CASE REPORT

Positive immunostaining for feline infectious peritonitis (FIP) in a Sphinx cat with cutaneous lesions and bilateral panuveitis

Bianca S. Bauer,* Moira E. Kerr,† Lynne S. Sandmeyer* and Bruce H. Grahn*

*Department of Small Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, 52 Campus Drive, Saskatoon, SK, Canada; and †Prairie Diagnostic Services, University of Saskatchewan, 52 Campus Drive, Saskatoon, SK, Canada

Address communications to:
B. Bauer
Tel.: 306.966.7083
Fax: 306.966.7156
e-mail: bianca.bauer@usask.ca

Abstract
Feline infectious peritonitis (FIP) is a common, fatal, systemic disease of cats. This case report describes the antemortem diagnosis of FIP in a 2-year-old spayed female Sphinx cat that presented with a bilateral panuveitis and multiple papular cutaneous lesions. Histopathologically, the skin lesions were characterized by perivascular infiltrates of macrophages, neutrophils, with fewer plasma cells, mast cells, and small lymphocytes in the mid- to deep dermis. Immunohistochemistry for intracellular feline coronavirus (FeCoV) antigen demonstrated positive staining in dermal macrophages providing an antemortem diagnosis of a moderate, nodular to diffuse, pyogranulomatous perivascular dermatitis due to FIP infection. Obtaining an antemortem diagnosis of FIP can be a challenge and cutaneous lesions are rare in the disease. Recognition and biopsy of any cutaneous lesions in cats with panuveitis and suspected FIP can help establish an antemortem diagnosis of the disease.

Key Words: feline infectious peritonitis, immunohistochemistry, panuveitis, skin

INTRODUCTION
Feline infectious peritonitis (FIP) is a fatal, systemic disease caused by a mutated feline corona virus (FCoV).1 The disease was first recognized in the 1950s2 and is characterized by a perivascular granulomatous to pyogranulomatous inflammation and vasculitis.3 Clinically, there are two main forms of FIP, ‘wet’ and ‘dry’, although occasionally cats can present with a mixture of both forms.4 Ocular involvement often occurs in the ‘dry’ form of the disease.5 The ocular manifestations of FIP were first described by Doherty6 in 1971 and include a pyogranulomatous panuveitis with fibrinous exudate in the anterior chamber, keratic precipitates, perivascular cuffing of retinal vessels, exudative retinal detachment, and optic neuritis.

Dermatologic lesions in association with spontaneous FIP are rare, with only three reports in the veterinary literature.7–9 Previously reported clinical lesions include truncal papules to nodules characterized by a pyogranulomatous vasculitis and folliculitis,9 small nodules over the neck and proximal forelimbs characterized by pyogranulomatous phlebitis in a cat with concurrent feline immunodeficiency virus (FIV) infection,7 and papular lesions over the neck and bilaterally over the thorax in a cat with FIP.8

The diagnosis of FIP is difficult, and typically, an antemortem diagnosis of FIP can be challenging, especially in noneffusive ‘dry’ cases.10 Histopathologic examination of biopsy or necropsy samples is considered the gold standard test, and immunohistochemistry (IHC) for the detection of intracellular FCoV antigen in macrophages is often required to confirm the disease.3,10–12 We report a case of the antemortem diagnosis of FIP based on positive immunostaining for intracellular FCoV in multiple skin lesions in a Sphinx cat with bilateral panuveitis.

CASE REPORT
A 2-year-old spayed female Sphinx cat presented to the Western College of Veterinary Medicine ophthalmology service for the evaluation of bilateral chemosis, prolapse of the third eyelids, sneezing and intermittent anorexia, and lethargy of 6-week duration. Three days prior to presentation, the owner noted multiple nonpruritic, raised skin lesions. Schirmer’s tear tests (Schirmer Tear Test Strips; Alcon Canada, Mississauga, ON, Canada) were 13 and 24 mm/min in the right (OD) and left eyes (OS), respectively. The intraocular pressures were

© 2013 American College of Veterinary Ophthalmologists
estimated with a rebound tonometer (TonoVet; Tiolat, Helsinki, Finland) and were 9 mmHg bilaterally. Slit-lamp biomicroscopy (Osram 64222; Carl Zeiss Canada, Don Mills, ON, Canada) revealed bilateral chemosis and a prolapsed left third eyelid. Aqueous flare was present bilaterally, and fibrin with blood was evident in the right anterior chamber (Fig. 1). Indirect ophthalmoscopic examination (Heine Omega 200; Heine Instruments Canada, Kitchener, ON, Canada) following dilation with 0.5% tropicamide (Mydriacyl, Alcon Canada) revealed multiple foci of chorioretinal cellular infiltration and retinal hemorrhage. The ophthalmic diagnosis was a bilateral panuveitis. Differential diagnoses included inflammatory, infectious, and neoplastic processes. On physical examination, multiple firm, nonpainful, 2–5 mm in diameter red papules were noted over the entire body (Fig. 2). Some of the papules were ulcerated. The remainder of the physical examination was unremarkable.

Ancillary diagnostics included evaluation of the following: complete blood cell count (CBC), serum biochemistry profile, urinalysis, serum protein electrophoresis, ELISA testing for FeLV and FIV, and FIP serum antibody titer. Abnormalities in the CBC included a mild anemia that was nonregenerative (Hct: 0.25 L/L; RI: 0.29-0.45 L/L) and a chronic inflammatory leukogram (moderate leukocytosis [37 × 10^9/L; RI: 3.9–18.0 × 10^9/L]; moderate neutrophilia [30.3 × 10^9/L; RI 2.1–15.0 × 10^9/L]; mild left shift [0.7 × 10^9/L; RI: 0.0–0.1 × 10^9/L]; and mild monocytosis [2.2 × 10^9/L; RI: 0.0–0.6 × 10^9/L]). An inflammatory serum protein profile (mild hypoalbuminemia [albumin: 26 g/L; RI 27–39 g/L]; mild hyperglobulinemia [globulin: 62 g/L; RI: 27–51 g/L]; and a low albumin to globulin ratio [0.42]) was noted, and a polyclonal gammopathy was present on serum protein electrophoresis. ELISA testing for FeLV and FIV was negative, and the FIP serum antibody titer was 1:51 200.

Two, six-millimeter punch skin biopsies were submitted for histopathologic examination, which revealed a nodular to diffuse, often perivascular, infiltrate of macrophages, neutrophils, with fewer plasma cells, mast cells, and small lymphocytes in mid- and deep dermis (Fig. 3a,b). Histochemical stains (PAS, Grocott, Fite and Gram stains) for infectious agents were negative. Immunohistochemistry for intracellular feline coronavirus (FeCoV) antigen (FIPV3-70, 1:500; Custom Monoclonals, West Sacramento, CA, USA) was positive in dermal macrophages (Fig. 3c). The histopathologic diagnosis was a moderate, nodular to diffuse, often perivascular pyogranulomatous dermatitis due to FIP infection.

Treatment with topical steroids (prednisolone acetate 1%) in both eyes four times daily was initiated as well as oral prednisolone (2 mg/kg/day) and human interferon-α (30 units once daily). Ten weeks after initial presentation, the cat was euthanized due to anorexia and progression of disease. The owner declined postmortem examination.

**DISCUSSION**

Feline corona viruses are transmitted by the fecal–oral route and typically cause mild enteric disease. After natural infection, cats begin to shed virus in their feces within 1 week and continue to shed for weeks or months with
some asymptomatic carriers shedding for life.\textsuperscript{13} The FIP virus (FIPV) originates by a spontaneous mutation of the FCoV in individual cats often under conditions of immune suppression.\textsuperscript{14} FIP most typically occurs in domestic cats between 3 months and 3 years of age\textsuperscript{15} and is more common in patients from multicat households, catteries, and shelters.\textsuperscript{16} Pure-bred cats have been reported to be at a higher risk of developing FIP.\textsuperscript{17} It has been reported that 5–12\% of cats seropositive for FCoV eventually develop FIP.\textsuperscript{18} There is no effective diagnostic protocol that can discriminate the avirulent FECV from the pathologic FIPV.\textsuperscript{16} The antemortem diagnosis of FIP is therefore difficult and should be based on a combination of history, signalment, clinical signs, and clinicopathological changes.\textsuperscript{10}

Laboratory findings that are common, but not pathognomonic for FIP include lymphopenia, nonregenerative anemia, increased total serum protein concentration, hyperglobulinemia, a low albumin/globulin ratio, high serum concentrations of the acute phase protein \(\alpha_1\)-acid glycoprotein, and high FCoV antibody titers.\textsuperscript{19} Typical ocular manifestations of FIP include ‘mutton fat’ keratic precipitates, hyphema, aqueous flare, and an iridocyclitis/exudative chorioretinitis that is often accompanied by perivascular retinal granulomas with retinal detachments and optic neuritis.\textsuperscript{6} When ocular signs are present, they typically coexist with other systemic signs such as fever, anorexia, lethargy, weight loss, or neurologic signs.\textsuperscript{4}

The history and clinical findings in this case were supportive of FIP although serum \(\alpha_1\)-acid glycoprotein levels supporting an inflammatory state were not measured and the FCoV antibody titers were at the high end of normal. RT-PCR may have provided additional diagnostic information to support FIP; however, a high percentage of cats that are RT-PCR positive will never develop FIP.\textsuperscript{20} The histopathologic demonstration of a pyogranulomatous to mixed perivasculitis is considered the gold standard for a conclusive diagnosis of FIP.\textsuperscript{10} The yield of histopathologic lesions in Tru-Cut biopsies (usually from kidney or liver) is low and limits the potential application of this approach for an antemortem diagnosis of FIP.\textsuperscript{21} Furthermore, invasive methods (i.e. laparotomy or laparoscopy) are usually necessary to obtain the tissue samples for histopathologic examination.

Methods of virus detection include the demonstration of FCoV antigen in macrophages in effusions or tissue samples by IHC. While FCoV may be present systemically in healthy cats, only in FIP cases will there be sufficient viral antigen in macrophages to result in positive staining.\textsuperscript{20} Demonstration of FCoV antigen in macrophages via IHC has a sensitivity of 57\%;\textsuperscript{20} however, IHC is 100\% predictive of FIP when positive staining of intracellular FCoV antigen in macrophages is demonstrated.\textsuperscript{22} Therefore, anti-FCoV IHC is mandatory to confirm/exclude the disease in doubtful cases.\textsuperscript{3,10–12} In this case, histopathologic examination of skin biopsies and positive

Figure 3. (a) Histopathology of skin lesion demonstrating nodular inflammatory infiltrate in mid- to deep dermis. Hematoxylin and eosin stain, 20\times (b) Histopathology of skin lesion demonstrating pyogranulomatous perivascular inflammatory reaction. Hematoxylin and eosin stain, 600\times (c) Immunohistochemical staining of skin lesion. Macrophages within the inflammatory infiltrate express feline coronavirus (FCoV) antigen. Streptavidin-biotin complex technique following protease pretreatment, 600\times.
immunostaining of intracellular FCoV antigen in dermal macrophages provided the antemortem diagnosis of FIP.

At present, there is no effective prevention or treatment for FIP. Supportive treatment for FIP is aimed at suppressing the inflammatory immune response, usually with corticosteroids. There are, however, no controlled studies demonstrating any beneficial effect of corticosteroids. Human interferon-α is an immuno-modulatory compound that has been demonstrated in vitro to have a direct antiviral effect protecting against viral replication; however, in vivo experiments failed to demonstrate a reduced mortality in treated cases. Although FIP is invariably progressive and fatal, temporary remission is possible.

The skin lesions in this case provided a definitive diagnosis of FIP and were easily visualized due to the lack of haircoat in this breed of cat. While a thorough physical examination is recommended in all cases of uveitis, careful examination and palpation of the skin and clipping of the fur may be rewarding in suspect cases of FIP. If cutaneous lesions are noted in a cat with a high clinical suspicion for FIP, then histopathologic examination of skin biopsies with IHC for intracellular FCoV antigen is strongly advocated.

REFERENCES

1. Vennema H, Poland A, Foley J et al. Feline infectious peritonitis viruses arise by mutation from endemic feline enteric coronaviruses. Virology 1998; 243: 150–157.
2. Holzworth J. Some important disorders of cats. The Cornell Veterinarian 1963; 53: 157–160.
3. Kipar A, May H, Menger S et al. Morphologic features and development of granulomatous vasculitis in feline infectious peritonitis. Veterinary Pathology 2005; 42: 321–330.
4. Hartmann K. Feline infectious peritonitis. Veterinary Clinics of North America Small Animal Practice 2005; 35: 59–79, vi.
5. Tsai HY, Chuh LL, Lin CN et al. Clinopathological findings and disease staging of feline infectious peritonitis: 51 cases from 2003 to 2009 in Taiwan. Journal of Feline Medicine and Surgery 2011; 13: 74–80.
6. Doherty MJ. Ocular manifestations of feline infectious peritonitis. Journal of the American Veterinary Medical Association 1971; 159: 417–424.
7. Cannon MJ, Silkstone MA, Kipar AM. Cutaneous lesions associated with coronavirus-induced vasculitis in a cat with feline infectious peritonitis and concurrent feline immunodeficiency virus infection. Journal of Feline Medicine and Surgery 2005; 7: 233–236.
8. Gross T. Pyogranulomatous vasculitis and mural folliculitis associated with feline infectious peritonitis in a Sphynx cat. Veterinary Pathology 1999; 36: 507. (Abstract).
9. Declercq J, De Bosschere H, Schwarzkopf I et al. Papular cutaneous lesions in a cat associated with feline infectious peritonitis. Veterinary Dermatology 2008; 19: 255–258.
10. Pedersen NC. A review of feline infectious peritonitis virus infection: 1963–2008. Journal of Feline Medicine and Surgery 2009; 11: 225–258.