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# Running head: FINDINGS IN DOGS WITH MUTLIPLE MYELOMA

1	Original Investigation
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3	Neurological signs and magnetic resonance imaging findings in twelve dogs with multiple
4	myeloma
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23	Keywords: canine, neoplasia, spinal.

#### **Abstract**

Vertebral lesions and associated neurological signs occur in dogs with multiple myeloma, however, veterinary literature describing magnetic resonance imaging (MRI) findings is currently lacking. The objective of this retrospective case series was to evaluate neurological signs and MRI findings in dogs with multiple myeloma, which presented for spinal pain or other neurological deficits.

Electronic records of four veterinary referral hospitals were reviewed. Dogs were included on the basis they had confirmed diagnosis of multiple myeloma, had presented for spinal pain or other neurological signs, and had undergone MRI of the vertebral column. MRI studies were evaluated and the anatomical location of lesion(s), signal intensity, presence of extra-dural material, degree of spinal cord compression, extent of vertebral lesions, and contrast enhancement were recorded.

Twelve dogs were included; most dogs (n = 8) had a chronic progressive history, with varying degrees of proprioceptive ataxia and paresis (n = 11), and spinal pain was a feature in all dogs. MRI findings were variable but more consistent features included the presence of multiple expansile vertebral lesions without extension beyond the outer cortical limits of affected vertebrae, and associated extradural material causing spinal cord compression. The majority of lesions were hyper- to isointense on T2 (n = 12) and T1-weighted (n = 8) sequences, with variable but homogenous contrast-enhancement (n = 12).

The MRI characteristics of multiple myeloma may be used to aid early identification and guide subsequent confirmatory diagnostic steps, to ultimately improve therapeutic approach and long-term outcome.

# Introduction

Multiple myeloma is a malignant disorder characterised by systemic proliferation of neoplastic plasma cells. <sup>1–3</sup> This haematopoietic neoplasm has a predilection for bone marrow of the axial skeleton and is the most important myeloma-related disorder in dogs based on incidence and severity. <sup>3</sup> Neoplastic cells involved with multiple myeloma are usually functional and secrete an overabundance of a single type or component of immunoglobulin, otherwise known as M-component. <sup>1,3</sup> Clinical signs ultimately depend on the location of neoplastic cellular infiltration as well as circulating levels of M-component. <sup>4</sup> Therefore, patients can present with variable or non-specific clinical signs including lethargy and weakness, which can be misleading and make diagnostic investigation challenging. <sup>1,5</sup>

The criteria for diagnosis of multiple myeloma includes at least two of the following: histopathological evidence of bone marrow plasmacytosis, detection of a monoclonal gammopathy in serum or urine, detection of light chain (Bence-Jones) proteinuria, and evidence of multiple osteolytic bone lesions. <sup>2,4</sup> Between 25-75% of dogs affected with multiple myeloma have radiographic evidence of bony lesions. <sup>3</sup> Furthermore, approximately 50% of dogs with vertebral involvement have neurological manifestation of disease; spinal pain with accompanying neurological deficits are common clinical findings. <sup>4,5</sup> Multiple myeloma is associated with a number of other clinicopathologic abnormalities including hyperviscosity syndrome (HVS), hypercalcaemia and renal insufficiency. <sup>1,3–5</sup>

Rusbridge and colleagues (1999) previously described clinical, neurological and radiographic findings in eight dogs affected by vertebral plasma cell tumours which presented with spinal pain and other neurological deficits.<sup>2</sup> None of the study subjects underwent magnetic resonance imaging (MRI) however. Kippenes and colleagues (1999)

previously reported MRI findings in dogs with vertebral tumours but only two of the dogs were diagnosed with vertebral plasmacytomas. MRI offers several advantages over radiography as a diagnostic imaging modality for investigation of spinal disease, and is considered part of the 'gold standard' imaging for human multiple myeloma patients. Veterinary literature describing MRI findings in dogs diagnosed with multiple myeloma is currently lacking.

By characterising the clinical and MRI features in dogs with multiple myeloma, this may aid early identification and guide subsequent confirmatory diagnostic steps; earlier diagnosis and treatment may improve long-term outcome. MRI examination features may also have prognostic implications and could prove useful in monitoring response to treatment. Purpose of this study was to retrospectively evaluate neurological signs and MRI findings in dogs diagnosed multiple myeloma, which presented for spinal pain or other neurological signs.

# **Materials and Methods**

Selection and description of subjects

The study is based on a retrospective case series design and was granted ethical approval by the Clinical Research Ethical Review Board of the primary study institution (protocol number URN 2016 1635b). The electronic records of four large veterinary referral hospitals in the UK were reviewed between March 2005 and July 2017 to identify dogs diagnosed with multiple myeloma. All study dogs were client-owned and had presented for further investigation of suspected spinal disease. Dogs were included on the basis they had a confirmed diagnosis of multiple myeloma based on previously published criteria.<sup>2,4</sup> had

presented for spinal pain or other neurological signs with or without additional signs of systemic illness, and had undergone MRI examination of the vertebral column. Dogs were excluded if medical records or imaging studies were incomplete, or if diagnostic criteria of multiple myeloma were not met.

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#### Magnetic resonance imaging studies

Although protocols and sequences could vary between institutions, MRI studies were completed with dogs under inhalational general anaesthesia using a 1.5 Tesla MRI unit (Intera, Philips Medical Systems, Eindhoven, Netherlands; Signa GE Medical Systems, Milwaukee, USA; Siemens Symphony, Camberley, UK; Siemens Magnetom, Erlangen, Germany). All dogs underwent 2D acquisition studies which included a minimum of fast spin-echo (FSE) T2-weighted (T2W) (time of repetition, TR 3000-3700ms/ time of echo, TE 83-120ms) and T1-weighted (T1W) (TR 400-620ms/ TE 8-15ms) sequences. FSE T1weighted sequences were also completed immediately following manual administration of intravenous gadolinium (T1WGd) (0.1mmol/kg gadopentetate dimeglumine). Sequences in sagittal and transverse planes were available in all dogs. Slice thickness was 2-4mm with an inter-slice gap of 2.3-4.3mm in the sagittal plane, and slice thickness was 2-5mm with an inter-slice gap of 3.3-5.3mm in the transverse plane. Where available, short-tau inversion recovery sequences (STIR) (TR 8.2-26ms/ TE 50-3420ms) were reviewed. All imaging studies were assessed using a PACS workstation DICOM viewer (Osirix Imaging Software, version 3.9.2, Bernex, Switzerland). MRI sequences were independently reviewed and described by a board-certified neurologist (E.B.), and a board-certified radiologist (M.P.), blinded to the clinical history and presenting signs of each case. Anatomical location of lesion(s), signal intensity, presence of extra-dural material, degree of spinal cord compression, extent of vertebral lesions, and contrast enhancement were recorded. Signal

intensity was subjectively categorised as hyperintense, isointense, or hypointense relative to normal spinal cord. The postcontrast enhancement was subjectively categorised as mild when there was contrast enhancement that was hypointense compared to fat tissue on T1W sequences, and marked when the contrast enhancement was isointense to fat tissue on T1W sequences. The contrast enhancement was categorized as homogenous when there was uniform enhancement and heterogeneous when it was dissimilar throughout the enhanced area. Extent of vertebral lesions was based on the presence of signal intensity changes involving one-third, two-thirds, or the entire vertebral structure. Furthermore, the character of vertebral lesions was recorded as either remaining largely within the outer cortical limits of affected vertebrae, or extending beyond them. Finally, degree of spinal cord compression was subjectively graded as mild, moderate or marked if there was a reduction in  $\leq 25\%$ ,  $\leq 50\%$  or > 50% respectively in cross-sectional area of the spinal cord, as measured in transverse section at the point of maximal compression.

#### Data recording and analysis

Information retrieved from medical records included: signalment, history, general physical and neurological examination at presentation, MRI examination findings, results of any adjunctive imaging studies (ultrasound, radiography, computed tomography (CT)), histopathology results, and bone marrow aspirate findings. Post mortem reports where available were reviewed. At the time of initial presentation all dogs were fully examined and their neurological status recorded by a board-certified neurologist or neurology resident-intraining under supervision. Dogs were retrospectively assigned a neurological grade at initial presentation (S.W.). Neurological grade was based on a previously validated system for evaluation of myelopathies as follows: 0, paraplegia with absent deep nociception; 1, paraplegia with absent superficial nociception; 2, paraplegia/ tetraplegia with intact

nociception; 3, non-ambulatory paraparesis/ tetraparesis; 4, ambulatory paraparesis/ tetraparesis and ataxia; 5, spinal pain only; and 6, no dysfunction.<sup>13</sup>

# **Results**

#### Case Subjects

Twelve dogs were included in the study. Dogs had a mean age of 7.7 years at initial presentation (median: 7.3 years, range: 4.4 - 11.9 years) and a mean body weight of 29 kg (median: 28.0 kg, range: 19 - 47 kg). Eight dogs were male (six neutered) and four were female (two neutered). Breeds included Golden Retriever (n = 3), Staffordshire Bull Terrier (n = 2), Cross Breed (n = 1), Doberman (n = 1), Scottish Terrier (n = 1), Cocker Spaniel (n = 1), Flat Coat Retriever (n = 1), Beagle (n = 1), and Rottweiler (n = 1).

#### Clinical Presentation

Duration of clinical signs prior to presentation ranged from one to 42 days (median: 14 days). Most dogs (n = 8) had a chronic progressive history, often with varying degrees of proprioceptive ataxia and paresis (n = 11), and spinal pain was a feature in all dogs. Onset of clinical signs was classified as acute and progressive in a further three dogs. One dog presented with a peracute onset paraplegia with intact nociception; this dog was diagnosed with a pathological compression fracture of the vertebral body of T10 in addition to a diagnosis of multiple myeloma. Neuroanatomical localisation varied but, in most dogs, clinical signs were consistent with a single neuroanatomical localisation (n = 8), and most frequently involved T3-L3 spinal cord segments (n = 7). One other dog exhibited signs consistent with a single neuroanatomical localisation which involved L4-S3 spinal cord segments. Four dogs demonstrated clinical signs which were consistent with a lesion

involving two different neuroanatomical locations based on neurological deficits and presence of spinal pain; these included C1-C5 and C6-T2 spinal cord segments in three dogs, and C1-C5 and L4-S3 spinal cord segments in one dog. An equal proportion of dogs showed evidence of lateralisation of clinical signs. Most dogs (n = 9) were assigned to grade 4 neurological status at initial presentation. One dog presented with spinal pain only and was therefore assigned a grade 5. One dog presented with non-ambulatory paraparesis and was therefore assigned a grade 3. One dog presented paraplegic with intact nociception and was assigned a grade 2. Regarding non-neurological findings, one dog presented with marked polyuria and polydipsia and was diagnosed with IRIS stage III renal failure, <sup>14</sup> two dogs had intermittent pyrexia, and eight dogs demonstrated non-specific signs of lethargy and inappetence.

# Imaging Findings

Solitary vertebral lesions were identified in three dogs (25%) while in the remaining nine dogs (75%), multiple vertebral lesions were identified on MRI. The most frequently affected region was T3-L3 vertebrae with all dogs demonstrating some evidence of pathological change. Seven dogs (58%) each had involvement of C1-C5 vertebrae and L4-S3 vertebrae, while five dogs (42%) had involvement of C6-T2 vertebrae. Eight dogs (67%) had lesions in more than one region of the vertebral column.

MRI appearance of vertebral lesions was associated with variable signal changes which showed no association with duration of clinical signs prior to presentation or any other clinical data. On T2W sequences, vertebral lesions were hyperintense in four dogs (33%), hyper- to isointense in seven dogs (58%), and isointense in one dog when compared to normal spinal cord (Fig. 1A, 2, 3A). On T1W sequences, vertebral lesions were hyperintense

in four dogs (33%), hyper- to isointense in three dogs (25%), iso- to hypointense in four dogs (33%), and isointense in one dog when compared to normal spinal cord (Fig. 1B, 3B). Additional STIR sequences were completed in eleven dogs and revealed lesions as hyperintense when compared to normal spinal cord in all of them (Fig. 3C). Contrast enhancement was present in all cases and was variable in intensity (from mild to marked) but homogeneous (Fig. 1C, 3D). Vertebral lesions were often asymmetrical, and although lesions variably affected all parts of the vertebrae, the vertebral body and arch tended to be more frequently involved. Lesions were often extensive involving two-thirds of vertebral structure in six dogs and the entire vertebral structure in three dogs. Vertebral lesions were generally consistent with expansile mass lesions which did not extend beyond the outer cortical limits of affected vertebra (n = 9) and were responsible for varying degrees of spinal cord compression (Fig. 1). The degree of spinal cord compression was categorised as moderate (n = 6) or marked (n = 6) and there was no association with neurological grade at presentation. One dog was also found to have a compression fracture of the vertebral body of T10.

In all cases on MRI there was evidence of extradural material extending into the vertebral canal causing variable spinal cord compression (Fig. 1). This was detected at a single site in eight dogs (67%) or multiple sites in four dogs (33%), and when present was always found at the same site as a vertebral lesion. Location of extradural material was in the region of T3-L3 vertebrae in nine dogs (75%). Other regions included C1-C5 vertebra in four dogs (33%), C6-T2 vertebra in five dogs (42%) and L4 vertebra to sacral vertebra in five dogs (42%). Extradural material was hyperintense in six dogs (50%), hyper- to isointense in five dogs (42%) and isointense in one dog when compared to normal spinal cord on T2W sequences. On T1W sequences, extradural material was hyperintense in seven dogs (58%), hyper- to isointense in four dogs (33%) and isointense in one dog when compared to normal

spinal cord. Mild to marked homogenous contrast enhancement of extradural material was present in all cases. MRI also identified additional bony lesions affecting ribs (n = 2), occipital bone of the skull (n = 1) and scapula (n = 2), along with enlarged thoracic lymph nodes and hepatic nodules in one case.

Three dogs had CT imaging of the abdomen and thorax following MRI. In two cases, this revealed further vertebral lesions in addition to those identified on MRI, as well as other lesions affecting ribs (n = 1), sacrum (n = 1), scapula (n = 1), and the ileum of the pelvis (n = 1). Seven dogs had radiographic imaging of the abdomen, thorax and vertebral column; lesions were identified affecting ribs, sternum, scapula, sacrum and pelvis and were consistent with those identified on MRI. Four dogs had abdominal ultrasound following MRI which revealed mass lesions affecting the liver (n = 2) and spleen (n = 1); cytological evaluation of fine needle aspirate samples collected from lesions was consistent with a diagnosis of round cell neoplasia in all cases.

Confirmatory antemortem histopathological diagnosis was achieved in nine dogs following biopsy of bony lesions taken from a variety of sites, as identified on diagnostic imaging studies. Biopsy sites included ileum of the pelvis, vertebrae, rib, and scapula. Four dogs were euthanised shortly after diagnosis; post mortem examination was consistent with a diagnosis of multiple myeloma in all cases.

#### Discussion

This study documents the neurological signs and MRI characteristics of dogs with multiple myeloma which presented with spinal pain or other neurological deficits. Although

there was a significant amount of variability in imaging characteristics detected on MRI, some more consistent features identified were the presence of extradural material and multiple expansile vertebral lesions which did not extend beyond the outer cortical limits of affected vertebra, and that were hyper- to isointense on T2W and T1W sequences, and variably but homogenously contrast-enhancing. The imaging features identified in this study may help to distinguish multiple myeloma from other differential diagnosis which include primary vertebral tumours or other less likely causes such as osteomyelitis. In comparison to multiple myeloma, vertebral neoplasms of an osseous lineage often disrupt cortices of affected vertebrae due to bony lysis and proliferation. 11 Primary bone tumours also more frequently involve a single vertebrae in comparison to multiple myeloma which typically resulted in involvement of multiple vertebral segments. 11 Regarding pathological signal intensity changes, replacement of normal bone marrow by oedema and inflammatory or neoplastic cells increases T2W relaxation and is reflected as areas of high signal intensity on T2W sequences. 19 These same pathological changes account for decreased T1W relaxation and hence reveal corresponding areas of low signal intensity, as in the case of osteomyelitis or other vertebral neoplastic lesions. <sup>6,19,20</sup> An unusual feature associated with multiple myeloma however was the fact most lesions showed variable evidence of hyperintensity on T1W sequences, which could be used as an additional identifying feature. This is consistent with previous reports which demonstrated that vertebral plasmacytomas were hyperintense on T1W sequences when compared to spinal cord parenchyma and when also compared to other types of vertebral tumour; one possible explanation is the presence of haemorrhage within myelomatous lesions of the vertebral bone marrow. 6,12,21 Other studies in the human literature have suggested that bone marrow fat cell content of patients affected with early stage multiple myeloma may be increased, which may account for the relative T1W hyperintensity of lesions in certain patients.<sup>8,10</sup> In the current study this theory was not

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supported as corresponding areas were hyperintense on STIR sequences and no association could be found with any imaging characteristics and duration of clinical signs prior to presentation. Repeat imaging to compare and monitor progression of lesion intensity, utilisation of additional MRI sequences such as T2W gradient echo, or histopathological evaluation of lesions would be beneficial to help determine the cause of signal intensity changes. The unique imaging features identified in this study may help to distinguish multiple myeloma from other types of vertebral neoplastic or other less likely infectious lesions and guide subsequent confirmatory diagnostic steps. <sup>6</sup>

The variability in imaging characteristics in the current study may reflect the differences in pathological bony changes associated with different stages of multiple myeloma. In the human literature, between three and five imaging patterns have previously been described based on MRI examination features. 8-10,12 These patterns include normal bone marrow, focal marrow lesions, diffuse homogenous marrow involvement, combined focal and diffuse marrow involvement, or variegated patterns with multiple small lesions on a background of normal marrow. 8-10 Interestingly, the presence of certain MRI patterns has previously been correlated with clinicopathological changes including the percentage bone marrow plasmacytosis and haemoglobin values. 12,22 In addition, MRI patterns also have reported in association with survival data and diffuse marrow infiltration has been correlated with more advanced disease features and increased tumour mass. 8,9,22,23 Due to the small numbers of cases in this study we were unable to consistently identify any specific MRI patterns or correlate lesion characteristics with outcome. Further research utilising a larger study population would be necessary to define any potential MRI patterns and their possible prognostic implications in dogs diagnosed with multiple myeloma which manifest with spinal pain or neurological signs as a presenting complaint.

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In the current study, neurological signs tended to be chronic, progressive, and associated with spinal pain, which is consistent with previous reports.<sup>2,5</sup> One dog was slightly unusual in its clinical presentation and presented with a peracute history. This dog was diagnosed with a pathological compression fracture of the vertebral body of T10 secondary to an osteolytic vertebral lesion. Pathological fractures have previously been reported in association with multiple myeloma.<sup>2</sup> It is important to be aware of this as a potential complication and not exclude the condition as a differential diagnosis despite the uncommon acute clinical presentation. An equal proportion of cases showed evidence of lateralisation of neurological signs and neuroanatomical localisation most frequently localised to T3-L3 spinal cord segments; this was consistent with imaging findings in which most lesions were identified within this region of the vertebral column. The degree of spinal cord compression did not reflect the neurological grade at presentation. This may be explained by the lack of contusive injury which is typically associated with acute spinal cord compressive lesions and can contribute to neurological deterioration. <sup>17</sup> Significant compression of the spinal cord can often be tolerated, particularly in those cases where it occurs slowly over an extended period, such as in the current study. 17,18

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The findings of the current study suggest that multiple myeloma is a condition which most frequently affects middle-aged to older dogs of medium to large breed, which is agreement with the findings from previous literature.<sup>5,15</sup> Earlier reports suggested the German Shepherd Dog breed may be overrepresented.<sup>5</sup> This was not something we appreciated however and this was not a breed represented in the current study. Although males constituted the majority of the study population, it is impossible to comment whether a sex

predilection exists based on the small numbers. Despite this, previous studies have suggested males may be overrepresented.<sup>16</sup>

The study is inherently limited by its retrospective design. The variation in clinical approach and diagnostic imaging protocols between different study organisations may also have introduced an element of systematic bias. This could ultimately have impacted on the conclusions drawn. The small study population also limits the conclusions drawn from the data. Future work utilising a larger study population with standardised diagnostic evaluation and imaging protocol would be of benefit. Based on operator experience in the current study along with previous literature, a minimum of T2W, STIR, T1W and T1WGd sequences should be utilised as standard when performing MRI examination of cases with suspected multiple myeloma. 12,24

In conclusion, the majority of dogs affected by multiple myeloma with vertebral involvement present with a chronic, progressive, painful T3-L3 myelopathy. The degree of spinal cord compression did not reflect the neurological grade of dogs affected. More consistent MRI features associated with multiple myeloma include the presence of extradural material and multiple vertebral lesions which largely remain within cortical limits, and are hyper- to isointense on T2W and T1W sequences, with variable but homogenous contrast enhancement. By recognising these distinguishable imaging characteristics, this may lead to earlier diagnosis and treatment with the possibility of improving long-term outcome. Further research is needed however to define the MRI features and prognostic implications in dogs diagnosed with multiple myeloma which manifest with spinal pain and neurological signs as a presenting complaint.

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352	(b) Acquisition of Data: Sophie Wyatt, Luisa De Risio, Colin Driver, Roberto José-López,
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354	(c) Analysis and Interpretation of Data: Sophie Wyatt, Luisa De Risio, Colin Driver, Roberto
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# **Figure Legends**

Fig. 1. Six-year six-month male entire Cocker Spaniel, presenting with a chronic, 439 440 progressive, painful, non-lateralised C1-T2 myelopathy. Transverse T2-weighted 441 (T2W), A, T1-weighted (T1W), B, and T1W post contrast (T1WGd), C, images. Note the single vertebral lesion which does not extend beyond the cortical limits of the 442 443 affected C4 vertebrae (arrow, 1A). The lesion is hyper- to isointense on T2W and T1W images relative to spinal cord, with moderate homogenous contrast enhancement. 444 There is associated extradural material (asterisk, 1C) causing moderate spinal cord 445 446 compression with extension into the left intervertebral foramen.

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Fig. 2. Ten-year two-month male neutered Scottish Terrier, presenting with a chronic, progressive, painful, non-lateralised T3-L3 myelopathy. Transverse T2-weighted (T2W) images at the level of L3 vertebrae, A, L4 vertebrae, B, L5 vertebrae, C, and L6 vertebrae, D. There are multiple vertebral lesions which largely remain within cortical limits of affected vertebrae (asterisk). Lesions are hyper- to isointense relative to spinal cord and cause variable spinal cord compression from none to marked.

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Fig. 3. Ten-year eight-month male neutered Golden Retriever, presenting with chronic progressive thoracolumbar spinal pain only. Sagittal T2-weighted (T2W), A, transverse T1-weighted (T1W), B, sagittal short tau inversion recovery (STIR), C, and transverse T1W post contrast (T1WGd), D, images. Note the single vertebral lesion affecting L2 vertebral body which is hyperintense on T2W and STIR images, hyper- to isointense on T1W images relative to spinal cord, with mild homogenous contrast enhancement, and marked spinal cord compression at this level (asterisk, 1D).