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 5mg/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 dimethyl-arginine (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 (×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 (×10^9/l)** | Adequate number* | Mildly increased* | Adequate number* | Adequate number* | 327 | 355 | 338 | 301 | Adequate number* | 300–800 |
| **Absolute reticulocyte count (×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 (×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 (×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 (×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 (×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 (×10^9/l)** | 0 | 0 | 0.70 | 0 | 0.32 | 0.31 | 0.92 | 0.76 | 0.46 | 0.0–1.5 |
| **Basophils (×10^9/l)** | 0 | 0 | 0 | 0 | 0 | 0.13 | 0.25 | 0 | 0.0–0.1 |
| **Agglutination**  | Positive | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |
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   | 37     | 202    | 139    | 176    | 133     | 94      | 43      | 45      | 30     |
| AST (IU/l)            |       | 349    | 142    | 81     |        |         |         |         |         | 0–66   |
| ALP (IU/l)            | 21    | 102    | 886    | 729    | 1251   | 752     | 426     | 85      | 58      | 42     |
| ALT (IU/l)            |       | 3      | 5 (0–2)*| 5 (0–2)*| 5     |         |         |         |         | 0–10   |
| GGT (IU/l)            | 8     | 29     | 101    | 101    | 101    | 5       | 5       | 4       | 4       | 2      |
| Bilirubin (µmol/l)    | 95    | 77     | 76     | 56     | 85     | 106     |         |         |         | 63–83  |
| Bile acids (µmol/l)   | 27    | 41     | 29     | 42     | 41     | 41      |         |         |         | 26–40  |
| Total protein (g/l)   | 68    | 44     | 44     | 44     | 44     | 44      |         |         |         | 27–49  |
| Albumin (g/l)         | 27    | 95     | 57     | 57     | 57     | 57      |         |         |         | 1.05   |
| Globulin (g/l)        | 27    | 41     | 29     | 42     | 41     | 41      |         |         |         | 41     |
| A:G ratio             | 0.39  | 1.16   |         |         | 0.93   | 0.86    |         |         |         | 0.6–1.6|
| Urea (mmol/l)         | 11.9  | 8.0    | 9.2    | 10.9   | 10.9   | 14.5    |         |         |         | 5.7–12.9|
| Creatinine (µmol/l)   | 209   | 80     | 91     | 91     | 91     | 91      |         |         |         | 70–159 |
| Phosphate (mmol/l)    | 1.56  | 1.23   | 1.32   | 1.32   | 1.32   | 1.32    |         |         |         | 1.30–2.80|
| Calcium (mmol/l)      | 2.24  | 2.66   | 3.13   | 3.13   | 3.13   | 3.13    |         |         |         | 1.81–2.70|
| Cholesterol (mmol/l)  | 2.9   | 4.3    | 5.9    | 8.1    | 8.1    | 7.9     |         |         |         | 1.5–6.0|
| Sodium (mmol/l)       | 147   | 156    | 150    | 150    | 150    | 150     |         |         |         | 147–156|
| Potassium (mmol/l)    | 3.8   | 4.3    | 4.5    | 4.5    | 4.5    | 4.5     |         |         |         | 3.5–5.0|
| Chloride (mmol/l)     | 1.15  | 105    | 104    | 104    | 104    | 104     |         |         |         | 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
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. 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. Gastrointestinal side effects were dose dependent; however, adverse effects, in general, were minimal. 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.2–6

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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Conflict of interest

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Ethical approval

This work involved the use of non-experimental animals only (owned or unowned), and followed established internationally recognised high standards (‘best practice’) of individual veterinary clinical patient care. Ethical approval from a committee was not necessarily required.

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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