Case Report

J Vet Intern Med 2008;22:666–670

Systemic Vasculitis with Severe Cutaneous Manifestation as a Suspected Idiosyncratic Hypersensitivity Reaction to Fenbendazole in a Cat

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A 16-month-old, 2.5 kg, spayed female domestic shorthaired cat was examined at The Queen Mother Hospital for Animals at The Royal Veterinary College (RVC) for severe anemia and pinnal lesions.

The cat presented to the referring veterinarian 6 days previously with a 2-day history of lethargy, swelling of the right pinna, and 1 episode of sneezing a sanguineous nasal discharge. The mucous membranes were pale and icteric, and the right pinna was inflamed and swollen. The manual packed cell volume (PCV) was 11%, and excessive hemorrhage occurred at venipuncture sites. Treatment with doxycycline[a] (8 mg/kg PO q12h) was instituted for possible hemotropic mycoplasmosis. After an apparent initial improvement, the cat's condition deteriorated 4 days later, prompting administration of prednisolone[b] (6 mg/kg PO q12h) for 24 hours before referral. The cat had previously been healthy, and fenbendazole[c] had been administered 24 hours before the onset of clinical signs as anthelminth prophylaxis. Fenbendazole had been administered once 12 months previously with no apparent adverse effects.

On presentation to the RVC, the cat was relatively bright but weak. The heart rate was 180 beats/min and a gallop sound was audible. The mucous membranes were very pale, and the cat was icteric. There was some increased upper respiratory tract noise. Pre-existing thickening of both pinnae had been exacerbated by hematoma formation secondary to auricular venipuncture and there was extensive bruising of the ventral neck after bilateral jugular venipuncture. A bilateral sanguineous nasal discharge was observed intermittently. Initial treatment consisted of a hemoglobin-based oxygen-carrying solution[d] at 3 mL/h IV. Administration of doxycycline was continued at 8 mg/kg PO q12h, and prednisolone was administered at a reduced dose rate of 2 mg/kg PO q24h.

The manual PCV was 10% and serum total solids were 6.5 g/dL. CBC revealed a severe macrocytic regenerative anemia (1.64×10^6 red blood cells [RBC]/μL; reference range, 5.0–10.0 $\times 10^6$ RBC/μL; 3.40 g/dL hemoglobin; reference range, 8.0–15.0 g/dL; 10.7% hematocrit; reference range, 24.0–45.0% and 236.160/μL total aggregate reticulocyte count). Moderate anisocytosis and polychromasia and mild spherocytosis and agglutination were noted. Moderate neutrophilia with slight left shift (29.44×10^3 neutrophils/μL; reference range, 2.50–12.50 $\times 10^3$ neutrophils/μL; 0.32×10^3 band neutrophils/μL; reference range, 0–0.30×10^3 band neutrophils/μL) was present, and a manual estimate of platelet count revealed thrombocytopenia (0.78×10^5 platelets/μL; reference range, 2.00–8.00×10^5 platelets/μL). A serum biochemistry profile revealed abnormalities of hyperbilirubinemia (1.80 mg/dL; reference range, 0–0.18 mg/dL) and hypoalbuminemia (2.14 g/dL; reference range, 2.80–4.2 g/dL). Coagulation testing with a point of care analyzer[e] revealed prolongation of both prothrombin time (PT) (> 100 seconds; reference range, 15–23 seconds) and activated partial thromboplastin time (APTT) (> 400 seconds; reference range, 70–120 seconds). The cat was of blood-type A.[f]

The next day the cat was more alert, but the proximal half of the tail was erythematous and swollen with no pain sensation or voluntary motor function. There was inflammation of the skin around the right hock. Bilateral fundic examination did not reveal abnormalities. Vitamin K[g] treatment was administered at 2 mg/kg SC q24h and infusion of the hemoglobin-based oxygen-carrying solution was stopped. Blood submitted for *Mycoplasma* polymerase chain reaction[h] was negative for *Mycoplasma hemofelis*, *M. coccoides*, and *M. hemominutum*. Conscious left and right lateral thoracic radiographs did not reveal abnormalities, and abdominal ultrasonography revealed a small volume of peritoneal fluid and mild mesenteric lymphadenomegaly.

Approximately 48 hours after admission, the cat's manual PCV was 21%. On day 5, the left pelvic limb was found to be diffusely erythematous and swollen. Pain sensation had returned to the proximal tail but voluntary motor function remained absent. Buprenorphine was administered at 0.01 mg/kg SC q6h. CBC revealed a moderate anemia with less regeneration (3.00×10^6 RBC/μL; 6.20 g/dL hemoglobin; 18.9% hematocrit; and 48,000/μL total aggregate reticulocyte count) with slight polychromasia, mild spherocytosis, and mild agglutination being noted. Moderate neutrophilia with slight left shift (25.12×10^3 neutrophils/μL; 0.32×10^3 band neutrophils/μL) was present, and a manual estimate of platelet count suggested adequate to increased numbers. Repeat PT and APTT measurements were within reference range. The next day, the proximal half of the tail had an irregular area of abrupt alopecia and

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Submitted August 7, 2007; Revised November 14, 2007; Accepted February 6, 2008.

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10.1111/j.1939-1676.2008.0092.x

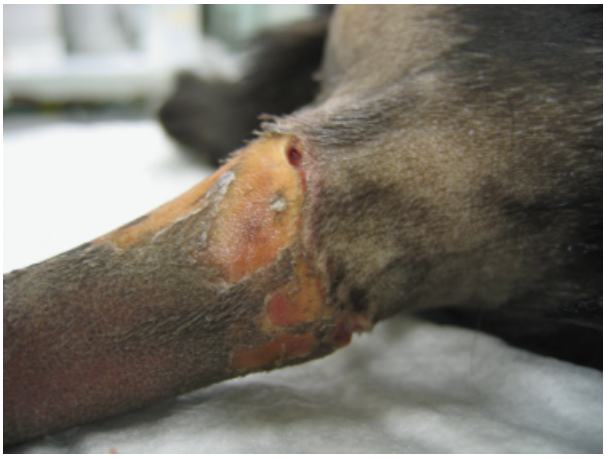

Fig 1. Dorsal aspect of tail base, clipped and cleaned. An irregular area of abrupt alopecia and discoloration (necrosis) borders a linear area of ulceration and separation between necrotic and viable tissue on the proximal edge of the lesion.

discoloration (necrosis) that bordered a linear area of ulceration and separation between necrotic and viable tissue on the proximal edge of the lesion. Similar changes were present on the dorsal (Fig 1) and ventral aspects. Bacterial culture of a microbiology swab taken from the tail lesion yielded a moderate growth of *Escherichia coli*, and amoxicillin-clavulanate[i] (20 mg/kg PO q12h for 7 days) was administered based on sensitivity testing. Both pinnae were necrotic.

Two weeks after admission, the cat was anesthetized and partial tail amputation and bilateral partial pinnectomy were performed. Histopathologic examination of both pinnae revealed ulcerative and necrotising dermatitis with neutrophilic exudation at the margin between necrotic and viable tissue. The changes were typical of ischemia secondary to thrombosis and were concentrated at the pinna margins (Figs 2 and 3). Previous vasculitis was suspected. Histology of decalcified sections of the tail revealed very similar changes to those in the pinnae, and thrombosis of blood vessels was identified (Fig 4).

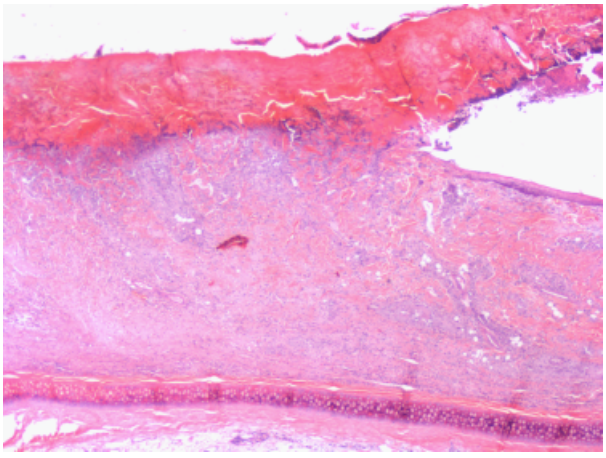

Fig 2. Ear pinna. Hematoxylin and eosin × 20. Ulcerative, exudative, and necrotizing dermatitis. Note abrupt demarcation between ulcerated lesion with adherent exudate and adjacent intact epidermis.

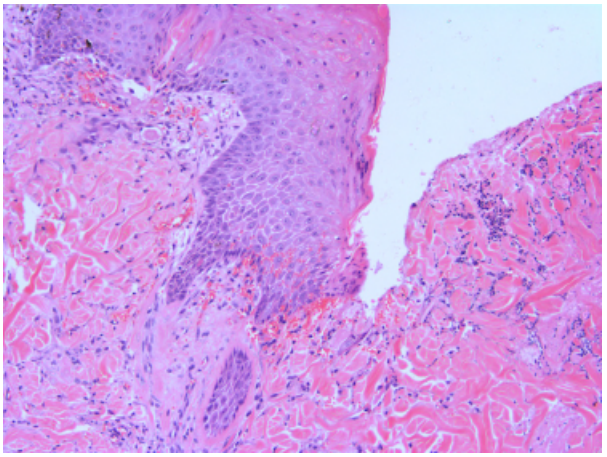

Fig 3. Ear pinna. Hematoxylin and eosin × 100. Ulcerative, exudative, and necrotizing dermatitis. Note abrupt demarcation between ulcerated epidermis with underlying necrotic dermis and adjacent intact and hyperplastic epidermis with underlying viable dermis.

Immunohistochemistry was performed on sections of both pinnae, but it failed to demonstrate immunoglobulin IgG or IgM deposition within blood vessel walls. Coombs testing[h] was negative for IgG and IgM at both 4 and 37 °C. The presumptive diagnosis was systemic vasculitis with severe cutaneous manifestation as an idiosyncratic allergic reaction to fenbendazole.

The cat was discharged 5 days after surgery with the instruction to administer prednisolone (2 mg/kg PO q24h until further advised), and was doing well when reexamined 3 days after discharge. All surgical wounds were healing satisfactorily; however, ulceration and necrosis had developed on the left pelvic foot (Fig 5) and on the caudal aspect of the left hock. Treatment with prednisolone as before and chlorambucil[j] (2 mg PO q72h) and aspirin[k] (75 mg PO q72h) was recommended. Two weeks later, the cat was reexamined and the lesions on the left pelvic limb were resolving. Serum biochemistry and CBC profiles did not reveal abnormalities, and feline coronavirus antibody titer measurement yielded a negative

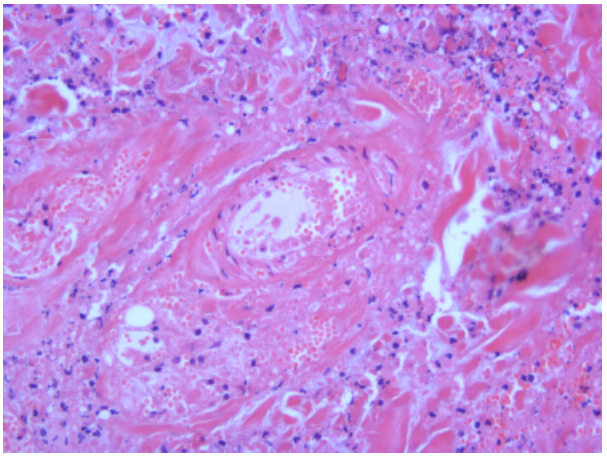

Fig 4. Ear pinna. Hematoxylin and eosin × 400. Necrotic blood vessel in dermis.

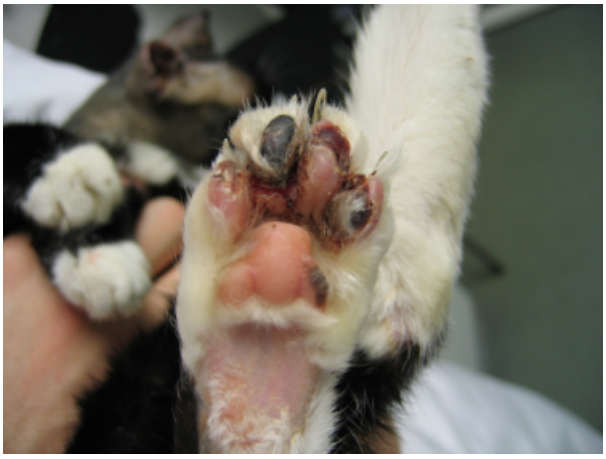

Fig 5. Ventral aspect of hind paw. Note blackening of footpads, suggestive of necrosis, and multifocal ulceration.

result. Aspirin administration was discontinued and the cat was administered pentoxifylline,[1] initially 15 mg/kg PO q8h but reduced to 15 mg/kg q12h because of compliance of the cat.

After 2 weeks, the prednisolone treatment was tapered and was discontinued 3 months after first being administered. Over the subsequent month, administration of first the chlorambucil and then the pentoxifylline was discontinued. Approximately 1 week later, the cat developed mild dermal changes on the left thoracic limb and the right pelvic foot, consistent with active vasculitis. Because of more reliable compliance, prednisolone treatment was recommenced at 2 mg/kg PO q24h in preference to pentoxifylline with a view to continuing treatment at the minimum effective dose for an extended period. The dermal changes did not progress and resolved over the next 2 weeks. Five months later, the cat had been weaned off all medical treatment and was free of signs of disease.

Adverse drug reactions are divided into a number of different groups, one of which encompasses idiosyncratic (nondose related) reactions of which hypersensitivity (allergic) drug reactions are 1 subset.[1] Hypersensitivity drug reactions are caused by an immune response either to the parent drug or to its metabolites.[1] Previous administration can initiate sensitization without apparent disease.[2] In a sensitized animal, signs of a hypersensitivity reaction can be seen within hours to days of repeat administration.[2,3] Fenbendazole has been widely used in cats for some time and is a safe drug in cats and other species in terms of dose-related adverse effects.[4,5] Cutaneous vasculitis has been reported as a rare idiosyncratic adverse reaction to fenbendazole in cats.[2,6] To the authors' knowledge, there are no reports in cats and 1 case report in a dog that documents such a reaction.[7] In the case reported here, the cat had been treated with fenbendazole 1 year previously. We speculate that this sensitized the cat with the development of clinical signs 24 hours after repeat administration. This history, together with histopathological changes consistent with recent cutaneous vasculitis and other findings consistent with systemic involvement, including anemia, thrombocytopenia, coagulopathy, and abdominal effusion or transudate, suggested a diagnosis of systemic vasculitis as an idiosyncratic hypersensitivity reaction to fenbendazole.

Inflammatory vasculopathies encompass a heterogeneous group of diseases characterized by inflammation and typical necrosis of vessel walls that differ with respect to their clinical and histological features, patterns of vessel involvement, and degree of severity. The presence of consistent histopathological changes is considered sufficient for a diagnosis of immune-mediated vasculitis.[2] Where active lesions are not sampled, as in the cat reported here, residual histopathological changes with consistent clinical signs may be reliably interpreted as being the result of previously active vascular inflammation.[8] The time delay between onset of disease and sampling in the cat reported here could account for the absence of demonstrable immunoglobulin in blood vessel walls.[9,10] Immunostaining for immune complex deposition in the basement membrane can provide further evidence for the diagnosis but has variable sensitivity.[2]

In both human and veterinary species, at least 50% of cases of vasculitis are classified as idiopathic.[8,11] However, drug-induced immune complex-mediated vasculitis is well recognized, and a temporal relationship with drug administration can be identified in dogs and cats.[8] Immune complexes in these cases constitute antigens derived from the parent drug or its metabolites coupled with host antibodies produced in response to these antigens. More recently, it has been suggested that the inflammation in some drug-induced vasculitides is associated at least in part with activation of neutrophils by circulating antineutrophil cytoplasmic autoantibodies.[12] This cause remains to be documented clinically in veterinary species. In virtually all instances, the diagnosis of an adverse drug reaction remains presumptive. Confirmation by repeat administration is ethically questionable and could have very serious and potentially fatal consequences.

Cutaneous signs are the most common clinical signs associated with immune complex-mediated vasculitis and can occur either as part of a localized process or as the most prominent and severe manifestation of systemic vasculitis. As in the cat reported here, skin overlying the extremities, including pinnae and feet, and over pressure points, including hocks, is most commonly affected.[2] A number of noncutaneous clinicopathological changes are identified in animals with systemic vasculitis, including hematological disorders such as anemia, thrombocytopenia and neutrophilia, protein-losing nephropathy, retinal changes, and musculoskeletal abnormalities.[2,3,13,14] Anemia, thrombocytopenia, and neutrophilia were all present in the cat under study, and the abdominal fluid identified was presumed to be secondary to intraperitoneal vasculitis.[15] The marked anemia at presentation was suspected to be principally secondary to immune-mediated hemolysis, although a blood loss component could not be excluded. Vasculitis-induced disseminated intravascular coagulation (DIC) was thought to be predominantly responsible for the

coagulopathy identified at presentation, and the thrombocytopenia was most likely due to both DIC and aggregation at sites of endothelial injury.[16,17]

Differential diagnoses included cold agglutinin disease, cryoglobulinemia, and coronavirus-induced systemic vasculitis. Cold agglutinin disease has been rarely reported in cats and was excluded on the basis of histopathology that was highly suggestive of primary vasculitis, the presence of marked hemolysis that is reportedly rare in this condition, and the proximal distribution of the tail pathology.[18] Clinicopathological findings consistent with cryoglobulinemia, such as white flocculent material in blood smears, centrifuged hematocrit tubes, or cooled serum, were not identified in this cat, and coronavirus antibody titer was negative.[19]

As with any adverse drug reaction, the administration of the suspected inciting agent must be discontinued in animals with drug-induced immune complex-mediated vasculitis and repeat administration must be avoided. Withdrawal of the agent does not always lead to rapid resolution, and treatment is therefore designed to modulate the inflammatory and immunogenic processes involved in the pathogenesis.[11] Corticosteroids are the most widely employed agents in the treatment of vasculitis because of their dose-dependent anti-inflammatory and immunosuppressive effects.[8,11] Immunosuppressive dosages are generally required to induce remission but treatment is then tapered to the minimum effective dose. Relapse after withdrawal of treatment is not uncommon.[11] Concomitant use of an additional immunosuppressive agent such as chlorambucil allows corticosteroids to be used more sparingly, thereby minimizing the associated adverse effects.[8,11] Pentoxifylline is a methylxanthine derivative with a variety of effects that include hemorheological, anti-inflammatory, immunomodulatory, profibrinolytic, and antithrombotic properties.[20,21] It has been used in a variety of diseases in humans, including a number of vasocclusive and cutaneous disorders, and its use in dogs with dermatological conditions has also been reported.[20,21,22,23] The use of pentoxifylline in the treatment of vasculitis is reported in both humans and dogs.[20,22] However, despite anecdotal reports of its clinical use in cats (Personal communication, Filippo de Bellis), to the authors' knowledge, no case reports exist in the veterinary literature on the use of pentoxifylline in the treatment of vasculitis in a cat. In dogs, a dosing regime of 15 mg/kg PO q8h may be most efficacious, but similar recommendations are not available for cats.[22] Both the dose and the dosing interval in the cat reported here were modified based on cat compliance. The drug appeared to be well tolerated with no clinical adverse effects reported during treatment.

Idiopathic adverse drug reactions have been infrequently reported in cats, and reports of cutaneous adverse drug reactions are rare.[2,24] Anecdotally, sulfonamides, penicillins, and cephalosporins may be most commonly implicated.[2] This report is the first to document vasculitis as a suspected idiosyncratic reaction to fenbendazole in a cat. It is also the 1st case report documenting the use of pentoxifylline in the treatment of feline vasculitis, which, after appropriate compounding, was administered successfully and appeared to be well tolerated.

Footnotes

[a] Ronaxan, Merial Animal Health, Harlow, Essex, UK
[b] Prednicare, Animalcare, Dunnington, York, UK
[c] Panacur, Intervet UK, Walton, Milton Keynes, UK
[d] Oxyglobin, Biopure, Cambridge, MA
[e] Synbiotics SCA 2000 Veterinary Coagulation Analyzer, Synbiotics, San Diego, CA
[f] RapidVet-H, DMS Laboratories Inc, Flemington, NJ
[g] Konakion MM Ampoules, Roche, Welwyn Garden City, Hertfordshire, UK
[h] Langford Veterinary Diagnostics, City and County of Bristol, UK
[i] Synulox, Pfizer, Sandwich, Kent, UK
[j] Leukeran, GlaxoSmithKline, Uxbridge, Middlesex, UK
[k] Aspirin, Aspar Pharmaceuticals Ltd, London, Middlesex, UK
[l] Trental 400, Aventis Pharma Ltd, West Malling, Kent, UK

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