypersensitivity as the underlying etiology.[426] Edematous plaques, pitting edema, and

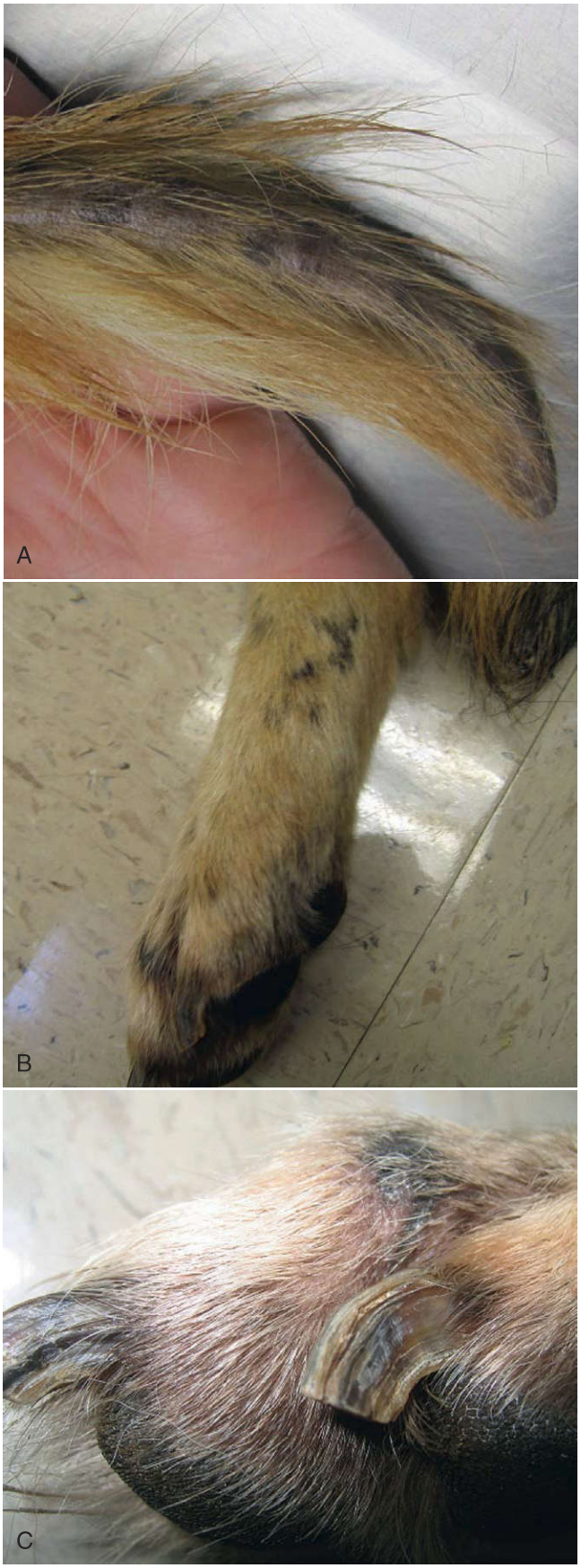


FIGURE 9-48 **A,** Tip of tail, a common site for vascular lesions, showing alopecia from ischemic dermatopathy. **B,** Linear lesions on distal leg in a dog with vasculitis. **C,** Same dog and leg showing onychodystrophy of claws.

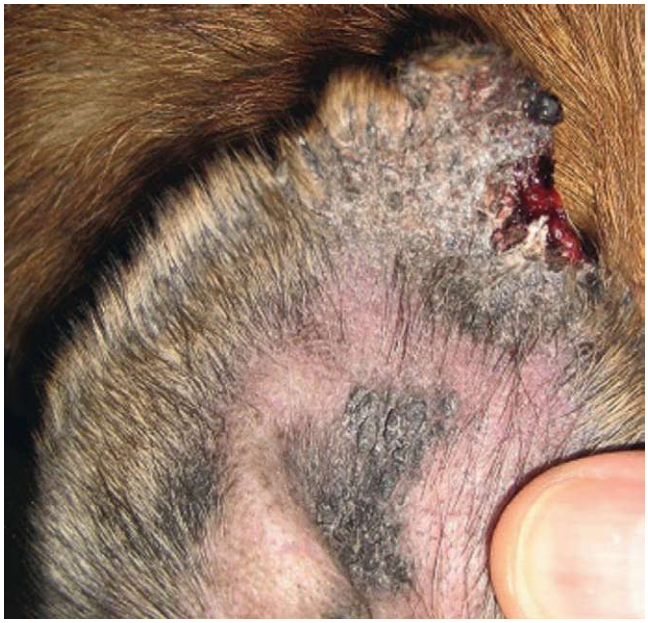
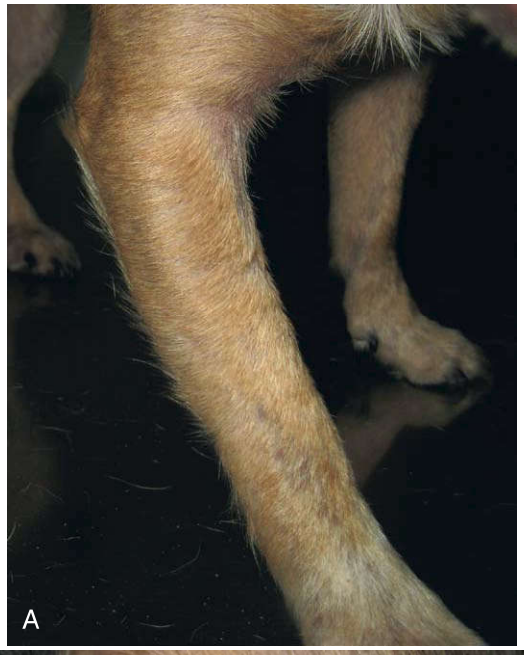


FIGURE 9-49 The pinna is a very common site for vasculitis lesions to occur, and this chronic case shows a variety of vascular lesions, alopecia, hyperpigmentation in a linear pattern, scarring, scale, ulceration, crusting, and necrosis, which has led to loss of tissue and altered shape to the apex of the pinna.



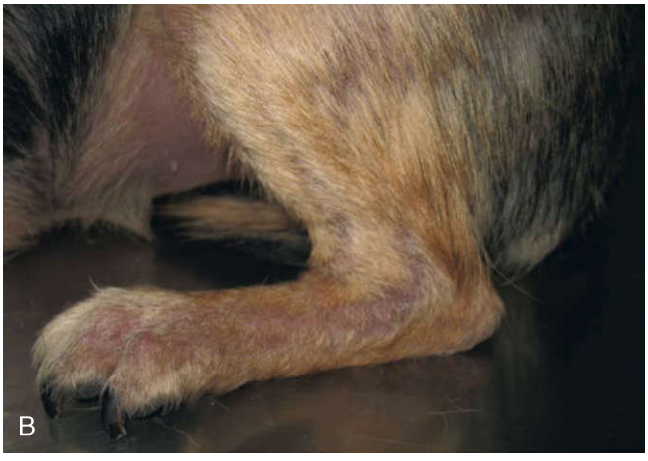


FIGURE 9-50 **A,** Front legs show linear lesions of alopecia and some erythema from elbows to top of paws on both front legs. **B,** Same case showing linear lesions on rear leg as well.

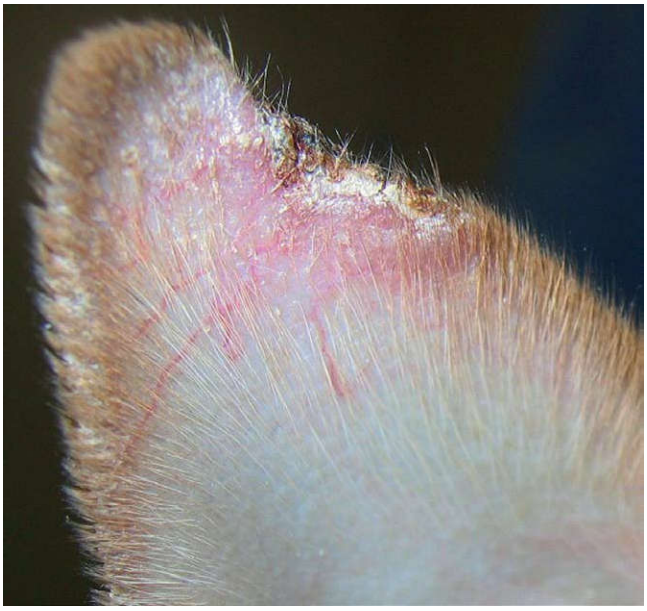


FIGURE 9-51 Apex pinnal lesions in a dog with proliferative thrombovascular necrosis. Note prominent blood vessels going to central lesion of necrosis and erythema.

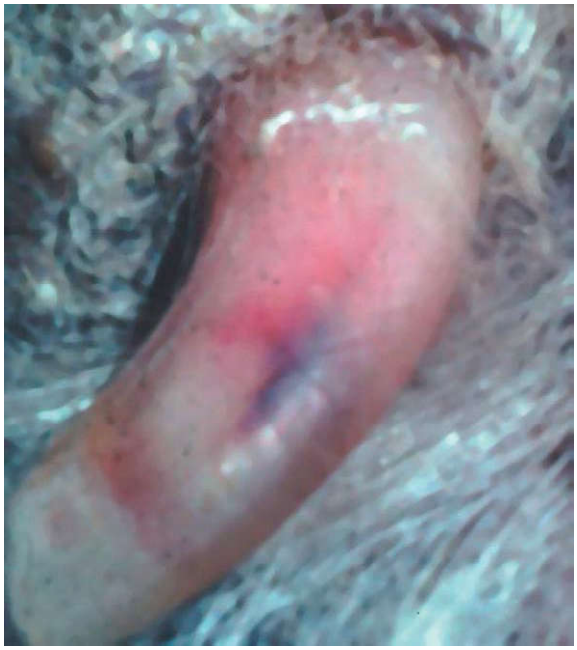


FIGURE 9-52 Petechial hemorrhage in a claw.

lymphedema may be present on the extremities or in the groin (see Fig. 9-47, *E*). The lesions may or may not be painful. In some animals, widespread erythema that may be purplish or cyanotic occurs. The erythematous skin does not blanch with diascopy, confirming its purpuric nature (Fig. 9-54). Rarely, subcutaneous nodules are noted, which represent panniculitis due to septal vasculitis.[497,500] Constitutional signs may be present, including anorexia, depression, and pyrexia. Although extracutaneous signs are uncommon, polyarthropathy, myopathy, neuropathy, hepatopathy, thrombocytopenia, and anemia have been reported in some dogs and cats. Any age, breed, or sex may be affected.

A *proliferative thrombovascular necrosis of the pinnae* has been recognized in dogs.[520] The etiology is unknown, but in one case report, fenbendazole drug reaction was associated with the disease.[405] There are no apparent age, breed, or sex predilections. Lesions begin on the apical margins of the pinnae and spread along the concave surface (Fig. 9-51). An elongated necrotic ulcer is at the center of the lesions. There is often a thickened, scaly, hyperpigmented zone surrounding the ulcers (Fig. 9-55). The lesions are wedge shaped, with the wide base at the pinnal apex. As the ulcer enlarges, the older areas undergo complete necrosis, resulting in a deformed pinnal margin.

A *proliferative arteritis of the nasal philtrum* that has classic presenting features has been recognized in dogs. The published cases include five Saint Bernards, one giant schnauzer, and one basset hound.[519,521] It has also been reported in a Doberman pinscher, Labrador retrievers, Newfoundland, and Samoyed dogs.[358,359] The authors have also seen the disease in multiple Saint Bernards, and similar to the original report, some of the dogs were related, so there does appear to be a genetic-based breed predilection in Saint Bernards. Generally, the dogs are young adults (2-6 years) at onset, and about equal numbers of males and females have been described to date, suggesting there is no sex predilection. The lesions are striking and even in long-standing disease are limited to the nasal philtrum; the rest of the nares are spared (Fig. 9-56). The lesion is a well-demarcated ulcer, generally linear to oval in shape, with the long axis parallel to the lip. They tend to be symmetrical, though some have affected mainly one side of the philtrum. The dogs have intermittent episodes of hemorrhage from the lesion.

A *solar vasculopathy* has been associated with solar damage in non- or lightly pigmented skin.[359] It has occurred in conjunction with discoid lupus erythematosus and vitiligo, and affected skin may also have other changes of solar dermatitis. No age, breed, or sex predilections are described. Lesions are described as generally well-demarcated areas of erythema, swelling, erosions, and ulcers and with chronicity, alopecia, and scarring. Since the disease occurs with solar light penetrating to the dermis, lesions are most commonly seen on the nose and face or other areas where hair loss has occurred, with underlying nonpigmented skin. Lesions may spread peripherally until pigmented skin is reached; inflammation results in alopecia and can even cause pigment loss, allowing further spread.

A *focal cutaneous vasculitis and alopecia at the sites of rabies vaccination* has been described in dogs.[358,420,522,523] Poodles and Yorkshire and silky terriers appear to be predisposed. Reactions are characterized by roughly annular areas of variable alopecia, hyperpigmentation, and less commonly, scaling or erythema overlying a variably indurated dermis and subcutis. The caudal or lateral thigh or the withers are typically affected (Fig. 9-57). The lesions generally appear 2 to 6 months after the subcutaneous administration of vaccine and persist for months to years. Mendelsohn reported that lesions may also develop at other typical vasculitis sites and still be associated with the typical localized lesion (Fig 9-57, *C,D*).[358] Usually the localized lesion develops prior to the other lesions, and these lesions have even resolved after surgical removal of the local rabies vaccine site lesion.[358]

A *cutaneous and renal glomerular vasculopathy* ("Alabama rot," "Greenetrack disease") has been described in kenneled and racing, related and unrelated, greyhounds (see Chap. 12).[514,524] A similar syndrome was also described in a Great Dane.[525] Usually young to middle-aged dogs are affected (6 months to 6 years), and there is no sex predilection. Palpable purpura, with lesions pinpoint to 10 cm in diameter, is characterized by reddened areas that rapidly become dark red to purple to black and then slough. Lesions are multiple and most commonly occur on the limbs and, less commonly, the groin and trunk (Fig. 9-58). Within 1 to 2 days, the lesions ulcerate and discharge a serosanguineous fluid. The ulcers are well demarcated and

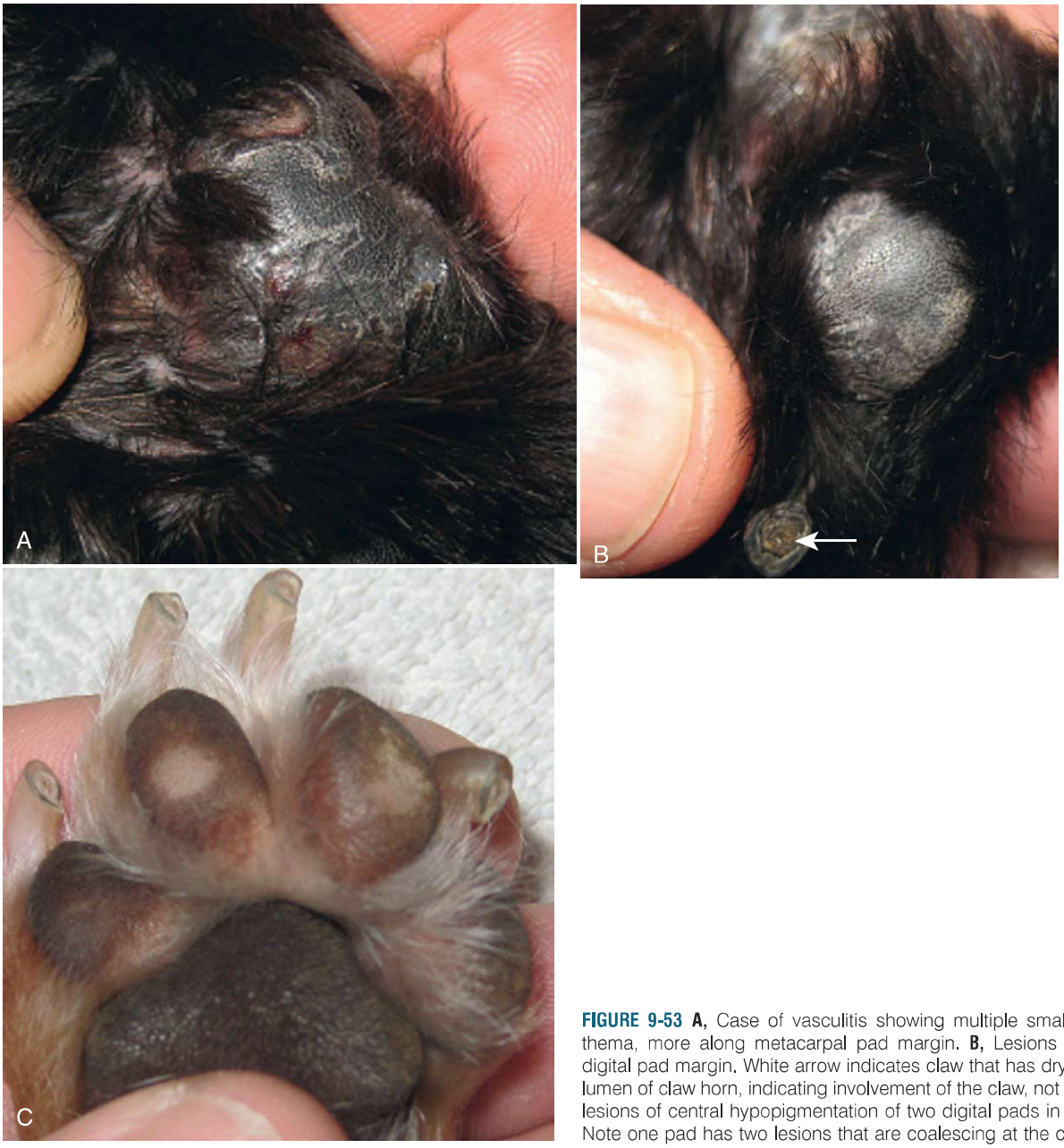


FIGURE 9-53 **A,** Case of vasculitis showing multiple small focal ulcers or erythema, more along metacarpal pad margin. **B,** Lesions of hyperkeratosis on digital pad margin. White arrow indicates claw that has dry crusty material filling lumen of claw horn, indicating involvement of the claw, not just pads. **C,** Vascular lesions of central hypopigmentation of two digital pads in a dog with vasculitis. Note one pad has two lesions that are coalescing at the center of the pad.

usually extend into the subcutis. Healing is slow, resulting in scar formation within 1 to 2 months. Many dogs experience pitting edema, especially distal to the stifle or elbow, on limbs that have ulcers. In most dogs, new lesions do not develop after the initial lesions resolve. Some dogs experience pyrexia, lethargy, polydipsia, polyuria, vomiting, dark or tarry stools, and acute renal failure. This syndrome is thought to be produced by verotoxin (Shiga-like toxin) elaborated by *Escherichia coli* in contaminated raw beef products (similar to the *hemolytic-uremic syndrome* in people).[524] A genetic predisposition may help explain the susceptibility of greyhounds.[524]

Familial (autosomal recessive trait) cutaneous vasculopathy of German shepherd dogs has been reported in young puppies, usually by 7 weeks age.[518] Similar lesions have been described in young fox terriers and miniature schnauzers.[359] The German shepherd dog puppies experience pyrexia and lethargy, most commonly associated with swollen depigmented footpads. Alopecia, crusts, and ulceration may also occur, involving the pinnae, tail, and nasal planum. Footpad biopsies demonstrate varying degrees and combinations of nodular dermatitis, collagenolysis, vascular degeneration, vasculitis, and cell-poor interface dermatitis with basal cell apoptosis. The changes may partly reflect the stage of disease at the time of biopsy. The cause is not determined, though a variety of immunologic test results have been normal. It has been suggested that similar lesions are seen in some vaccine-induced vasculitis cases, and possibly this played a role.[359]

Ischemic dermatopathy is a syndrome that results from loss of blood supply from either vasculitis or vasculopathy. Dermatopathologists include several vascular syndromes in this category they refer to as *cell-poor vasculitis*.[359,470] In some cases, a relationship between vasculitis and vasculopathy is present, because both histopathologic lesions may occur in the same case and may reflect stage of lesion development at time of sampling.[470] The original description and what is considered the prototypical forms of ischemic dermatopathy are post–rabies vaccination scarring, alopecia, and dermatomyositis.[425,526,527] Similar histologic cell-poor vasculitis changes are seen with familial German shepherd dog vasculopathy, some "lupoid" dermatoses, and the disease in greyhounds.[470]

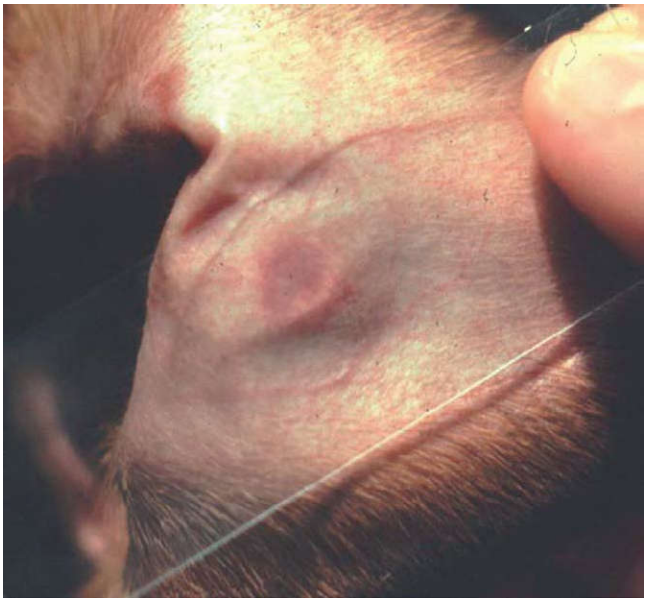


FIGURE 9-54 Positive diascopy on the pinna of a dog with vasculitis. The erythema did not resolve when pressure of the glass slide was applied to the lesion, indicating the blood is in the dermis and not just vessels.

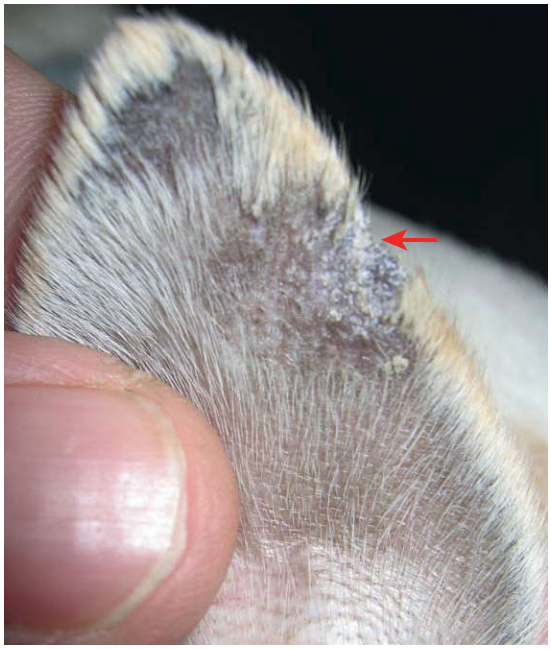


FIGURE 9-55 Proliferative thrombovascular necrosis with alopecia, scaling, and hyperpigmentation of pinna apex. Red arrow is where pinnal tissue is missing from prior necrosis.

The clinical presentation of ischemic dermatopathy has been described as taking one of five forms.[359] Two forms are dermatomyositis, with the first being in known familially predisposed breeds (see Chap. 12) and the second being juvenile-onset dermatomyositis in nonfamilial recognized breeds. The third form is post–rabies vaccination panniculitis; the fourth is generalized vaccine-induced ischemic dermatopathy; the fifth are adult-onset ischemic dermatopathy lesions, but no temporal association with vaccinations as a cause. It is believed that the vascular disease is relatively mild or more subtle in onset or severity, leading to tissue hypoxia. The tissue hypoxia leads to follicular, dermal, and epidermal changes without the more typical vascular changes of hemorrhage, edema, and necrosis.[359,470] The types of lesions seen with this "less severe" or more slowly

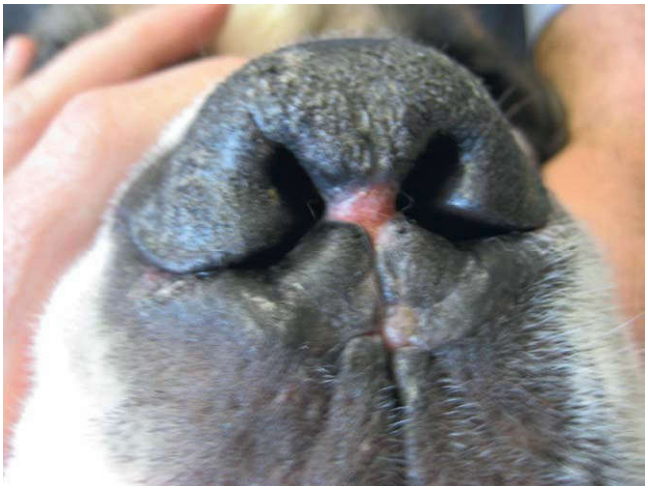


FIGURE 9-56 Saint Bernard with a healing lesion of nasal arteritis being treated with topical application of tacrolimus. Classic lesion location is the central philtrum of nares.

progressive vascular damage may induce scarring alopecia, shiny scaly skin, and comedones (Fig. 9-59).

Vaccine-associated lesions usually start 2 to 8 months after the vaccination. The lesions are various combinations of plaques, nodules, alopecia, scale, erosions, ulcers, crusts, hyperpigmentation, and scarring. Lesions may occur at the site of vaccination, pinnae (usually the apex and often the concave surface, especially at the pinnal margins), face, paw pads, tip of the tail, periocular region, and over bony prominences (see Fig. 9-57). Erosions and ulcers may be seen on the tongue. An associated ischemic atrophic myopathy may be present.

DIAGNOSIS

The differential diagnosis is variable depending on what types of lesions predominate. The more classic linear vascular pattern with ecchymosis or petechia includes coagulopathy, systemic lupus erythematosus, cold agglutinin disease, frostbite, disseminated intravascular coagulation, and lymphoreticular neoplasia. Acute necrotic lesions and ulceration would also include other ulcerative disease such as subepidermal bullous diseases, burns, and some deep pyoderma cases. When urticarial lesions predominate, hypersensitivity disorders not associated with vasculitis are also differential diagnoses. Ischemic dermatopathy, especially early focal lesions, would have a differential diagnosis including *Demodex* and dermatophytosis, discoid lupus erythematosus, and dermatomyositis. Definitive diagnosis is based on history, physical examination, and skin biopsy.

It is important to attempt to determine the cause of any vasculitis case; a thorough drug and vaccine history is indicated. It is also important to consider the timing in relation to vaccination; lesions often develop 2 to 6 months following an inciting vaccine. A search for any source of a septic vasculitis is indicated and would include diseases such as deep pyoderma, cellulitis, and bacterial endocarditis. Vector-borne infectious diseases including members of the genera *Babesia*, *Ehrlichia/Anaplasma*, and *Bartonella*, as well as *Rickettsia rickettsii*, *Borrelia burgdorferi*, and *Leishmania infantum*, should be tested for with PCR or antibody testing. Identification for some of these infections does not prove they caused the vasculitis but would be suspicious and warrant appropriate therapy.

Histopathologic findings will vary depending on which vascular syndrome is present, age of the lesion biopsied related to the vascular damage, and secondary infections. As previously discussed, the vascular lesions may be marked or mild and

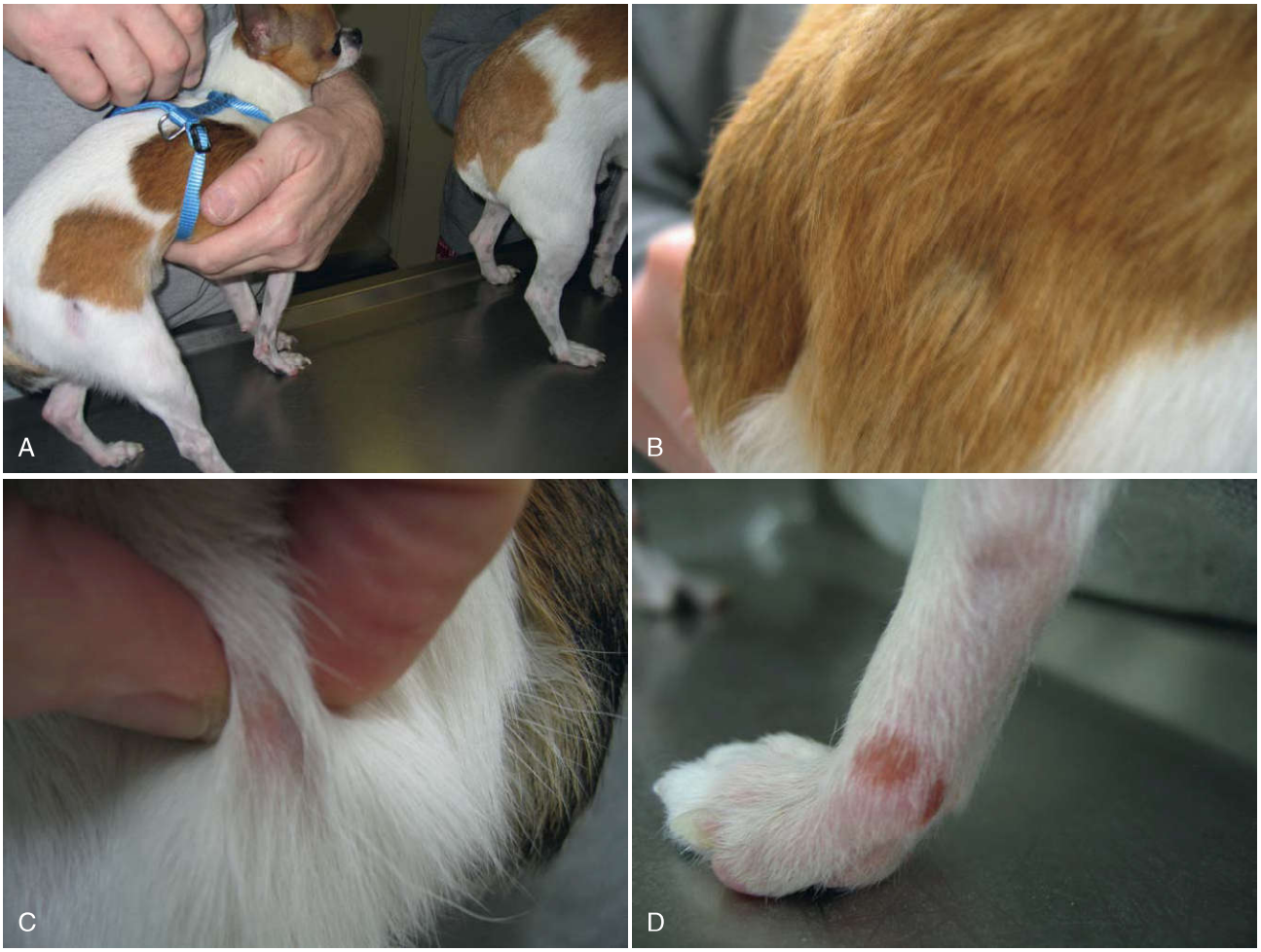


FIGURE 9-57 **A,** Two related Chihuahuas, same parents but 1 year apart. Both dogs developed rabies vaccine reactions on the right lateral hip. **B,** Close view of the more mildly affected dog showing alopecia and hair already regrowing. **C,** More severely affected dog with thicker nodule and some erythema present. **D,** More severely affected dog also had more erythematous lesions on lower legs.

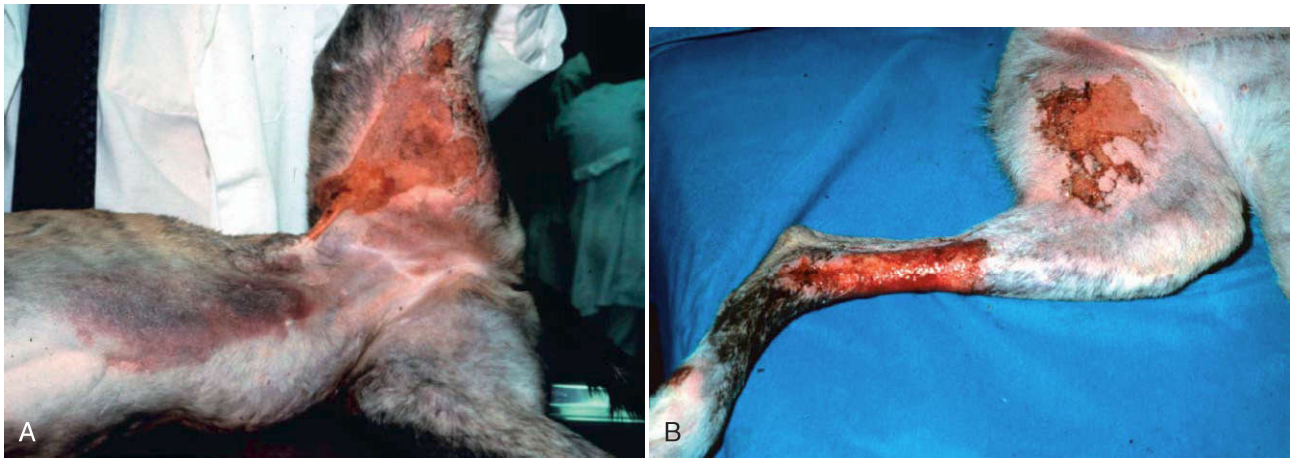


FIGURE 9-58 **A,** Cutaneous vasculopathy in a greyhound. Large area of purpura on ventral abdomen and well-circumscribed necrosis and ulceration of left medial thigh. **B,** Cutaneous vasculopathy in a greyhound. Marked lymphedema of left hind leg, and multifocal necrosis and ulceration of right hind leg. *(**A** courtesy B. Fenwick.)*

associated with different types of inflammatory cells or be cell poor. Considering the variation and subtle vascular changes that may be seen, or the follicular, dermal, and epidermal changes suggestive of hypoxia, it is important that the clinician take extra care in submitting biopsy samples. It is essential that a good description of the pet's lesions and differential diagnosis including vascular disease be included with the pathology submission. A pathologist alerted to a differential diagnosis of vascular disease is more likely to find subtle changes. If possible, the sample should be submitted to a veterinary pathologist with an interest in dermatopathology.

Many vasculitis cases will have thrombus formation, and subsequently the fibrin in the thrombus is broken down, and this results in formation of fibrin degradation products known as *D-dimers*. A monoclonal antibody–based assay is available that detects D-dimers in the blood. This test was evaluated in

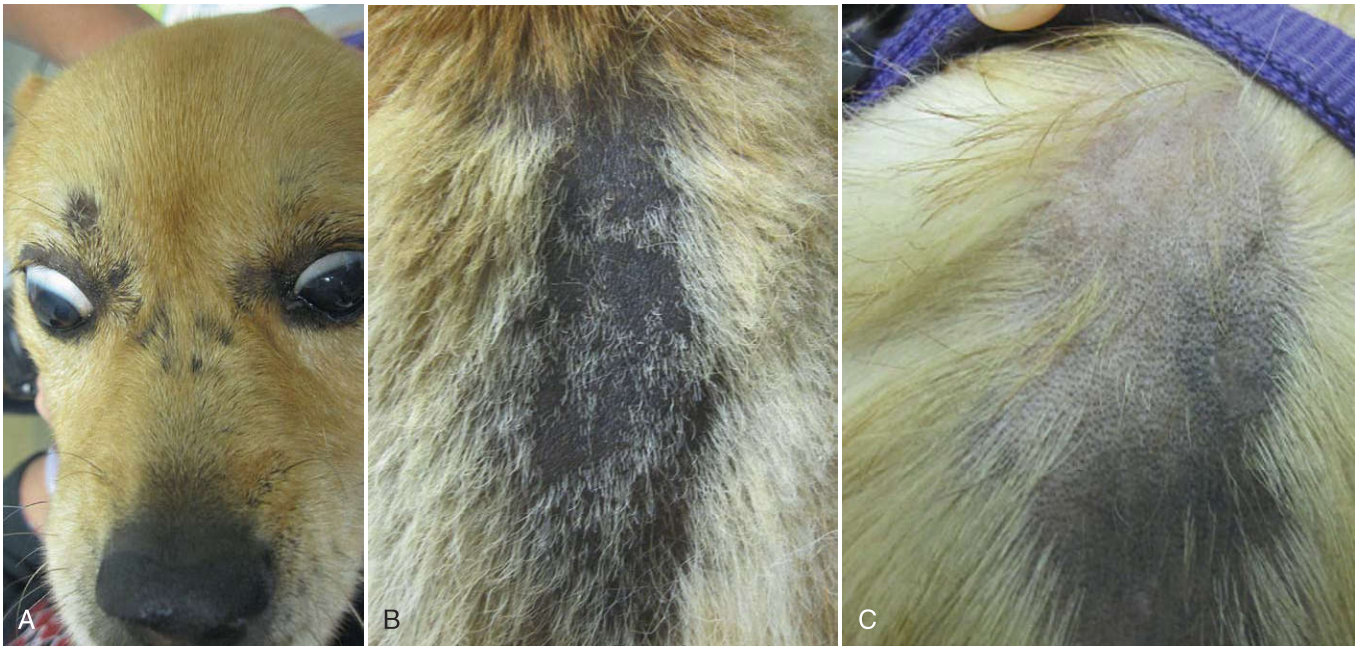


FIGURE 9-59 Ischemic dermatopathy. **A,** Facial alopecia and scarring. **B,** Thickened hyperpigmented hypertrophic scarring alopecia. **C,** Alopecia with hyperpigmented comedones.

10 dogs with allergic skin disease and 26 dogs with cutaneous vasculitis.[528] Fifteen vasculitis dogs had thrombi present in their skin biopsy, and 11 had vasculitis but no thrombi detected. The 15 dogs with thrombus all had D-dimer levels greater than 500 ng/mL. The dogs with no detectable thrombus varied, with 4 having values below 250 ng/mL, 3 having 250-500 ng/mL, and 4 having values greater than 500 ng/mL. Using a cutoff of greater than 500 ng/mL for vasculitis, there was a specificity of 100% and sensitivity of 64%. This study also evaluated fibrinogen levels, and all 26 vasculitis dogs had elevated levels greater than the normal level of 287 mg/dL.

Direct immunofluorescence or immunohistochemical testing may demonstrate immunoglobulin, complement, or both in vessel walls and occasionally at the BMZ in both the neutrophilic and lymphocytic forms of cutaneous vasculitis.[25] These tests are usually not needed, however, and are not particularly useful for diagnosis. If they are performed, they are best done within the first 4 hours after lesion formation and no later than 24 hours.[529]

One might suspect that immune complex levels would be elevated in at least some dogs with vasculitis. Though controlled studies evaluating this have not been published, a study evaluating immune complex levels in dogs with other skin diseases including staphylococcal pyoderma and generalized *Demodex* did show elevations, so positive tests are not specific.[530]

CLINICAL MANAGEMENT

The clinical course varies depending on the vasculitis syndrome and cause for the vascular disease. A single episode lasting a few weeks may occur, or the disorder may be chronic and lifelong or recurrent. The outcome depends on the extent of internal organ involvement (especially renal and neurologic) and the underlying or precipitating factor(s). Certainly, if a cause is found, the initial treatment is to eliminate it by whatever means are most effective for the primary cause. However, once immune complexes and the immune system has been stimulated, even controlling the primary cause (e.g., an infectious agent) may not immediately resolve the vasculitis, and other therapies as discussed later may be needed.

Treatment of vasculitis may require immunomodulatory drug treatment. In less severe cases, doxycycline or pentoxifylline is recommended. Doxycycline is often prescribed while waiting for results of biopsy reports and PCR or antibody titers for infectious diseases. In less severe cases, initial therapy with pentoxifylline is indicated because of its relative lack of side effects and some reports of success (see Chap. 3). Pentoxifylline was apparently effective in four of seven rabies vaccine–associated vasculitides (which required 2-5 months of therapy) but was of no benefit in leukocytoclastic vasculitides.[425,426] It also was suspected to have some benefit in a case of traction alopecia associated with vasculitis.[510] In more severe cases of vasculitis, especially neutrophilic types, systemic prednisone or prednisolone (2-4 mg/kg PO every 24 hours) is initially used, with or without pentoxifylline. For cases refractory to glucocorticoids, generally immune suppressive drugs such as azathioprine or cyclosporine are added to the treatment regimen. Some cases have been difficult to control with glucocorticoids alone, or the combination glucocorticoid and azathioprine or cyclosporine; then combinations of three or more drugs may be used. Glucocorticoid, azathioprine, cyclosporine, and pentoxifylline have all been used together in some difficult cases treated by the authors and others.[358] Old reports have shown that sulfones such as dapsone (1 mg/kg PO every 8 hours in dogs; 1 mg/kg PO every 24 hours with caution in cats) or sulfasalazine (20-40 mg/kg PO every 8 hours in dogs) may be effective.[515,531] The combination of glucocorticoid and dapsone may be synergistic.[515] Large doses of vitamin E may be a useful adjunctive therapy, as may tetracycline and niacinamide.[515,532] In some cases, therapy can be stopped after 4 to 6 months of treatment. Other patients require long-term maintenance therapy with lower drug doses and reduced frequency of administration (see Chap. 3).

Proliferative thrombovascular necrosis of the pinnae is slowly progressive and usually unresponsive to most medical therapies, though some cases have responded to pentoxifylline. If pentoxifylline is ineffective, the treatment of choice is partial surgical removal of the pinna. Relapses have occurred only when attempts were made to save as much tissue as possible.

Focal cutaneous vasculitis and alopecia subsequent to injections may also respond (up to 75% reduction in lesion size) to pentoxifylline or may be treated by complete surgical excision, or it occasionally spontaneously resolves. Topical tacrolimus (0.1%) is also an effective treatment for some cases. It would be logical to *not* repeat the incriminated vaccine unless required by law, because repeat reactions have been seen.[358]

Solar vasculopathy cases merit minimized exposure to UV radiation. Though the assumption has been that mainly UVB should be avoided, it is unknown whether UVA is benign or also involved in the pathogenesis, so avoiding both may be necessary in some cases. Solar radiation avoidance is accomplished by keeping the pet indoors and even minimizing sun exposure through glass during the day. Use of sunscreens (SPF 30 or greater) containing UVA blockers and solar-protective garments would be indicated (see Chap. 16).

AMYLOIDOSIS

Amyloidosis is a generic term that signifies the abnormal extracellular deposition of one of a family of low-molecular-weight protein fibrils that share certain characteristic staining properties and ultrastructural features.[533-535] Amyloidosis is not a single disease entity, and amyloid may accumulate as a result of a variety of different pathogenetic mechanisms. In the dog and cat, most cases of amyloidosis are related to deposition of immunoglobulin light chains and are systemic in nature, without skin involvement.[349,536] Skin disease may be seen and very rarely may be the only organ affected.[537]

CAUSE AND PATHOGENESIS

Different amino acid compositions of amyloid may occur.[534,538] Amyloid deposits contain a nonfibrillar protein called *amyloid-P*, which is identical to a normal circulating plasma globulin known as *serum amyloid-P* (an elastase inhibitor that may help protect amyloid deposits from degradation and phagocytosis). Primary and myeloma-associated systemic amyloidosis have immunoglobulin light chains (mostly the lambda type) as precursors to the amyloid fibril protein, which is called *amyloid-L*. In secondary systemic amyloidosis (associated with chronic inflammation), a serum precursor protein, serum amyloid-A (a high-density lipoprotein and acute-phase reactant), forms the fibrils in the amyloid deposits. Serum amyloid-A is thought to be cleaved proteolytically by macrophages to amyloid-A and excreted extracellularly.

Although the pathogenesis of amyloidosis is unclear, it is morphologically related to cells of the mononuclear phagocytic system, plasma cells, and keratinocytes. Functional studies suggest that such cells play at least a partial role in the genesis of amyloidosis. Ultimately, amyloid deposits lead to changes in tissue architecture and function. In dogs and cats, amyloidosis is usually associated with chronic inflammatory disease, neoplasia, and accumulations of plasma cells.[349,533,536] It has also been associated with a vasculitic syndrome.[539] A familial tendency has been detected in Chinese Shar-Pei and beagle dogs and in Abyssinian and Siamese cats.[533,538-540] It has also been suggested that the cocker spaniel may be predisposed to primary cutaneous amyloidosis and extramedullary plasmacytoma resulting in cutaneous amyloidosis.[537]

CLINICAL FEATURES

Most commonly, amyloidosis is an internal disease, usually affecting the kidneys, spleen, and liver, with death often resulting from the renal involvement.[349,533] Cutaneous lesions are described in dogs with systemic amyloidosis and cutaneous disease and rarely as the only lesions.[537] Primary nodular cutaneous amyloidosis has been described as the most common type of cutaneous amyloidosis in dogs and cats.[537] Solitary or grouped dermal or subcutaneous papules or nodules may occur anywhere but more commonly involve the ear. Some nodules may ulcerate secondary to necrosis. Purpuric macules have also been described.[541] Cutaneous lesions with systemic amyloidosis associated with a monoclonal gammopathy was reported in an adult female cocker spaniel.[542] Cutaneous hemorrhage could be induced by flicking the abdominal skin briskly with a finger or by removing hair (Fig. 9-60). If the skin was traumatized severely, blood oozed through the skin within seconds and clotted immediately. Skin biopsy revealed an amorphous, homogeneous, eosinophilic superficial dermis. The walls of the blood vessels in the involved area were thickened by deposition of the homogeneous eosinophilic material. The material was Congo red positive (congophilia), and a green birefringence of the material was visible in Congo red–stained sections examined with polarized light (dichroism). A monoclonal serum IgG paraprotein was found. No treatment was given, and the dog remained unchanged for 14 months.

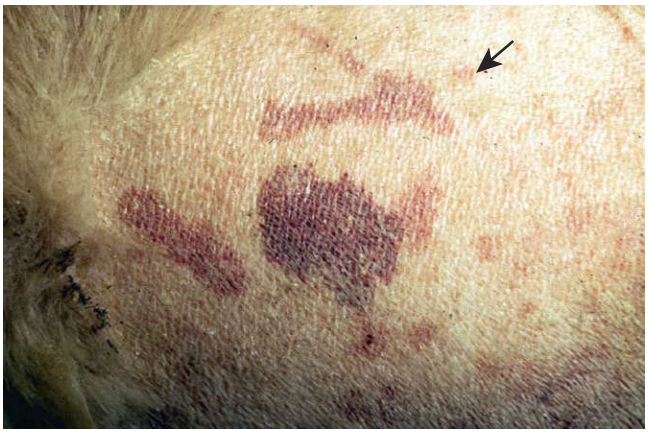


FIGURE 9-60 Canine cutaneous amyloidosis. Ecchymoses produced by traumatizing the skin (pinch purpura) *(arrows)*. *(Courtesy R. M. Schwartzman.)*

A case of generalized amyloidosis was described in a 10-week-old German shepherd puppy.[543] It presented with swollen erythematous pads and reluctance to walk. Though amyloidosis was found at necropsy, the pads only showed chronic exudative inflammation.

DIAGNOSIS

The differential diagnosis for these lesions would be neoplasia, cysts, and infectious or sterile nodular granulomas. The diagnosis of amyloidosis is confirmed by biopsy. Light-microscopic examination reveals the deposition of an eosinophilic amorphous substance that is congophilic and birefringent when polarized.[534] Secondary—but not primary and myeloma-associated—amyloid loses its congophilia after pretreatment with potassium permanganate. Electron-microscopic examination reveals the characteristic presence of 7.5- to 10-nm-wide linear, nonbranching tubular fibrils, each fibril being composed of several filaments arranged in a β-pleated sheet configuration.[534]

CLINICAL MANAGEMENT

Solitary nodules unassociated with systemic disease can be successfully excised. Successful treatment of multiple lesions is not reported. In humans, skin lesions of both primary and myeloma-associated amyloidosis have responded to DMSO, which may inhibit amyloid synthesis or act to promote amyloid degradation.[534]