CASE REPORT
Companion or pet animals

Caecal gastrointestinal stromal tumour with secondary immune-mediated haemolytic anaemia in a cocker spaniel

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Abstract
The present case report documents a paraneoplastic immune-mediated haemolytic anaemia secondary to a gastrointestinal stromal tumour of the caecum in a female neutered cocker spaniel. The dog was presented with a history of acute onset lethargy and anorexia. Investigations revealed a mildly regenerative, Coombs’ test-positive anaemia with spherocytosis and auto-agglutination. Abdominal ultrasonography documented a concurrent focal caecal mass. Surgical resection of the mass resulted in complete resolution of the immune-mediated haemolytic anaemia; immunosuppressive treatment was not required at any stage. The histopathological and immunohistochemical findings supported the diagnosis of a gastrointestinal stromal tumour. To the authors’ knowledge, this is the first report of a paraneoplastic immune-mediated haemolytic anaemia secondary to a gastrointestinal stromal tumour in a dog and demonstrates a rare case of remission of immune-mediated haemolytic anaemia in response to surgical resection of the tumour alone.

BACKGROUND

Immune-mediated haemolytic anaemia (IMHA) can be referred to as primary (idiopathic) or secondary to underlying neoplastic disease, infectious disease, exposure to drugs, vaccines and toxins. IMHA is characterised by destruction of erythrocytes due to anti-erythrocyte antibody production, both intravascularly (mediated by IgM and complement activation) or extravascularly (IgG-mediated haemolysis by macrophages in the reticulo-endothelial system of the liver and spleen). Studies have suggested that approximately 60%–75% of IMHA cases in dogs are thought to be ‘primary’ or, as more recently termed, ‘non-associative’ in origin.

Paraneoplastic IMHA, described as paraneoplastic autoimmune haemolytic anaemia (AIHA) in humans, has been documented in previous literature. It has been described most commonly in relation to human haematopoietic neoplasms, particularly Hodgkin and non-Hodgkin lymphoma. The frequency of autoimmune perturbations in lymphoproliferative diseases was deemed to be significantly higher than in myeloproliferative diseases in humans overall (8% and 1.7%, respectively). In contrast, in a study of 1083 human patients with solid tumours, only 1.29% presented with a paraneoplastic syndrome; of these, 21% were associated with AIHA. Erythrocyte autoantibodies have been detected in a variety of human carcinomas, particularly those of the breast, lung, colon, rectum, renal, prostatic and ovarian tissues. They have been most commonly linked with the presence of a large tumour mass and/or metastatic disease. Other solid tumours such as adenocarcinoma (gastric, pancreatic and pulmonary), gastric stromal tumour and Kaposi sarcoma have also been associated with IMHA.

The veterinary literature documenting paraneoplastic IMHA is sparse and consists mainly of case reports; it has been reported in association with a sarcoma in a flat-coated retriever, phaeochromocytoma, mast cell tumour, in two sibling cats with multicentric lymphoblastic infiltration and an intestinal leiomyosarcoma in a dog whereby surgical resection achieved complete remission. There has also been mention of involvement with other canine tumours such as carcinomas, lymphoma, leukaemia, myeloid neoplasias and multiple myelomas, although the temporal association in these cases is less clear. According to the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on the diagnosis of IMHA in dogs and cats, at present there is very little evidence to support a definitive causal link between neoplasia and IMHA in veterinary medicine.

Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms of the gastrointestinal tract of dogs; in one
study they were found to occur most commonly in the large intestine, followed by the small intestine and stomach. They arise from stem cells phenotypically similar to the interstitial cells of Cajal; these are the autonomic pacemakers of gastrointestinal motility, and transformation is thought to be driven by activating mutations of the tyrosine kinase c-Kit proto-oncogene. c-Kit exon 11 mutations have been found to occur frequently in canine GISTs; this is similar to humans whereby exon 11 mutations occur in 50%–60% of cases.

Complete remission of Evans syndrome (immune-mediated destruction of erythrocytes, neutrophils and/or platelets) was achieved with surgical resection of a human lung papillary adenocarcinoma, while in another report IMHA resolved in response to resection of a human gastric stromal tumour. These cases, alongside the report of complete remission of IMHA following resection of an intestinal leiomyosarcoma in a dog, highlight the potential that treatment of the underlying neoplasia can result in complete remission without immunosuppression. The present case report documents the presentation, findings, treatment and outcome of IMHA secondary to a caecal GIST in a female cocker spaniel that achieved complete remission with surgical resection.

CASE PRESENTATION

A 9-year 8-month-old, female, spayed cocker spaniel was referred to the Queen’s Veterinary School Hospital (QVSH), Cambridge, after an acute onset lethargy and anorexia. Twenty-four hours prior, the referring veterinarian had documented a mildly regenerative anaemia, which was suspected to be immune-mediated due to the presence of spherocytosis on blood film and a positive Coombs’ test result. On abdominal imaging, there was a focal thickening of the small intestine. Upon presentation to the QVSH, the clinical examination revealed pale pink mucous membranes and a temperature of 39.3°C; however, the rest of the examination was within normal limits. The dog had not been exposed to any medications or known toxins in the preceding weeks before referral. It was up to date with core vaccinations, but had not received a booster vaccination for at least 10 months.

INVESTIGATIONS

A complete blood count (CBC) documented a moderate, macrocytic, hypochromic regenerative anaemia with a packed cell volume (PCV) of 25% (reference interval 37–55) and a reticulocytosis of 156.9 x 10^9/L (reference interval 0–70) (Table 1). Blood film analysis performed by a board-certified clinical pathologist at a commercial laboratory was consistent with moderate polychromasia, spherocytosis (one to three spherocytes per high-power field [HPF]), anisocytosis and mild agglutination. Performance of an in-saline agglutination test was unfortunately not documented at the time. Biochemistry was within normal limits apart from an elevated C-reactive protein (28.9 mg/L, reference interval 0–8.2). Blood-borne parasites (e.g., Babesia spp.) were not detected on peripheral blood film analysis, and infectious disease testing (4Dx SNAP; Idexx) for antibodies to Borrelia burgdorferi, Ehrlichia canis/ewingii, Anaplasma phagocytophilum/platys and Dirofilaria immitis antigen was negative. A moderate bilirubinuria was present on urinalysis with a urine specific gravity of 1.046.

Abdominal ultrasonography documented a focal, rounded and well-defined eccentrically positioned mass lesion on the caecum (measuring 1.82 × 1.36 cm), which was homogeneously hypoechoic and minimally vascular on colour flow Doppler (Figure 1). The mass was extending into the muscularis layer with an intact hyperechoic submucosal layer deep into it, suggestive of a mesenchymal neoplasm. A splenic nodule was identified (deemed most likely extramedullary haematopoiesis or lymphoid hyperplasia); however, the rest of the abdominal ultrasound was within normal limits. Thoracic radiographs were normal. Fine-needle aspirate cytology of the mass was also strongly suggestive of a mesenchymal neoplasm. The smears contained low to moderate numbers of medium-sized cells with moderate amounts of medium to deep blue cytoplasm and indistinct cell borders. They were frequently arranged in variably sized, cohesive aggregates associated with abundant extracellular pink matrix. The cells had round to oval, and occasionally elongated nuclei, with finely stippled chromatin and indistinct to occasionally visible, prominent, medium-sized nucleoli. There was mild anisokaryosis.

DIFFERENTIAL DIAGNOSIS

Given the presence of contemporaneous immune-mediated haemolytic anaemia and an intestinal mass, the pathological process was deemed most likely compatible with a secondary, paraneoplastic IMHA. The main differential diagnoses for the mass were a GIST, leiomyoma or a well-differentiated leiomyosarcoma.

TREATMENT

During the initial hospitalisation period, clopidogrel (1.8 mg/kg orally [PO] once daily) was initiated. The patient remained stable and 48 hours after initial presentation to the QVSH, a marginal typhlectomy was performed. The excised
**TABLE 1** Complete blood count results on admission, 24 hours and 7 days postoperatively

<table>
<thead>
<tr>
<th>Parameter (Unit)</th>
<th>On Admission</th>
<th>24 Hours Postoperatively</th>
<th>7 Days Postoperatively</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC ($\times 10^9$/L)</td>
<td>10.66</td>
<td>10.13</td>
<td>5.99*</td>
<td>6–17</td>
</tr>
<tr>
<td>Neutrophils ($\times 10^9$/L)</td>
<td>8.85</td>
<td>8.73</td>
<td>4.17</td>
<td>3–11.5</td>
</tr>
<tr>
<td>Lymphocytes ($\times 10^9$/L)</td>
<td>0.5*</td>
<td>1.1</td>
<td>1.2</td>
<td>1–4.3</td>
</tr>
<tr>
<td>Monocytes ($\times 10^9$/L)</td>
<td>0.64</td>
<td>0.56</td>
<td>0.48</td>
<td>0.2–1.5</td>
</tr>
<tr>
<td>Eosinophils ($\times 10^9$/L)</td>
<td>0.11</td>
<td>0.13</td>
<td>0.12</td>
<td>0.1–1.3</td>
</tr>
<tr>
<td>Basophils ($\times 10^9$/L)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>0–0.5</td>
</tr>
<tr>
<td>RBC ($\times 10^{12}$/L)</td>
<td>3.07*</td>
<td>3.53*</td>
<td>5.56</td>
<td>5.5–8.5</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>7.7*</td>
<td>8.5*</td>
<td>13.6</td>
<td>12–18</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>24.2*</td>
<td>26.7*</td>
<td>40.7</td>
<td>37–55</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>78.8*</td>
<td>75.6</td>
<td>73.2</td>
<td>60–77</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>25.1*</td>
<td>24.1</td>
<td>24.5</td>
<td>19.5–24.5</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>31.8*</td>
<td>31.8*</td>
<td>33.4</td>
<td>32–37</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>14.4</td>
<td>14.1</td>
<td>14.9</td>
<td>13.2–17.8</td>
</tr>
<tr>
<td>Platelets ($\times 10^9$/L)</td>
<td>140*</td>
<td>232</td>
<td>497</td>
<td>175–500</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>25*</td>
<td>26*</td>
<td>43</td>
<td>37–55</td>
</tr>
<tr>
<td>PP (g/L)</td>
<td>70</td>
<td>62</td>
<td>76</td>
<td>60–80</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>5.11*</td>
<td>5.85*</td>
<td>3.01*</td>
<td>0–1.5</td>
</tr>
<tr>
<td>Reticulocytes ($\times 10^9$/L)</td>
<td>156.9*</td>
<td>206.5*</td>
<td>167.4*</td>
<td>0–70</td>
</tr>
</tbody>
</table>

Blood film analysis

- **WBC:** few early neutrophils seen. WBC: normal morphology. WBC: normal morphology.
- **RBC:** moderate polychromasia, occasional NRBC seen, mild anisocytosis; mildly regenerative anaemia. 1–3 spherocytes per HPF. Mild agglutination
- **RBC:** mild polychromasia, occasional NRBC, marked anisocytosis; moderately regenerative anaemia. 2–5 Spherocytes per HPF

Abbreviations: Hb, haemoglobin; HCT, haematocrit; HPF, high-power field; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; MCV, mean cell volume; NRBC, nucleated red blood cell; PCV, packed cell volume; PP, plasma protein; RBC, red blood cells; RDW, red cell distribution width; WBC, white blood cells.

*Indicates a value outside of the reference interval.

**FIGURE 1** Ultrasoundographic view of the caecal mass. A focal, rounded and well-defined eccentrically positioned mass lesion on the caecum (measuring 1.82 x 1.36 cm) that was homogenously hypoechoic and minimally vascular on colour Doppler. The mass appeared to be extending into the muscularis layer with an intact hyperechoic submucosal layer deep to it.

caecal mass was subsequently submitted for histopathology (Figure 2). Twenty-four hours postoperatively, the PCV was measured to be 26%; however, the spherocytosis increased to two to five per HPF (Table 1); this was attributed to a degree of ongoing low-grade haemolysis in the immediate postoperative period. Intravenous opioid analgesia (methadone 0.2 mg/kg every 4 hours, followed by buprenorphine 0.02 mg/kg every 6 hours) and paracetamol (10 mg/kg twice daily) were also initiated. The patient was discharged 2 days postoperatively to continue oral medications at home; these included clopidogrel (1.8 mg/kg once daily for 10 days) and paracetamol (10 mg/kg twice daily for 10 days). Immunosuppressive treatment was not initiated at any stage.

**OUTCOME AND FOLLOW-UP**

Preliminary histopathology of the caecal mass was consistent with an intestinal spindle cell tumour (Figure 3). This nodular mass occupied the muscularis externa with partial infiltration into the submucosa. The neoplastic cells were arranged in interlacing streams, bundles and herring-bone patterns with
occasional nuclear palisading and were supported by moderately scant fibrous stroma. The individual neoplastic cells were of moderate size, spindle-shaped, with indistinct cell borders and scant eosinophilic, mildly vacuolated cytoplasm. The nuclei were oval or fusiform, centrally located with finely stippled to vesicular slightly hyperchromatic chromatin and one or two small, eosinophilic and variably distinct nucleoli. There were 11 mitoses per 10 HPF (2.37 mm²). Small numbers of bizarre mitoses were seen multifocally. Anisocytosis, anisokaryosis and nuclear pleomorphism were moderate. Sections taken from the adjacent caecum were histologically normal; the surgical margins were deemed to be clean.

In order to characterise the mass further, immunohistochemistry was performed. This revealed a diffusely weak to moderately strong staining for CD117(c-Kit); 60%–70% of neoplastic cells with predominantly membranous and, to a lesser extent, cytoplasmic staining. Additionally, there was diffusely weak staining for smooth muscle actin (SMA); 40% of neoplastic cells had cytoplasmic staining (Figure 4). These results were supportive of the diagnosis of a GIST of the caecum.¹⁸,²⁰–²³

The patient was re-examined at the QVSH 7 days, 39 days and 16 weeks postoperatively. CBC (Table 1) had largely normalised by day 7 (PCV 43% [reference interval 37%–55%], one spherocyte per three to four HPFs) and continued to remain within normal limits thereafter. Coombs' tests performed on Day 39 and week 16 were negative, with no evidence of spherocytosis. A repeat abdominal ultrasound performed at week 16 did not document any overt signs of tumour recurrence or progression. No further treatment was indicated at this stage, although repeat abdominal ultrasonography was recommended in the 3 and 6 months to follow. The patient was reported to be asymptomatic and doing well nearly 2 years after the initial presentation.

**DISCUSSION**

The present case report documents a paraneoplastic IMHA secondary to a GIST of the caecum; surgical resection of the mass resulted in complete resolution of the IMHA. Immunosuppressive medication was not required at any stage during treatment.

In the present case, IMHA was diagnosed according to the ACVIM consensus statement on the diagnosis of IMHA in dogs and cats.¹ Confidence in the diagnosis of IMHA requires the presence of two or more signs of immune-mediated destruction of erythrocytes (including spherocytosis, positive saline agglutination, positive Coombs’ test) and one or more signs of haemolysis (including hyperbilirubinaemia, bilirubinuria, haemoglobinuria, haemoglobinaemia and erythrocyte ghosts). In this case study, spherocytosis, positive Coombs’ test and bilirubinuria were consistent with the diagnosis of IMHA. The spherocytosis was initially documented to be one to three, and later two to five spherocytes/×100 oil immersion field can be considered supportive of a diagnosis of IMHA (sensitivity 63%, specificity 95%); however, three to four spherocytes/×100

**FIGURE 2** Photo of the caecal mass (gastrointestinal stromal tumour). Gross appearance of the caecal mass in situ just before surgical excision via marginal typhlectomy

**FIGURE 3** The neoplastic cells are arranged in broad interlacing streams, bundles and herring-bone patterns. Haematoxylin and eosin stain; scale bar = 400 µm
oil immersion field also may be consistent with IMHA (sensitivity 74%, specificity 81%), provided no other cause of spherocytosis is identified. Although the Coombs’ test (direct antiglobulin test, DAT) has been reviewed to have a sensitivity ranging 61%–82% in dogs, the specificity is deemed to be 94%–100%. Ultimately, to truly establish a link between IMHA and a solid tumour, it is important to first exclude other possible underlying diseases such as drug intake, infections, autoimmune diseases and haematological malignancies.

In the present case, the history, blood testing and imaging performed were supportive of this link and no other concurrent disease was found. Complete resolution of the IMHA in response to surgical resection of the mass is further supportive of causality.

The authors are aware that clopidogrel was initiated before the decision to proceed with surgical intervention. Clopidogrel treatment in the present case was initiated based on the ACVIM Guidelines for the treatment of IMHA whereby the risk of thrombosis is recognised as a leading cause of morbidity and mortality in dogs with IMHA. At present, the use of clopidogrel peri-operatively is controversial in humans. One study identified no increased peri-operative bleeding risk in humans undergoing general surgery when clopidogrel was continued. Another human study documenting an increased risk of postoperative bleeding with the use of clopidogrel recommends cessation of the drug at least 7 days before elective abdominal surgery. However, most episodes of bleeding encountered in this study were successfully managed by transfusion without an increase in bleeding-related mortality or the necessity for revisional surgery. The Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE) in small animals suggests that alteration of antithrombotic treatment before surgery should be based on balancing the risk of haemorrhage and thrombosis. According to these guidelines, diseases with clear and consistent evidence for thrombosis as a complication of disease should be deemed ‘high risk.’ The recommendation is that antiplatelet therapy with a single agent (such as clopidogrel) should be continued before a surgical procedure in ‘high-risk’ patients.

Although rare, neoplasia has been proposed to have a role in development of IMHA through mechanisms that can be divided into three broad categories: disruption of central tolerance (e.g., B- and T-lymphocyte escape of ‘forbidden clones’), peripheral tolerance (e.g., upregulated co-stimulation for T-cell activation resulting in aberrant activation) and alteration of self-antigens (e.g., modification of red cell antigens by the tumour, immune complex formation against tumour antigens and subsequent binding to erythrocytes with complement activation, immune cross-reactivity between antigens of malignant and normal tissues).

Another human paper describes the production of anti-platelet antibodies (IgM) by lymphoma tissue in a case of lymphoplasmacytic lymphoma with paraneoplastic autoimmune thrombocytopenia; the production of auto-antibodies by the tumour is therefore another potential mechanism by which paraneoplastic immune-mediated disease may be triggered in haematological malignancies. There is evidence to suggest that the presence of a paraneoplastic process is likely to impact on long-term prognosis of these cases. In humans, it has been found that concurrent paraneoplastic haematological syndromes secondary to lung cancer are associated with a poorer prognosis. AIHA can be a marker of tumour recurrence when the tumour was originally associated with AIHA. However, AIHA may also occur as a de novo paraneoplastic syndrome at the time of recurrence.

GISTs in dogs have been found to develop more commonly in the colon, caecum and small intestine compared to the stomach and mesentery. Their biologic behaviour varies from benign to malignant, with a previously reported metastatic rate of 29% to the liver or abdominal cavity (spleen, mesentery, serosa, mesenteric lymph nodes) in dogs. In humans, they also typically possess the ability to metastasise to the liver and abdominal cavity, but do not generally result in obstruction. Immunohistochemistry plays an essential role in the diagnosis of GIST, as has been described in the present case. A major difficulty when encountering mesenchymal gastrointestinal tumours is that GISTs are often erroneously diagnosed as leiomyomas or
leiomyosarcomas, with many having been retrospectively reclassified as GISTs. The correct diagnosis has considerable implications on prognosis; in one study, the median survival times for dogs with surgically resected GISTs compared to leiomyosarcomas were 11.6 and 7.8 months, respectively. This highlights the importance of the use of immunohistochemical techniques to distinguish between these neoplasms given that the appearance under light microscopy can be identical. Immunohistochemical criteria specific to the diagnosis of GISTs typically includes strong c-Kit/CD117 and vimentin immunoreactivity, although it is also possible to detect expression of the less specific alpha SMA, desmin and S-100 expression. Leiomysarcomas are usually positive for SMA and desmin, but negative for c-Kit and can therefore be differentiated from GISTs in this way.

Several prognostic indicators have been variably identified in human GIST, including tumour size, mitotic rate, ability to completely resect the tumour and location. In one study, tumour type, location, histopathological or immunohistochemical characteristics were not recognised as prognostic indicators in dogs. However, more recently, tumour location and size have been recognised as prognostic indicators. Small intestinal GISTs and those with a diameter of greater than or equal to 10 cm have been associated with a poorer prognosis in dogs. The small intestinal GISTs had a higher mitotic index, which may explain the poorer prognosis. The median overall survival of surgically resected caecal versus small intestinal lesions was 22 and 6 months, respectively.

In the present case, treatment of the underlying neoplasia was favoured over the use of immunosuppressive therapy; the authors believe there is evidence in the literature to support this rationale. In humans, it has been suggested that tumours preceding paraneoplastic haematological syndromes should be treated first. In a review of 52 human patients with solid tumours and concurrent AIHA, 11 of these were non-metastatic solid tumours (including one gastric stromal tumour). Nine of 11 patients received primary immunosuppressive steroid treatment, with five having no or poor response. Nine out of 11 of these same patients underwent radical cancer surgery with achievement of complete remission in all cases; response to surgery was thought to reflect a reduction in antigenic load. However, it is important to note that three of these patients also underwent a splenectomy at the same time, and therefore complete remission cannot be attributed solely to tumour removal. In another human case study, corticosteroid treatment of IMHA secondary to a gastric stromal tumour was initially successful for 6 months. AIHA recurred upon cessation of treatment; however, surgery to excise the mass (albeit with a splenectomy) resulted in remission. Interestingly, a retrospective analysis of various lymphomas associated with AIHA proposed that anti-lymphoma treatment was more effective against AIHA than conventional therapy with steroids or immunoglobulin.

To the authors' knowledge, in dogs, there has been one case of an intestinal leiomyosarcoma with paraneoplastic IMHA whereby surgical resection of the tumour led to complete remission of the IMHA. Of course, it is important to note that patients with more severe manifestations of IMHA may not be immediate candidates for surgery; immunosuppressive therapy and/or transfusion support may therefore be considered to attempt initial stabilisation. Patients with disseminated neoplastic disease or non-resectable tumours may not achieve remission from surgery, although there has been some evidence in humans to suggest that resection of a primary tumour has beneficial effects in some metastatic cancers.

Chemotherapeutic treatment for unresectable or metastatic GISTs in humans may include tyrosine kinase inhibitors, although the literature for this in dogs is lacking. In one retrospective study, five out of seven dogs with gross disease experienced a clinical benefit when treated with toceranib. In another case report, a dog with a large GIST of the caecum with widespread metastasis (albeit negative for mutations in exon 8 and exon 11 of the receptor tyrosine kinase c-Kit proto-oncogene [KIT]) was successfully treated with toceranib phosphate (Palladia; Pfizer) and achieved a complete response for at least 9 months after diagnosis. However, it is important to note that the development of resistance to tyrosine kinase inhibitors has been described in the human literature. The mechanisms by which this occurs are thought to involve new molecular abnormalities or mutations associated with KIT and platelet-derived growth factor receptor alpha (PDGFRα) signalling pathways. On the other hand, successful surgical resection of GISTs (with clean margins) has been documented and is considered to be the treatment of choice for focal neoplasms at present; although there has been some preliminary evidence in humans to suggest that imatinib (tyrosine kinase inhibitor) may be used in conjunction with surgery in focal GISTs to improve recurrence-free survival. In the present case, several factors such as the location, size, lack of metastasis and ability to completely resect the mass provided a favourable long-term prognosis; the use of adjuvant chemotherapeutic treatment was therefore not deemed necessary, which is consistent with guidelines in humans. Recurrence of caecal GISTs has been reported in up to 37% of dogs, so these drugs may represent a future treatment option for this patient.

It is also important to discuss the timeframes for remission and recurrence postoperatively as these influence monitoring strategies and, ultimately, prognosis. In the present case, the PCV normalised within 7 days postoperatively, albeit with the presence of very rare spherocytosis. Roughly, one spherocyte per three to four HPFs was observed; this remained below the range supportive of IMHA described in the ACVIM Guidelines. Complete remission of the IMHA was determined more definitively on day 39 with a normal haematology (including blood film analysis) and Coombs' negativity. The dog's neoplasia and IMHA are in clinical remission approximately 2 years after surgery. The time to remission of IMHA is consistent with the findings of the aforementioned study whereby removal of an intestinal leiomyosarcoma in a dog led to remission of IMHA 14 days after surgery; the PCV recovered to 40% with no evidence of spherocytosis and a repeat Coombs' test was negative. However, unlike the present study, this patient was lost to long-term follow-up. In the review of 52 human patients, complete remission of AIHA occurred very early (2–4 weeks postoperatively) in seven of nine patients who underwent surgical resection of non-metastatic solid tumours, whereas the remaining two wereascertained later (likely as a result of delayed monitoring). Four of nine cases had a long-term follow-up; two of these cases sustained complete remission of the AIHA and tumour at 2 and 5 years, whereas two patients exhibited recurrence of
the AIHA and tumour at 11 months and 1 year, respectively. Serological remission was noted in 75% of cases. To the authors’ knowledge, this is the first report of a paraneoplastic IMHA associated with GIST in a dog and one of very few cases that achieved complete remission of IMHA in response to surgical resection of a tumour without concurrent use of immunosuppressive medication. The dog responded rapidly to surgical treatment, while demonstrating a very good long-term prognosis. These findings add support to a growing body of evidence for paraneoplastic IMHA and are a stimulus for further research in this area to elucidate the underlying pathophysiological processes, methods of treatment and prognosis.

AUTHOR CONTRIBUTIONS
Giulia Cattaneo analysed the case, conducted research around the subject and wrote the case report. Luca Schiavo, Katie E. McCallum and Jane M. Dobson were involved in clinical management of the case, reviewed the case report and research. Diana Bochyr'ska and Katherine Hughes produced the histopathological report, histopathological images and reviewed the case report.

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CONFLICTS OF INTEREST
The authors declare they have no conflicts of interest.

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ETHICS STATEMENT
Ethics approval was not required for the present case report; informed consent was obtained and anonymity maintained.

REFERENCES


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