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COMPANION OR PET ANIMALS

# Marked paraneoplastic hypereosinophilia associated with a low-grade, metastatic canine mast cell tumour

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Received 25 October 2017  
Revised 16 March 2018  
Accepted 25 April 2018

## SUMMARY

An 11-year-old, female, spayed labrador retriever was presented to the Iowa State University Oncology Service for evaluation of a rapidly expanding mass located near the right prescapular lymph node. A Patnaik grade I mast cell tumour (mitotic index <3/10 high-power fields) had been completely excised from the right antebrachium five months before presentation. Cytological evaluation of aspirates from the healed incision site and the new mass revealed mast cells with marked eosinophilic infiltration consistent with local recurrence and presumed lymph node metastasis. A complete blood count revealed markedly elevated eosinophils ( $23.96 \times 10^3$  cells/ $\mu$ l, reference interval 0–0.75). The patient was diagnosed with a histologically low-grade, biologically high-grade cutaneous, metastatic mast cell tumour with paraneoplastic hypereosinophilia. Changes in the magnitude of peripheral hypereosinophilia frequently paralleled tumour response to treatment with multiple antineoplastic agents. Nine months after initiating chemotherapy, treatment was discontinued due to declining quality of life.

## BACKGROUND

Mast cell tumours (MCTs) are round cell neoplasms that occur most commonly in the skin and represent 16–21 per cent of all cutaneous tumours in dogs and 20 per cent of all cutaneous tumours in cats.<sup>1</sup> They are less commonly reported in human beings,<sup>2</sup> horses<sup>3</sup> and cattle.<sup>4</sup> Mast cells originate from the bone marrow and are widely distributed throughout the body as normal components of the immune system and allergic response. They also concentrate at sites of haematological malignancies and at the margins of several solid tumours.<sup>5</sup> Mast cells contain granules that are rich in histamine, heparin, prostaglandins, proinflammatory cytokines (specifically interleukin-5 (IL-5)) and numerous other mediators.<sup>6–8</sup> The function and composition of mast cell granules depend on the microenvironment in which they mature.<sup>6</sup>

Eosinophils are a cellular component of the immune system recruited during allergic reactions, autoimmune disorders and neoplastic processes.<sup>5</sup> Similar to mast cells, eosinophils originate in the bone marrow and contain granules rich in cytokines, specifically IL-5, and prostaglandins that drive the allergic response in addition to interactions with surrounding mast cells.<sup>8</sup> When in close contact, mast cells and eosinophils form the allergic effector unit, which leads to a hyperactive state and the release of soluble mediators from the granules of both cells.<sup>5</sup> Mast cell granule products, such as

IL-5, modulate eosinophil functions, and stem cell factor (SCF) released from eosinophils helps to activate mast cells, thus stimulating bidirectional mast cell–eosinophil interactions.<sup>5</sup>

Human mastocytosis is a malignancy comprised of an abnormal mast cell expansion that accumulates in the bone marrow and skin. Fifteen to twenty-eight per cent of patients with systemic mastocytosis also have a peripheral paraneoplastic eosinophilia.<sup>5</sup> This paraneoplastic syndrome has also been reported with human nasal carcinoma, colorectal carcinoma, oral squamous cell carcinoma and Hodgkin's lymphoma.<sup>5</sup>

Peripheral paraneoplastic eosinophilia has been reported sporadically in the veterinary literature. It has been found to be associated with canine cutaneous and visceral mast cell disease,<sup>9–11</sup> canine pericardial leiomyosarcoma,<sup>12</sup> intestinal T-cell lymphoma in both dogs and cats,<sup>13 14</sup> canine anaplastic mammary carcinoma,<sup>15</sup> canine oral fibrosarcoma,<sup>16</sup> and in one case of a cat with transitional cell carcinoma of the urinary bladder.<sup>17</sup> Eosinophilic effusions have also been found in dogs and cats with cancer and non-cancerous conditions alike. Interestingly, in these cases the eosinophil counts in the blood were not linearly related to the eosinophil count in the effusions, and in some cases the number of eosinophils in the effusion exceeded that in the blood.<sup>18</sup> The cause of paraneoplastic eosinophilia is not well understood but likely results through stimulation by various interleukins, eotaxins and cytokines. The most important of these substances is likely IL-5, which is produced by multiple neoplastic cells, including mast cells.<sup>19</sup>

Although paraneoplastic eosinophilia has been reported previously, to the authors' knowledge, this is the first report of severe hypereosinophilia associated with a low-grade, metastatic cutaneous MCT that responded to chemotherapy treatment, and where hypereosinophilia recrudescence often signalled progression of the disease.

## CASE PRESENTATION

An 11-year-old, female, spayed labrador retriever was referred to the Iowa State University Lloyd Veterinary Medical Center (ISU LVMC) for evaluation of a rapidly expanding mass located in the area of the right prescapular lymph node. A Patnaik grade I, Kiupel low-grade MCT (mitotic index <3/10 high-power fields (hpf)) with eosinophilic infiltration had been completely excised from the right antebrachium five months before presentation. A complete blood count (CBC) completed just before



**To cite:** Musser M, Berger E, Flaherty HA, et al. *Vet Rec Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/vetreccr-2017-000563

surgery revealed an eosinophil count of  $3.63 \times 10^3$  cells/ $\mu$ l (reference interval (RI) 0.10–1.49) but was otherwise unremarkable. No additional prognostic testing was pursued at the time of excision. No clinical signs were reported at presentation to the ISU LVMC. On physical examination, the patient weighed 44.6 kg with a body condition score of 6/9. The previous surgical site on the right antebrachium appeared to be well healed; however, a small, firm 2-cm mass was present 0.5 cm lateral to the surgical scar. This mass had not been noted on physical examination two days prior at the family veterinarian, and no inflammatory reaction was noted around the mass. An 11-cm, firm subcutaneous mass was noted in the anatomical position of the right prescapular lymph node. The remainder of the physical examination was unremarkable. On presentation, the patient was receiving carprofen for chronic arthritis, and flea/tick and heartworm preventives May through November of each calendar year. No other medications were reported.

## INVESTIGATIONS

A CBC, serum biochemical analysis and urinalysis were performed. A moderate leucocytosis ( $35.24 \times 10^3$  cells/ $\mu$ l, RI 6.0–17.0) was present, characterised by a marked eosinophilia ( $23.96 \times 10^3$  cells/ $\mu$ l, RI 0–0.75) with normal morphology. Serum biochemistry revealed hypernatraemia (153 mEq/l, RI 141–151), hypobicarbonataemia (17.0 mEq/l, RI 19–25), increased serum alkaline phosphatase activity (1057 iu/l, RI 20–150), increased serum alanine aminotransferase activity (344 iu/l, RI 24–90) and hyperbilirubinaemia (0.88 mg/dl, RI <0.1–0.6). The liver enzyme elevations were historical before the diagnosis of MCT. Voided urinalysis detected trace bilirubin and moderate protein (2+) with a urine specific gravity of 1.020.

Cytological evaluation of aspirate samples from the 2-cm mass lateral to the surgical scar over the right antebrachium and the right prescapular mass was performed. Neoplastic mast cells with marked eosinophilic infiltration were identified within the antebrachial mass, confirming MCT recurrence, and in the samples from the right prescapular mass, indicating metastatic disease.

Thoracic radiographs identified a right prescapular mass displacing the trachea to the left but were otherwise unremarkable. An abdominal ultrasound was performed to evaluate the liver, spleen and lymph nodes. A single anechoic nodule within the liver was noted (0.53 cm in diameter). Numerous ill-defined hypoechoic nodules measuring up to 1.03 cm were observed in the spleen. Ultrasound-guided spleen and liver aspirate samples, including the general parenchyma and direct aspirates of the nodules noted in each organ, were obtained without incident. Cytological examination of the liver revealed low numbers of well-granulated mast cells, considered within normal limits. Cytological examination of the spleen revealed a mild increase of well to poorly granulated mast cells; however, this was not diagnostic for splenic metastasis as cytologically the mast cells were normal and they appeared as individual cells without clustering, as has been previously described in normal splenic parenchyma.<sup>20</sup> Moderate to marked numbers of eosinophils were observed in both liver and splenic aspirate samples. A bone marrow aspirate was recommended, but declined.

An MCT prognostic panel was submitted on the primary tumour removed five months before presentation. The MCT tested positive for an activating duplication mutation in exon 11 of *KIT*, a tyrosine kinase receptor. In addition, the MCT was noted to have c-kit staining pattern 2, Ki67 labelling of 30 cells/grid (>23 is associated with a decreased survival time)<sup>21</sup> and an

AgNOR x Ki67 index of 84 (>54 is associated with a decreased survival time).<sup>21</sup>

## DIFFERENTIAL DIAGNOSIS

Canine peripheral hypereosinophilia (typically defined as  $>5.0 \times 10^3$  cells/ $\mu$ l)<sup>22</sup> can be caused by a plethora of neoplastic and non-neoplastic conditions. These include parasitic infections (eg, hookworms, heartworm disease, respiratory helminth infections), allergic conditions (eg, flea allergy dermatitis), breed predispositions (eg, rottweilers), pulmonary infiltrates with eosinophils (eosinophilic bronchopneumonia), pulmonary aspergillosis, bacterial pneumonia, acute and chronic gastrointestinal disease, idiopathic hypereosinophilic syndrome, and eosinophilic leukaemia.<sup>19–22</sup> Heartworm antigen and tick testing (AccuPlex 4, Antech Diagnostics) were completed 17 months before presentation, and both were negative. Intermittent heartworm prevention (Heartgard Plus) and flea/tick prevention (Activyl Tick Plus) were administered at home (May through November of each calendar year; the patient had received both preventives for the four consecutive months before presentation). No significant travel history, clinical history of allergies, or current clinical signs of pneumonia or gastrointestinal disease were noted. Bloodwork 6 months before surgical removal of the primary MCT had a normal eosinophil count ( $0.4 \times 10^3$  cells/ $\mu$ l, RI 0.10–1.49). A CBC completed just before surgery revealed an eosinophil count of  $3.63 \times 10^3$  cells/ $\mu$ l. Given the negative results of available diagnostics and risk factors for other causes of hypereosinophilia, the lack of hypereosinophilia before identification of the primary MCT, and the significant eosinophilic infiltration of both the primary MCT incision site and metastatic lymph node, the severe peripheral hypereosinophilia was determined to be a paraneoplastic syndrome.

## TREATMENT

A guarded prognosis of weeks to months was given based upon the diagnosis of a biologically high-grade MCT.<sup>23</sup> Aggressive surgical removal of the affected lymph node and amputation of the right forelimb were offered but declined. Thus, a staged initiation of therapy was planned with the informed and written consent of the owner. This approach was elected due to the severity of disease to try to avoid significant adverse clinical side effects following initiation of treatment. The patient was discharged the day of presentation with prednisone (30 mg/m<sup>2</sup> every 24 hours, orally), omeprazole (1 mg/kg every 24 hours, orally) and diphenhydramine (2.2 mg/kg every 12 hours, orally). The right prescapular metastatic MCT responded well to prednisone based on the solid tumour response evaluation criteria (Tables 1 and 2, Fig 1).<sup>24</sup> In addition, the peripheral eosinophil count and the size of the original antebrachial mass decreased significantly (Fig 1, Table 2). Chemotherapy (vinblastine, 3 mg/m<sup>2</sup> intravenously) commenced the following week, which also resulted in a further decrease in the size of the right prescapular metastatic MCT, antebrachial MCT and eosinophil count. Thus an additional dose of vinblastine was given.

After two doses of vinblastine, it was elected to switch therapy to toceranib phosphate (2.45 mg/kg Monday, Wednesday, Friday, orally) for owner's convenience and based on the presence of a mutation in *KIT*. Prednisone (mean dose 28 mg/m<sup>2</sup>; Table 2), omeprazole (1 mg/kg every 24 hours, orally) and diphenhydramine (2.2 mg/kg every 12 hours, orally) were continued throughout the treatment. Over the course of nine months, the patient received a variety of chemotherapy treatments, including

**TABLE 1:** Summary of Response Evaluation Criteria in Solid Tumours V.1.0 (RECIST)<sup>23</sup>

Complete response (CR)	Disappearance of all target lesions; pathological lymph nodes <10 mm short axis
Partial response (PR)	≥30% decrease in sum diameters of target lesions, taking as reference the baseline sum
Stable disease (SD)	<30% reduction (PR) or 20% increase (PD) in the sum diameters of target lesions, taking as reference the smallest sum of diameters while on study
Progressive disease (PD)	≥20% increase in sum diameter of target lesions taking as reference the smallest sum of diameters while on study; the sum increase must be ≥5 mm, OR the appearance of one or more new lesions

vinblastine, toceranib phosphate, lomustine (73–78 mg/m<sup>2</sup> every 3 weeks, orally) and vinorelbine (15 mg/m<sup>2</sup>, intravenously) (Table 2). At each visit, the longest diameter of the prescapular tumour and antebrachial tumour (if possible) was measured, and an eosinophil count was completed. The diameter of the prescapular mass fluctuated with response to treatment, and alongside this the peripheral eosinophil count, for the most part, changed accordingly. On two occasions, at day 195 and day 250, the eosinophil count increased without a significant change in the size of the prescapular tumour, possibly indicating that systemic disease was developing driving the increase in eosinophils, or that a normal fluctuation in eosinophil count

had occurred (Fig 1, Table 2). The most dramatic decrease in eosinophil count was noted following the initiation of treatment with prednisone (Fig 1, Table 2). During treatment, no other haematological side effects (neutropenia, thrombocytopenia or anaemia) were observed.

**OUTCOME AND FOLLOW-UP**

The patient responded positively to initial therapy with prednisone, vinblastine and toceranib phosphate, with the size of the right prescapular mass decreasing significantly (from 11 cm to 1.1 cm). The recurrent antebrachial mass resolved entirely, and the eosinophil count decreased (Fig 1, Table 2). However, after approximately three months, resistance to toceranib phosphate was noted as both the right prescapular mass diameter and eosinophil count increased (the recurrent antebrachial tumour remained resolved). The patient was continued on a variety of differing cytotoxic chemotherapeutics for an additional six months before the client elected to discontinue treatment due to minimal tumour response, severe hindlimb weakness of which the aetiology was unknown, and overall poor perceived quality of life. The patient was humanely euthanased four weeks after the final chemotherapy treatment and approximately ten months following treatment initiation (overall survival time from treatment initiation: 291 days). Postmortem examination was not performed.

**TABLE 2:** Summary of treatment, lymph node measurements and eosinophil counts

Days from treatment initiation	Right prescapular lymph node longest diameter (cm)	Response (RECIST)*	Eosinophil count (×10 <sup>3</sup> /µl); reference interval: 0.0–0.75×10 <sup>3</sup> /µl	Previous cycle treatment(s)
0	11	Initial baseline	23.96	None
7	7.5	PR	3.68	Prednisone 32 mg/m <sup>2</sup> orally every 24 hours
15	4.5	PR	0.61	Vinblastine 3 mg/m <sup>2</sup> intravenously Prednisone 32 mg/m <sup>2</sup> orally every 24 hours
22	1.1	CR	1.69	Vinblastine 2.7 mg/m <sup>2</sup> intravenously Prednisone 25 mg/m <sup>2</sup> orally every 24 hours
55	1.2	CR	0.08	Toceranib 2.4 mg/kg orally every 48 hours Prednisone 25 mg/m <sup>2</sup> orally every 24 hours
90	1.3	CR	0.38	Toceranib 2.45 mg/kg orally M, W, F Prednisone 17 mg/m <sup>2</sup> orally every 24 hours
118	6.4	PD New baseline	5.96	Toceranib 2.45 mg/kg orally M, W, F Prednisone 17 mg/m <sup>2</sup> orally T, Th, Sa
125	6.9	SD	2.42	Vinblastine 2.7 mg/m <sup>2</sup> intravenously Prednisone 34 mg/m <sup>2</sup> orally every 24 hours
133	9.4	PD New baseline	5.50	Vinblastine 2.7 mg/m <sup>2</sup> intravenously Prednisone 34 mg/m <sup>2</sup> orally every 24 hours
153	10.8	SD	1.73	Lomustine 73 mg/m <sup>2</sup> orally Prednisone 34 mg/m <sup>2</sup> orally every 24 hours
174	11.2	SD	2.01	Lomustine 77 mg/m <sup>2</sup> orally Prednisone 34 mg/m <sup>2</sup> orally every 24 hours
195	10.7	SD	4.05	Lomustine 77 mg/m <sup>2</sup> orally Prednisone 34 mg/m <sup>2</sup> orally every 24 hours
217	11.9	PD	2.29	Lomustine 78 mg/m <sup>2</sup> orally Prednisone 35 mg/m <sup>2</sup> orally every 24 hours
237	13.5	PD New baseline	3.44	Lomustine 78 mg/m <sup>2</sup> orally Prednisone 35 mg/m <sup>2</sup> orally every 24 hours
250	13.0	SD	11.98	Vinorelbine 15 mg/m <sup>2</sup> intravenously Prednisone 18 mg/m <sup>2</sup> orally every 24 hours
265	13.2	SD	8.81	Vinorelbine 15 mg/m <sup>2</sup> intravenously Prednisone 18 mg/m <sup>2</sup> orally every 24 hours

\*See Table 1 for RECIST response criteria.

F, Friday; M, Monday; Sa, Saturday; T, Tuesday; Th, Thursday; W, Wednesday of each week.

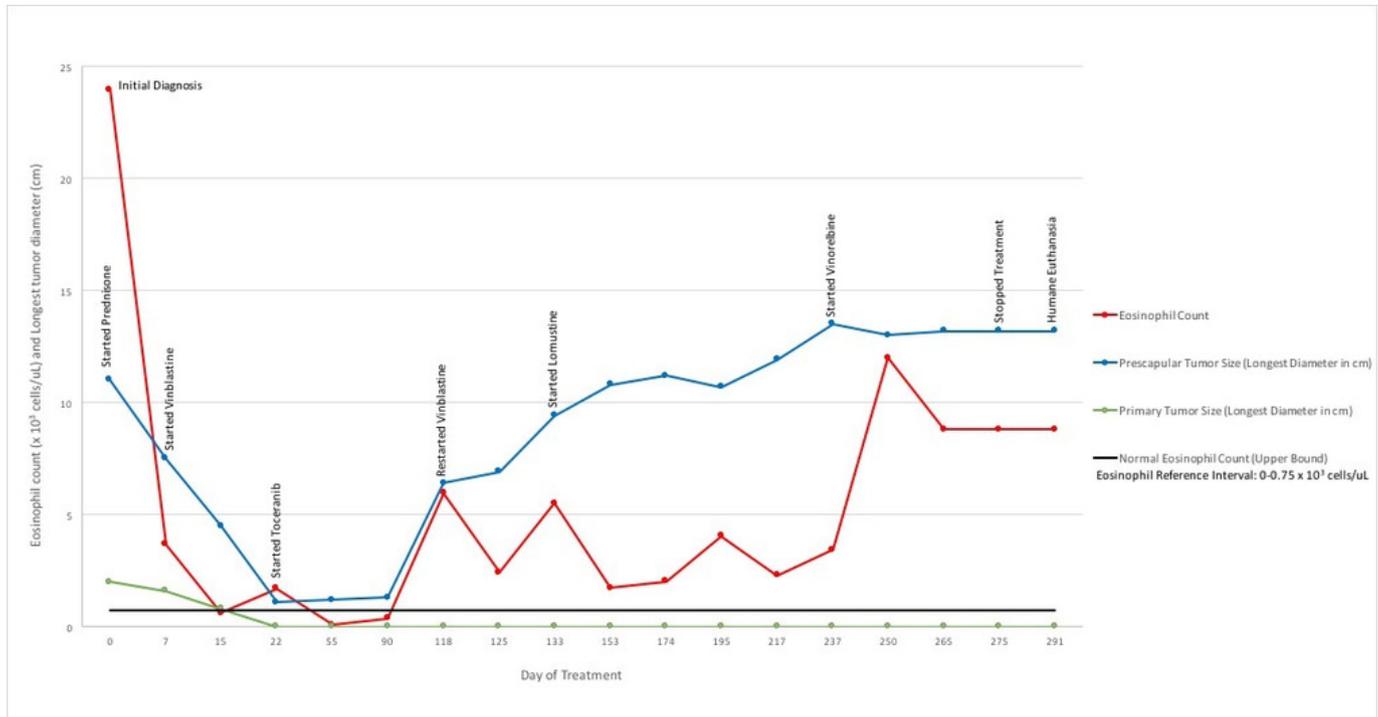


FIG 1: Changes in eosinophil count, primary tumour longest diameter and prescapular tumour longest diameter over time.

**DISCUSSION**

Paraneoplastic hypereosinophilia has been reported frequently within the human literature, but studies investigating the role of eosinophils are mixed. Some studies have found that hypereosinophilia correlates to a better prognosis in tumours such as colorectal, bladder and prostatic carcinomas,<sup>5</sup> whereas other studies, including those evaluating Hodgkin’s lymphoma, oral squamous cell carcinoma and cervical carcinoma, have found hypereosinophilia to be linked to a poorer prognosis.<sup>5</sup> Within the human literature it appears that paraneoplastic hypereosinophilia is more likely to be caused by extensive metastatic disease as compared with a primary tumour.<sup>25</sup> The veterinary literature has described cases associated with both primary and metastatic cancers.<sup>9–15</sup>

Human mastocytosis is a clonal proliferation of mast cells that can accumulate in the skin, blood or multiple organs.<sup>26</sup> Paraneoplastic hypereosinophilia is especially common in cases of systemic mastocytosis and indicates an aggressive course of the disease and poor prognosis.<sup>27</sup> However, paraneoplastic hypereosinophilia has rarely been reported in mastocytosis confined to the skin.<sup>28</sup> Similarly, in dogs the vast majority of case reports describing paraneoplastic peripheral hypereosinophilia associated with mast cell disease are from patients with extensive visceral or systemic disease.<sup>10, 29</sup> In addition, it has been determined that hypereosinophilia positively correlates to the likelihood of systemic bone marrow involvement, implying a more extensive and severe disease.<sup>11</sup> The authors believe that this case is one of the first to demonstrate severe hypereosinophilia due to a low-grade, locally metastatic MCT without obvious evidence of systemic spread of the disease or visceral involvement. A limitation of this case is that a bone marrow aspirate was not completed (the owner declined) to confirm lack of systemic disease within the bone marrow. However, a previous study showed that dogs with bone marrow involvement either have visceral disease, peripheral blood cytopenias or both.<sup>30</sup> Based on the very mild elevations of cytologically normal mast cells noted

in the spleen (not consistent with overt metastatic disease), the unremarkable liver aspirates and the lack of peripheral blood cytopenias in the patient of the present case, the authors believe the disease was likely confined to the right antebrachium and right prescapular lymph node.

In normal mature mast cells, activation of the c-kit receptor by its ligand SCF leads to increased proliferation, prolonged survival and intensified release of mediators. In human patients with mastocytosis, these functions are often directed by overexpression of SCF and a gain-of-function mutation in the *KIT* gene resulting in autocrine dysregulation.<sup>8</sup>

Canine MCTs have also been shown to have several gain-of-function mutations in the *KIT* gene, specifically in exons 8 and 11,<sup>31</sup> and those with a mutation in exon 11 have a significantly shorter disease-free interval compared with patients without a mutation.<sup>32</sup>

In addition, a correlation between the pattern of c-kit receptor expression and prognosis has been found: MCTs with c-kit pattern 1 (membranous staining only) have not been associated with a poor prognosis, whereas MCTs with c-kit patterns 2 and 3 (increased cytoplasmic staining) have an increased rate of local disease recurrence and a decreased overall survival rate.<sup>33</sup> However, MCTs with c-kit patterns 2 and 3 are most likely to respond to tyrosine kinase inhibitor drugs (ie, toceranib phosphate).<sup>34</sup> Similarly, MCTs that have a high proliferation activity measured via AgNOR or Ki67 expression have been associated with a significantly worse prognosis and decreased survival times.<sup>21</sup> In studies comparing proliferation indices with survival time, MCTs with an AgNOR x Ki67 index greater than 54 or a Ki67 index greater than 23 cells/grid were associated with an increased risk of death. In addition, those tumours with an AgNOR x Ki67 of greater than 54 were associated with an increased rate of reoccurrence at the original surgical site.<sup>21</sup>

In the present case, initial grading of the patient’s tumour from the right antebrachium was consistent with a Patnaik grade I (mitotic index <3/10 hpf), Kiupel low-grade MCT. Historically,

a mitotic index of greater than 5/10 hpf correlated with a shorter median survival time.<sup>1</sup> The Kiupel grading scheme uses a mitotic index of greater than 7/10 hpf to differentiate high grade from low grade, which correlates with a shorter survival time.<sup>35</sup> A recent study suggested a mitotic index of greater than 2/10 hpf was more sensitive for predicting death of a patient due to their MCT.<sup>36</sup> In the present case, the patient's mitotic index was less than 3/10 hpf, potentially suggesting an increased risk of death from the MCT. However, this lower mitotic index (>2/10 hpf) has not been fully validated for impact on survival, and thus caution is necessary in drawing conclusions in this case based on mitotic index alone. The MCT prognostic panel revealed a *KIT* mutation in exon 11, c-kit staining pattern 2, Ki67 index of 30 and an AgNOR x Ki67 index of 84, all indicative of an aggressive tumour phenotype. Although aggressive behaviour is not common for a low-grade MCT, 15–30 per cent of low-grade tumours prove to be aggressive,<sup>1</sup> and thus in the present case the MCT prognostic panel becomes an indispensable part of the patient's evaluation for treatment and prognostic considerations.

In order to properly diagnose the patient, it was necessary to eliminate other causes of hypereosinophilia. Upon presentation to the ISU LVMC, there was no clinical evidence of allergic disease, the patient was heartworm-negative and had been on a preventive, and had no clinical evidence of respiratory or gastrointestinal disease. In addition, previous bloodwork showed a normal eosinophil count until the development of the primary MCT. Eosinophilic leukaemia is rare and difficult to differentiate from a reactive population. Having a monoclonal population of eosinophils would help to differentiate the two, but such evaluation is not yet validated for the dog, to the authors' knowledge. Having eliminated other possible causes of hypereosinophilia, it is most logical to conclude that the recurrent MCT and regional lymph node metastasis (both exhibiting marked eosinophilic infiltrate on cytology) were the source of peripheral hypereosinophilia. In addition, the fluctuation in eosinophil count that frequently paralleled the decreasing and increasing size in tumour diameter further supported the MCT as the source of the patient's hypereosinophilia.

While MCTs are a common occurrence in dogs, they rarely have been associated with such a marked paraneoplastic hypereosinophilia.<sup>11</sup> Based on previous literature, it seems likely that the primary MCT and/or metastatic lymph node influenced the development of the hypereosinophilia via the release of IL-5 and stimulation of eosinophils,<sup>19</sup> although further molecular studies are necessary to support that conclusion. The unique combination of a histologically low-grade, biologically high-grade primary MCT paired with marked peripheral hypereosinophilia makes this a notable case, and cutaneous MCT should be a differential for canine patients with severe peripheral hypereosinophilia.

**Contributors** MM contributed to the data collection, analysis of the data and writing of the manuscript. EB contributed to the management of the case, data collection and writing of the manuscript. HAF evaluated the clinical pathology data and contributed to the writing of the manuscript. LF contributed to the management of the case and writing of the manuscript. CMJ contributed to case management, data collection and preparation of the manuscript. All authors reviewed the final version of this manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** CMJ is a former employee of Pfizer Animal Health and has served as a member of the Zoetis (formerly Pfizer Animal Health) Oncology Advisory Board and occasionally receives honoraria for these activities.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** This is a descriptive case report and therefore all data generated has been included in the manuscript.

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