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A retrospective study of canine and feline cutaneous vasculitis

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Abstract Twenty-one cases of cutaneous vasculitis in small animals (dogs and cats) were reviewed, and cases were divided by clinical signs into five groups. An attempt was made to correlate clinical types of vasculitis with histological inflammatory patterns, response to therapeutic drugs and prognosis. Greater than 50% of the cases were idiopathic, whereas five were induced by rabies vaccine, two were associated with hypersensitivity to beef, one was associated with lymphosarcoma and two were associated with the administration of oral drugs (ivermectin and itraconazole). Only the cases of rabies vaccine-induced vasculitis in dogs had a consistent histological inflammatory pattern (mononuclear/nonleukocytoclastic) and were responsive to combination therapy with prednisone and pentoxifylline, or to prednisone alone. Most cases with neutrophilic or neutrophilic/eosinophilic inflammatory patterns histologically did not respond to pentoxifylline, but responded to sulfone/sulfonamide drugs, prednisone, or a combination of the two.

Keywords: cat, cutaneous vasculitis, dapsone, dog, pentoxifylline, sulfasalazine.

INTRODUCTION

Cutaneous necrotizing vasculitis is a rare disorder of dogs and cats which is generally defined as a disease process characterized by inflammation and subsequent destruction of blood vessels resulting in ischaemic necrosis of recipient tissue. Clinical lesions of small vessel cutaneous vasculitis in animals often present as purpura or haemorrhagic bullae. Progression of the disease results in the formation of well-demarcated ulcers, especially involving the paws, pinnae, lips, tail and oral mucosa.[1] Neutrophilic vasculitis is the most common form and may be either leukocytoclastic or nonleukocytoclastic. Lymphocytic, eosinophilic and granulomatous vasculitides are reportedly uncommon in companion animals.[1–3]

In human medicine, classification systems for cutaneous vasculitis have been developed and revised for decades, in an attempt to predict aetiology, therapeutic response and prognosis. Revisions have often been necessary because of the recognition of 'new' syndromes, the development of assays that recognize autoantibodies correlating with disease activity, and the cumulative experience gained in managing distinct subtypes of vascular disease.[4–7] Classification systems have been proposed based upon vessel size, the histological pattern and type of inflammatory cell infiltrate, and the coexistence of other primary (or secondary) cutaneous or systemic diseases. However, despite recommendations from several independent groups, a single system that successfully and consistently predicts aetiologic, prognostic and therapeutic outcomes has not been achieved, leading one author to lament that 'Common sense is sometimes sacrificed in favour of criteria that are simply reproducible.'[4] Still, classification systems provide valuable templates for investigation and discussion, as well as patient management.[5]

In veterinary medicine, vasculitis is usually classified according to the histological inflammatory pattern, and most cases affect the small cutaneous vessels.[2,3] Histological findings necessary to diagnose vasculitis include varying degrees of neutrophilic, eosinophilic and mononuclear cell invasion of vessel walls along with endothelial cell swelling, fibrinoid degeneration, extravasation of red blood cells and, at times, leukocytoclasia ('nuclear dust') located within or near vessel walls.[7] In human beings, leukocytoclastic vasculitis (LCCV) affects small dermal vessels (post capillary venules, capillaries, arterioles, small arteries) and in its acute phase is characterized histologically by neutrophilic inflammation.[5] It is important to recognize, however, that histological lesions have 'life spans' and mixed inflammatory infiltrates are common in 'aged' lesions. Serial histological examination of human LCCV lesions has shown that the granulocytic infiltrate gives

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way to a predominantly mononuclear population within 24–48 h.[8,9]

The majority of LCCV cases are thought to result from a hypersensitivity response. Immunological dogma has long held that 'hypersensitivity vasculitis' is the result of a type III hypersensitivity reaction to foreign antigen/antibody complexes lodged in vessel walls (the prototypical Arthus reaction), in which activation of complement provokes an influx of neutrophils.[10] In human medicine, numerous aetiologies have been attributed to small-vessel LCCV. In theory, any foreign antigen capable of inciting an antibody response should be considered as a potential cause, including infectious organisms (bacterial, mycobacterial, viral, rickettsial, fungal), neoplasia, drugs and food additives, sera (serum sickness syndrome) and sources of autoantibody, such as cryoglobulins and collagen vascular diseases (e.g. lupus vasculitis, rheumatoid arthritis-associated vasculitis).[5,6,11,12] Food sensitivity has also been reported to cause LCCV in people.[13]

Forms of small vessel cutaneous vasculitis that are mononuclear from the onset also occur in human beings and may represent a different aetiology and pathogenesis of disease.[8] Perhaps the best described form of mononuclear vasculitis occurring in domestic animals is that associated with the subcutaneous administration of killed rabies virus vaccine in dogs.[14]

Therefore, cutaneous vasculitis should not be thought of as a diagnosis, but rather as a clinical problem with a seemingly endless list of aetiological possibilities. However, of all cases of small-vessel cutaneous vasculitis occurring in human beings, 50% or more are attributed to idiopathy.[4,15]

A large retrospective case series of cutaneous vasculitis in animals has not been reported previously, so information on aetiology, therapy and prognosis has been limited. The purpose of this retrospective study was to identify the most common clinical presentations of cutaneous vasculitis in dogs and cats and to attempt to correlate these with histological inflammatory patterns, aetiology, responses to drug therapy and ultimately, prognosis.

METHODS

Records of all canine and feline patients examined at a small animal dermatology referral clinic between 1994 and 1997 were reviewed, and animals with a histological diagnosis of cutaneous vasculitis were identified. Records were examined for information regarding physical examination findings, laboratory analyses, aetiologies, treatment protocols, responses to therapy and morbidity/mortality data. Based upon clinical characteristics of the vasculitic lesions, patients were divided into five groups and the retrospective information used to infer prognostic factors for each group.

A minimum database consisting of complete blood count with differential, serum biochemical analysis, urinalysis, rickettsial screen (dogs) and virology (cats) had been performed for all patient groups except dogs with clinical lesions typical of rabies virus vaccine-induced vasculitis with alopecia. The rickettsial screen included serology for *Rickettsia rickettsii*, *Ehrlichia canis* and *Borrelia burgdorferi*, whereas the viral screen included serology for feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV).

RESULTS

Twenty-one patients with cutaneous vasculitis were identified. These represented 0.76% of all new patients (2753) examined during this period. Nineteen dogs (1 male, intact; 11 male, castrated; 1 female, intact; 6 female, spayed) and two cats (female, spayed) were represented. The dogs ranged in age from 1 years to 12 years (mean 5.7 years); and the cats were 1 and 7 years of age.

Fourteen pure-bred and five mixed-breed individuals were represented in the canine study population. Breeds represented included Bichon Frise,[2] miniature Dachshund,[2] and one each of Pug, Labrador Retriever, Golden Retriever, Dalmatian, Maltese, Miniature Poodle, Miniature Schnauzer, Jack Russell Terrier, Greyhound and Yorkshire Terrier. One domestic short-hair and one domestic long-hair cat was represented.

The first clinical group consisted of eight dogs and one cat with pinnal and/or footpad lesions. In two dogs of this group (Nos 1 and 2), the pinnae alone were affected. In two dogs and one cat (Nos 3, 4 and 5), the pads alone were affected. Four dogs (Nos 6, 7, 8 and 9) had both pinnal and pad involvement.

Histopathological findings proved neutrophilic leukocytoclastic vasculitis to be the predominant inflammatory pattern in five dogs and the one cat in this group, whereas two dogs had a neutrophilic nonleukocytoclastic vasculitis, and one dog had both neutrophilic and eosinophilic nonleukocytoclastic patterns. None of these cases exhibited a mononuclear cell infiltrate (Table 1).

In six of the animals the aetiology of the cutaneous vasculitis was undetermined. In addition to the minimum database, Cases 2, 7 and 9 had elimination diet trials performed (Innovative Veterinary Diets® venison/potato, Nature's Recipe Pet Foods, Corona, CA, USA) for a minimum of 8 weeks without clinical improvement. One dog (No. 4) developed pinnal and pedal lesions along with clinical signs of gastrointestinal disease; an abdominal exploratory revealed mesenteric lymphosarcoma. One cat (No. 5) acutely developed pedal lesions, pyrexia and inappetence within 24 h of rabies vaccination. The aetiology of the vasculitis in Case 9 was thought to be drug reaction due to a close temporal relationship with the oral administration of 1% ivermectin (Cattle Ivomec®, MSD-AgVet, Rahway, NJ, USA). Lesions began within 48 following the oral administration of 300 $\mu g\ kg^{-1}$ ivermectin for suspected sarcoptic acariasis. Lesions

Table 1. Summary of 21 patients with histopathological evidence of cutaneous vasculitis

Case	Signalment	Histopathology	Clinical signs	Aetiology
Group 1				
1	12 year MC Dalmatian	A	Focal erosive plaque, ulcerated pinnal margins	Idiopathic
2	9.5 year MC Yorkshire Terrier	A	Linear, ulcerative pinnal lesions with crusting on pinnal margins	Idiopathic
3	10 year MC Greyhound	B	Swollen, painful footpads	Idiopathic
4	3 year MC canine mix	C	Ulcerative footpads	Lymphosarcoma
5	1 year FS DLH	A	Crusting dermatitis of central footpad margins	Rabies vaccine
6	6 year F Dachshund	A	Ulcerative pinnal and footpad lesions	Idiopathic
7	7.5 year MC Dachshund	A	Ulcerative pinnal and footpad lesions	Idiopathic
8	12 year MC canine mix	B	Ulcerative pinnal, pedal, and footpad lesions	Idiopathic
9	4 year MC canine mix	A	Ulcerative pinnal margins, footpads, pressure points	Ivermectin
Group 2				
10	3 year FS Miniature Poodle	D	Focal alopecic area on shoulder	Rabies vaccine
11	8 year FS Maltese	D	Focal alopecic area on shoulder	Rabies vaccine
12	4.5 year FS Bichon Frise	E	Two adjacent lesions of alopecia on shoulder	Rabies vaccine
13	3.5 year MC Bichon Frise	D	Focal alopecic area on flank	Rabies vaccine
Group 3				
14	4.5 year MC Pug	B	Generalized erythematous wheals	Food allergy
15	3.5 year MC Labrador Retriever	C	Generalized erythematous wheals	Food allergy
16	7 year FS miniature Schnauzer	A	Generalized erythematous wheals	Idiopathic
Group 4				
17	3 year MC canine mix	A, C	Annular, ulcerative lesions of carpus	Itraconazole
18	1 year FS Golden Retriever	A	Solitary, crateriform ulcer on flank	Idiopathic
19	1 year M Jack Russell Terrier	B	Ulcerative lesions of face and scrotum	Idiopathic
20	7 year FS DSH	B	Focal ulcerative lesion over right shoulder area	Idiopathic
21	5 year FS canine mix	A	Unilateral ulcerative glossitis, cheilitis, facial dermatitis, paronychia	Idiopathic

Letters denote histopathological pattern of cutaneous vasculitis as described: A, neutrophilic leukocytoclastic vasculitis; B, neutrophilic nonleukocytoclastic vasculitis; C, neutrophilic, eosinophilic non-leukocytoclastic vasculitis; D, lymphohistiocytic vasculitis; E, lymphoplasmacytic vasculitis.

became markedly worse after repeated administration of this same dosage 7 days later.

Treatment and therapeutic outcomes varied within this group, but some general patterns were apparent. Three dogs (Nos 2, 7 and 8) responded to treatment with a combination of prednisone and sulfasalazine (Azulfidine®, Pharmacia & Upjohn, Kalamazoo, MI, USA). Pentoxifylline (Trental®, Hoechst-Marion-Roussel, Kansas City, MO, USA) at a dosage of 10–15 mg kg^{-1} twice daily was used initially in all three of these dogs for a minimum of 6 weeks. When the dosage of prednisone was tapered, all cases relapsed and the adjunctive therapy was changed to sulfasalazine. Interestingly, the histological inflammatory pattern was predominantly neutrophilic in each of these cases.

Case 2 was initially treated with prednisone (1 mg kg^{-1} twice daily, tapered to 0.5 mg kg^{-1} every other day for 3 months) and pentoxifylline (15 mg kg^{-1} twice daily for 3 months). The vasculitis improved at the higher prednisone dosage but relapse of clinical signs occurred once the dose was tapered. At this point, both drugs were discontinued and sulfasalazine was initiated at a dosage of 25 mg kg^{-1} three times daily. The skin lesions improved immediately; however, 3 weeks after starting therapy the dog developed keratoconjunctivitis sicca (KCS). The frequency of sulfasalazine was then decreased to 25 mg kg^{-1} once daily and within 3 weeks the KCS had resolved but the pinnal vasculitis had returned. A serum biochemical panel performed at this time revealed elevations in all hepatic enzymes; therefore, sulfasalazine therapy was discontinued and dexamethasone therapy was initiated at a dosage of 0.05 mg kg^{-1} twice daily and tapered to 0.05 mg kg^{-1} twice weekly over a 4-week period. This protocol controlled the vasculitic signs in the dog. A follow-up serum biochemical profile performed 3 weeks after discontinuation of the sulfasalazine revealed that all hepatic enzymes had reverted to within normal limits.

Case 7 developed acute irreversible hepatotoxicity 1 month after initiating sulfasalazine therapy at a dosage of 15 mg kg^{-1} three times daily and was euthanized.

Case 8 (Fig. 1a,b) was treated initially with a combination of pentoxifylline (15 mg kg^{-1} twice daily for 6 weeks) and prednisone (initial dosage of 0.75 mg kg^{-1} twice daily). After 6 weeks of therapy, a decrease in lesions was observed; however, new lesions continued to form. Pentoxifylline was discontinued and sulfasalazine was initiated at a dose of 20 mg kg^{-1} three times daily. Within 10 days, the older lesions resolved with no formation of new lesions. Five years after initial diagnosis, the dog's cutaneous vasculitis continues to be successfully controlled with sulfasalazine (20 mg kg^{-1} twice daily) alone.

Case 6 was administered a combination of prednisone (1 mg kg^{-1} twice daily tapered to 0.5 mg kg^{-1} every other day) and pentoxifylline (15 mg kg^{-1} twice daily) prior to being lost to follow-up at 6 weeks. At the time of final physical examination, the dog appeared to be free of vasculitic lesions.

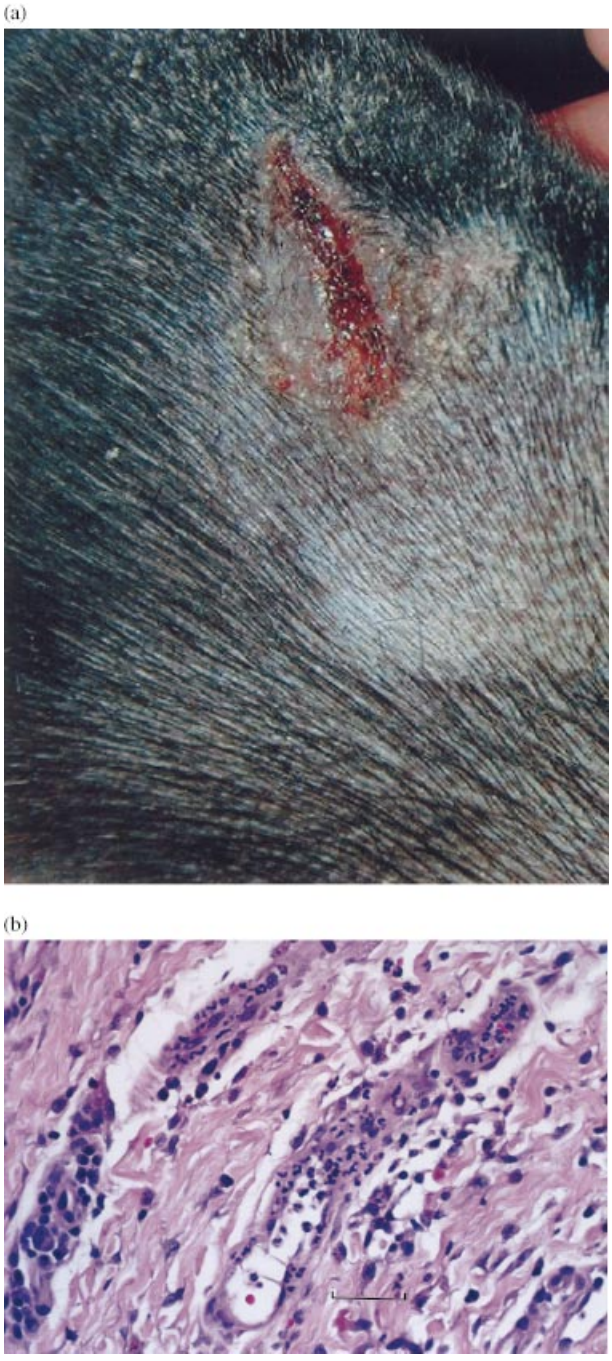

Figure 1. (a) Ulcerative pinnal lesion of Case 8, due to neutrophilic nonleukocytoclastic vasculitis of unknown aetiology. (b) Large dermal venule exhibiting neutrophilic margination and intramural inflammation without significant leukocytoclasia (haematoxylin and eosin; bar = 14.2 μm).

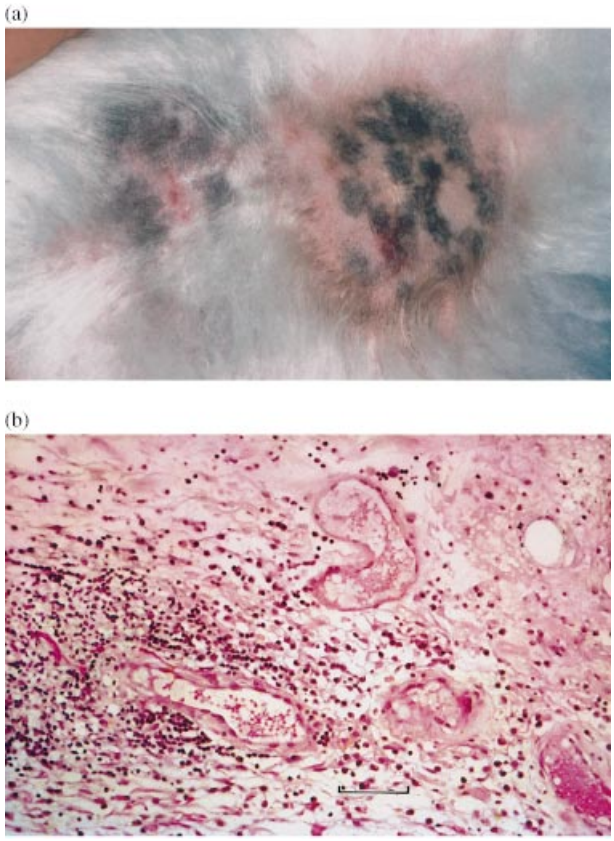

Figure 2. (a) Focal patch of alopecia with mild erythema and post-inflammatory hyperpigmentation following rabies vaccination in Case 12. The excoriated area is iatrogenic, due to a skin scraping to rule out *Demodex canis*. (b) Moderate to marked lymphoplasmacytic perivascular inflammation of a large venule, with interstitial oedema and fibrin deposition. Rare intramural inflammatory cells were also present (not shown) (haematoxylin and eosin; bar = 31 μm).

Two dogs and one cat in this group were treated successfully with drug monotherapy. In Case 1 complete resolution of lesions occurred with 6 weeks use of pentoxifylline (10 mg kg^{-1} twice daily) and therapy was discontinued after 5 months without recurrence of clinical signs during an 8-month period of follow-up. Cases 3 and 5 resolved with prednisone alone (initial dosages of 0.5 mg kg^{-1} twice daily and 1 mg kg^{-1} twice daily, respectively). Case 3 was lost to long-term follow-up. Case 5 discontinued prednisone therapy after 6 weeks and remained lesion free for a 12-month period of follow-up.

Of the remaining dogs in this group, one was euthanized (No. 9), and one died from its primary disease (No. 4).

The second clinical group consisted of four dogs presenting with focal alopecic lesions of the trunk. Three of these patients had lesions over the dorsal interscapular area, whereas the fourth had a lesion located on the flank. Two of the dogs were Bichon Frises (same sire and dam but from different litters), one was a Maltese and one a Miniature Poodle. Lesions were 2–5 cm in diameter, and were alopecic, variably inflamed, centrally hyperpigmented and flat to slightly indurated on palpation (Fig. 2a). Two of the lesions also had mild scaling and epilation of hair at the periphery. All four dogs had received subcutaneous rabies vaccine within 3 months of initial observation of lesions. The vaccines were administered over the interscapular space in three dogs and in the flank of the remaining dog. Histopathological findings revealed a lymphohistiocytic vasculitis in three of the dogs (Nos 10, 11 and 13) and a lymphoplasmacytic pattern in the fourth (No. 12; Fig. 2b). Because active vasculitis was present and the alopecic areas were expanding at the time of histological

diagnosis, three of the dogs (Nos. 11, 12 and 13) were treated with prednisone (0.5–1.0 mg kg^{-1} twice daily tapered to 0.5 mg kg^{-1} every other day for 12–16 weeks) and pentoxifylline (15 mg kg^{-1} twice daily for 12–16 weeks), whereas Case 10 received only prednisone (initial dosage of 0.4 mg kg^{-1} twice daily tapered to 0.4 mg kg^{-1} every other day over 4 weeks). This latter case was lost to follow-up, but lesion expansion ceased within 3 weeks in the remaining three dogs. Two of these dogs had complete regrowth of hair at the affected sites after discontinuation of therapy, whereas the remaining dog developed only partial hair regrowth.

The third clinical group consisted of three dogs with urticarial vasculitic lesions (nonpitting erythematous wheals). These three dogs presented for acute onset of intense erythroderma with coalescing erythematous wheals that failed to blanche with diascopy. Cases 14 and 15 presented with lesions while receiving glucocorticoid therapy (20 mg methylprednisolone acetate intramuscularly and 1 mg kg^{-1} prednisone once daily for 4 days, respectively). The lesions resolved in each dog within 1 week of changing the diet to novel protein sources (Prescription Diet D/D®, Hill's Pet Nutrition Inc., Topeka, KS, USA and Innovative Veterinary Diets® venison/potato, respectively). Both dogs had recurrence when challenged with beef. Case 15 also had recurrence of lesions on several occasions when other commercial foods were offered.

The cause of the urticarial vasculitis in Case 16 remains unknown. This dog had a history of recurrent urticarial episodes following visits to a groomer; however, this episode was much more severe and was not associated with grooming (Fig. 3a,b). In addition, the dog was anorectic, febrile, dehydrated and lethargic. Serum biochemical assay revealed markedly elevated hepatic enzymes (alanine aminotransferase enzyme 860 U L^{-1}, normal range 16–91 U L^{-1}; and aspartine aminotransferase 255 U L^{-1}, normal range 23–65 U L^{-1}) suggestive of an acute hepatocellular insult. These signs resolved with fluid replacement therapy, and the skin lesions resolved within 10 days upon initiation of short-term prednisone therapy (initial dosage of 1 mg kg^{-1} twice daily for 3 days tapered to 1 mg kg^{-1} every other day for three dosages) and did not return. The histopathological inflammatory pattern varied in all three cases (Table 1).

The fourth clinical group consisted of three dogs and one cat presenting with localized ulcerative lesions. Case 17 involved a dog with localized sporotrichosis being treated with itraconazole (Sporanox®, Janssen Pharm. Inc., Titusville, NJ, USA; 4 mg kg^{-1} twice daily). The dog had been treated with itraconazole for 8 weeks and the fungal infection was resolving, when an annular ulcerative lesion developed on the carpus at the site of prior infection. Neutrophilic leukocytoclastic vasculitis and neutrophilic, eosinophilic leukocytoclastic vasculitis were the predominant histopathologic inflammatory patterns in this lesion (Fig. 4a,b). The drug was discontinued and the lesion resolved within

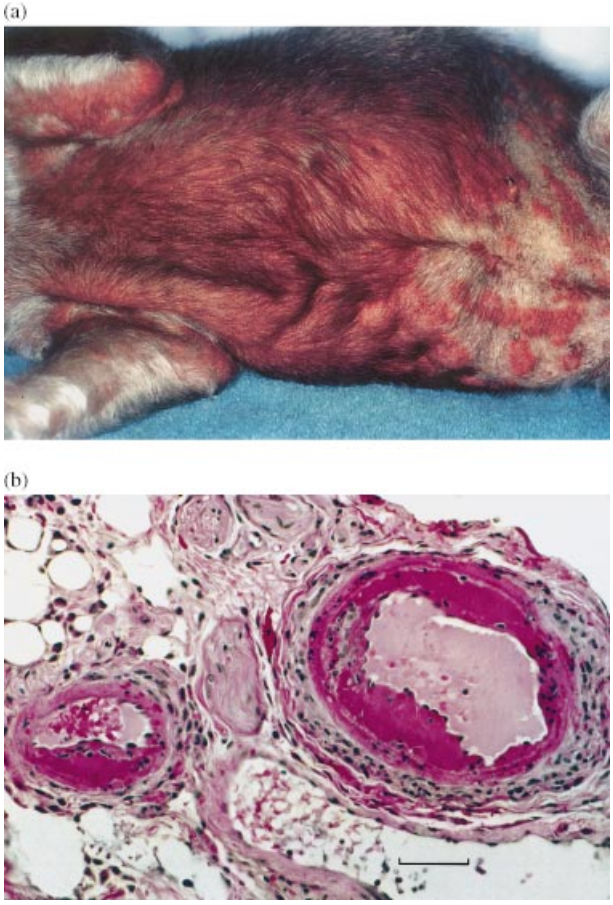

Figure 3. (a) Coalescing wheals (caudal abdomen) and diffuse erythema/angioedema (cranial abdomen) of Case 16 due to leukocytoclastic vasculitis of unknown aetiology. (b) Small dermal arterioles exhibit necrosis of endothelial cells, marked fibrinoid degeneration of the tunica media, intramural neutrophilic inflammation, leukocytoclasia (nuclear dust), and extravasation of erythrocytes (periodic acid Schiff; bar = 16 μm).

2 weeks, suggesting a vasculitic reaction to itraconazole consistent with prior clinical reports.[16,17]

Case 18 involved a dog that presented with a crateriform ulcer on the left flank. The aetiology of the vasculitis was not identified, however, the lesion resolved in 5 weeks with a tapering prednisone regimen (initial dose of 1 mg kg^{-1} twice daily tapered to 0.5 mg kg^{-1} every other day) and there was no recurrence. A follow-up telephone conversation with the owner confirmed that there was no hair regrowth at the affected site.

Case 19 involved a Jack Russell Terrier with ulcerations of the face and scrotum that were determined to be due to neutrophilic, nonleukocytoclastic vasculitis histologically. Therapy with prednisone (1.5 mg kg^{-1} twice daily) in combination with pentoxifylline (20 mg kg^{-1} twice daily), and then azathioprine (Imuran®, Glaxo Wellcome Inc., Research Triangle Park, NC, USA; 2 mg kg^{-1} every other day) was unsuccessful. Ultimately, control of the vasculitis was achieved with a combination of prednisone (0.75 mg kg^{-1}) and the sulfone Dapsone® (Jacobus Pharm., Princeton, NJ, USA; 1 mg kg^{-1}) on an alternate day dosing schedule. Subsequently, lesions have been

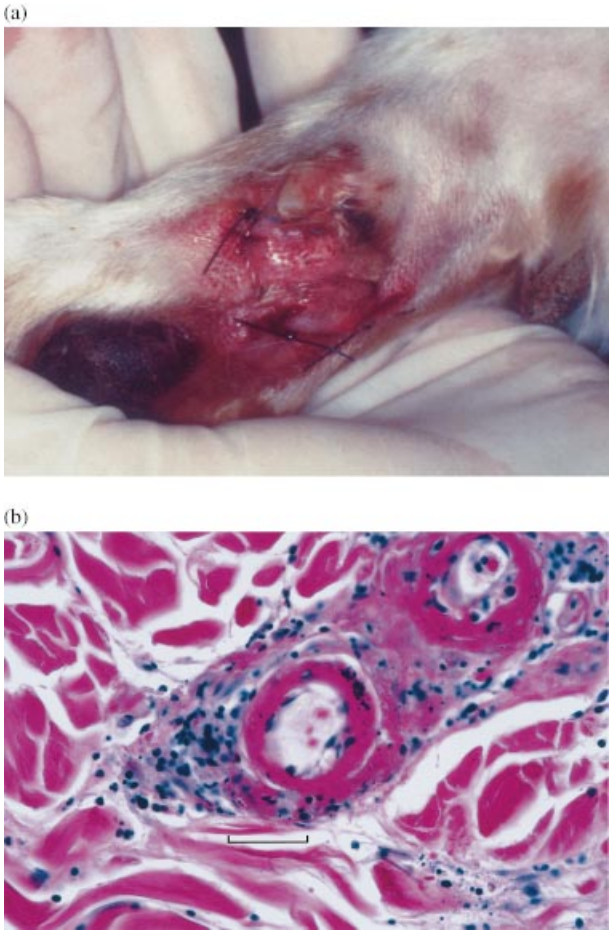

Figure 4. (a) Nodular/ulcerative dermatitis of the plantar carpal surface of Case 17, due to itraconazole administration. (b) Perivascular and intramural neutrophilic inflammation of dermal arterioles, with marked leukocytoclasia and fibrinoid degeneration (haematoxylin and eosin; bar = 14 μm).

controlled for 5 years with dapsone monotherapy (1 mg kg^{-1} administered twice weekly). Discontinuation of the drug resulted in recurrence of lesions.

Also present in this group was a cat (No. 20) with an acute focal ulcerative/necrotizing lesion over the right shoulder and cervical area. The cat had received numerous oral and parenteral treatments for hepatic lipidosis and died shortly after the diagnosis of neutrophilic, nonleukocytoclastic vasculitis was made. A reaction to subcutaneous injection (drug unknown) could not be ruled out.

A final case that was dissimilar to all others involved a dog presenting with unilateral ulcerative glossitis and facial dermatitis and paronychia limited to the right front and hind limbs. The dog was febrile, anorectic and lethargic. Shortly after histological confirmation of vasculitis, the hind-limbs became markedly oedematous and the dog died suddenly at home. Necropsy revealed necrosis and gas pockets within the subcutis; a *Clostridium* sp. was grown on anaerobic culture of the affected tissue. Contamination of biopsy sites could not be ruled out. Even though a definitive cause of the vasculitis could not be proven, there was a potential temporal relationship with the administration of metronidazole, 500 mg twice daily for 1 week preceding the development of skin lesions.

DISCUSSION

Cutaneous vasculitis was diagnosed in 21 animals based on clinical signs consistent with purpuric or ulcerative dermatitis, and definitive histopathological changes. Although vasculitis may occur in blood vessels of any size, thus potentially affecting multiple organ systems, our case series was limited to cutaneous vasculitis which usually involves small vessels such as capillaries, postcapillary venules and small arterioles.[2]

The most widely accepted pathomechanism of vasculitis is thought to be an immune-mediated (type III hypersensitivity) response. In this reaction, soluble circulating antigen–antibody immune complexes (formed in antigen excess) become lodged in blood vessel endothelium due to incomplete clearance by the reticuloendothelial system.[10,15] In addition to being the largest immunological barrier surface in the body, the endothelium is also responsible for homeostatic mechanisms such as the maintenance of a nonthrombotic environment.[18] Complex entrapment between endothelial cells activates the complement cascade via the classic pathway and the C5a component of complement initiates polymorphonuclear cell recruitment to the vessel wall. The polymorphonuclear cells infiltrate the blood vessel wall and release lysosomal enzymes (collagenase and elastase), along with toxic oxygen radicals which damage endothelial cells. Thrombosis results from fibrin deposition, with tissue necrosis and extravasation of erythrocytes being the end result.[19,20]

The historically recommended therapies for vasculitis in human medicine have included the identification and elimination of antigenic stimulus and control of the aberrant immune response while providing supportive care.[10] In this regard, it is imperative to distinguish between primary (idiopathic) and secondary vasculitides.

Cutaneous vasculitis in animals is often compared with LCCV (hypersensitivity vasculitis) of humans.[21–26] Because of the self-limiting nature of this condition in many people, initial treatment is often dependent upon the severity of the symptoms. When a drug or infectious organism is thought to be the offending antigen, treatment is centred upon removal of drugs, treatment of infections and bed-rest. Should skin lesions prove to be recurrent, nonsteroidal anti-inflammatory therapies, such as dapsone, may be implemented. Aggressive therapy with glucocorticoids and other immunosuppressive drugs is typically reserved for chronic relapsing and systemic forms of vasculitis.[27,28]

The exact mechanism(s) by which glucocorticoids act on vasculitis have not been completely ascertained but glucocorticoids are known to inhibit the chemotactic

response of neutrophils and monocyte–macrophages and may also act to inhibit their binding to vascular endothelium at sites of inflammation.[29,30]

In both human and veterinary medicine, anti-inflammatory agents such as sulfones, sulfonamides and pentoxifylline, have been used to treat vasculitis.[6,31] The mechanism(s) of action of sulfones and sulfonamides are still not fully understood; however, these drugs are thought to interfere with the neutrophil myeloperoxidase system, thereby negating the formation of superoxide radicals and their potentially destructive action in tissue.[32,33] Dapsone is also capable of inhibiting neutrophil chemotaxis[34] and mitogen-stimulated lymphocyte transformation.[35]

Sulfasalazine is often preferred by veterinary clinicians over dapsone because of the latter's reputation for toxicity (agranulocytosis, anaemia, hypersensitivity reactions). Sulfasalazine is converted in the colon to sulfapyridine and 5-aminosalicylic acid via bacterial action on the azo linkage. Therapeutic benefit for vasculitis is dependent upon the sulfapyradine moiety, which undergoes significant systemic absorption in the colon.[32] Potential side effects of sulfa drugs have been well documented in both humans and animals, especially during the induction phase. Mild anaemia and leukopenia, as well as elevations of serum ALT, may be expected to occur during this period. More serious potential side effects include blood dyscrasias, cutaneous eruptions, nephrotoxicity and neuropathies, which may or may not be reversible upon discontinuation of the drug. The most common side effect observed with long-term administration of sulfones and sulfonamides is KCS. This condition has been shown to be reversible with reduction of either the drug dosage or frequency of administration.[32,33]

Pentoxifylline, a methylxanthine derivative, has proven to be of significant benefit for the treatment of numerous dermatoses of human beings. In the treatment of cutaneous vasculitis, the most substantial effect of this drug may be its potent haemorrheologic properties which increase erythrocyte deformability, thus allowing the cells to more readily pass through compromised blood vessels.[36] Pentoxifylline has also shown significant anti-inflammatory effects due to inhibition of pro-inflammatory cytokines [interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α], direct inhibition of leukocyte adhesion to endothelial cells, inhibition of chemokines and inhibition of leukocyte adhesion to keratinocytes, thus effectively interfering with the amplification process of skin inflammation.[37] Of therapeutic concern is the potentially long latency period for clinical response to treatment. In human beings, this time frame has been reported to range from 2 weeks to 14 months depending upon the disease process being treated.[36] With regard to combination therapies, studies have shown synergistic effect of pentoxifylline with both the fluoroquinolone ciprofloxacin and with glucocorticoids. The mechanism of this synergy may be the inhibition of TNF-α, of which all three are capable.[36,38] Side effects are reportedly very rare in dogs, and appear to be limited to gastrointestinal disturbances and hyperactivity in the experience of the authors.

Immunosuppressive agents such as cyclophosphamide, chlorambucil, azathioprine, methotrexate and cyclosporin A have been used primarily to treat systemic vasculitis with cutaneous involvement in humans. A more complete review of their mechanisms in vasculitic disease is available.[39]

In this case series most dogs presenting with pinnal and/or pedal lesions received a final diagnosis of idiopathy (6/9). In a majority of cases in this group, combination therapy was initiated with glucocorticoids (due to their known efficacy) and pentoxifylline (due to its minimal side effect profile). The pentoxifylline was used with the goal of achieving a steroid-sparing effect should on-going therapy be necessary. Altogether, seven dogs in this group were treated with pentoxifylline with only one (No. 1) exhibiting a definitively favourable response. Although Case 6 responded well to a combination of prednisone and pentoxifylline prior to being lost to follow-up after 6 weeks of therapy, it was not possible to determine what role, if any, the pentoxifylline played in lesional improvement.

Potential considerations for lack of response to pentoxifylline may include a prolonged lag phase for effect, incorrect dosing and inappropriate case selection (i.e. based upon the inflammatory cell infiltrate). Although it may seem unlikely that the latter would be problematic as the favourable dampening effects on neutrophil-mediated inflammation have been well documented experimentally, it is also known that the majority of these effects on neutrophils are due to pentoxifylline-mediated inhibition of TNF-α.[25] This cytokine is produced predominantly by mononuclear cells, which should play no direct role in the initiation of complement-mediated neutrophilic inflammation. In our cases of neutrophilic leukocytoclastic and nonleukocytoclastic vasculitis, mononuclear cells were either absent or a very minor part of the inflammatory infiltrate.

The dosage of pentoxifylline (10–15 mg kg^{-1}) used in our cases was based upon the dosage reported anecdotally to be effective for the treatment of canine familial dermatomyositis, an inflammatory disease in which microvascular vasculopathy is thought to play a role. The dosing interval (twice daily) was chosen due to the personal experiences of the authors gained in treating dermatomyositis. However, a recent pharmacokinetic study suggests that an oral dosage of 15 mg kg^{-1} thrice daily should be used due to a short plasma half-life of the drug.[41]

Dapsone and sulfasalazine were not the first drugs chosen due to their reported side effect profiles.[32,33] Nonetheless, the use of sulfasalazine was implemented in three dogs (Nos 2, 7 and 8) that did not respond to the initial combination. Sulfasalazine was chosen over dapsone because of fewer potential side effects.[32] The cutaneous vasculitic lesions of all three of these dogs

improved significantly with its use, although one dog (No. 7) developed irreversible hepatotoxicity and another (No. 2) developed KCS within 3 weeks and elevated liver enzymes within 6 weeks of its use. Because of these potential side effects, tear production, complete blood count and serum biochemical analysis should be monitored periodically.

Case 8 tolerated sulfasalazine therapy well, and has continued to receive it. Case 19, a Jack Russell Terrier with LCCV, required initial combination therapy with prednisone and dapsone, but has been maintained with dapsone monotherapy for several years. The drug was selected based upon a published report of its successful use in the treatment of idiopathic cutaneous vasculitis in Jack Russell Terriers.[42]

Although our case numbers are too low to permit statistical analysis, it is interesting to note that all cases responding to sulfone/sulfonamide therapy (and which were unresponsive to pentoxifylline) had predominantly neutrophilic inflammatory cell infiltrates histologically. This favourable response is not unexpected considering the mechanisms of action of the sulfones/sulfonamides.

The finding of focal cutaneous vasculitic lesions at rabies vaccination sites has been documented previously.[14] Similarities that are apparent between the referenced study and our study include the breeds involved, the time interval between vaccine administration and observation of lesions, and the finding of a mononuclear, nonleukocytoclastic histopathological pattern of inflammation. The significance of two affected dogs being offspring of the same parentage is unknown, but cases in littermates have also been reported.[6]

Three of four dogs presenting with these lesions responded well to prednisone and pentoxifylline combination therapy. Because none of the dogs in this group was treated with pentoxifylline alone, it is not possible to retrospectively determine what effect, if any, this drug had on our cases of rabies vaccine-induced cutaneous vasculitis with alopecia. However, favourable responses to pentoxifylline in combination with vitamin E, but without concurrent steroid use, have been reported for two dogs with rabies vaccine-associated ischaemic dermatopathy.[43]

Three of the 21 cases reviewed presented with urticarial vasculitis, and food sensitivity was proven in two of these by dietary elimination trials with provocative exposure to beef. Although urticarial vasculitis is a recognized entity in human beings it has not been associated with food sensitivity.[44,45] However, other clinical presentations of leukocytoclastic vasculitis in people have been reported in association with food antigens and additives.[11,12,46]

Of all the clinical lesions presented in this retrospective, only the cases involving the rabies-induced vasculitis presented with a consistent histopathological pattern. The other cases involved mixed patterns with neutrophilic leukocytoclastic and nonleukocytoclastic infiltrates predominating. The relevance of the lack of leukocytoclasia in some of our cases is unknown. Neutrophilic nonleukocytoclastic vasculitis has been reported in conjunction with Rocky Mountain spotted fever.[2] However, our cases were serologically negative for rickettsiae. Neutrophilic vasculitis has also been associated with staphylococcal pyoderma in dogs, in which case it is thought to represent a hypersensitivity reaction to bacterial antigens.[47] Tissue cultures were not performed in all cases with granulocytic inflammatory patterns, however, pyoderma was ruled out with empirical anti-staphylococcal therapy when lesions suggestive of pyoderma were noted clinically. In none of the cases were concurrent bacterial folliculitis or epidermitis noted histologically.

Overall, 11 of 21 cases (52.3%) were assigned a diagnosis of idiopathy by exclusion. This finding concurs with the frequency of idiopathy reported for cutaneous small-vessel vasculitis in human beings. Of the remaining cases, rabies vaccine reactions (four dogs and one cat), oral drug reactions (ivermectin and itraconazole) and neoplasia (lymphosarcoma) were associated with the vasculitis. Regarding the latter, there was nothing novel about the inflammatory pattern to suggest internal disease. Despite previous anecdotal impressions in human beings, it has now been shown that the severity of the inflammatory infiltrate of LCCV is not predictive of extracutaneous involvement.[49] Finally, despite the close temporal relationships to drug administration in two other cases, too many confounding factors were present to make a definitive diagnosis of drug induction and these were classified as idiopathy. A potential association with drugs is especially problematic as withdrawal of an offending drug does not always lead to rapid resolution of the inflammatory process, confusing the diagnostic process. Several hypotheses for the pathomechanism of this prolonged response have been proposed for T-cell-mediated injury. These include persistence of drug metabolites (hapten-carrier conjugates) in body tissues, and the uncovering of 'cryptic' peptides that provoke T-cell autoreactivity.[50] It seems plausible that similar conditions could provoke antibody-mediated reactions as well.

The complete diagnosis of a case of cutaneous vasculitis can therefore be a challenge. An extensive history to rule out drug-induced and polysystemic disease should be pursued, and be accompanied by a thorough physical examination (including ophthalmologic). The authors now consider the minimum database to include a complete blood count with differential, serum biochemical assay, urinalysis and histopathology. Coagulation profiles and more specific testing of immune status (antinuclear antibody, Coombs, rheumatoid factor) may be reserved for use on a case-by-case basis. Infectious disease should be ruled out depending upon the clinical history and physical signs. Tissue culture should be performed on nodular or granulomatous lesions, and blood culture may be indicated in cases with clinical or laboratory evidence of sepsis. Viral serology (FIV, FeLV) should be considered in cats, and rickettsial serology is important for canine patients in many regions of the world.

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Résumé Vingt et un cas de vasculite cutanée sont rapportés chez des chiens et des chats. Les cas ont été divisés en fonction des signes cliniques en cinq groupes distincts. L'aspect clinique des lésions a été corrélé avec le type d'inflammation à l'examen histopathologique, la réponse au traitement et le pronostic. Plus de 50% des cas étaient idiopathiques, cinq étaient dûs à une vaccination antirabique, deux associés à une hypersensibilité au boeuf, un à un lymhosarcome, et deux à l'administration orale de médicaments (ivermectine et itraconazole). Seuls les cas de vasculite induite par une vaccination antirabique présentaient un type constant d'inflammation à l'examen histologique (mononucléé/non leucocytoclasique) et une bonne réponse au traitement par l'association prednisone/pentoxifylline ou par la prednisone seule. La plupart des cas caractérisés par une inflammation neutrophilique ou neutrophilique/éosinophilique n'ont pas répondu à la pentoxifylline, mais ont été contrôlés par les sulfones/sulfonamides, la prednisone ou l'association de ces molécules. [Nichols, P. R., Morris, D. O., Beale, K. M. *A retrospective study of canine and feline cutaneous vasculitis*. (Etude rétrospective de vasculites cutanées canines et félines.) *Veterinary Dermatology* **12**: 255–264.]

Resumen Se revisaron veintiún casos de vasculitis cutánea en animales domésticos (perros y gatos), y se dividieron los casos según los síntomas clínicos en cinco grupos. Se intentó correlacionar los tipos clínicos de vasculitis con los patrones de inflamación histológica, respuesta a la terapia con fármacos y el pronóstico. Más del 50% de los casos fueron idiopáticos, mientras que cinco fueron inducidos por la vacunación de la rabia, dos se asociaron a una hipersensibilidad a la ternera, uno se asoció a linfosarcoma y dos se asociaron a la administración de fármacos orales (ivermectina e itraconazol). Sólo los casos de vasculitis inducida por la vacunación de rabia en perros tuvieron un patrón histológico de inflamación constante (mononuclear/no-leucocitoclástico) y respondieron a la combinación terapéutica de prednisona y pentoxifilina, o a la prednisona sola. La mayoría de casos con patrones histológicos de inflamación neutrofílica o neutrofílica/eosinofílica no respondieron a la pentoxifilina, pero respondieron a la sulfona/sulfonamida, prednisona, o a una combinación de los dos. [Nichols, P. R., Morris, D. O., Beale, K. M. *A retrospective study of canine and feline cutaneous vasculitis*. (Estudio retrospectivo de la vasculitis cutánea felina y canina.) *Veterinary Dermatology* **12**: 255–264.]

Zusammenfassung Einundzwanzig Fälle kutaner Vaskulitis bei Kleintieren (Hunde und Katzen) wurden überprüft und auf Grund klinischer Symptome in fünf Gruppen unterteilt. Es wurde versucht, klinische Typen der Vaskulitis mit histologischen Entzündungsmustern, Besserung auf Grund medikamenteller Behandlung und Prognose zu korrelieren. Über 50% der Fälle waren idiopathisch, fünf waren durch Tollwutimpfungen verursacht, zwei mit einer Überempfindlichkeit gegen Rindfleisch, ein Fall mit Lymphosarkom und zwei mit der Verabreichung oraler Medikamente (Ivermektin und Itrakonazol) verbunden. Nur die Fälle der durch Tollwutimpfung verursachten Vaskulitis zeigten ein klassisches Entzündungsmuster (mononukleär/nicht-leukozytoklastisch) und sprachen auf Kombinationstherapie mit Prednison und Pentoxyphyllin oder auf Prednison allein an. Die meisten Fälle mit histologischen neutrophilen oder neutrophilen/eosinophilen Entzündungsmustern sprachen nicht auf Pentoxyphyllin, aber auf Sulfone/Sulfonamide, Prednison oder eine Kombination dieser Medikamente an. [Nichols, P. R., Morris, D. O., Beale, K. M. *A retrospective study of canine and feline cutaneous vasculitis.* (Eine retrospective Studie kutaner Vaskulitis bei Hund und Katze.) *Veterinary Dermatology* **12**: 255–264.]