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CASE REPORT
Cutaneous lesions associated with coronavirus-induced vasculitis in a cat with feline infectious peritonitis and concurrent feline immunodeficiency virus infection

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This report describes a clinical case of feline infectious peritonitis (FIP) with multisystemic involvement, including multiple nodular cutaneous lesions, in a cat that was co-infected with feline coronavirus and feline immunodeficiency virus. The skin lesions were caused by a pyogranulomatous-necrotising dermal phlebitis and periphlebitis. Immunohistology demonstrated the presence of coronavirus antigen in macrophages within these lesions.

The pathogenesis of FIP involves a viral associated, disseminated phlebitis and periphlebitis which can arise at many sites. Target organs frequently include the eyes, abdominal organs, pleural and peritoneal membranes, and central nervous tissues, but cutaneous lesions have not previously been reported.

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A 1-year-old domestic shorthair cat was presented with a 2-week history of pyrexia, lethargy, inappetence and weight loss, sneezing, bilateral nasal and ocular discharge and conjunctivitis. These signs had not responded to treatment with amoxycillin/clavulanic acid (Synulox; Pfizer) or doxycycline (Ronaxan; Merial Animal Health). Some improvement was seen following treatment with dexamethasone (Azium; Schering Plough Animal Health). Four days before presentation the cat had suffered sudden onset blindness and had developed a number of small skin nodules over the neck and forelimbs.

Clinical examination revealed bilateral mydriasis with severe iritis and extensive areas of retinal detachment. There were also bilateral serous ocular and nasal discharges. On abdominal palpation the right kidney was painful and irregular in outline. The skin over the ventral and lateral aspects of the cat's neck and the proximal forelimbs exhibited multiple well-circumscribed slightly raised, red nodules of approximately 2 mm diameter, which were associated with partial alopecia, but were non-painful and non-pruritic.

The major differential diagnoses were diseases that are expected to have multisystemic involvement and which may involve both the eye and the kidney. The most likely differential diagnoses were considered to be feline infectious peritonitis (FIP), multifocal lymphosarcoma, feline immunodeficiency virus-associated disease, feline leukaemia virus-associated disease or toxoplasmosis. A concurrent upper respiratory tract virus infection was suspected as the most likely cause of the nasal and ocular discharges and the sneezing. The cat was treated with oral clindamycin (Antirobe; Pharmacia and Upjohn, 50 mg twice daily) and with prednisolone eye drops (Pred forte; Allergan, one drop to each eye three times daily), pending the results of further diagnostic tests.

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Serum biochemistry revealed mild hyperbilirubinaemia (total bilirubin 12.0 μmol/l, reference range 0–8.6 μmol/l) and an elevation in α1-acid glycoprotein (3.26 g/l, reference range 0.1–0.48 g/l). The levels of total protein (76 g/l, reference range 57–89 g/l), albumin (26 g/l, reference range 26–39 g/l) and globulin (50 g/l, reference range 28–51 g/l) were within reference range and the albumin:globulin ratio was 0.52. Routine haematology indicated mild normocytic, normochromic anaemia (red blood cell count 4.7×10^{12}/l, MCHC 35.2 g/l, MCV 45.7 fl) and profound lymphopenia (0.1×10^{9}/l, reference range $1.5–7.0 \times 10^{9}$/l). Urinalysis was unremarkable and indicated normal renal concentrating ability (specific gravity > 1.050). Culture from ocular and oropharyngeal swabs was negative for feline herpesvirus, feline calicivirus and *Chlamydophila felis* (Clinical Pathology Diagnostic Service, University of Bristol), but rapid immunomigration tests (Witness, Rhone-Merieux) revealed that the cat was feline immunodeficiency virus (FIV) antibody positive and feline leukaemia virus antigen negative. The coronavirus antibody titre was zero (Companion Animal Diagnostic Laboratory, University of Glasgow) and the *Toxoplasma gondii* IgG titre was negative (<8 iu/ml; Scottish Toxoplasma Reference Laboratory, Inverness).

The cat remained non-pyrexic but over the next 2 days right-sided renomegaly became apparent. Ultrasound examination of the right kidney revealed multiple hypoechoic areas throughout the renal cortex and foci of increased echogenicity within the medulla. The cat was anaesthetised and biopsies were taken from skin lesions and right kidney. Biopsies were fixed in 10% neutralised formalin and submitted for histopathological examination.

Histopathology revealed a severe extensive pyogranulomatous nephritis. In the skin, a multifocal pyogranulomatous perivascular infiltration and phlebitis was seen in the mid and deep dermis, centred around mid dermal and deep dermal vascular plexuses (Figs 1, 2a). There was intense degeneration and necrosis of infiltrating cells. Additionally, moderate atrophy of adnexae and epidermis was seen.

Immunohistology for feline coronavirus (FCoV) antigen, using a mouse monoclonal antibody (FCV3-70, Custom Monoclonals International, West Sacramento, USA), was performed on renal and skin biopsies as previously described (Kipar et al 1998, in press). Scattered macrophages expressing low amounts of FCoV antigen were identified in the renal infiltrates. In the skin lesions, numerous FCoV antigen-positive cells were found (Fig 2b). The histological and immunohistological findings together confirmed the diagnosis of FIP.

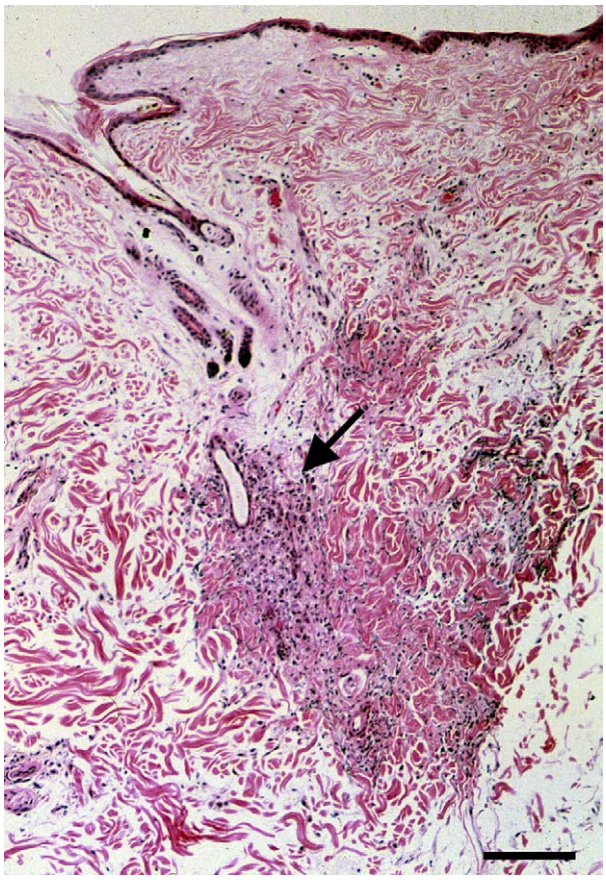

Fig 1. Skin biopsy, exhibiting a focal pyogranulomatous inflammatory infiltration in the mid to deep dermis. Haematoxylin and eosin stain. Bar = 100 μm.

Palliative treatment was instituted using immunosuppressive doses of methyl-prednisolone (Medrone V; Pharmacia and Upjohn; 8 mg twice daily). The cat's respiratory signs improved and the uveitis was less severe, but 6 days later a neuropathy developed, with flaccid paralysis of the tail and proprioceptive deficits of the hindlimbs. Treatment was maintained at the owner's request until the cat died 3 days later. A post-mortem examination was not performed.

This is the first reported case of FIP in which skin lesions have been recognised as a feature of the disease. The nodular erythematous skin lesions were associated with pyogranulomatous phlebitis and periphlebitis in the dermis. The presence of FCoV antigen within a significant proportion of macrophages in these infiltrates demonstrated their association with FIP.

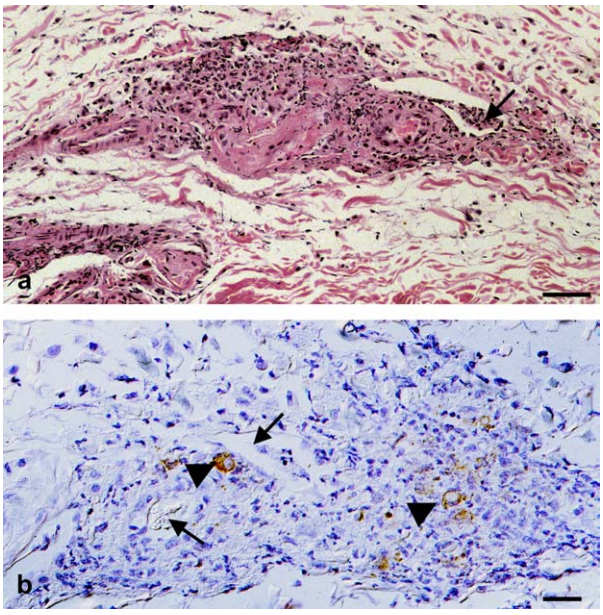

Fig 2. Deep dermis. (a) Pyogranulomatous inflammatory infiltration centred around blood vessels, with pyogranulomatous phlebitis (arrow). Haematoxylin and eosin stain. Bar = 40 μm. (b) Macrophages within the inflammatory infiltrate express FCoV antigen (arrowheads; veins: arrows). Peroxidase anti-peroxidase method, Papanicolaou's haematoxylin counterstain. Bar = 20 μm.

This case also illustrates the important role of histopathology and immunohistology for the premortem diagnosis of FIP. In this case the clinical signs were consistent with a number of possible diagnoses, the most likely of which were considered to be FIP, lymphosarcoma, feline leukaemia virus-associated disease, feline immunodeficiency virus-associated disease and toxoplasmosis. FIP was suspected because of the presence of clinical, clinicopathological and histopathological findings that were consistent with the disease. The diagnosis was confirmed by the presence of numerous FCoV antigen-positive macrophages within the granulomatous lesions, a finding only seen in, and therefore pathognomonic for, FIP (Kipar et al 1998, in press).

Clinicopathological findings that were consistent with FIP included the presence of elevated α_1-glycoprotein concentration, an albumin:globulin ratio of less than 0.6, mild non-regenerative anaemia, lymphopenia and mild hyperbilirubinaemia. An elevated α_1-glycoprotein concentration is frequently seen in cats with FIP, but is a non-specific feature of inflammatory diseases in general, and is also found in terminal stages of FIV (Duthie et al 1997). An albumin:globulin ratio of less than 0.6, mild non-regenerative anaemia, lymphopenia and mild hyperbilirubinaemia are also common findings with FIP but are not specific to the disease (Sparkes et al 1994). In this cat the CoV antibody titre was zero and this was an unusual feature of the case. A positive CoV antibody titre is not a universal finding in cats with FIP (Sparkes et al 1994, Gaskell and Dawson 2000, Lappin 2003) and negative CoV antibody titres may occur in cats affected by either 'effusive' or 'non-effusive' forms of the disease (Sparkes et al 1991, Harvey et al 1996, Paltrinieri et al 1998). A number of explanations have been postulated, including lack of circulating CoV antibodies due to immune-complexing with CoV antigen and loss of ability to produce antibodies in the terminal stages of disease (Hoskins 2001).

Taken together, the clinical signs, clinical pathology, histological changes and immunohistological findings in this case confirm that the cat had a 'non-effusive form' of FIP, with involvement of the kidneys, skin and most likely brain and eyes.

This cat was found to be FIV positive using an 'in-house' test kit (Witness RIM; Rhone-Merieux), but in view of the cat's clinical condition and the histopathological findings, confirmation of this finding by Western blot was not pursued. The apparent presence of concurrent FIV infection in this case might have predisposed the cat to the development of FIP, as it has been shown that immunosuppression, eg, due to FIV infection, is associated with a higher risk of mutation of non-pathogenic FCoV to pathogenic, FIP-inducing FCoV mutants (Poland et al 1996). Other possible differential diagnoses were not identified by the initial clinicopathological and routine histopathological findings in this case. Further detailed investigations would have been required to rule out their presence as concurrent diseases in addition to the presence of FIP in this cat, but these tests were not undertaken.

FIP is a systemic, FCoV-induced disease which has long been regarded as an immune complex-mediated, type III hypersensitivity disease (Hayashi et al 1977, Pedersen and Boyle 1980, Weiss et al 1980). One of the morphological hallmarks of FIP is a granulomatous to necrotising phlebitis and periphlebitis (Hayashi et al 1977, Weiss et al 1980, Kipar et al 1998, in press) which was recently shown to be triggered by activated monocytes which attach to venous endothelial cells, migrate out of the veins, thereby destroying the basal lamina, and then accumulate perivascularly (Kipar et al in press). The process appears to be cytokine-mediated (Kipar et al in press).

The morphological features (predominance of macrophages) and distribution (only veins are affected) of vascular lesions in FIP do not support a primarily immune complex-mediated development of vasculitis, although FCoV immune complexes may well participate in the disease (Jennette and Falk 1995, Kipar et al in press).

Animals with FIP exhibit generalised activation of venous and, to a lesser extent, arterial endothelial cells, likely mediating selective adhesiveness of monocytes (Kipar et al in press). A selective endothelial cell reactivity to systemic cytokines could explain why FIP-associated phlebitis is not seen in all organs, but predominantly occurs in leptomeninges, renal cortex and eyes (Hayashi et al 1977, Weiss et al 1980, Male et al 1990, Kipar et al 1998, in press). However, phlebitis in, for example, lungs and liver has been shown (Hayashi et al 1977, Weiss et al 1980, Kipar et al in press) and the present report demonstrates that dermal veins can also be affected.

This report indicates that a differential diagnosis of FIP should be considered in cats showing nodular erythematous skin lesions, especially where these occur in conjunction with signs of systemic disease that are consistent with the diagnosis.

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