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#### SPONTANEOUSLY ARISING DISEASE

## Association Between Pancreatitis and Immune-mediated Haemolytic Anaemia in Cats: A Cross-sectional Study

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#### Summary

In most cases, the underlying causes of feline pancreatitis and feline immune-mediated haemolytic anaemia (IMHA) remain unknown. Following the observation that some cats present with both diseases concurrently, the aim of this cross-sectional study was to investigate if the two disorders were associated statistically in this species. A residency case log of all cases seen at the Small Animal Hospital, University of Glasgow, Glasgow, UK, between July 2004 and December 2007, was used as the database for this study and an association between these two disorders was assessed by Fisher's exact test. Of the 155 sick cats included in the study, nine were diagnosed at the time of presentation with pancreatitis (prevalence of 5.8%) and 11 with IMHA (prevalence of 7.1%). In three of these cats both conditions were present concurrently at the time of presentation (prevalence of 1.9%). A significant association between these two disease was found (Odds Risk 8.63, exact 95% confidence interval 1.15–49.31, P = 0.0178). Two possible biological explanations for the statistical association found between these two diseases are that one of these conditions may represent the cause for the onset of the other or that an underlying disorder of the immune system may concurrently target feline red blood cells and the exocrine pancreas.

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Pancreatitis is a common disease in cats (De Cock *et al.*, 2007), but in most cases the underlying causes remain unknown. Biliary tract disease such as cholangitis, stricture, neoplasia and calculus (Hill and Van Winkle, 1993; Weiss *et al.*, 1996; Mayhew *et al.*, 2002), inflammatory bowel disease (Weiss *et al.*, 1996), pancreatic flukes (Fox *et al.*, 1981), *Toxoplasma gondii* (Dubey and Carpenter, 1993), trauma (Westermarck and Saario, 1989), organophosphate poisoning (Hill and Van Winkle, 1993) and lipodystrophy (Ryan and Howard, 1981) have all been associated with pancreatitis in cats. Nevertheless, there are no studies demonstrating a causative effect between any of these conditions and naturally occurring pancreatitis, and

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studies demonstrating at least a statistical association between these conditions and naturally occurring pancreatitis are scarce (Weiss *et al.*, 1996). Similar to pancreatitis, the causes of feline immune-mediated haemolytic anaemia (IMHA) are also not yet entirely identified. Reported causes of IMHA in cats include infectious agents (Scott *et al.*, 1973; Maede and Hata, 1975; Werner and Gorman, 1984), drugs or tumours (Scott *et al.*, 1973; Peterson *et al.*, 1984; Werner and Gorman, 1984), systemic lupus erythematosus and blood transfusions from incompatible donors (Auer and Bell, 1983; Lusson *et al.*, 1999). If the cause cannot be identified, the anaemia is called primary or idiopathic IMHA (Kohn *et al.*, 2006).

Following the observation that some cats present with both of these diseases concurrently, the aim of

0021-9975/\$ - see front matter http://dx.doi.org/10.1016/j.jcpa.2017.02.003 © 2017 Elsevier Ltd. All rights reserved.

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The first author's residency case log of all cases seen at the Small Animal Hospital, University of Glasgow, Glasgow, UK, between July 2004 and December 2007 was used as the database for this cross-sectional study. The first author had been assigned randomly to 20% of the feline patients referred in that time period to the Internal Medicine Department, which accepted all of the stable and emergency cases referred in the following disciplines: cardiology, endocrinology, gastroenterology/hepatology, haematology, immunology, urology, medical neurology, oncology and pulmonology. Cats were not included in the study if they did not have a final diagnosis explaining the presenting complaints. For all cats, the minimal diagnostic evaluation consisted of history, clinical examination, complete blood count including microscopical evaluation of a blood smear, a biochemistry profile and a full urinalysis. Further specific tests were performed on each cat included in the study in accordance with clinical requirements.

All cats with a clinical diagnosis of pancreatitis also underwent abdominal ultrasonography and determination of serum feline pancreatic lipase concentration (fPLI; Gastrointestinal Laboratory, College of Veterinary Medicine, Texas A&M University, College Station, Texas, USA) or serum feline trypsin-like immunoreactivity (fTLI; IDEXX Laboratories, Wetherby, UK). A clinical diagnosis of pancreatitis was made if a cat had two or more of the following abnormalities: (1) historical and clinical signs consistent with pancreatitis (i.e. three or more of the following: lethargy, partial anorexia or anorexia, dehydration, hypothermia, abdominal pain, vomiting, weight loss, jaundice and presence of a cranial abdominal mass) (Hill and Van Winkle, 1993), (2) abdominal ultrasonographical changes suggestive of pancreatitis (i.e. two or more of the following: pancreatic enlargement or irregular pancreatic contours, decreased echogenicity and nearby presence of free fluid or hyperechoic peritoneum) (Saunders et al., 2002), and (3) a fPLI or fTLI equal to or above the value consistent with pancreatitis (i.e.  $\geq 12.0 \ \mu g/ml$ , reference interval: 2.0-6.8  $\mu$ g/ml;  $\geq$ 400 ng/ml, reference interval: 35-139 mg/ml; respectively), with a concurrent serum creatinine concentration within the laboratory reference interval (i.e. 91–180 µmol/l) (Forman et al., 2004; Gerhardt et al., 2011).

All cats with a diagnosis of IMHA also underwent thoracic radiography and abdominal ultrasonography, direct Coombs test (ImmonO<sup>TM</sup>, Feline Antiglobulin Test, MP Biomedicals, Strasbourg, France), manual reticulocyte count, feline leukaemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody detection (SNAP<sup>®</sup> FIV/FeLV Combo Test, IDEXX Laboratories) and blood smear evaluation for haemotropic *Mycoplasma* spp. In some cats, polymerase chain reaction (PCR) testing for *Mycoplasma haemofelis* was also used. In several cats, cytology was performed using fine-needle aspirates of the liver, spleen, lymph nodes or bone marrow. Immune-mediated haemolytic anaemia was diagnosed based on the presence of a haematocrit  $\leq 14\%$  (reference interval: 30-45%), plasma protein  $\geq 60$  g/l (reference interval: 60-85 g/l), a positive direct Coombs test, exclusion of other concurrent diseases as the cause of the anaemia, and evidence of haemolysis (in the form of hyperbilirubinaemia, bilirubinuria, haemoglobinaemia and haemoglobinuria).

To assess the association between pancreatitis and IMHA, a 2 × 2 contingency table was created using the entire feline population included in the study. Fisher's exact test was used to analyse the significance of this association. The level of significance was set at P < 0.05.

One hundred and fifty-five client-owned cats were included in the study. At the time of presentation, nine cats were diagnosed with pancreatitis (prevalence of 5.8%) and 11 with IMHA (prevalence of 7.1%). In three of these cats both diseases were present concurrently (prevalence of 1.9%; Table 1). Cats with pancreatitis comprised five neutered male cats and four neutered female cats. Eight cats were domestic short hair (DSH) and one was a Burmese. Ages ranged from three to 16 years (mean  $11.1 \pm 9.2$  years). Presenting complaints for these cats were: anorexia (n = 5) or partial anorexia (n = 3), lethargy (n = 7), vomiting (n = 4), weight loss (n = 3), hypothermia (n = 2), jaundice (n = 2), abdominal discomfort (n = 1) and a cranial abdominal mass (n = 1). Five out of the nine cats with a final diagnosis of pancreatitis had three or more clinical signs consistent with this disorder (Hill and Van Winkle, 1993), and abdominal ultrasound was also considered consistent with pancreatitis in five of these nine cats. Feline TLI was run in six of the nine cats with pancreatitis, and in five of them it was elevated above the minimal threshold, consistent with pancreatitis. Feline PLI

Table 1
$2 \times 2$ contingency table created to assess the association
between pancreatitis and IMHA

	IMHA +	IMHA –	Total
Pancreatitis +	3	6	9
Pancreatitis –	8	138	146
Total	11	144	155

Data presented represent number of cats. +, with the disease; -, without the disease; IMHA, immune-mediated haemolytic anaemia.

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