DOI: 10.1002/vms3.927

CASE REPORT

WILEY

# Multiple myeloma involving the gastrointestinal tract in an English Springer Spaniel

Emma Roberts[1] | Alex Shirlow[1] | Alistair Cox[2] | Owen Davies[1]

[1]Highcroft Veterinary Referrals, Bristol, United Kingdom

[2]Finn Pathologists, Harleston, United Kingdom

**Correspondence**
Emma Roberts, Highcroft Veterinary Referrals, Bristol, United Kingdom.
Email: emma.roberts@cvsvets.com

## Abstract

A 10-year-old, entire male, English Springer Spaniel was referred for evaluation of weight loss, polyuria, polydipsia and gastrointestinal tract signs including melena/haematochezia for the previous six months. Results of serum protein electrophoresis, urine analysis, computed tomography of the thorax/abdomen, bone marrow aspiration and core biopsy, and splenic and mesenteric lymph node cytology were consistent with multiple myeloma. Endoscopically obtained gastrointestinal tract biopsies identified marked plasma cell infiltration within the duodenum, ileum and colon; immunohistochemistry showed positive labelling to MUM1 and Lambda confirming clonal plasma cell involvement. The dog entered complete clinical remission seven weeks after starting a melphalan/prednisolone protocol. The dog was euthanised 475 days after starting treatment due to cervical pain and collapse. At the time of euthanasia, blood work was not supportive of a relapse of multiple myeloma. To the authors' knowledge, this is the first report of multiple myeloma involving the gastrointestinal tract in a dog.

KEYWORDS
haematochezia, Kappa, Lambda, melena, MUM1, plasma cell

## 1 | INTRODUCTION

Multiple myeloma is a neoplasm resulting from systemic proliferation of malignant plasma cells or their precursors and accounts for 8% of canine haematopoietic tumours (Matus et al., 1986). Dogs with multiple myeloma commonly have bleeding diatheses and of those, gastrointestinal tract bleeding is documented in approximately 20% of cases (Caldin et al., 2019). The cause of bleeding is thought to be multifactorial, but important mechanisms include an excess of complete or incomplete serum immunoglobulin molecules (the M component), which impede platelet aggregation, and cause serum hyperviscosity, which reduces availability of clotting factors; thrombocytopenia also occurs in some cases (Matus et al., 1986). However, specific evaluation of the cause of bleeding from the gastrointestinal tract has not been performed to date.

We report the clinical presentation, investigative findings and successful treatment of a dog with multiple myeloma that also included involvement of its gastrointestinal tract.

## 2 | CASE HISTORY

A 10-year-old, entire male, English Springer Spaniel, was referred for evaluation of a six month history of diarrhoea, gastrointestinal tract

blood loss (melena and haematochezia), weight loss, polyuria and polydipsia. The dog had been rescued from within the United Kingdom and was under the care of a charity at the time of referral.

Investigations performed two weeks prior to referral had demonstrated hyperglobulinaemia, hypoalbuminaemia, hypocholesterolaemia, a mild non-regenerative anaemia and an increased urine protein:creatinine ratio (UPCR). Treatment had included metronidazole (Metrobactin; Dechra) administration, resulting in improvement of the diarrhoea; however, relapse had recurred rapidly following treatment cessation. A hydrolysed diet trial (Hill's Prescription Diet z/d) had not resulted in clinical improvement.

On referral to our institution, pertinent findings included bilaterally enlarged and torturous retinal vasculature and a body condition score of 3/9.

Venous blood gas analysis, blood coagulation testing (prothrombin time and activated partial thromboplastin time), testing for *Angiostrongylus vasorum* (Angio Detect, Idexx UK), *Dirofilaria immitis*, *Ehrlichia canis* and *ewingii*, *Anaplasma phagocytophilum* and *platus*, and *Borrelia burgdoferi* (SNAP 4Dx, Idexx UK) were unremarkable and the dog was normotensive. Complete blood count, serum biochemistry and urine analysis/culture documented an ongoing progressive non-regenerative anaemia (packed cell volume [PCV] 24.7%; reference interval [RI] 37.0–55.0%), hyperglobulinaemia (99.9 g/L; RI 19–46 g/L), hypoalbuminaemia (15.3 g/L; RI 26–40 g/L), hypocholesterolaemia (1.8 mmol/L; RI 2.8–8.3 mmol/L), hypotriglyceridaemia (0.28 mmol/l; RI 0.34–1.97 mmol/l) and proteinuria (UPCR 2.26; RI 0-0.5). A *Leishmania* ELISA was negative and serum protein electrophoresis detected a tall double peak spanning the beta/gamma junction. A computed tomography scan of the neck, thorax and abdomen identified osteolytic lesions of the right 7th rib, left 5th rib, 6th and 9th thoracic vertebrae, right humeral head, and left wing of the 1st sacral vertebra, mild splenomegaly, abdominal lymphadenopathy and bilateral renal infarcts. There was no evidence of gastrointestinal tract mass lesions and ultrasonography of the gastrointestinal tract was unremarkable. Splenic and mesenteric lymph node cytology detected a predominance of plasma cells, present in clusters and individually with occasional binucleated forms present. Cytology and histopathology from the bone marrow showed plasmacytosis >20%; both myeloid and erythroid lineages were orderly and complete.

An upper and lower gastrointestinal tract endoscopy detected diffuse superficial mucosal haemorrhages throughout the duodenum, ileum, ascending, transverse and descending colon (Figure 1). Duodenal endoscopic biopsies demonstrated evidence of mild villous blunting and a marked increase in plasma cells within the lamina propria and to a lesser degree, lymphocytes. In the ileum, the villi were broadened and the lamina propria was infiltrated with well-differentiated monomorphic plasmacytoid cells. This cellular infiltrate extended into the deep lamina propria, resulting in marked separation of the crypts, which were reduced in numbers. In the colon, there was marked expansion of the lamina propria by large numbers of monomorphic, well-differentiated plasmacytoid cells, again resulting in crypt separation. Immunohistochemistry of the duodenal, ileal and colonic biopsies detected diffuse strong positive labelling of the plasmacytoid population to MUM1 and 100% of the infiltrating round cell population labelled positively to Lambda but did not label to Kappa (Figures 2–4).

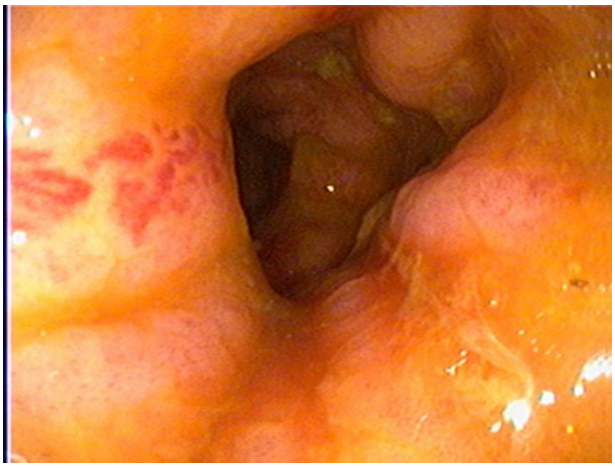

**FIGURE 1** Endoscopic photo of the colon demonstrating the multifocal mucosal haemorrhages that were identified

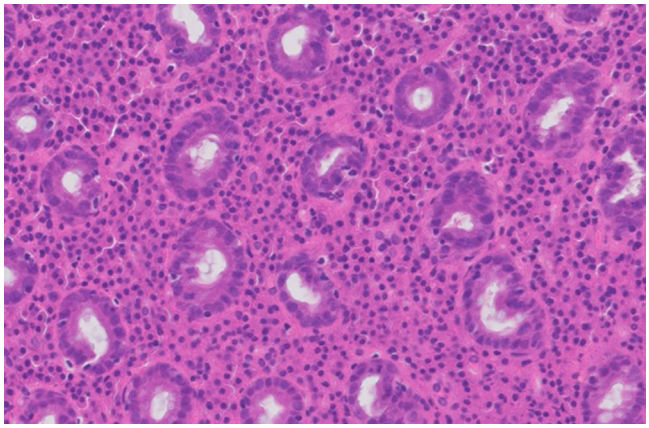

**FIGURE 2** Histopathology image of the colonic biopsies, demonstrating the dense plasma cell infiltrates (magnification ×40)

The dog was diagnosed with multiple myeloma and serum hyperviscosity syndrome, with secondary involvement of the gastrointestinal tract. He was started on prednisolone (2 mg/kg, per os [PO] q 24 h) (Prednidale; Dechra) and melphalan (2 mg, PO q 24 h, reducing to 2 mg PO q 48 h after two weeks) (Alkeran, Veenak) and a short course of metronidazole (10 mg/kg PO q 12 h) was given on initiation of treatment. Complete resolution of clinical signs occurred, and the dog gained weight. However, due to diarrhoea relapse, a repeat course of metronidazole was prescribed leading to acute resolution. The dog was in complete clinical remission seven weeks after starting melphalan/prednisolone, with resolution of the previous haematological/biochemical alterations and proteinuria present at diagnosis and the prednisolone dose was tapered. The dog had intermittent diarrhoea relapses, which resolved each time with short courses of metronidazole.

The dog was euthanised 475 days after starting treatment for multiple myeloma at the referring veterinary practice, due to acute collapse

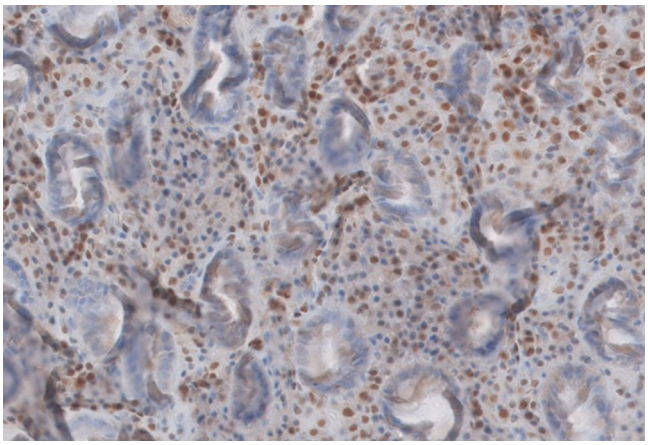

**FIGURE 3** Histopathology image of the colonic biopsies, demonstrating the positive staining to MUM1 (magnification ×40)

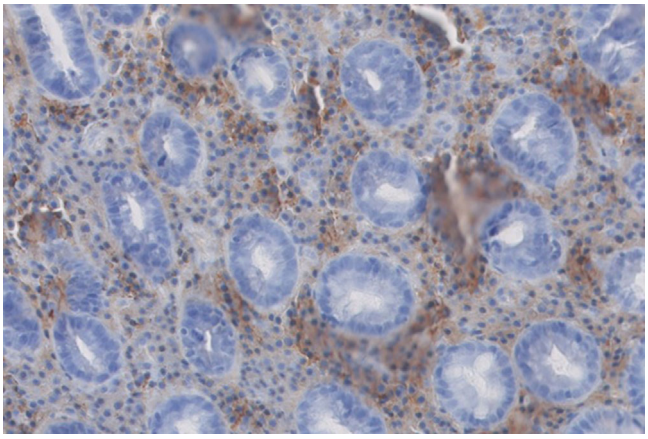

**FIGURE 4** Histopathology image of the colonic biopsies, demonstrating the positive staining to Lambda (magnification ×40)

and development of neck pain. At the time of euthanasia, the dog was still receiving melphalan (2 mg, PO q 48 h) and prednisolone (0.25 mg/kg PO q 72 h). Blood work at this time was not supportive of multiple myeloma relapse but this could not be definitively excluded based on the investigations performed at the time.

## 3 | DISCUSSION

Dogs with multiple myeloma commonly have evidence of bleeding diatheses at diagnosis, with a frequency of 18–42% reported and of those, approximately 20% have gastrointestinal tract involvement (Caldin et al., 2019; Fernández & Chon, 2018; Matus et al., 1986). Dogs with bleeding diatheses appear to have an improved short-term prognosis compared to those without (Caldin et al., 2019). The cause of bleeding is thought to be due to serum hyperviscosity leading to reduction in coagulation factors, the inhibitory interference of the M component on platelet aggregation and thrombocytopenia but specific research into this has not been performed (Matus et al., 1986). In this case, thrombocytopenia was not present and coagulation times were normal, as such, the bleeding was presumed to have occurred from multiple myeloma infiltration of the gastrointestinal tract due to the evidence of endoscopic mucosal haemorrhages.

Although gastrointestinal tract inflammation can result in an increase in plasma cell numbers within the lamina propria of the mucosa in dogs, this is accompanied by a concurrent lymphocytic infiltrate (Washabau et al., 2010). The polyclonal nature of lymphocytic-plasmacytic inflammation, will involve both Lambda and Kappa light chain-producing plasma cells, compared to neoplastic plasma cell infiltration, in which monotypic light chain production occurs (Foiani et al., 2020). In this case, the marked plasma cell infiltration of the gastrointestinal tract mucosa, which only labelled to Lambda not Kappa, was not accompanied by a concurrent similar lymphocytic infiltration, supporting the conclusion that the dog had a clonal plasma cell infiltration secondary to multiple myeloma, rather than an inflammatory enteropathy.

In humans, multiple myeloma involvement of the gastrointestinal tract is rare and results in development of plasmacytoma formation, rather than diffuse plasma cell infiltration of the intestinal tract (Gravina et al., 2013; Suvannasankha et al., 2008; Yasuda et al., 2001). Gastrointestinal tract involvement occurs later in the disease course and is associated with shorter periods of remission (Talamo et al., 2006).

Neoplastic plasma cell involvement of the gastrointestinal tract has been previously documented in dogs, but to date, only the formation of discrete, extramedullary plasmacytomas have been reported; these can be IgG-secreting, resulting in a monoclonal gammopathy, and can metastasise to local lymph nodes in the manner of a solid tumour, rather than forming part of a systemic, multiorgan disease process (Atherton et al., 2017; Jackson et al., 1994; Trevor et al., 1993). To the authors' knowledge, involvement of the gastrointestinal tract secondary to multiple myeloma in the dog has not been previously reported, nor has neoplastic intestinal plasma cell infiltration been documented in the absence of mass lesions. In this case, neither gastrointestinal tract involvement nor bleeding significantly affected the dog's prognosis, since not only was clinical remission obtained shortly after starting treatment, but the dog survived for >15 months following diagnosis (Matus et al., 1986).

Although clinical and biochemical remission was achieved in this case, intermittent flares of diarrhoea that responded to metronidazole did occur. In humans with multiple myeloma, not only can dysbiosis result in progression of disease but additionally melphalan use can affect the gastrointestinal tract microbiome, with the faecal bacteriome being found to correlate with the incidence of diarrhoea occurring in these patients (Ahmed et al., 2020; El Jurdi et al., 2019). It is possible that this also occurs in dogs, which could be why our case responded to metronidazole. However, further studies assessing the faecal microbiome in dogs with multiple myeloma and during treatment with melphalan would need to be conducted to define this further.

In conclusion, this report documents that multiple myeloma can involve diffuse infiltration of the canine gastrointestinal tract and demonstrates that endoscopy be considered as part of the

investigations when gastrointestinal tract signs are present. An additional, and key component of the gastrointestinal haemorrhage in these cases may be due to direct infiltration of the gastrointestinal tract, rather than M component mediated effects. Involvement of the gastrointestinal tract does not appear to influence prognosis as clinical remission can still be achieved and there does not appear to be an effect on short to mid-term prognosis.

## AUTHOR CONTRIBUTIONS

Emma Roberts: Conceptualisation; investigation; writing – original draft. Alex Shirlow: Investigation; writing – review & editing. Alistair Cox: Investigation; writing – review & editing. Owen Davies: Investigation; writing – review & editing.

## ACKNOWLEDGEMENTS

The authors of the paper would like to thank the charity 'Spaniel Aid UK', Jessica Reader (the veterinary surgeon in charge of this case in primary care practice), as well as Elizabeth J Reeve, for her help with the diagnostic imaging performed in this case.

## CONFLICT OF INTEREST

No external funding was received, and the authors declare that there were no conflicts of interest.

## FUNDING STATEMENT

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

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required due to the nature of this case report.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.927.

## ORCID

*Emma Roberts* https://orcid.org/0000-0002-3157-9671

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**How to cite this article:** Roberts, E., Shirlow, A., Cox, A., & Davies, O. (2022). Multiple myeloma involving the gastrointestinal tract in an English Springer Spaniel. *Veterinary Medicine and Science*, *8*, 2273–2276. https://doi.org/10.1002/vms3.927