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Suspected hepatopathy and pancreatitis associated with mycophenolate mofetil use in a cat with immune-mediated haemolytic anaemia

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Abstract

Case summary A 5-year-old spayed female domestic shorthair cat was referred for severe anaemia. Findings on initial work-up were consistent with a diagnosis of idiopathic immune-mediated haemolytic anaemia. A combination of prednisolone and mycophenolate mofetil (MMF) was instituted. On revisit approximately 2 months later, red blood cell parameters were normal, but the plasma was described as icteric, prompting further investigation. Concurrent hepatopathy and pancreatitis were diagnosed, suspected as being adverse reactions to MMF, as has been reported with use of the drug in humans. Resolution of serum biochemistry abnormalities took approximately 2 months, following discontinuing MMF. At the time of writing, the cat remained clinically well 1 year after initial presentation.

Relevance and novel information With increasing use of MMF as an immunosuppressive agent in cats, clinicians should be aware of both common and potentially rare adverse effects, such as those described herein. In addition, suitable monitoring tools need to be in place to facilitate early detection and appropriate management.

Keywords: Adverse reaction; hepatotoxicity; immune-mediated haemolytic anaemia; IMHA; immunosuppressive therapy; monitoring; mycophenolic acid; side effect

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Case description

A 5-year-old spayed female domestic shorthair cat was referred to our veterinary teaching hospital (VTH) for further investigation into a severe non-regenerative anaemia. Treatment instituted prior to referral included doxycycline (VibraVet 100 Paste [Zoetis]) at approximately 5 mg/kg PO q12h for 8 days as management for potential *Mycoplasma haemofelis*, based on the suspicion of the presence of haemotropic mycoplasmas on a blood smear.

On initial presentation, apart from moderate tachycardia, oral mucous membrane pallor and detection of a gallop rhythm on thoracic auscultation, no further abnormalities were identified on physical examination. Body condition score was 3/9. Haematology revealed a severe, macrocytic, normochromic, non-regenerative anaemia, along with a moderate leukopenia with a mild neutropenia (Table 1, day 1). In-saline agglutination was positive. Blood smear evaluation identified occasional Howell-Jolly bodies and ghost cells, with no evidence of haemotropic mycoplasmas. Severe hyperproteinaemia, consisting of severe hyperglobulinaemia and low normal albumin count, along with a moderate azotaemia and concurrent moderate increase in symmetric dimethylarginine (Table 2, day 1), and a mild hyperbilirubinaemia, were noted on serum biochemistry. Retroviral testing was negative (feline immunodeficiency virus [antibody], feline leukaemia virus [antigen]; IDEXX SNAP FIV/FeLV

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Table 1 Serial monitoring of haematological parameters in a cat with immune-mediated haemolytic anaemia treated with a combination of prednisolone and mycophenolate mofetil

	Day 1	Day 24	Day 58	Day 76	Day 97	Day 111	Day 125	Day 146	Day 167	RI
RBC ($\times 10^{12}$/l)	1.0	5.1	7.6	7.6	6.9	6.8	6.6	7.3	7.1	5.0–10.0
Haemoglobin (g/l)	23	81	98	97	105	93	99	93	98	80–150
HCT (l/l)	0.06	0.27	0.30	0.31	0.32	0.31	0.30	0.29	0.34	0.24–0.45
MCV (fl)	69	52	39	42	46	46	45	40	47	39–55
MCHC (g/l)	343	306	331	309	333	299	336	321	292	290–360
Platelets ($\times 10^9$/l)	Adequate number*	Mildly increased*	Adequate number*	Adequate number*	327	355	338	301	Adequate number*	300–800
Absolute reticulocyte count ($\times 10^9$/l)	19	51	39	104	146	84	60	50	51	19–107
NRBC	1	0	0	0	0	0	0	0	0	0–0
WBC ($\times 10^9$/l)	4.0	12.2	11.7	16.7	15.9	15.5	13.2	12.7	9.2	5.5–19.5
Segmented neutrophils ($\times 10^9$/l)	1.8	10.49	8.89	14.86	13.67	13.49	9.9	9.78	7.08	2.4–12.5
Lymphocytes ($\times 10^9$/l)	2.2	1.46	1.40	1.34	1.43	1.24	2.11	1.65	1.47	1.5–7.0
Monocytes ($\times 10^9$/l)	0	0.24	0.70	0.50	0.48	0.47	0.13	0.25	0.18	0.0–0.9
Eosinophils ($\times 10^9$/l)	0	0	0.70	0	0.32	0.31	0.92	0.76	0.46	0.0–1.5
Basophils ($\times 10^9$/l)	0	0	0	0	0	0	0.13	0.25	0	0.0–0.1
Agglutination	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	

*Platelet number estimated when clumping present, precluding automated count
RI = reference interval; RBC = red blood cell count; HCT = haematocrit; MCV = mean cell volume; MCHC = mean cell haemoglobin concentration; NRBC = nucleated red blood cell count; WBC = white blood cell count

Table 2 Serial monitoring of serum biochemical parameters in a cat with immune-mediated haemolytic anaemia treated with a combination of prednisolone and mycophenolate mofetil

Analyte	Day 1	Day 62	Day 71	Day 76	Day 97	Day 111	Day 125	Day 146	Day 167	RI
SDMA (µg/dl)	28				11	11		<5		0–14
CK (IU/l)	107				156	190		250		0–344
AST (IU/l)	37	306			349	142		81		0–66
ALP (IU/l)	21	202	139 (10–90)*	176 (10–90)*	133	94	43	45	30	0–85
ALT (IU/l)	102	886	729 (20–100)*	1251 (20–100)*	752	426	85	58	42	0–100
GGT (IU/l)		3	5 (0–2)*	5 (0–2)*						0–10
Bilirubin (µmol/l)	8	39	29 (2–10)*	22 (2–10)*	5	5	4	4	2	0–5
Bile acids (µmol/l)			101 (0–25)*	96 (0–25)*						
Total protein (g/l)	95	77	76 (54–82)*	92 (54–82)*	85	106		81		63–83
Albumin (g/l)	27	41	29 (22–44)*	40 (29–44)*	41	49		41	41	26–40
Globulin (g/l)	68	36			44	57		40		27–49
A:G ratio	0.39	1.16			0.93	0.86		1.05		0.6–1.6
Urea (mmol/l)	11.9		8.0 (3.6–10.7)*	9.2 (3.6–10.7)*	10.9	14.5		9.9		5.7–12.9
Creatinine (µmol/l)	209				80	91		79		70–159
Phosphate (mmol/l)	1.56		1.23		1.32	1.38		1.12		1.30–2.80
Calcium (mmol/l)	2.24				2.66	3.13		2.59		1.81–2.70
Cholesterol (mmol/l)	2.9		4.3 (2.3–5.3)*	5.9 (2.3–5.3)*	8.1	7.9		8.4		1.5–6.0
Sodium (mmol/l)	147				156	150		151		147–156
Potassium (mmol/l)	3.8				4.3	4.5		4.4		3.5–5.0
Chloride (mmol/l)	115				105	104		109		108–128

*Alternate chemistry analyser used, reference interval (RI) included in brackets
SDMA = symmetric dimethylarginine; CK = creatine kinase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; A:G ratio = albumin:globulin ratio

Combo Test, IDEXX Laboratories). Survey thoracic and abdominal radiographs were both reported as normal. No significant findings were described on abdominal ultrasound. Cytology of a bone marrow aspirate demonstrated bone marrow hyperplasia, with a myeloid:toerythroid ratio of 1.73. There was evidence of mild dysplasia and lymphocytosis (morphologically normal lymphocytes), consistent with an immune-mediated process and attempts at a regenerative erythroid and myeloid response.

With the above findings consistent with a diagnosis of primary/idiopathic immune-mediated haemolytic anaemia (IMHA), immunosuppressive therapy was instituted in the form of dexamethasone sodium phosphate (Dexadreson [MSD Animal Health] 0.3 mg/kg IV q12h) during hospitalisation. Considering the severity of the anaemia identified on haematology, blood collection was kept to a minimum so as to limit further contribution to this. As a result, packed cell volume (PCV) was used as an estimate of haematocrit. The PCV was 13% at discharge on day 5. At this time, the cat was transitioned onto prednisolone sodium phosphate (Redipred [Aspen] 2 mg/kg PO q12h), along with mycophenolate mofetil (MMF) (compounded suspension [Optimus] 10 mg/kg PO q12h), given the reported success of such a combination recently in two similar cases.[1] In addition, clopidogrel (Arrow-Clopid [Teva Pharma] 18.75 mg/cat PO q24h) was instituted as prophylaxis against thromboembolic disease.

On day 24 following implementation of the above therapy, the cat was presented to the referring veterinarian for repeat haematology. This revealed marked improvement in the anaemia, with a low normal haematocrit, and all white blood cell parameters except the lymphocyte count having returned to within the reference interval (RI; Table 1, day 24).

At a further revisit for repeat haematology (Table 1, day 58) with the referring veterinary clinic, approximately 2 months following commencement of the above therapy, red blood cell parameters were normal, but the plasma was described as icteric, prompting repeat serum biochemistry. The latter revealed moderate increases in aspartate aminotransferase and alkaline phosphatase, moderate hyperbilirubinaemia and severely increased alanine aminotransferase (Table 2, day 62). In-house testing of prothrombin and partial thromboplastin times were found to be within normal limits. With concurrent hyporexia and lethargy (day 62), there was concern about a potential infection secondary to the immunosuppressive therapy, such as toxoplasmosis or bacterial cholangitis. The cat was started on clindamycin hydrochloride (Antirobe [Zoetis] approximately 12.5 mg/kg PO q12h for 3 days) and enrofloxacin (Baytril [Bayer Animal Health] approximately 5 mg/kg PO q24h for 3 days; at the time, this was the only licensed small animal veterinary quinolone in the country of practice). Clopidogrel was withdrawn so that hepatic fine-needle aspiration could subsequently be performed with lower risk.

Three days later the cat was referred for further investigation into the newly identified hepatopathy. To minimise travel the cat was seen by a feline medicine specialist. At this time the owners also described vomiting following introduction of the antibiotic therapy, leading to discontinuation of both these drugs. Abdominal palpation identified the liver extending beyond the costal arch; it was palpably firm but non-painful. Generalised hepatomegaly with a diffuse increase in echogenicity was appreciated on abdominal ultrasound, along with the right lobe of the pancreas being mildly enlarged; however, no changes involving the peripancreatic fat were noted. Cytology of fine-needle aspirates obtained from the liver were consistent with mild-to-moderate hepatocellular degenerative changes and cholestasis. Serology for toxoplasmosis using a latex agglutination assay that detects IgM and IgG, but cannot distinguish between the two (Mast Group; this is the available serological test for toxoplasmosis in the country of practice), revealed a titre of 1:128. This was interpreted as a low positive titre; however, given the absence of other supporting evidence for clinical toxoplasmosis and the cat's clinical improvement after cessation of clindamycin, it was not considered significant. Quantitative feline pancreatic lipase immunoreactivity was consistent with a diagnosis of pancreatitis (6.5 µg/l; RI ⩽3.5 µg/l). Antinuclear antibody titres were negative. PCR for feline immunodeficiency virus was negative.

With the hepatopathy and presumed pancreatitis suspected as being adverse reactions to MMF, as has been reported with use of the drug in humans, MMF was discontinued.[2–4] In addition, liver supportive therapy was introduced. This included ursodeoxycholic acid (Ursosan [PRO.MED.CS Praha a.s.] 15 mg/kg PO q24h), and a liver supplement containing silybin, vitamin E and vitamin C (Samylin [VetPlus] one small-breed tablet PO q24h). Clinical signs improved within the following week; however, resolution of serum biochemistry abnormalities took approximately 2 months (Table 2). The anaemia was successfully managed with a tapering dose of prednisolone. At the time of writing, the cat remained clinically well a year after initial presentation.

Discussion

A recent study by Slovak and Villarino demonstrated that MMF was tolerated by healthy cats at an intravenous dosage of 10 mg/kg q12h for 3 days, and an oral dosage ⩽15 mg/kg q12h for up to 7 days.[5] Gastrointestinal side effects were dose dependent; however, adverse effects, in general, were minimal.[5] That being said, several other studies have described a highly variable disposition of mycophenolic acid (MPA; MMF being the prodrug of MPA) in the plasma of cats treated with MMF,

which could result in significant interindividual variability in both drug safety and efficacy.[6–8]

With the currently limited, albeit growing, experience with the use of MMF, the adverse effect profile is not well established.[9] Currently recognised side effects include gastrointestinal signs (diarrhoea, vomiting, anorexia), lethargy/reduced activity, lymphopenia, papillomatosis and increased rates of dermal infections.[9] Attributable to MMF's immunosuppressive activity, increased systemic infection and malignancy rates are also possible, particularly with long-term use.[9]

In humans, in addition to the adverse effects described above, MMF has been associated with the development of hepatitis/hepatotoxicity and acute pancreatitis.[2–4,10–12] As far as we are aware, no such reports of a hepatopathy and/or pancreatitis associated with MMF have been described in cats. That being said, the true incidence may currently be underestimated. As is often the practice, in our VTH at least, with follow-up on IMHA cases, repeat blood work is generally limited to haematology alone. Serum biochemistry is rarely performed, often because of financial constraints, and also owing to a lack of evidence to support any prognostic value for monitoring serum biochemistry parameters. Thus, we suspect that such findings may, in fact, be more common (i.e, subclinical), particularly with long-term use. Taking this into consideration, it may therefore be prudent to consider implementing appropriate monitoring tools for such adverse effects of MMF, especially given its increasing use in managing immune-mediated diseases in both cats and dogs.[1,13–20]

Several limitations were acknowledged with the current report. Firstly, the lack of liver and pancreatic biopsies, along with culture and sensitivity testing of both liver tissue and bile to definitively rule in/out a secondary infection, was considered a limitation. Secondly, compounding of MMF may have also played a role, potentially affecting the bioavailability of the drug, the dosage administered and resultant toxicity. Finally, the lack of re-challenge with MMF, was another limitation, and although useful to consider, it is difficult to justify in this context given the potential clinical implications with repeat hepatotoxicity, if confirmed.

Hepatopathy has also rarely been described as an adverse effect with the use of clopidogrel in humans.[21] Clopidogrel has also been found to increase the risk of acute pancreatitis in humans actively using it.[22] Although to our knowledge it has not been associated with either hepatopathy or pancreatitis in cats, it potentially could have contributed in this case. With respect to the use of clindamycin and enrofloxacin – again both drugs have been associated with hepatotoxicity – these were instituted after detection of the hepatopathy. While they may, although unlikely, have contributed to the hepatotoxicity, they were not considered to be the inciting cause for the hepatopathy described herein.

It is also worth mentioning that an association has been identified between pancreatitis and IMHA in cats.[23] While it is certainly worth considering in a case such as the one described herein, this association typically refers to the diagnosis of both diseases concurrently.[23] In contrast to this, the diagnosis of a hepatopathy and pancreatitis in this cat was made approximately 2 months after the initial diagnosis of IMHA, when the last was considered to be well-controlled.

Conclusions

With increasing use of MMF as an immunosuppressive agent in cats, clinicians should be aware of both common and potentially rare adverse effects, such as those described herein. In addition, suitable monitoring tools need to be in place to facilitate early detection and appropriate management.

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Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work for the procedure(s) undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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