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Cutaneous Vasculitis in Small Animals

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KEYWORDS

• Cutaneous vasculitis • Necrotizing vasculitis • Neutrophilic vasculitis
• Immune mediated • Cutaneous adverse drug reactions • Canine • Dog • Cat

KEY POINTS

- Cutaneous vasculitis is a reaction pattern and not a disease in itself.
- A thorough workup to identify underlying triggers should always be made.
- The diagnosis must be confirmed histologically, and one should obtain deep tissue samples to make sure vascular damage is not missed.
- If a drug is suspected or confirmed as the cause of vasculitis, withdrawal and future avoidance is the most important treatment.
- Very high doses of steroids may not be the best treatment for patients presenting with large areas of ulcerated skin, because this increases the risk of secondary wound infections and delays wound healing.

Vasculitis is a reaction pattern, characterized by an aberrant immune response directed toward blood vessels.[1] The pathophysiology is not fully understood, and is most likely complex, involving a variety of mechanisms acting in concert to induce necrotizing inflammatory changes in the blood vessel wall.[2]

Clinical presentation of patients affected by this multifactorial reaction pattern depends mainly on the extent of vascular destruction, and both cutaneous and systemic forms have been reported.[1] Impaired vascular function may lead to edema formation, hemorrhage, and purpura. Full-thickness skin necrosis and crateriform ulcers may follow. Patients affected with systemic or cutaneous vasculitis are most often sick, presenting with constitutional signs. A varying degree of pain is common and may range from mild to severe. Extensive ulcerations of large areas of skin predispose these patients to secondary bacterial wound infections and sepsis, much like a patient presenting with extensive burns, so proper wound management is essential.

Numerous triggering factors have been identified as a cause of vasculitides in dogs and cats; therefore, a thorough drug history and early workup for underlying ongoing disease processes are important steps when presented with these patients.[1,3] Diagnosis should be based on history and clinical findings along with compatible histopathology reports.

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Treatment must be tailored to the individual patient, and should be based on underlying triggering factors as well as the extent and severity of cutaneous lesions.

Vasculitic diseases currently recognized in dogs and cats, including cutaneous necrotizing vasculitis or neutrophilic immunologic vasculitis, are covered herein. Specific familial vasculitides will also be reviewed briefly. For information about ischemic dermatopathies please refer to the article by Morris elsewhere in this issue.

IMMUNOPATHOGENESIS

The primary immunopathogenic events that initiate the process of vascular inflammation and blood vessel damage are poorly understood in both people and animals; however, immunologic mechanisms appear to play an active role.[2]

Applying the traditional Gell-Coombs classification of hypersensitivity reactions, it is thought that immediate hypersensitivity reactions as well as type II and type III reactions may all be involved in the immunopathogenesis of vasculitic diseases.[4] This immunologic heterogeneity also illustrates the importance of not viewing vasculitic diseases as a diagnosis in itself, but a reaction pattern that warrants further investigations to achieve a proper diagnosis and prognosis for the individual patient.

Type I Hypersensitivity Reactions

Immediate hypersensitivity reactions, characterized by the formation of immunoglobulin E antibodies have been stated to be involved especially in the early stages of cutaneous vasculitides in animals[5]; however, type I reactions are unlikely to be the major player in most cases of canine and feline vasculitides.[1]

Type II Hypersensitivity Reactions

In a classical type II hypersensitivity reactions, antigen–antibody interactions result in the local production of anaphylotoxin (C5a), the recruitment of polymorphonuclear leukocytes, and subsequent tissue injury owing to the release of hydrolytic neutrophil enzymes after their autolysis. In human medicine, a subset of vasculitides are characterized by the formation of autoantibodies; so called antineutrophil cytoplasmic antibodies (ANCA) and the diseases associated with the production of these antibodies are referred to as ANCA vasculitides. In ANCA vasculitides (Wegener's granulomatosis [WG], Churg–Strauss syndrome, and polyarteritis nodosa), ANCA bind directly to neutrophil granules and the release of toxic mediators leads to a direct damage of vessel walls.[1,2]

Human antibody-associated vasculitides, where antibodies bind directly to the vessel walls, are thus classical examples of type II reactions.[2]

Type III Hypersensitivity

Immune complex reactions occur when antibodies present in the blood result in the formation and deposition of antigen–antibody complexes. The very presence of these complexes lodged in blood vessels, in addition to the polymorphonuclear leukocytes attracted by complement activation, results in tissue injury and compromised function. Vasculitis associated with connective tissue diseases such as systemic lupus erythematosus are examples of a type III hypersensitivity reaction.[1,6] This is currently the most widely accepted pathomechanism of cutaneous vasculitis in animals.

HISTOLOGIC FEATURES

Histologic examination is needed to confirm a diagnosis of cutaneous vasculitis, and samples from affected patients show pathologic changes in the vascular structures of

the dermis or sometimes deep panniculus, as well as secondary changes that can be related to tissue hypoxia.[5] True vasculitis is separated histologically from *vasculopathy*, the latter being a term used to describe thromboembolic accidents and occlusion of vessels by fibrin thrombi, usually as a result of sepsis and vascular toxins.[7]

In cases of "true" vasculitis, a differentiation between leukocytoclastic and non-leukocytoclastic vasculitis is made. Leukocytoclasia is a histologic term referring to pyknosis and karyorrhexis of nuclei. This can be visualized histologically as fragmented nuclear debris around blood vessels, often referred to as "nuclear dust." Leukocytoclasia may range from subtle to severe and can sometimes be the only evidence of a vascular insult[5]; however, a diagnosis of leukocytoclastic vasculitis requires several other criteria to be satisfied: Intramural inflammation (visualized as inflammatory cells transmigrating the vessel histologically), endothelial cell swelling, leukocytoclasia, hemorrhage, and fibrinoid necrosis of the vessel wall.[7] The dominant inflammatory infiltrate may be neutrophilic (majority of cases), eosinophilic, or lymphocytic. Leukocytoclasia is normally a feature of vasculitis affecting small or medium sized vessels.[5]

Damage to dermal vessels usually leads to the development of hemorrhage and edema within the tissues. Hypoxic changes with pale collagen ("smudging of the collagen") along with faded hair follicles and adnexal structures may be seen as well. Epidermal lesions such as exudation, crusting, and ulceration may also develop owing to tissue ischemia.[7]

CLASSIFICATION

Classification of vasculitides in animals has traditionally been based on histologic inflammatory patterns. Currently, no classification system taking into account the clinical presentation of the individual patient is recognized in veterinary medicine. Based on such histologic classification, vasculitides in animals are categorized as either leukocytoclastic or non-leukocytoclastic, and then subdivided as neutrophilic, eosinophilic, or lymphocytic.[5] Correlations have also been made between histologic classifications and the different triggering factors leading to the vasculitic event; however, one should keep in mind that histologic lesions may evolve and change over time.[7] This has been thoroughly documented in human patients, where serial evaluations of human leukocytoclastic cutaneous vasculitis has shown that the granulocytic infiltrate gives way to a predominantly mononuclear population within 48 hours.[7]

It is the personal opinion of the author that the current classification alone is unsatisfactory from a clinical standpoint, because it does not help to predict the outcome of the disease for the individual patient.

CLINICAL FINDINGS

Dermatologic Presentation

Disruption of adequate blood flow and tissue oxygenation may lead to a wide range of clinical signs. Dermatologic lesions may be the only clinical sign, but it is not uncommon for constitutional signs to antedate cutaneous changes.[8]

Palpable purpura, plaques and hemorrhagic bullae, and wheals and serpentine papules, alone or in combination with pitting edema, are common presenting signs.[1] Purpura, a symptom indicating an ongoing hemorrhagic event in the skin, may also become darker with time.[8] It is imperative that purpura is differentiated from erythema. This can easily be done by applying a glass slide to the lesion with slight pressure. If the lesion does not blanch, purpura can be confirmed. This diagnostic test is commonly referred to as diascopy (**Fig. 1**).[5]

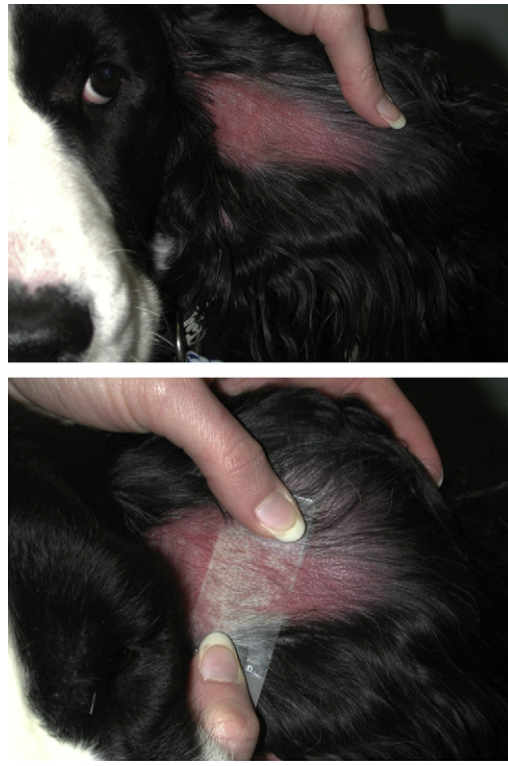

Fig. 1. Diascopy is performed by pressing a transparent glass slide onto the skin. Using this simple diagnostic test will help to differentiate between erythema and purpura (hemorrhage).

With severe vascular injury and subsequent hypoxia or ischemia of the tissue, resulting lesions in the form of full-thickness necrosis and "punched out" crateriform ulcers or even eschars may develop. Devitalized tissue may be firm, discolored, and cool to the touch.

If the vasculitic event targets vessels of subcutaneous adipose tissue, a process referred to as *septal vasculitis*, palpable, firm subcutaneous nodules, and swellings may be present.[5] Acrocyanosis, a bluish discoloration of the extremities, has also been reported in some affected dogs.[8]

Atypical presentation with target lesions and a clinical picture mimicking erythema multiforme was observed in 1 patient with confirmed vasculitis histologically (personal observation). Some patients, especially if food allergy is an inciting trigger of the vasculitis, may also present with a generalized, sometimes chronic urticaria.[3]

Lesions may develop at any site of the body, including the oral cavity and mucous membranes. Independent of body site, it is not uncommon that lesions are distributed in a linear fashion, reflecting the vascular anatomy of the patient. This may be a striking feature, especially when the tail or extremities are affected, that should alert the clinician to a possible ongoing vasculitic event.[8] The clinician needs to keep in mind that the cutaneous lesions resulting from an ischemic event in the skin may evolve over time. Patients presenting early may develop ulcers only several days later, and pitting edema along with constitutional clinical signs, which may be the only finding in the early stage of the disease. See **Figs. 2–6** for examples of dermatologic presentations.

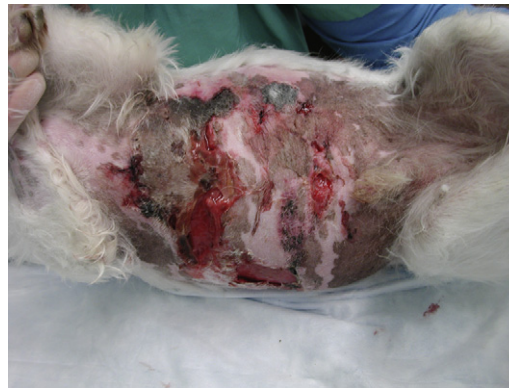

Fig. 2. Severe necrotizing vasculitis in a 7-year-old Jack Russell Terrier mix. Note the extensive deep ulceration, devitalized tissue in the cranial parts of the abdomen, and a punched out eschar on the right lateral aspect of the umbilicus region.

Palpation of the skin is imperative to detect pitting edema, unusual firmness of the skin, or temperature changes that may occur as a result of a deficient blood supply. Patients with a long hair coat should be clipped to allow better visualization of the affected skin and thus better monitoring of disease progression and response to treatment. Marking the edges of the lesions with a waterproof marker is a simple but effective tool for monitoring progression of disease when lesions are extensive.

Systemic Clinical Signs

Patients may present with a range of clinical symptoms and constitutional signs, such as anorexia, depression, malaise, and pyrexia.[8] In a retrospective evaluation of 36 patients with histologically confirmed cutaneous necrotizing vasculitis, 34 of 36 patients presented with signs of systemic illness (Marie Innerå, unpublished data, 2011). In the same group, a majority of patients suffering from vasculitis also displayed

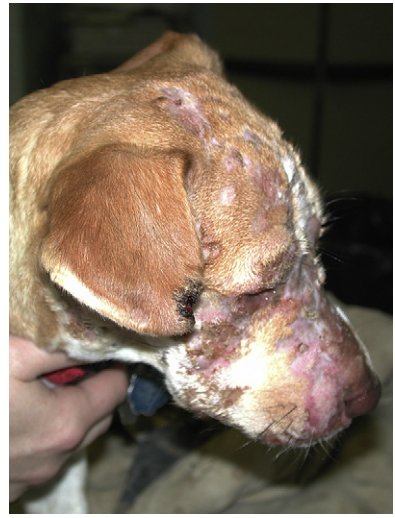

Fig. 3. Generalized vasculitis in an 8-month-old mixed breed dog. No triggers could be identified in this patient, but the dog was managed on 5 mg/kg cyclosporine.

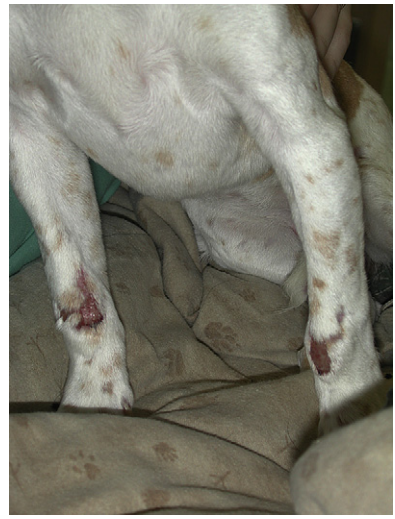

Fig. 4. Same dog as in **Fig. 3**. Full-thickness ulceration of the front legs below the anastomosis of the proximal palmar venous arch and the accessory cephalic arch (where the vessels are narrower). The lesions follow the vasculature in a linear and symmetric fashion. This is commonly seen in patients suffering from cutaneous vasculitis.

signs of generalized or diffuse pain. This is particularly common during the initial phase of the disease; however, degree of pain may be highly individual. Pain may be related to the skin as a single organ system and in certain cases may be so severe that it becomes difficult to evaluate whether or not other organs are involved, for example, involvement of the ventral abdomen may cause the animal to walk with a stiff gait or avoid lying down. It may also be challenging to palpate the abdomen or perform a routine abdominal ultrasound, even under sedation, when the skin of the abdomen is severely affected

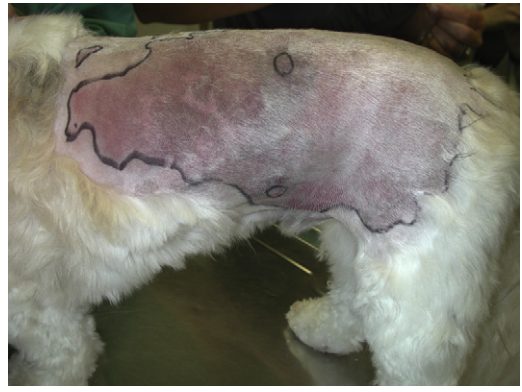

Fig. 5. This 5-year-old Shi Tzu originally presented as an emergency owing to ocular vasculitis and hyphema a day after visiting the groomer. On recheck with the ophthalmologist 3 weeks later, the dog developed these confluent purpuric lesions that rapidly expanded while being examined by the ophthalmologist. A thorough drug history revealed that the owner would give the dog acepromazine before car rides. Acepromazin was thus the likely trigger in this dog, because it had been administered both before the visit to the groomer and before seeing the ophthalmologist for a recheck.

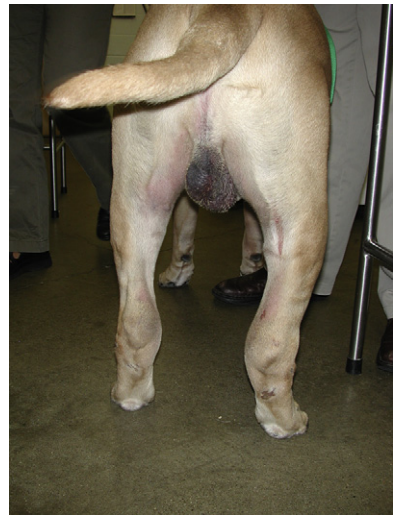

Fig. 6. Pitting edema is a common finding in vasculitis patients. This 9-year-old Mastiff presented with pitting edema of both hind legs and intensely painful purpuric lesions of the groin and scrotum. The dog was diagnosed with lymphoma.

and painful. Dogs with a thick hair coat may only show signs of severe pain when touched or handled and the lesions may not become evident to the owners or clinician until the skin itself is more thoroughly examined. Oral lesions, when present, may cause the animal to salivate, become anorexic, or to be reluctant to open its mouth.

Polyarthropathy, myopathy, and neuropathy has also been described in patients with cutaneous necrotizing vasculitis. It is common to see moderate elevations liver enzymes (50% of patients in an unpublished study, Marie Innerå, 2011). Glomerular disease, pleuritis, pericarditis, and gastrointestinal inflammation may also be present. These findings correspond with what is seen in human cases of leukocytoclastic cutaneous vasculitis.[8]

In contrast with ischemic dermatopathies (also known as cell-poor vasculopathy or cell-poor vasculitis), patients presenting with true cutaneous vasculitis are usually sick dogs that require a thorough workup and careful monitoring. Early recognition of clinical symptoms and a tentative working diagnosis of cutaneous vasculitis allows for a better prognosis for the patient, so that appropriate actions can be taken in the early stage of the disease process.

DIAGNOSIS

A thorough history should always be obtained when vasculitis is suspected and should include information about exposure to drugs and/or xenobiotic substances administered to the pet either systemically, topically or added to the animals diet within the last 2 to 4 months (Dr Edmund Rosser, personal communication, 2009). A drug history should also include routine vaccinations and dietary supplements. Information should also be obtained with regard to current and previous diets (including treats and people food) that the animal has been exposed to, so that an appropriate elimination diet can be selected if necessary.

A comprehensive physical examination must be performed, including a thorough dermatologic examination. A minimum database should include a complete blood

count with differential, a serum chemistry profile, and urinalysis. Tick titers should be evaluated, especially when the patient is living in or traveling to areas where tick-borne illnesses are endemic.

Cutaneous hemorrhagic events may be the only symptom of certain coagulation disorders or ongoing immune-mediated hematologic processes. Such diseases are important differentials for cutaneous vasculitis, and a coagulation profile as well as more specific immunologic testing may be necessary (antinuclear antibody testing, Coombs tests, and rheumatoid arthritis factor).

One of the most important and critical steps in the workup of patients suffering from vasculitis is differentiating between infectious and non-infectious disease processes. If sepsis is suspected, blood cultures are indicated. However, it can often take some time to get the results of these tests and the same is true for histopathology reports. When faced with acutely ill patients, additional diagnostic tools can therefore be of value in an emergency setting. The author finds fine-needle aspiration biopsies from edematous areas to be a helpful in such situations. Aspiration of edematous skin lesions and subsequent staining with a Romanowsky type stain such as Diff Quick or Hemacolor can provide an impression of the nature of the cutaneous infiltrate. More important, bacterial organisms may be visualized on such smears.

D-Dimer, if available, may also be of value in this early stage of decision making, because this test predicts thrombus formation in dogs with cutaneous vasculitis.[9–11] This test, however, will not differentiate between infectious and non-infectious processes so a positive D-dimer only reflects thrombus formation and does not replace histopathology as a means of diagnosing vasculitis.

Histology is essential to confirm the diagnosis, regardless of fine-needle aspiration biopsy results, and it is advised to obtain biopsies that are representative of different stages of the disease process. One should make an effort to include the deeper layers of the skin as well as the epidermis in the biopsy, because vascular disease processes may be more easily observed here. Taking skin biopsies at an early stage allows for a more rapid diagnosis. A sterile punch biopsy should be obtained simultaneously and submitted for macerated tissue culture and susceptibility testing (bacterial and fungal) to rule out infectious processes (**Box 1**).

DIFFERENTIAL DIAGNOSES

Several diseases may mimic cutaneous vasculitis both clinically and histologically. Vascular damage, vasculopathy, and thrombosis of blood vessels are features of several infectious diseases. This highlights the importance of ruling out infectious causes of vasculitis before making a diagnosis of true vasculitis.

The principal clinical differentials that needs to be considered before making a diagnosis of true vasculitis includes sepsis (which can lead to thrombosis and/or vasculopathy), disseminated intravascular coagulation, cryoglobulinemia, cryofibrinogenemia (cold agglutinin disease), and frostbite.[5] Sepsis can lead to thrombosis and vasculopathy secondary to infections of the skin, such as deep pyoderma when it complicates demodicosis, or as a result of internal infections such as bacterial endocarditis.[5] Other, less common differentials include erysopleothrix rhusiopathie infections and Rocky Mountain spotted fever. These diagnoses are, however, not common in dogs.[5,12]

TRIGGERS AND UNDERLYING DISEASES

The list of underlying causes that can result in an aberrant immune response directed toward the vascular endothelium is exhausting and summarized in **Box 2**.[1,3,5]

Box 1
Diagnostic testing for cutaneous and systemic vasculitis in dogs

Minimum Database

- Complete blood count with differential
- Serum chemistry assay
- Urinalysis
- Tick titers
- Cytology (fine-needle aspiration biopsy)
- Histopathology
- Culture (fungal and bacterial)

Additional diagnostic tests

- Coagulation profile
- Blood cultures
- Coombs test
- Antinuclear antibody test (ANA)
- Rheumatoid arthritis factor
- Diagnostic imaging
- Elimination diet

Drugs

Drugs may act as antigens triggering a number of cutaneous adverse drug reactions. The antigen may be the drug itself, one of its metabolites, or a drug–protein or metabolite–protein complex.[6] In all cases of cutaneous adverse drug reactions, a drug could

Box 2
Underlying causes of vasculitis in dogs

1. Drugs
2. Insect bites
3. Infectious causes
   a. Viral
   b. Bacterial
   c. Mycobacterial
   d. Fungal
   e. Protozoal
   f. Rickettsial
4. Neoplastic processes
5. Adverse reactions to food
6. Autoimmune diseases
7. Genetic/familial forms
8. Idiopathic forms

also be defined as any "drug-like substance" and not necessarily only licensed medication intended for the treatment of animals. This is important, because the trend for supplementing and treating companion animals with holistic or alternative medications is gaining popularity. Such supplements might sometimes be included in the animal's diet. In addition, with the recent technological developments, owners are relying more on information from various other sources than their regular veterinarian when it comes to treatment of various maladies in their pets. The list of remedies an animal may have been exposed to before an adverse event could therefore be extensive.

When presented with a patient suffering from an adverse drug reaction, a thorough drug history is of crucial importance, because the most important therapy is drug withdrawal, including all drugs or drug-like substances administered to the patient within the last 4 to 6 months.[6]

Determining whether or not a drug is in fact the trigger may be problematic, especially in patients receiving multiple medications, and there are few solid reports of specific drugs implicated as triggers of vasculitis. This may stem from the fact that proving a relationship between a drug and a specific adverse drug reaction can be challenging. Patients commonly receive multiple drugs simultaneously and when a reaction to a drug produces a severe life-threatening reaction, rechallenge runs the risk of being fatal and is therefore not advisable. Specific diagnostic tests aimed at documenting immunologically based reactions to specific medications are not commercially available for dogs and cats at the moment. This "lack of solid proof" may well be one of the reasons for the sparse amount of literature being published on the subject of cutaneous vasculitis and one can probably make the assumption that these diseases are underreported. Much of the currently available information is thus based on an association between previous drug exposure and development of clinical signs along with exclusion of other possible triggers.

Itraconazole is a well-known, dose-dependent trigger of vasculitis in dogs. In a report from 1996, Legendre and coworkers reported that 7.5% of dogs receiving a 10 mg/kg dose of itraconazole developed vasculitis, whereas dogs receiving lower doses (5 mg/kg) did not develop lesions.[13]

Recently, nonsteroidal anti-inflammatory drugs have been associated with vasculitis in dogs. Meloxicam was suspected as a trigger of vasculitis in a 10-year-old mixed breed dog from Portugal treated with the drug awaiting surgical repair of a cranial cruciate ligament injury.[14]

An association between meloxicam exposure and cutaneous vasculitis was seen in 3 of 36 dogs in an unpublished retrospective review of canine cutaneous vasculitis (Marie Innerå, unpublished data, 2011); however, a true connection between the drug and the clinical disease was difficult to assess in 2 out of 3 cases because 1 patient had a history of recent exposure to both meloxicam and deracoxib, and another dog received allergen-specific immunotherapy for atopic dermatitis as well as cephalexin at the time of the vasculitic event. A true connection between nonsteroidal anti-inflammatory drugs and cutaneous vasculitis may thus be difficult to assess, owing to the common practice of co-administering of additional medications. However, in the same retrospective study, a 5-year-old Shih Tzu developed cutaneous eosinophilic vasculitis 3 days post administration of beef-flavored chewable firocoxib tablets. Eosinophilic vasculitis has previously been associated with food antigens as a trigger of vasculitis.[3] Whether or not the drug or the flavoring ingredient was the true trigger in this patient remains unknown.

Drugs that have been associated with cutaneous vasculitis in dogs are listed in **Box 3**.

Box 3
Drugs Associated with Cutaneous Vasculitis in Dogs and Cats

- Antibiotics (Cephalexin)
- Ivermectin
- Vaccines
- Metronidazole
- Phenobarbital
- Furosemide
- Itraconazole
- Phenylbutazone
- Enalapril
- Imodium
- Metoclopramide
- Fenbendazole
- NSAIDs (Meloxicam)
- Acempromazin

Refs.[14,57]

Feline vasculitides have also been associated with drugs. A case of systemic vasculitis with cutaneous involvement was reported in a cat after having received fenbendazole[15] and another cat was reported to have developed cutaneous vasculitis as a result of oral cimetidine administration.[16]

Insect Bites

In addition to having an important role as vectors of certain diseases, biting, stinging, or hematophagous insects and ticks may elicit numerous immune responses when stinging or feeding on their hosts.[8] Venomous insects express toxins that may damage tissues directly. When bees and wasps sting, they deposit the tip of their abdomen into the skin and the entire poison apparatus is left in the wound. Salivary antigens from different insects and ticks may also be deposited into the skin during feeding. Thus, there are numerous ways in which insects can introduce foreign antigens into the skin, and in this way trigger immune responses in their hosts.[8]

Infectious Causes

Infectious causes of cutaneous or systemic vasculitis may develop owing to direct invasion of the vessel wall by a pathogen, as a result of immune complex deposition on the vascular endothelium, or via activation of B or T cells.[17]

In human medicine, a distinction is often made between primary and secondary vasculitides, with primary vasculitis representing immunologic or autoimmune diseases with no identifiable infectious agent, and secondary vasculitis representing those vasculitic diseases that should be considered a symptom or clinical feature of an infectious disease by itself.[17] Before the development of advanced molecular diagnostic methods, idiopathic human vasculitides were considered common. However, with recent developments in diagnostic methods, an increasing body of evidence is mounting for the potential role of microbial agents and infections in the pathogenesis

of diseases previously considered to be strictly immune mediated.[18] To exemplify this, tissue destruction caused by different microbial agents during an infectious process may lead to formation of autoantibodies directed against various cells, including vascular endothelium. The role of viruses, heat shock proteins, superantigens, and various underlying comorbidities as possible initiators of different immune-mediated diseases is still not fully understood. However, new insight into this area may substantially increase our understanding of these diseases in the future.[17,19]

Viral infections

In dogs, the list of infectious diseases associated with cutaneous vasculitis is extensive. However, a true relationship between viral diseases and cutaneous vasculitis has not been made in canines. In cats, on the other hand, cases of cutaneous vasculitis have been documented in patients suffering from feline infectious peritonitis.

Progression from feline coronavirus infection to the development of feline infectious peritonitis is determined not only by mutations of the virus, but by the animal's immune response and characterized by Immune complex deposition in various organs.[20] Although rare, cats suffering from feline infectious peritonitis have presented with dermatologic clinical signs consisting of slightly raised demarcated and erythematous intradermal nodules or non-pruritic papules along with other organ system involvement.[21–23] In 1 cat, lesions were transient and probably recognized because the affected cat belonged to a hairless breed.[23]

A leukocytoclastic immunologic vasculitis was reported in one of these cases, whereas a pyogranulomatous infiltrate was described in 2 others. Changes restricted to the mid and deep dermis with severe edema and multifocal pyogranulomas, often centered around vessels, along with dermal necrosis and hemorrhage was observed. In addition to dermal vascular pathology, adnexal structures were affected in all 3 cases.[21–23] In 2 out of 3 cases, feline coronavirus antigen was confirmed in both kidney and skin tissues using a mouse monoclonal antibody.[21,22]

Bacterial infections

Bacterial pyoderma was reported to be associated with canine vasculitis in 1978 and a hypersensitivity reaction to bacterial antigens was proposed as the most likely triggering event.[24] In people, nasal carriage of *Staphylococcus aureus* (including methicillin-resistant *S aureus*) has a known affinity for vascular endothelium, and *Staphylococcus aureus* carriage is capable of modulating the expression of WG, a type of human neutrophilic vasculitis. Patients suffering from WG are also more likely to carry *S aureus* (nasal colonization) than normal healthy individuals. Although the majority of patients suffering from WG are nasal carriers of *S aureus*, the corresponding prevalence for the general population is approximately 25%.[25]

The exact pathomechanisms leading to an increased carriage of *S aureus* in human patients suffering from this type of vasculitis and the role of *S aureus* as a cause of exacerbations and flares of WG is unknown. However, several hypotheses have been proposed, including molecular mimicry, binding of cationic staphylococcal enzymes to glomerular endothelial cells, and a direct activation or priming of neutrophils. Patients carrying strains of *Staphylococcus* that produce superantigens, such as toxic shock syndrome superantigen-1 carry a particular strong risk for relapse of their vasculitic disease.[18,25]

Whether or not staphylococcal organisms are of importance in immune-mediated diseases in dogs and cats is not known; however, *Staphylococcus pseudintermedius*, the dominant staphylococcal organism of dogs and cats, has the capacity of producing exotoxins with superantigenic properties.[26]

Gram-negative toxin-producing bacteria has been linked with a specific form of systemic vasculitis mainly occurring in racing Greyhounds fed a diet consisting of undercooked beef. In idiopathic cutaneous and renal glomerular vasculopathy in racing Greyhounds (also known as green track disease and Alabama rot), an association has been made between verotoxin-producing strains of *Escherichia coli* O157:H7 and idiopathic cutaneous and renal glomerular vasculopathy in racing Greyhounds.[1] A purely infectious nature of this syndrome could, however, not be confirmed because oral and intravenous inoculation of adult greyhounds with high doses of idiopathic cutaneous and renal glomerular vasculopathy in racing Greyhounds-producing strains of *E coli* alone failed to produce the disease.[27] Unidentified genetic factors may also be involved, but this acute and potentially lethal syndrome has also been recognized in other breeds such as Great Danes.[28] The true etiology of this disease thus remains unproved.

Affected dogs present with cutaneous lesions consisting of multifocal erythematous cutaneous swellings that may drain a serosanguinous fluid, and affected animals are usually lethargic and febrile. Lesions evolve into sharply demarcated ulcers, and pitting edema of the distal limbs may be present in some dogs. The ventral abdomen and extremities are most commonly affected, sparing the head and dorsum. Gastrointestinal symptoms and signs of acute renal failure may also be present. Some cases present with strictly cutaneous involvement.[1,8]

Fibrinoid necrosis of small dermal arterioles along with full thickness necrosis of the epidermis is the typical dermatohistopathologic finding and renal biopsy specimens usually reveal glomerular lesions with thrombotic microangiopathy and necrosis. Glomerular changes resemble the childhood form of hemorrhagic uremic syndrome in humans; however, children do not develop cutaneous clinical signs.[29]

Bartonella infections may lead to a condition called bacillary angiomatosis in dogs and people. This is a disease in which the vessels are directly invaded by the bacteria, producing lesions that may resemble vasculitis (*pseudovasculitis*). Bacillary angiomatosis was recently described in an immunosuppressed dog, and may in fact be an underdiagnosed disease because it requires special staining to detect the organisms in tissue sections[30]

Tick-transmitted pathogens Associations between different tick-borne diseases and cutaneous vasculitides has long been proposed, but solid evidence of a true correlation between the 2 may be difficult to prove scientifically. There are several reasons for this. First, there may be a failure to recognize the importance of ticks as disease agents themselves.[31] Also, a substantial number of animals may be seropositive for specific tick-borne pathogens in endemic areas, making a true correlation between vasculitic diseases and tick-transmitted pathogens difficult to prove.[32]

Classical symptoms of the different tick-borne illnesses are usually easily recognized in endemic areas. However, animals with an incomplete protective immune response commonly develop persistent subclinical infection, which can recrudesce with stress or concurrent disease.[33] In these cases, low numbers of organisms and cryptic infections make diagnosis difficult using standard methods. Continued antigenemia can lead to the induction of polysystemic, immune-mediated disease such as cyclic anemia, thrombocytopenia, polyarthropathy, uveitis, and vasculitis. Infected animals commonly have high serum globulin levels with monoclonal or polyclonal gammopathies and immune complex formation.[34]

The true prevalence of tick-transmitted pathogens as triggers of canine cutaneous vasculitis is unknown. However, in a recent review of 36 cases of cutaneous necrotizing vasculitis, tick titers were performed as part of the workup for their vasculitic

disease in 10 of the 36 dogs. Three of these 10 dogs showed significant elevation in tick titers. One had elevated *Ehrlichia* titers, 1 had a significantly elevated *Anaplasma phagocytophilum* titer, and 1 young dog presented with a *Borrelia burgdorferi* titer of 1:2560 (reference range >80 considered negative). In the latter dog, a convalescent tick titer was performed 4 weeks after initiating treatment with anti-inflammatory doses of prednisolone and standard doses of doxycycline, and a significant titer reduction was observed along with clinical resolution of cutaneous clinical signs.

Another retrospective study involving 21 cases of cutaneous vasculitis failed to identify cases associated with elevated tick titers, but this study also included a substantial number of patients suffering from ischemic dermatopathies.[3]

Although tick-transmitted pathogens have different target cells, most of them are deposited directly into the skin of their host during a blood meal. *B burgdorferi* in particular replicate in the skin before systemic dissemination.[35]

Beagles experimentally infected with *B burgdorferi* organisms were shown to harbor *B burgdorferi* in their skin as measured by polymerase chain reaction and skin cultures as late as 14 months (end of study) after initial inoculation. An even longer period of tissue replication could potentially be expected, which would mean that these patients experience chronic ongoing antigen stimulation lasting several months to several years.[33]

An established relationship between canine granulocytic anaplasmosis and cutaneous vasculitis has yet to be documented, but anecdotal reports of cases presenting with cutaneous vasculitis and significantly elevated *A phagocytophilum* antibody titer are occasionally encountered by clinicians in different countries.

A study evaluating a possible association between *A phagocytophilum* infection as measured by positive serologic antibody titers and skin lesions in dogs was recently conducted. Of 12 seropositive dogs presenting with skin lesions, DNA for *A phagocytophilum* could be detected in the cutaneous tissue of 3 dogs using molecular diagnostic techniques (polymerase chain reaction). The histologic findings of these dogs were characterized by moderate to severe edema with variable hemorrhage. A superficial and periadnexal mixed cell infiltrate and multifocal nodules, composed of neutrophils and macrophages were seen as well. Established vasculitic criteria, however, could not be confirmed on examined skin biopsies from these dogs.[36]

Neoplastic Processes

Vasculitis presenting as a paraneoplastic syndrome secondary to various underlying malignancies, both solid tumors and hematopoietic cancers does occur but is inconsistently documented most likely owing to the inability of collecting larger case series for systematic reviews. In general, paraneoplastic syndromes may antedate the neoplasm, may occur simultaneously, or may become apparent during the late stages of the malignant disease.[37] Diagnostic imaging at the time of initial presentation is advised in older patients presenting with cutaneous necrotizing vasculitis, because treatment with immunosuppressive agents may delay a diagnosis of hematopoietic cancers particularly.

No definite connection has been made between particular neoplastic processes and the development of vasculitides in canine or feline patients so far.

Adverse Reactions to Food

Cutaneous vasculitis may be the only presenting clinical sign of an adverse reaction to food in dogs.[3] It has so far not been described in the cat.

The mechanism by which food antigens trigger this cutaneous reaction pattern is not known. The majority of these food allergic dogs have presented with an urticarial

form of vasculitis with dermatologic findings presenting as intense erythroderma and generalized erythematous serpentine wheals that fail to blanch on diascopy (**Fig. 1**).[3] A chronic angioedema that often fails to respond to glucocorticoid treatment may be the dominant clinical symptom in some patients, and gastrointestinal signs with soft stools, large bowel diarrhea, flatulence, and frequent bowel movements (>3 per day) may or may not accompany the dermatologic signs. More typical signs of cutaneous necrotizing vasculitis with erythroderma skin necrosis and deep crateriform cutaneous ulcers have also been observed (author's unpublished observations, 2007).

In cases where urticarial vasculitis was the primary presenting clinical sign, histology often revealed an eosinophilic infiltrate; however vasculitis triggered by food may as well be neutrophilic (author's unpublished observations, 2009–2011).

When presented with cases of cutaneous vasculitis, 1 or more elimination and provocation diets should be performed if other triggers cannot be identified. A home-cooked, novel protein diet is recommended; however, hydrolyzed protein diets may also be attempted.

Autoimmune Diseases

Multisystemic involvement associated with cutaneous lesions compatible with vasculitis should alert the clinician to a possible systemic autoimmune disease process as systemic and cutaneous vasculitis may be a feature of such diseases. In dogs, vasculitis has been associated with systemic lupus erythematosus, discoid lupus erythematosus, and rheumatoid arthritis.[7]

Genetic/Familial Forms

Familial pyogranuloma and vasculitis of Scottish Terriers

In 1991, Pedersen and Scott reported a disease in related Scottish Terriers from Denmark in which young animals presented with severe non-painful ulcerations affecting both the nasal planum and the nasal cartilage itself. Affected dogs ranged in age from 3 weeks to 6 months and also showed constitutional signs such as lethargy, depression, and intermittent fever. Both genders were affected and all dogs were from the same breeder. Histologic findings consisted of pyogranulomatous inflammation along with a leukocytoclastic vasculitis. Attempted treatment with prednisolone in 1 case proved to be ineffective and all dogs were eventually humanely killed.[38]

Additional cases have since been reported in other countries—1 case from Argentina and 1 from the United States. The ethiopathogenesis of this disease is currently unknown. Based on preliminary pedigree analyses, the disease is suspected to represent an autosomal-dominant genodermatosis.[39]

Acute febrile neutrophilic vasculitis of the skin of young Shar-Pei dogs

In 2002, Malik and coworkers described 3 cases of necrotizing neutrophilic vasculitis in young Shar Pei dogs. All the affected dogs presented with constitutional signs of before the onset of, or along with the development of, cutaneous lesions. Extensive edema, especially of the face and extremities, that subsequently developed into multifocal, full-thickness skin necrosis and deep cutaneous ulcerations was seen dermatologically. Two dogs responded to treatment with steroids and various antibiotics, whereas 1 dog showed a better response to enrofloxacin than a combination of immunosuppressive treatment, clavulanate-potentiated amoxicillin, and cephalexin along with injectable dexamethasone. A pedigree analysis was not possible to perform in these cases and a genetic etiology could not be confirmed. Two of these 3 dogs had been vaccinated with a live virus vaccine 3 weeks before the onset of illness, and 2 dog dogs had also been exposed to antibacterial treatment with a combination of amoxicillin

and clavulanic acid. Whether this disease represents a genodermatosis in the Chinese Shar Pei is currently unknown. Additional cases have not been reported so far.[40]

Proliferative arteritis of the nasal philtrum

A highly distinctive arteritis affecting only the nasal philtrum was originally described in 4 St Bernards and a Giant Schnauzer.[41] Subsequently, the disease has also been described in a Newfoundland and a Basset Hound. A genetic predisposition seems to exist in the St Bernard.[5,42]

The typical appearance is of a solitary, well-circumscribed, round, or sometimes V-shaped ulcer that is neither painful nor pruritic. Episodes of arterial bleeding may occur in affected dogs, a situation that often warrants emergency interventions.[5,42]

The visual appearance of this distinct disease of the St. Bernard is striking, but diagnosis should still be confirmed histologically to differentiate it from other disease processes that may affect the nasal cartilage.

Histologically, changes are highly characteristic and not comparable with the other vasculitides covered within this article. The disease targets the deep dermal arteries, and subendothelial spindle cell proliferation is seen within these vessels. A marked extracellular matrix deposition containing mucin and collagen may also be seen subjacent to the ulcer. This leads to intimal thickening and stenosis of dermal arteries and arterioles. Immunohistochemical studies have shown that spindle cells proliferating within this thickened area of vascular intima are positive for smooth muscle actin and vimentin and negative for factor VIII-related antigen, suggesting either myofibroblast or smooth muscle-like differentiation of the proliferating cells. Superficial changes have included neutrophilic dermal inflammation and lymphoplasmacytic dermatitis.[7]

Long-term treatment with immunosuppressive therapies have been used, including prednisolone, topical fluocinolone in dimethyl sulphoxide, a combination of tetracycline and niacinamide, and fish oil.[42] In the author's experience, topical tacrolimus ointment applied 2 or 3 times a day for extended period has been effective as well. Surgical treatment options for this disease has also been proposed[42]

Idiopathic

Idiopathic vasculitis is clearly a diagnosis of exclusion. If no triggering agent can be detected, a diagnosis of idiopathic vasculitis can be made. In a retrospective study of vasculitis in dogs and cats, the diagnosis was idiopathic in 10 of 21 cases. The corresponding numbers from a recent unpublished study concluded with idiopathy in 9 of 36 cases.

TREATMENT

Treatment must be tailored to the individual patient and should be based on history, clinical findings, identification of the inciting cause, and whether or not the disease is progressing or regressing. In patients suffering severe and extensive cutaneous ulcerations, adequate wound care is essential to prevent secondary bacterial infections and sepsis.

Treatment should not lead to a worsening of the patient's prognosis and care should be taken to make sure underlying diseases and comorbidities that may affect the outcome are not missed.[1] Treatment may in some cases be guided by the histologic inflammatory pattern.[3,7]

Avoidance of Triggers

If drugs or "drug-like substances" are suspected, the most important treatment is removal and future avoidance of such agents. Keep in mind that the inciting agent can also be the vehicle of a drug and not only the drug itself (eg, capsules containing

gelatin may be the triggering factor of hypersensitivity vasculitis in a beef-allergic dog). In patients suffering from vasculitis triggered by an adverse reaction to drugs, removal of the drug along with close patient monitoring may in fact be the only treatment necessary. This may also be true for patients presenting with severe and extensive ulcerations of the skin. As an example, a patient presenting with severe ulcerations affecting 20% of the total body surface with a particular drug as the only triggering factor may not benefit from glucocorticoid treatment unless the disease is progressing, because this may only serve to delay wound healing and increase the risk of wound infection and sepsis. Such patients may benefit more from drug withdrawal and proper wound care along with future avoidance of the offending drug.

Care should, therefore, be taken when planning treatment of these patients and therapy should be based on the individual patient's needs. Close monitoring of the patient during the early phase of the disease is essential to decide on a proper treatment regiment suitable for each individual case.

Glucocorticoids

If no underlying trigger of vasculitis can be identified, and the disease is progressing during the initial 24 to 48 hours of monitoring glucocorticoid therapy should be considered. Older literature has recommended immunosuppressive doses ranging between 2 and 4 mg/kg of prednisolone.[8] However, the author prefers starting at a lower dose of 0.5 to 1 mg/kg of prednisolone. Starting at lower doses makes sense because prednisolone doses can easily be increased if necessary, higher doses are associated with severe side effects and poor wound healing, and significant immunosuppression may predispose animals with severe and extensive cutaneous ulcerations to secondary (wound) infections and sepsis. Furthermore, in the early phase of the disease, several diagnostic tests may still be pending, including tests for infectious conditions (blood cultures, tick titers, and tissue cultures). Administering high doses of steroids during this phase of disease could therefore have detrimental effects and negatively affect treatment outcome if it is later discovered that the animal was suffering from an infectious condition.

When a dose sufficient of halting progression of clinical signs has been established, the patient is kept on this dose until clinical remission is achieved. Slow tapering with a 25% dose reduction every 14 days is then attempted.[1]

Oral prednisone or prednisolone are both alternatives for dogs; however, prednisone has a relative bioavailability of 65% compared with prednisolone because it needs to be actively converted in the liver.[43] Oral prednisolone is the drug of choice in cats.[44] Cases refractory to prednisolone may benefit from triamcinolone or dexamethasone.

Patient follow-up Patients on long-term glucocorticoid treatment should have a complete blood count, serum chemistry profile, urinalysis, and a urine culture performed at least every 6 months[45,46]

Calcineurin inhibitors

Cyclosporine A is a systemic immunosuppressant licensed for systemic administration to both dogs and cats. In recent years, it has been used off label for the treatment of an increasing spectrum of immune-mediated and inflammatory diseases. Cyclosporine exerts its effect by blocking transcription of genes required for T-cell activation.[47,48] See article bv Palmeiro elsewhere in this issue for details on mechanisms of action and dose regimens. There are, however, no solid studies evaluating efficacy of this medication for the treatment of cutaneous vasculitis in dogs and cats. Based on anecdotal reports, cyclosporine may be effective in the treatment of some cases of cutaneous vasculitis.[1,7] The author would consider this drug in patients that require

long-term medical management of idiopathic vasculitis, especially in patients that cannot tolerate glucocorticoid therapy.

Cytotoxic agents

Use of cytotoxic agents for the treatment of cutaneous vasculitis may be necessary when other therapeutic measures have failed or are otherwise contraindicated[1,7]

Azathioprine, a prodrug of 6-mercaptopurine, is an immunosuppressant and corticosteroid-sparing agent used for the treatment of several immune mediated diseases in dogs. Thiopurine antimetabolites compete with endogenous purines for incorporation into RNA and DNA, resulting in nonsense sequences. DNA and RNA syntheses are thus inhibited, and mitosis and cellular metabolism disrupted.[49]

Azathioprine is a potent cytotoxic agent that may be considered as a steroid-sparing agent in cases refractory to empiric anti-inflammatory therapy to reduce side effects associated with persistent high-dose corticosteroid therapy. Some dogs may experience life-threatening myelosupression, consisting of profound neutropenias, lymphopenias, and thrombocytopenias, as a result of standard azathioprine dosing.[50] Weekly or biweekly complete blood counts should be performed in all patients treated with azathioprine. Other uncommon adverse effects include hepatotoxicity, pancreatitis and gastrointestinal distress.[47] Myelosupression occurs more frequently in the cat preventing the widespread use of this drug in feline patients.[49]

The clinician needs to keep in mind that there may be a considerable lag time before full effect of this drug is reached; 1 to 6 weeks have been reported.[1,51] Once the patient is clinically stable, tapering to the lowest necessary dose should be attempted to minimize side effects.[1] The author prefers to start with a dose of 1 to 2 mg/kg, and uses the lower range of the dose in schnauzers or related breeds.[52] The dose is then tapered down slowly (every 14–21 days) to a dose of 1 or 0.5 mg/kg before tapering down further to every 48 hours and if possible every 72 hours.

Patient follow-up A complete blood count, serum chemistry profile, and urinalysis is performed before starting therapy. A complete blood count is then performed weekly in the initial phase of treatment.[1]

Chlorambucil may be used in cases incapable of tolerating azathioprine. The starting dose is 0.1 to 0.2 mg/kg orally once daily or every other day. Side effects and patient follow-up are as for azathioprine.[1]

Xanthin derivatives

Pentoxiphylline is a methylxanthine derivative with both hemorheologic (changes the conformation of erythrocytes, improves microcirculatory blood flow, and tissue oxygenation) and immunomodulatory effects that traditionally has been recommended as a suitable treatment option for cutaneous vasculitides.[8] Its value in the treatment of true cutaneous vasculitis is difficult to assess, because it is more commonly used in combination with other treatments. Some clinicians, including the author, find it to be a valuable drug when dealing with ischemic dermatopathies (see article by Morris elsewhere in this issue), but it is rarely effective as a single agent for the treatment of neutrophilic vasculitis.[53] The onset of action is slow, and several weeks to months may be required before clinical response is seen.[1,54] Pentoxiphylline is, however, a safe drug, is associated with few side effects in dogs, and should not be discarded as a steroid-sparing agent in patients that require long-term management of their disease. Gastrointestinal irritation, although rare, has been reported as a side effect.

Drugs targeting neutrophil function

Tetracycline/niacinamide The combination of tetracycline and niacinamide could be considered a treatment in milder cases of cutaneous vasculitis.[1,7] Tetracyclines

(tetracycline, doxycycline, monocycline) exert a variety of anti-inflammatory and immunomodulating properties by themselves or in combination with niacinamide (synonyms are nicotinamide and nicotinic acid amide). The combination of tetracyclines and niacinamide has the ability to inhibit blast transformation of lymphocytes and chemotaxis of neutrophils and eosinophils; however, their exact mechanism of action in immune-mediated diseases is not completely understood.[55]

Dosing alternatives

Tetracycline/niacinamide For dogs weighing less than 10 kg, give 250 mg/dog of each drug orally every 8 hours with food. For dogs weighing more than 10 kg, give 500 mg/dog of each drug orally every 8 hours with food.[56] Alternatively, a dosage of 22 mg/kg every 8 to 12 hours, rounded to the nearest convenient tablet size (tablets are easily halved or quartered), may be calculated (Dr Daniel O. Morris, personal communication, 2012). Tetracycline has recently become unavailable in the United States, and doxycycline may be substituted for it at a dosage of 5 to 10 mg/kg every 12 hours. Niacinamide should still be administered every 8 hours when possible, until remission is established, but can often be tapered thereafter.

Patient follow-up This drug combination is usually well-tolerated by most dogs, but side effects have been reported, most commonly owing to niacinamide. Vomiting, lethargy, anorexia, diarrhea, and elevated liver values have been observed.[57] Tetracyclines are also capable of lowering seizure thresholds in epileptics and may induce hepatopathy.[1]

Sulfasalazine and dapsone Sulfonamide drugs can be highly effective in treatment of neutrophilic cutaneous vasculitis failing to respond to other alternative therapies. Sulfasalazine is usually preferred over dapsone, because the latter has been associated with more severe hepatotoxicities[3,7]

Side effects associated with sulfa drugs are well-documented in dogs and includes anemia, leukopenia, keratoconjunctivitis sicca, and hepatotoxicity. Blood dyscrasias, cutaneous eruptions, nephrotoxicity, and neuropathies can also occur. Keratoconjunctivitis sicca has been shown to be reversible with reduction of either dosage or frequency of administration.[7]

For sulfasalazine, a dose of 25 mg/kg 3 times per day has been recommended. It is advised not to exceed a total dose of 3 g per day. Dapsone is dosed at 1 mg/kg by mouth once daily.

Patient follow-up A complete blood count, serum chemistry profile, and Schirmer tear test should be performed every 2 weeks for the initial 2 months of treatment. If no adverse events are observed during this period, follow-up can be reduced to once every 30 days for 2 months and then every 3 months as long as the dog remains on the treatment.[1]

SUMMARY

Cutaneous vasculitis is an inflammatory process targeting blood vessels. A number of underlying factors may be associated with vasculitides in dogs and cats, including drugs, infectious diseases, adverse reactions to food, malignancies, and immune-mediated diseases. Vasculitis should thus be regarded as a reaction pattern that warrants an extensive workup of the patient to identify such triggers. Affected patients present with a variety of symptoms, such as purpura, pitting edema, and ulcerations of the skin. Constitutional signs such as fever, depression, and anorexia are common and seem to be present in the majority of patients. Once a diagnosis is confirmed by compatible histologic findings, treatment, and follow-up must be tailored to the individual

patient. High doses of immunosuppressive medications are only recommended once infectious diseases capable of producing a similar constellation of clinical signs have been ruled out.

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