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Source: Journal of Feline Medicine and Surgery Open Reports, 3(2)

Published By: SAGE Publishing

URL: <https://doi.org/10.1177/2055116917730180>

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Marked paraneoplastic basophilia accompanying eosinophilia in a cat with alimentary T-cell lymphoma

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Journal of Feline Medicine and Surgery Open Reports
1–6

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DOI: 10.1177/2055116917730180

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Abstract

Case summary A 5-year-old male neutered domestic shorthair cat was referred with a history of persistent pyrexia, pica, soft faeces, inappetence, intermittent vomiting, mild-to-moderate granulocytosis and mild hypercalcaemia. No significant improvement was noted after antibiotic and corticosteroid treatment, except that the hypercalcaemia resolved. Physical examination, including thoracic auscultation, and abdominal and peripheral lymph node palpation, were unremarkable. On admission, haematology revealed moderate leukocytosis ($36.8 \times 10^9/l$) with moderate-to-marked eosinophilia ($21.3 \times 10^9/l$) and marked basophilia ($4.04 \times 10^9/l$), the latter identified microscopically. Lymphocytes were markedly decreased ($0.37 \times 10^9/l$). Blood smear examination revealed 58% eosinophils, 28% neutrophils, 11% basophils, 2% monocytes, 1% lymphocytes and marked, diffuse platelet clumping. Biochemistry abnormalities indicated mild pancreatitis, dehydration and anorexia with mildly increased pancreatic lipase, mild hypernatraemia (157 mmol/l), a moderate decrease in urea (3.1 mmol/l) and a slight decrease in phosphate (1.32 mmol/l). Ultrasound and radiographic imaging revealed enlargement of the mesenteric lymph nodes. Fine-needle aspiration, a Tru-cut biopsy and immunohistochemistry were performed. Cytological examination revealed ~65–75% lymphocytes (~80% were larger than a neutrophil), ~25–35% eosinophils and occasional basophils. Lymphocytes had single, small ($<1/3$ red blood cells), prominent nucleoli and increased pale, mildly vacuolated cytoplasm. On histopathology, cells were monomorphic, large, with prominent nucleoli, and mild, multifocal, staining for T-cell marker CD3. Smaller cells were strongly CD3-positive. Cells were negative for B-cell marker CD45R.

Relevance and novel information This is the most severe case of paraneoplastic basophilia reported with feline alimentary T-cell lymphoma with accompanying eosinophilia and lymph node infiltration. Feline basophil prevalence is reported for the first time.

Accepted: 15 August 2017

Case description

A 5-year-old male neutered domestic shorthair cat was referred to the University College Dublin Veterinary Hospital (UCDVH) with a 6 week history of lethargy, inappetence and pica. Pyrexia of 1 month's duration, a recent history of soft faeces and intermittent vomiting were also reported. No improvement was noted after antibiotic and corticosteroid treatment, and the patient was referred for further investigations. On physical examination the cat was quiet, alert and responsive, with a body condition score of 5/5 and weighing 7.6 kg. The mucous membranes were pink with a capillary refill time <2 s. Thoracic auscultation and abdominal palpation

were unremarkable. Rectal temperature was 40.1°C and the peripheral lymph nodes were normal.

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Table 1 Haematology and plasma biochemistry panel from the referring veterinarian and on admission to University College Dublin Veterinary Hospital (UCDVH)

Parameter	Referring practice	Reference interval	UCDVH	Reference interval
Haematology				
Haematocrit (l/l)	0.27	0.30–0.45	0.26	0.24–0.45
Haemoglobin (g/l)	97	90–151	86	81–142
RBCs ($\times 10^{12}/l$)	5.7	5–10	5.4	5–10
MCH (pg)	17	12–20	15.9	12–16
MCHC (g/l)	356	290–375	334	300–360
MCV (fl)	47.7	41–58	47.7	39–55
Platelets ($\times 10^9/l$)	>200	175–600	53	180–550
MPV (fl)	5.5	–	22.7	8.6–18.9
WBCs ($\times 10^9/l$)	51.9	5.5–19.5	36.8	6–18
Segmented neutrophils	39.8	2.5–12.5	10.3	2.5–12.5
Band neutrophils	–	–	0.0	0.0–0.0
Lymphocytes	1.37	0.4–6.8	0.37	1.5–7
Monocytes	8.13	0.15–1.7	0.74	0.04–0.85
Eosinophils	2.4	0.1–0.79	21.3	0–1.5
Basophils	0.2	0.0–0.1	4.04	0–0.04
PT (s)	–	–	18	9–14
aPTT (s)	–	–	16.8	10–15
Biochemistry				
Total protein (g/l)	70	57–89	71.1	59–78
Albumin (g/l)	29	22–40	33.7	25–35
Globulin (g/l)	41	28–51	37.4	24–40
Calcium (mmol/l)	2.98	1.95–2.83	2.4	1.5–3.3
Urea (mmol/l)	3.9	5.7–12.9	3.1	6.6–10
Creatinine ($\mu\text{mol/l}$)	115	71–212	98	40–170
Phosphate (mmol/l)	1.84	1.0–2.42	1.32	1.4–2.5
GLDH (U/l)	–	–	16	0–17
ALT (U/l)	32	12–130	31	0–45
Sodium (mmol/l)	–	–	157.1	147–156
Chloride (mmol/l)	–	–	117.2	108–122
Potassium (mmol/l)	–	–	3.96	4–4.5
Cobalamin (ng/l)	–	–	>1000	≥ 275
Folate ($\mu\text{g/l}$)	–	–	12.8	8.2–13.5

RBCs = red blood cells; MCH = mean cell haemoglobin; MCHC = mean cell haemoglobin concentration; MCV = mean cell volume; MPV = mean platelet volume; WBCs = white blood cells; PT = prothrombin time; aPTT = activated partial thromboplastin time; GLDH = glutamate dehydrogenase; ALT = alanine aminotransferase

Salient blood results from both the referring veterinarian (LaserCyte; IDEXX Laboratories) and on admission to UCDVH (Advia 2120; Siemens Healthcare Diagnostics) revealed persistent eosinophilia and basophilia, with values significantly increased at the time of referral ($21.32 \times 10^9/l$ and $4.04 \times 10^9/l$, respectively). Erythron and platelet values indicated borderline anaemia and marked thrombocytopenia. Mild hypercalcaemia was identified before referral, whereas urea was moderately decreased before and after admission. While hospitalized, feline pancreatic-like immunoreactivity test (IDEXX Laboratories) revealed pancreatitis ($5.7 \mu\text{g/l}$; reference interval [RI] $0.1\text{--}3.5 \mu\text{g/l}$). Urine culture revealed no growth and the patient was negative for *Toxoplasma gondii*, feline immunodeficiency virus/feline leukaemia virus and *Giardia* species infection. Table 1

summarises the haematology and biochemistry data obtained from the referring veterinary practice and on admission to UCDVH.

Microscopic examination of the blood smear revealed a differential count of 58% eosinophils, 28% neutrophils, 11% basophils, 2% monocytes and 1% lymphocytes (Figure 1). Basophils were identified exclusively by routine microscopic examination of the smear. They were occasionally larger than an eosinophil, with a ribbon-like, sometimes bi- or tri-lobed, and rarely U-shaped nucleus with moderately condensed chromatin and numerous relatively uniform, round, lavender cytoplasmic granules. Basophil morphology was compared with that of healthy cats and was found to be unremarkable, with no significant differences in granule size, number and staining, or differences in nuclear segmentation or

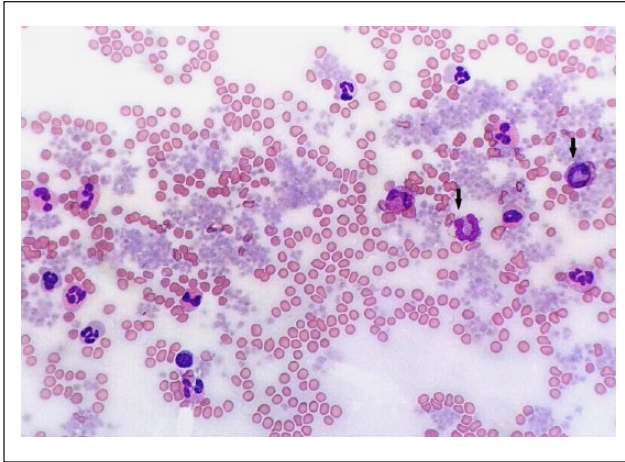


Figure 1 Blood smear. Numerous granulocytes, of which two are basophils (arrows), and marked, diffuse platelet clumping. Objective $\times 40$. Romanowsky stain

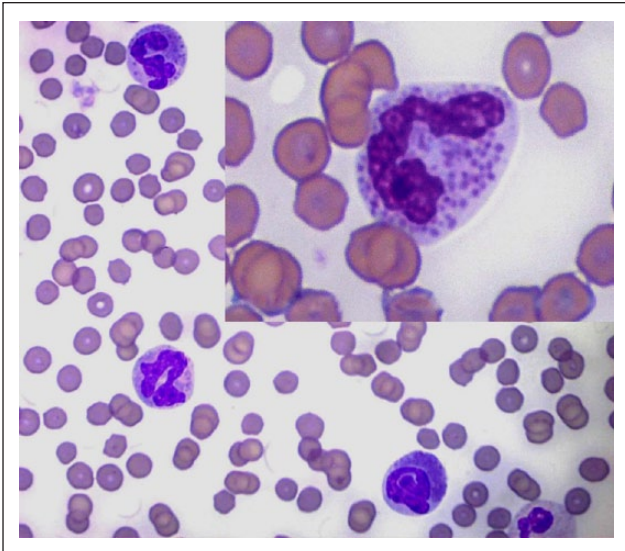


Figure 2 Blood smear. Three feline basophils. Inset: detail of the cytoplasmic granules. Objective $\times 100$. Romanowsky stain

chromatin pattern. More than 95% of basophils were well granulated with prominent, individual granules (Figure 2, inset), rarely with peripheralised or poorly stained granules (Figure 2). Also, there were large numbers of well-granulated eosinophils with segmented nuclei and abundant orange, rod-shaped granules. Rare eosinophilic metamyelocytes were observed (not shown). Marked and diffuse platelet clumping was also noted throughout the smear area.

Further tests included radiographic imaging and abdominal ultrasound, both of which identified a mid-abdominal mass consistent with markedly enlarged mesenteric lymph nodes. Samples for cytological evaluation were obtained by fine-needle aspiration (FNA) from the mesenteric and sternal lymph nodes and spleen, and

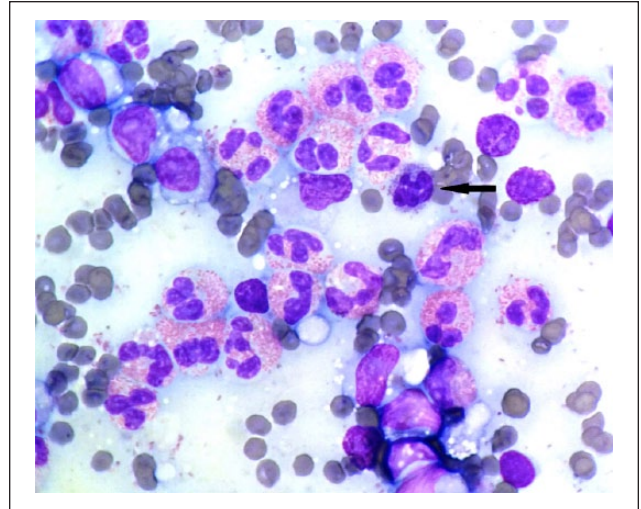


Figure 3 Photomicrograph of the mesenteric lymph node. Marked eosinophilic infiltration, one basophil (arrow) and medium-sized lymphocytes with prominent nucleoli. Objective $\times 100$. Romanowsky stain

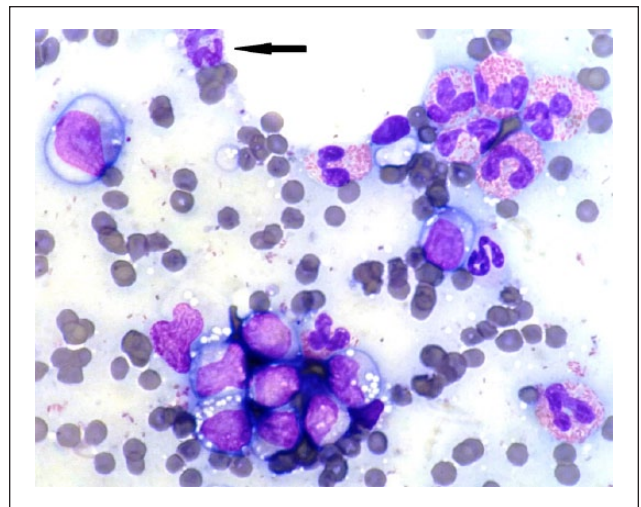


Figure 4 Photomicrograph of the mesenteric lymph node. Medium-sized and large lymphocytes with irregular, indented nuclei, fine chromatin pattern and increased, pale blue cytoplasm with small, clear vacuoles. Frequent eosinophils and one basophil observed (arrow). Objective $\times 100$. Romanowsky stain

submitted for analysis. The mesenteric lymph node (Figures 3 and 4) was highly cellular with good cell preservation in a haemodiluted background. Approximately one-third, occasionally up to half, of nucleated cells were well-granulated eosinophils, markedly out of proportion to the blood contamination (Figure 3). Occasional basophils were noted (Figures 3 and 4). The lymphoid population consisted of mostly ($>80\%$) medium-sized lymphocytes (2–2.5 red blood cells [RBCs] in diameter) with round-to-oval, often irregular, indented and off-centre nuclei, fine chromatin and usually single small

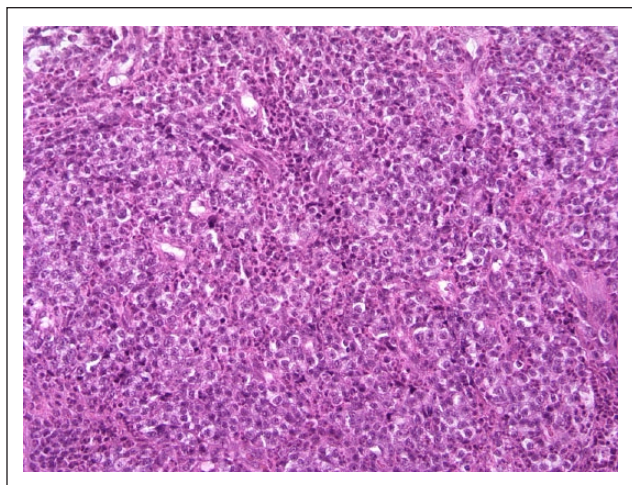


Figure 5 Tru-cut section of the mesenteric lymph node. Diffuse infiltrate of round cells and frequent eosinophils. Objective $\times 40$. Hematoxylin and eosin stain

(<1/3 RBCs) and prominent nucleoli (Figure 4). Occasionally, lymphocytes were >3 RBCs in diameter. Light blue cytoplasm was in moderate amounts, frequently with small, clear vacuoles. Large macrophages with phagocytosed cellular debris or intact eosinophils were occasionally noted. The cytological features of the FNA of the sternal lymph node were similar to that of the mesenteric, with a lower cell yield and a lower eosinophilic infiltration (20%). There was a mixed population of lymphocytes with one-third to half being medium-sized, as described previously. Occasional basophils, rare eosinophilic metamyelocytes and rare mast cells were observed. The splenic aspirate revealed frequent eosinophils (25%) and basophils (10%) in a background of fresh blood. The lymphoid population was mixed, with mostly small lymphocytes (<1.5 RBCs in diameter), whereas one-third had nuclear diameters larger than two RBCs. Frequent metarubricytes, rubricytes, rare rubriblasts and rare eosinophilic metamyelocytes were also noted. The cytological diagnosis was lymphoma of both mesenteric and sternal lymph nodes with marked and moderate eosinophilic infiltration, respectively, mild basophilic infiltration for both, and accompanying moderate extramedullary haematopoiesis of the spleen.

To further characterise the tumour, immunocytochemistry and polymerase antigen receptor rearrangement tests were performed. While both examinations proved inconclusive owing to insufficient material recovered, a faint band suggestive of a clonal population was noted on the electropherogram. A Tru-cut biopsy of the mesenteric lymph node was later submitted for analysis. Prior to sampling, repeat coagulation values remained mildly prolonged.

Histopathological examination revealed a diffuse infiltrate of round cells admixed with large numbers of

intact, degranulated eosinophils (Figure 5). Morphologic similarities with the cytological sample included a monomorphic population of round cells with large, round-to-ovoid nuclei with prominent nucleoli and stippled chromatin. The cells typically exhibited finely granular, pale-basophilic to clear cytoplasm, anisocytosis and occasional nuclear hyperchromasia. Mitotic activity was minimal (<1 per 10 high-power fields). Immunohistochemistry (University of Liverpool, Veterinary Laboratory Services) revealed smaller diameter lymphocytes to be strongly positive for CD3, a pan T-cell marker, whereas the larger lymphocytes were diffusely and multifocally mildly positive. Both the small lymphocytes and the neoplastic cells were positive for major histocompatibility complex II antigen, a macrophage and dendritic lineage marker, whereas the latter were negative for CD45R, a specific pan-B-cell marker for cats. Toluidine blue staining and CD117 (C-kit), mast cell markers, were negative, ruling out a visceral mastocytoma. A final diagnosis of alimentary T-cell lymphoma was made.

While hospitalised, the cat received fluid therapy and remained alert with a body temperature below 40°C. There was no evidence of bleeding from the biopsy sites. Unfortunately, after discharge and a mild episode of anorexia at home, the owner opted for euthanasia, which was carried out by the referring veterinarian. The remains were not available for post-mortem examination.

Discussion

Feline paraneoplastic basophilia has rarely been documented.¹⁻⁵ Non-neoplastic causes of basophilia are primarily attributed to allergic reactions and parasitism, previously reported with heartworm infection and polycythemia vera.^{1,5,6} Other inflammatory disorders such as food allergy, flea dermatitis, eosinophilic granuloma and asthma are observed during IgE-mediated hypersensitivity reactions, and typically accompany eosinophilia.^{6,7} The main cytokines responsible for the production and proliferation of basophils are interleukin (IL)-3 and granulocyte macrophage colony-stimulating factor, whereas IL-4 is the major cytokine responsible for tissue infiltration.⁶

In cats, paraneoplastic basophilia has previously been reported with intestinal and epitheliotropic lymphoma of T-cell origin,^{1,2} feline large granular lymphocyte lymphoma,⁸ acute and chronic myelogenous leukaemia,^{3,4} and malignant mesenchymal tumour.⁵

Lymphoma is one of the most common neoplasms reported in cats.⁹ In this patient, the cytological diagnosis was based on the proportion and size of the lymphocytes,¹⁰ as >50% had irregular, eccentric nuclei exceeding 10 μ m in diameter with prominent nucleoli and increased cytoplasm.¹¹ This was confirmed on histopathology, and, coupled with the referring hypercalcaemia, persistent eosinophilia and basophilia, persistent pyrexia, clinical signs, negative staining for CD45R and the positive

staining for CD3, was identified as T-cell in origin. Likely due to the steroid treatment, the hypercalcaemia was only identified before admission to UCDVH. The clinical signs and biochemistry results indicated anorexia, mild dehydration and mild pancreatitis, and the thrombocytopenia was artefactual, due to the marked, diffuse aggregates observed microscopically.

In feline patients, lymphoma is located predominantly in the gastrointestinal (GI) tract, where up to 25% are T-cell in origin (CD3+).^{12,13} It can be associated with mild-to-severe peripheral eosinophilia and eosinophilic infiltrates of the duodenum and the mesenteric lymph nodes.^{1,2,7,14} Paraneoplastic eosinophilia is typically a feature of mast cell tumours, also reported in cats with myeloproliferative disease, transitional cell carcinoma and lymphoma.^{2,3} While hypereosinophilia and T-cell lymphoma are well documented in humans, only rare cases have been reported in cats and dogs.^{14,15} Non-neoplastic eosinophil values can range from $23.5 \times 10^9/l$ to $46.2 \times 10^9/l$, reported in cats with flea allergy and eosinophilic granuloma complex, respectively.¹⁶ Values $>50 \times 10^9/l$ are characteristically seen in rare disorders such as idiopathic hypereosinophilic syndrome and eosinophilic leukaemia.¹⁶ In this case, the cause of the increased circulating eosinophils was attributed to the confirmed alimentary T-cell lymphoma, whereas other inflammatory conditions were eliminated based on history and clinical signs. Neither eosinophilic nor basophilic leukaemia were suspected in the present case as circulating granulocytes were mature, well differentiated with rare band forms and rare eosinophilic metamyelocytes, and no blast cells were noted during the blood smear examination. Eosinophilic leukaemia is rare in the feline patient,^{16–18} whereas basophilic leukaemia as a primary neoplasm has been reported exclusively in dogs and humans.^{19–21}

Electronic records from the UCDVH Clinical Pathology laboratory identified only five cases of basophilia from approximately 7000 cats in the past 7 years. Values ranged from $0.6\text{--}3.49 \times 10^9/l$ (RI $0\text{--}0.04 \times 10^9/l$). In the same time period, only one canine patient was identified with a value of $1.18 \times 10^9/l$. Internal records also revealed that basophil relative counts of $\leq 1\%$ and absolute values of $\leq 0.3 \times 10^9/l$ have a prevalence of 8–10% in the feline population.

Special consideration should be given to both automated and manual counts, as basophils can often be misinterpreted. When performing manual counts, emphasis should be put on differentiating basophils from monocytes or toxic neutrophils by their cytoplasmic characteristics,²² and from mast cells based on their nuclear morphology.²³ In one study, three haematology analysers were evaluated with respect to their ability to detect canine, feline and leporine basophils, considered to be resistant to acid lysis, differentiating them from the rest of the white cell population. Canine basophils were not

detected by the Sysmex XT-2000iV or CELL-DYN 3500 analysers,^{22,24} and neither canine nor feline basophils were identified by the Advia 2120.²² Scattergram cluster interpretation for basophils and eosinophils is predominantly useful in cats for the Sysmex XT-2000iV.^{5,24}

Paraneoplastic basophilia and eosinophilia in cats have been rarely reported together, predominantly with haemolymphatic malignancies, and usually accompanied by clinical signs of GI disease.^{1–4} Feline basophils had mild-to-moderate increases, ranging from $0.2 \times 10^9/l$ with chronic myeloid leukaemia,⁴ $0.28 \times 10^9/l$ with the acute form,³ and up to $0.58 \times 10^9/l$ with intestinal T-cell lymphoma.² The highest reported value was $2.8 \times 10^9/l$,¹ also documented in a case of intestinal lymphoma. Eosinophil counts in these cases were 7.7, 10.7, 2.6 and $4.3 \times 10^9/l$, respectively. In dogs, rare papers have reported basophilia with thymoma,^{25,26} accompanied by lymphocytosis, GI T-cell lymphoma and visceral mastocytoma.^{27,28} Basophil values ranged from 0.3 and 0.68 to $2.8 \times 10^9/l$,^{26–28} with $4.8 \times 10^9/l$ being the highest reported value in a dog with probable essential thrombocythemia.²⁹ The eosinophil counts were 2.9, 0.5, 35.8 and $1.0 \times 10^9/l$, respectively.

Conclusions

A literature review identified only five feline cases of paraneoplastic peripheral basophilia with associated eosinophilia, two of which were reported with intestinal lymphoma, and one identified as T cell in origin. This is the most severe case of paraneoplastic basophilia reported with feline alimentary T-cell lymphoma with accompanying eosinophilia and lymph node infiltration. Identified exclusively during microscopic evaluation of blood smears, slight basophilia ($\leq 1\%$ or $\leq 0.3 \times 10^9/l$) has a prevalence of 8–10% in the feline population. Eosinophilia cases should be manually screened for basophilia, and both relative and absolute basophil increases should prompt suspicion of an underlying lymphoid neoplasm in the feline patient.

Acknowledgements The authors wish to thank Jeremiah O'Connor and Oaklawns Veterinary Surgery Clinic for their collaboration; Dr Lorenzo Ressel and Valerie Tilston from the University of Liverpool for carrying out and interpreting the immunohistochemistry; ECVIM-CA Diplomate Barbara Gallagher for her management of the case; Brian Cloak for his assistance with the photomicrographs; and all technical staff in the University College Dublin Veterinary Hospital clinical pathology laboratory.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

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