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TITLE: Clinical presentation, diagnostic findings and outcome in dogs diagnosed with presumptive spinal-only meningoencephalomyelitis of unknown origin

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1 MANUSCRIPT

2

3 **Structured summary**

4

5 **Objectives** - Although difficult to clinically diagnose, presumptive meningomyelitis
6 of unknown origin (MMUO) is an important differential diagnosis for dogs presenting
7 with signs of spinal cord dysfunction. The aim of this study was to evaluate clinical
8 presentation, diagnostic findings and long-term outcome for dogs clinically diagnosed
9 with MMUO.

10 **Methods** - Medical records were reviewed for dogs diagnosed with presumptive
11 MMUO between 2006 and 2015.

12 **Results** - Twenty-one dogs met the inclusion criteria. The majority of dogs presented
13 with an acute (43%) or chronic (52%) onset of neurological signs. Ambulatory paresis
14 was the most common neurological presentation (67%). Neurological examination
15 most commonly revealed a T3-L3 myelopathy, and spinal hyperaesthesia was a
16 common finding (71%). A spinal cord lesion was visible in 90% of cases on MR
17 imaging. Lesions were typically extensive, ill-defined, hyperintense on T2-weighted
18 and isointense on T1-weighted images. Eighteen lesions (86%) showed parenchymal
19 contrast enhancement and 17 lesions (81%) showed contrast enhancement of
20 overlying meninges. All dogs were treated with immunosuppressive doses of
21 glucocorticosteroids, sometimes combined with cytosine arabinoside. At time of data
22 capture, 10/21 dogs (48%) had died or been euthanized because of MMUO. Overall
23 median survival time was 669 days.

24 **Impact** - MMUO should be considered in the differential diagnosis of dogs
25 presenting with an acute or chronic, progressive, and potentially painful myelopathy.

26 MRI features can possible help to distinguish presumptive MMUO from other more
27 common spinal diseases. Overall, long-term survival is guarded, approximately 50%
28 of dogs will die or be euthanized because of MMUO regardless of
29 immunosuppressive treatment.

30

31 **Keywords**

32 MRI, inflammatory CNS disease, GME, cytosine arabinoside, glucocorticosteroids

33

34 **Introduction**

35 Pure myelitis (inflammation of spinal cord parenchyma) or meningomyelitis
36 (inflammation of spinal cord parenchyma and surrounding meninges) are rare
37 diseases in small animals and occur commonly in combination with inflammatory
38 brain disease (Tipold and Stein 2010). Viruses (canine distemper virus, feline
39 coronavirus), bacteria (*Staphylococcus* spp., *Streptococcus* spp., *Pasteurella*,
40 coliforms, *Actinomyces*, *Nocardia* spp.), fungi (*Cryptococcus*, *Coccidioides* spp.,
41 *Blastomyces*, *Histoplasma*), rickettsiae (*Ehrlichia*, *Rickettsia*, Rocky Mountain
42 spotted fever), protozoa (*Toxoplasma gondii*, *Neospora caninum*), parasites
43 (*Dirofilaria immitis*, *Cuterebra*, *Angiostrongylus vasorum*) and algae (*Prototheca*
44 *wickerhamii*, *Prototheca zopfii*) are known causes for meningomyelitis in dogs and
45 cats, with or without concurrent intracranial signs (Dewey 2016; Csebi *et al.* 2010;
46 Parry *et al.* 2009; Griffin *et al.* 2008). Apart from infectious causes, non-infectious
47 meningomyelitis including granulomatous meningoencephalomyelitis,
48 pyogranulomatous meningoencephalomyelitis and steroid-responsive meningitis-
49 arteritis (SRMA) are described (Dewey 2016; Parry *et al.* 2009; Griffin *et al.* 2008;
50 Meric 1988). In agreement with the terminology for meningoencephalitis of unknown
51 origin (MUO), dogs clinically diagnosed with non-infectious inflammatory myelitis
52 that did not have positive infectious disease testing, that were not classified as SRMA
53 or eosinophilic meningomyelitis, and that were not histopathologically confirmed,
54 were named meningomyelitis of unknown origin (MMUO). A clinical diagnosis of
55 MMUO is typically made by a combination of clinical presentation, imaging of the
56 vertebral column, and results of cerebrospinal fluid (CSF) analysis (Griffin *et al.*
57 2008).

58 Currently, only one previous study has focused specifically on the clinical
59 presentation, diagnostic findings, and outcome in dogs with meningomyelitis caused
60 by a variety of underlying aetiologies (Griffin *et al.* 2008). Twenty-eight cases were
61 included, of which 15 dogs were diagnosed with MMUO. Clinical signs were
62 reflected by the affected spinal cord segments, and younger dogs, toy breeds, and
63 hound breeds were suggested to be predisposed for meningomyelitis. Although results
64 of myelography, computed tomography (CT), and CT-myelography have been
65 reported, little is known about magnetic resonance imaging (MRI) findings in dogs
66 with MMUO. The aims of this study were therefore to describe the signalment,
67 clinical presentation, diagnostic findings, including results of MRI, and long-term
68 survival in dogs diagnosed with presumptive MMUO without concurrent clinical
69 signs of intracranial (Deleted: It was hypothesized that dogs diagnosed with MMUO
70 could be of any breed, gender or age, that they would present generally with severe
71 neurological dysfunction but without spinal hyperaesthesia and that their long-term
72 prognosis is guarded to good).

73

74

75

76 **Materials and methods**

77 *Case selection*

78 The electronic medical database was searched between March 2006 and February
79 2015 for dogs diagnosed with “MUA”, “MUO”, “GME”, “myelitis”, “inflammatory
80 spinal cord disease”. Dogs were included based on the criteria used by Granger *et al.*
81 (2010), if they had (1) complete medical records available, (2) a complete
82 neurological examination performed leading to a spinal cord localisation, (3)

83 inflammatory CSF analysis, (4) MRI of the spinal cord, and if (5) long-term follow-up
84 information was available through revision of medical records or through contacting
85 the referring veterinarian by telephone. Dogs were excluded if (1) the clinical records
86 or imaging studies were incomplete or not available for review, (2) dogs showed
87 clinical or neurological signs of intracranial involvement at time of presentation, (3)
88 they had a peracute onset of clinical signs that were not progressive after 12-24 hours,
89 (4) they had signs of extradural or extradural/intramedullary spinal cord compression
90 on MRI and if (5) they had positive infectious disease titres or if clinical presentation,
91 CSF analysis or necropsy findings were suggestive of SRMA or eosinophilic
92 meningoencephalomyelitis (>10% eosinophils in CSF) (Dewey 2016). Typical
93 clinical presentation for SRMA was considered to be a dog less than 2 years of age of
94 a typical dog breed (Boxer, Beagle, Bernese Mountain dog, Nova Scotia Duck Tolling
95 Retriever, Golden Retriever, German Shorthaired Pointed) presenting with pyrexia
96 and cervical hyperesthesia. CSF analysis in SRMA is typically revealing a
97 predominantly neutrophilic pleocytosis (Dewey 2016). Dogs with histopathological
98 confirmation of the disease (granulomatous meningo(encephalo)myelitis (GMEM) or
99 necrotising meningo(encephalo)myelitis (NMEM)) only needed to fulfil inclusion
100 criteria (1) and (5). Information retrieved from the medical records included breed,
101 gender, age at diagnosis, body weight, results of neurological examination including
102 neuroanatomical localisation, duration of clinical signs prior to diagnosis, results of
103 complete blood count (CBC) and biochemistry profile, results of CSF analysis
104 including total nucleated cell count (TNCC), white blood cell differentiation and total
105 protein (TP) concentration, treatment received, and outcome. (Deleted: Based on body
106 weight, dogs were divided in small/medium (<15kg) and large breed dogs (>15kg).
107 For dog breeds in which the body weight varied around 15kg, mean body weight for

108 male and female dogs as reported on the Kennel Club website
109 (<http://www.thekennelclub.org.uk/services/public/breed/standard-find.aspx>) were
110 used to consider them large or medium/small breed dogs). Duration of clinical signs
111 prior to diagnosis (days) was classified as peracute (<2 days), acute (2–7 days) or
112 chronic (>7 days). For dogs that had CSF analysis performed, site of collection
113 (cisternal or lumbar), TNCC, TP and cytological differentiation were recorded. Total
114 nucleated cell count was considered normal if < 5 cells/mm³. Protein concentration
115 was considered normal for a cisternal collection if < 0,25 g/l and for a lumbar
116 collection if < 0,4 g/l.

117

118 *Neurological assessment*

119 The neurological status was classified from 0 to 5 according to the clinical
120 examination (adapted from Scott *et al.* 1997): grade 0 = neurologically normal; grade
121 1 = spinal hyperesthesia without neurological deficits; grade 2 = ataxia, ambulatory
122 para- or tetraparesis; grade 3 = non- ambulatory para- or tetraparesis; grade 4 = para-
123 or tetraplegia with or with- out bladder control, and intact deep pain sensation; grade
124 5 = para- or tetraplegia, urine retention or overflow, and deep pain sensation loss.
125 Possible neuroanatomical localizations included C1-C5, C6-T2, T3-L3 or L4-S3
126 spinal cord segments. Dogs were diagnosed with a focal lesion if only one spinal cord
127 segment was affected, and with a multifocal lesion if more then one spinal cord
128 segment appeared to be affected on the neurological examination.

129

130 *Magnetic resonance imaging*

131 Magnetic resonance imaging was performed under general anaesthesia with a
132 permanent 1.5T magnet (Intera, Philips Medical Systems, Eindhoven, the

133 Netherlands) and all images were reviewed by the corresponding author using Osirix
134 Dicom viewer (Osirix Foundation, V.5.5.2 Geneva, Switzerland). Sequences could
135 vary, but studies included a minimum of T2-weighted (T2W) (repetition time (ms)
136 (TR)/echo time (ms) (TE), 3000/120) and T1-weighted (T1W) (TR/TE, 400/8) images
137 of the affected spinal cord region in a sagittal and transverse plane. The T1W images
138 were acquired before and after IV administration of paramagnetic contrast medium
139 (0,1 mg/kg, gadoterate meglumine, Dotarem, Guerbet). If MR images of the brain
140 were present, they were reviewed concurrently. Variables recorded were lesion
141 intensity on T2W and T1W images, lesion localization and distribution, lesion length
142 and presence of parenchymal and/or meningeal contrast enhancement. Lesion length
143 was measured using Osirix Dicom viewer, and performed on sagittal T2W images for
144 dogs that had focal lesions. Lesion length was measured twice, and the mean value
145 between both was used. To compensate for differences in body size, values were
146 corrected towards length of vertebral body of C6 (for cervical lesions) or L2 (for
147 thoracolumbar lesions). Vertebral body length was measured on T1W sagittal images.
148

149 *Treatment and follow-up*

150 For all dogs, the specific treatment protocol was recorded. During hospitalisation, all
151 dogs underwent daily at least one general physical and complete neurological
152 examination by a board-certified neurologist or neurology resident. The results of the
153 neurological examination as well as response to treatment (improvement,
154 deterioration or static status) were systematically recorded on the kennel sheets.
155 Follow-up information during hospitalisation was collected from the medical records,
156 and afterwards through medical records of re-examination visits or telephone contact
157 with the referring veterinarian. A successful outcome was defined as the dog being

158 ambulatory, fecal and urinary continent and, according to the owners, without signs of
159 overt spinal hyperaesthesia. An unsuccessful outcome was defined as (1) deterioration
160 in neurological status by one or more grades after diagnosis and treatment, or (2) if
161 the dog was not independently ambulatory, possibly with previously non-existing or
162 worsening fecal and/or urinary incontinence, or was experiencing spinal
163 hyperaesthesia as defined by the owner.

164

165 *Statistical analysis*

166 Data analysis was performed with the aid of a standard statistical software package
167 (Prism, Graphpad Software Inc). (Deleted: A Mann-Whitney *U* test was used to
168 compare age, duration of clinical signs prior to diagnosis, and TNCC in CSF between
169 small/medium and large breed dogs. A fisher's exact test was used to compare
170 differences in sex and neuroanatomical localization between small/medium and large
171 breed dogs.) Regarding outcome, a Mann-Whitney *U* test was used to evaluate effect
172 of relative lesion length on long-term outcome. A fisher's exact test was used to
173 evaluate the effect of pain, presence of lymphopenia and additional administration of
174 cytosine arabinoside on outcome. Numeric variables were expressed as median and
175 interquartile ranges (IQR). Values of $P < 0.05$ were considered significant. Survival
176 analysis was performed using both a Log-rank (Mantel-Cox) and Gehan-Breslow-
177 Wilcoxin test, resulting in median survival time (MST) calculation and a Kaplan-
178 Meier survival curve. (Deleted: comparing survival percentage in small/medium and
179 large breed dogs, and presenting overall survival
180 One-way NOVA was used to evaluate significant differences between affected
181 regions on neurological examination.) Survival was defined as time from diagnosis to
182 death or euthanasia, including whether this happened because of disease progression

183 or due to unrelated causes, or time from diagnosis to data collection for dogs that
184 were alive at time of data capture. Dogs that died because of unrelated causes and
185 dogs that were still alive at time of data capture were censored for survival analysis.

186

187 **Results**

188 *Signalment*

189 Twenty-one dogs were included in the study. (Deleted: Thirteen dogs (62%) were
190 large breeds and 8 dogs (38%) were considered small/medium breed dogs)
191 Represented breeds included French Bulldog (n=2), Jack Russell Terrier (n=2), Lhasa
192 Apso (n=2) and one each of Akita, Bearded Collie, Boxer, Bull Mastiff, Chihuahua,
193 cross breed, English Springer Spaniel, Giant Schnauzer, Labrador Retriever, Maltese
194 Terrier, Rhodesian Ridgeback, Rottweiler, Shih Tzu, West Highland White Terrier
195 and Yorkshire Terrier. Overall, median age at presentation was 56 months (10 – 128
196 months). (Deleted: There was no significant difference in age at presentation between
197 small/medium and large breed dogs (P=0.358).)Thirteen dogs (62%) were male and 8
198 dogs (38%) were female. Compared to the general hospital population between March
199 2006 and February 2015, there was no significant difference in sex distribution in the
200 group of dogs with MMUO (P=0.075). Median duration of clinical signs prior to
201 diagnosis was 8 days (ranging from 1-90 days). One dog (5%) presented with
202 peracute, 9 dogs (43%) with acute and 11 dogs (52%) with a chronic onset of
203 neurological signs.

204

205 *Neurological examination*

206 Thirteen (62%) and 8 (38%) dogs were diagnosed with a focal and multifocal spinal
207 lesion on neurological examination, respectively. (Deleted: Small/medium breed dogs

208 presented significantly more with a focal spinal cord lesion on the neuroanatomical
209 localisation compared to large breed dogs (P=0.049.) Regarding dogs with focal
210 spinal lesions (n=13), 3 dogs were diagnosed with a lesion affecting the C1-C5 spinal
211 cord segments, 2 dogs with a lesion affecting the C6-T2 spinal cord segments, 6 dogs
212 with a lesion affecting the T3-L3 spinal cord segments and 2 dogs with a lesion
213 affecting the L4-S3 spinal cord segments. At time of diagnosis, no dogs presented as
214 grade 0; 2 dogs (10%) were grade 1; 14 dogs (67%) grade 2; and 5 dogs (24%) grade
215 3. No dogs were found to have paraplegia or tetraplegia at time of presentation. Pain
216 on direct spinal palpation was present in 15 (71%) dogs. Urinary retention was seen in
217 2 dogs (10%), and a combination of urinary and faecal incontinence was noticed in 2
218 dogs (10%). One dog (5%) developed seizures 669 days after diagnosis of MMUO.
219 An overview of the clinical findings of the 21 included dogs, can be consulted in table
220 1.

221

222 *Diagnostic findings*

223 As required by the inclusion criteria, CSF collection revealed a pleocytosis in all
224 cases. Overall, median TNCC was 209 cells/mm³ (ranging from 6 – 6000). Total
225 protein measurement was performed in all but 3 CSF samples, and was above
226 reference values in 17/18 dogs (94%). The median TP concentration was 1.67 g/l
227 (ranging from 0.21-16.3 g/l). Complete blood count and serum biochemistry results
228 were available in 16 dogs (76%). Leucocytosis was only present in 2 dogs (10%) and
229 lymphopenia was present in 6 dogs (29%). Infectious disease testing based on
230 serology and/or polymerase chain reaction (PCR) on CSF for Canine Distemper Virus
231 (CDV), *Toxoplasma gondii*, and *Neospora caninum* was not performed in 2 (10%)

232 dogs and was negative in the remaining 19 (90%) dogs. In the 2 dogs with lacking
233 infectious disease testing, full necropsy was performed, revealing GMEM.

234

235 *Magnetic resonance imaging*

236 Magnetic resonance imaging of the spinal cord was available in all cases, revealing a
237 focal lesion in 15 dogs (71%), a multifocal lesion in 4 dogs (19%) and no lesion was
238 visible on sagittal T2W or T1W images in 2 dogs (10%). Lesion length was measured
239 in the focal cases only. Median lesion/vertebral body ratio was 4.8 (ranging from 0.6
240 – 10.9). All visible lesions were ill-defined, intramedullary, hyperintense on T2W
241 images and isointense on T1W images (Figure 1 and 2). Lesions showed parenchymal
242 contrast enhancement in 18 dogs (86%), and contrast enhancement of overlying
243 meninges in 17 dogs (81%). In dogs presenting with spinal hyperaesthesia (n= 15),
244 there was no significant association with the presence of meningeal contrast
245 enhancement on MRI (P=0.24). In the 2 cases where no lesion was visible on sagittal
246 T2W and T1W images, no parenchymal contrast enhancement was seen, but 1 dog
247 only showed meningeal contrast enhancement. In 2 dogs (10%) intracranial images
248 were present within the field of view of the cervical spinal cord images (T2W
249 transverse and sagittal images), revealing multiple T2W hyperintensities in the
250 forebrain and/or brainstem. Neither of those dogs had clinical or neurological signs of
251 intracranial involvement at time of diagnosis. The first dog, a 56-month-old Jack
252 Russell Terrier, never recovered from general anaesthesia after diagnostic procedures,
253 and full necropsy revealed GMEM. The second dog, a 123-month-old Rhodesian
254 Ridgeback, developed seizures 669 days after diagnosis and was euthanized without
255 further investigations.

256

257 *Treatment and outcome*

258 As required by the inclusion criteria, outcome was available in all dogs. As described
259 above, one dog never recovered from general anaesthesia for MRI of the spinal cord,
260 and this dog was censored for survival analysis. Mean duration of hospitalisation was
261 5 days (ranging from 1 – 19 days), with 17 dogs (81%) showing improvement in
262 neurological status within those days. One dog (5%) remained neurologically stable
263 (no improvement nor deterioration), and 3 dogs (14%) showed deterioration of their
264 neurological status. All dogs, including the dog that never recovered from
265 anaesthesia, were treated with immunosuppressive doses of glucocorticosteroids
266 immediately after diagnosis. This consisted of IV dexamethasone (dose ranging from
267 0.3 – 0.5 mg/kg/day) in 9 dogs (43%), and oral prednisolone (dose ranging from 2 – 4
268 mg/kg/day) in 12 dogs (57%). Fourteen dogs (67%) received additional treatment
269 with cytosine arabinoside as a constant rate infusion (CRI) of 200mg/m² over 8 hours
270 in 1 dog (7%) and as 4 subcutaneous (SC) injections of 50mg/m² every 12 hours for 2
271 consecutive days in 13 dogs (93%).

272 Twenty dogs (95%) survived to discharge. Of these dogs, 9 dogs (45%) were still
273 alive at time of data capture. Of these 9 dogs, 8 dogs were neurologically normal
274 according to follow-up information, and 1 dog was still showing ataxia and
275 ambulatory paraparesis. Of the 8 normal dogs, 2 dogs were still receiving
276 cyclosporine 5mg/kg every 24 hours, 1 dog was receiving cytosine arabinoside 50mg/
277 m² every 12 hours for 2 consecutive days every 9 weeks, 1 dog was receiving
278 prednisolone 0.2mg/kg every 24 hours, 1 dog was receiving prednisolone 1mg/kg
279 every 24 hours and cytosine arabinoside 50mg/ m² every 12 hours for 2 consecutive
280 days every 4 weeks, and 3 dogs were not receiving any treatment at time of data
281 capture. The dog that was still showing neurological abnormalities was receiving

282 0.5mg/kg prednisolone every other day and cytosine arabinoside 50mg/ m² every 12
283 hours for 2 consecutive days every 5 weeks. Regarding the 11/20 dogs (55%) that had
284 deceased at time of data capture, 3 dogs died or were euthanized because of disease
285 progression, 6 dogs were euthanized because of acute neurological deterioration after
286 initial neurological improvement, and 2 dogs were euthanized because of unrelated
287 causes (complications after stifle surgery and development of aggression). Dogs that
288 showed acute neurological deterioration after initial improvement did so within a
289 median of 171 days after diagnosis (ranging from 30 – 669 days). Of those 6 dogs, 1
290 dog showed acute deterioration after discontinuation of prednisolone treatment, and 5
291 dogs were still receiving treatment consisting of prednisolone 1mg/kg every 24 hours,
292 prednisolone 0.5mg/kg every 24 hours, prednisolone 2mg/kg every 24 hours and
293 azathioprine 2mg/kg every 24 hours, or cytosine arabinoside 50mg/ m² every 12 hours
294 for 2 consecutive days every 7 weeks. Overall, we can conclude that 10/21 dogs
295 (48%) died or were euthanized because of MMUO.

296 No difference was seen in long-term survival between dogs receiving sole
297 prednisolone therapy or combination therapy with cytosine arabinoside (P=0.31).
298 Overall, the MST was 669 days (ranging from 1 – 2250 days) (Figure 3). (Deleted:
299 There was no difference in survival time (ST) between small/medium and large breed
300 dogs with MMUO (P=0.47) (Figure 2).) No significant difference was seen in relative
301 lesion length on MR imaging between dogs that are alive and dogs that died or were
302 euthanized because of MMUO (P=0.91). Post mortem confirmation was available in 3
303 dogs, revealing GMEM in 2 dogs and necrotising meningomyelitis in 1 dog. All
304 clinical data are summarized in tables 1 and 2.

305

306 **Discussion**

307

308 This study evaluated the clinical presentation, diagnostic findings and long-term
309 survival in 21 dogs diagnosed with presumptive MMUO. Dogs had a median age of 5
310 years at time of diagnosis. A lesion affecting the T3-L3 spinal cord segments resulting
311 in ambulatory paraparesis was considered the most common clinical presentation.
312 However the overall MST was 669 days, 48% of dogs diagnosed with MMUO died or
313 were euthanized because of MMUO, indicating a guarded long-term prognosis.

314

315 To be included in the study, dogs were not allowed to have clinical signs or
316 neurological examination abnormalities suggestive of intracranial involvement.
317 Interestingly, additional MR images of the brain were included in the field of view of
318 the cervical MRI in 2 dogs, showing additional lesions in both cases. One of those
319 dogs, a 123-month-old Rhodesian Ridgeback, developed seizures 669 days after
320 diagnosis despite on-going cytosine arabinoside treatment, and was therefore
321 euthanized. No necropsy was performed, but because intracranial lesions were already
322 present at time of diagnosis, development of MUO was assumed. The other dog, a 56-
323 month-old Jack Russell Terrier, never recovered from general anaesthesia for MR
324 imaging. Necropsy was performed, revealing the presence of GMEM. Because
325 intracranial MR images were only available in 2 dogs, it is currently unclear (1) if
326 these brain abnormalities represent a multifocal nature of the disease or cranial
327 extension of the cervical inflammatory lesions, and (2) if inflammatory brain lesions
328 are currently underdiagnosed in dogs with MMUO and if MMUO could therefore be
329 considered a more generalised inflammatory disease process, a
330 meningoencephalomyelitis.

331

332 Pain on direct spinal palpation was present in 71% of dogs. Spinal pain reflects the
333 involvement of the meninges, and/or vertebrae (vertebral periosteum), and/or nerve
334 roots or spinal nerves (Da Costa 2012). In the present study, the lesions showed
335 meningeal contrast enhancement in 18/21 dogs, but there was no significant
336 association between spinal hyperaesthesia and the presence of meningeal
337 enhancement on MR imaging.

338

339 MRI of the spinal cord revealed no lesion on sagittal T2W and T1W images in 10%
340 of dogs (n=2), which appears similar to the 7% described for the brain in dogs with
341 MUO (Granger *et al.* 2010). In the retrospective study of Griffin *et al.* (2008), only 1
342 dog with meningomyelitis had MRI performed, revealing no abnormalities. Based on
343 these findings, presence of MMUO cannot be ruled out based on unremarkable MRI
344 findings. The first dog was a 42-month-old Bull Mastiff with a one-month history of
345 slowly progressive T3-L3 spinal cord lesion. After diagnostic procedures, the dog was
346 treated with oral prednisolone but continued to deteriorate and was euthanized after 6
347 days. No necropsy was performed. The second dog was a 136-month-old Bearded
348 Collie with a one-week history of a progressive multifocal spinal cord
349 neuroanatomical localisation (T3-S3 spinal cord lesion). The dog showed
350 improvement on treatment with prednisolone and cytosine arabinoside (see table 1)
351 after diagnostic investigations, and was still alive without current treatment 1100 days
352 after diagnosis. Both dogs had inflammatory CSF analysis (increased TNCC and TP
353 concentration). For both dogs, the presence of vascular, degenerative and neoplastic
354 spinal cord lesions can't be excluded. As both dogs had a progressive disease course,
355 a vascular (ischaemic) lesion seemed less likely. A neoplastic lesion cannot be
356 excluded, although this seems rather unlikely in the Bull Mastiff considering his very

357 young age. The second dog had a lymphocytic pleocytosis on CFS analysis, but no
358 signs of lymphoma were seen on microscopical examination, however no specific test
359 to look for clonality was performed.

360 If a lesion was visible on MRI, all lesions were extensive, ill-defined, intramedullary,
361 hyperintense on T2W images and isointense on T1W images. Other spinal conditions,
362 including acute non-compressive nucleus pulposus extrusions (ANNPE) and
363 ischaemic myelopathy (IM), are also associated with intraparenchymal
364 hyperintensities on MRI. These conditions are however associated with other clinical
365 and MRI characteristics, which could potentially aid in differentiating between these
366 conditions (Cardy *et al.* 2015; Fenn *et al.* 2016). Looking into a recent study (Cardy *et*
367 *al.* 2015), the clinical presentation of dogs with spinal cord dysfunction, IM (most
368 commonly fibrocartilagenous embolic myelopathy (FCEM)) and ANNPE are
369 typically characterised by a peracute onset of non-progressive clinical signs and
370 affected dogs do not commonly demonstrate overt spinal hyperaesthesia at time of
371 admission. This is in contrast with the clinical presentation of dogs with MMUO,
372 which was characterised by an acute onset of progressive and mainly symmetrical
373 neurological deficits, with pain on spinal palpation or manipulation in 86% of dogs
374 (Cardy *et al.* 2015), which is comparable with the 71% of dogs presenting with spinal
375 hyperaesthesia in the presented study. (Deleted: Typical MRI characteristics of dogs
376 with ANNPE include a focal area of intramedullary spinal cord hyperintensity on
377 T2W images overlying an intervertebral disc space, a reduction in volume of the T2W
378 hyperintense nucleus pulposus signal, mild narrowing of the associated disk space,
379 presence of extradural material or signal intensity change with minimal or no spinal
380 cord compression at this level, and are more likely to be lateralised (De Risio *et al.*
381 2015; Fenn *et al.* 2016). Diagnosis of IM (or presumed FCEM) is based on the

382 presence of a focal, relatively well-demarcated intramedullary T2W hyperintense
383 lesion, mainly affecting grey matter, with an absence of the above criteria used to
384 diagnose ANNPE and mainly showing no lateralization (De Risio *et al.* 2015; Fenn *et*
385 *al.* 2016). In the presented study, dogs diagnosed with MMUO all showed presence of
386 an extensive, ill-defined, intramedullary hyperintensity over multiple vertebral bodies,
387 without concurrent presence of disk space narrowing or reduction in the nucleus
388 pulposus signal. In a study looking at MRI findings in dogs with suspected ischemic
389 myelopathy, contrast enhancement was seen in a small proportion of affected dogs
390 (De Risio *et al.* 2007). Additionally, lesions of dogs with IM have been reported to
391 have a median lesion to vertebral body ration of 1.6 and 2.2 for lesions in the cervical
392 (compared to C6) and thoracolumbar region (compared to L2), respectively (De Risio
393 *et al.* 2007). Compared to the present study, revealing an overall lesion/vertebral body
394 ratio of 4.8, the lesions in dogs with MMUO seem to be remarkably longer than the
395 intraparenchymal hyperintense lesions seen in dogs with IM or ANNPE.) Although
396 CSF analysis in dogs with IM is most often within normal limits, affected dogs can
397 demonstrate an increased TP concentration and mild neutrophilic or mixed cell
398 pleocytosis with a median TNCC of 12 WBC/microL (De Risio *et al.* 2007). A
399 marked pleocytosis with a median TNCC of 209 WBC/mm³ was seen in the presented
400 study, although results should be interpreted with caution as presence of a CSF
401 pleocytosis was considered one of the inclusion criteria. To conclude, the presentation
402 of a dog with an acute or chronic onset of a progressive and painful T3-L3
403 myelopathy in combination with an extensive, ill-defined, intramedullary lesion with
404 presence of parenchymal and/or meningeal contrast enhancement on MRI, and
405 presence of a marked pleocytosis on CSF analysis, can be presumptively diagnosed
406 with MMUO. The importance of differentiating between these conditions is

407 highlighted by the differences in treatment and prognosis between dogs with
408 presumptive MMUO and dogs with ANNPE or IM.

409

410 A previous study demonstrated that short tau inversion recovery (STIR)
411 hyperintensities in the cervical epaxial musculature of dogs with
412 meningoencephalomyelitis had a sensitivity of 78% and a specificity of 92% in
413 predicting inflammatory CSF results (Eminaga *et al.* 2013). In the presented study,
414 STIR images were unfortunately only available in 3/21 cases. Adding this sequence to
415 the protocol in dogs with presence of a focal or multifocal, ill-defined T2W
416 intramedullary hyperintensity might be considered in the future.

417

418 Several studies have evaluated survival times of dogs diagnosed with MUO (Granger
419 *et al.* 2010, Coates and Jeffery 2014). Overall, dogs with MUO appear to have a
420 guarded prognosis. A large meta-analysis of dogs with MUO revealed an overall
421 reported MST of 240-590 days in 96 dogs treated with corticosteroids plus any other
422 immunosuppressive protocol, compared to a MST of 28-357 days for 43 dogs
423 receiving corticosteroids alone (Granger *et al.* 2010). In the presented study, dogs
424 with presumptive MMUO had a MST of 669 days (2 years), but ultimately, 48% of
425 dogs died or were euthanized because of MMUO, indicating a more guarded long-
426 term prognosis.

427

428 Limitations of this study are the relative small sample size and retrospective character,
429 which limited standardisation of patient assessment and treatment. Although dogs
430 were all treated with glucocorticosteroids, it cannot be excluded that specific
431 differences in treatment have influenced our results. Despite including cases over a

432 relative large period and from a busy referral hospital, only 21 dogs could be
433 included. This could indicate that MMUO should be considered a rare disorder and
434 this is in agreement with previously reported findings (Cardy *et al.* 2015), which
435 indicated that MMUO represents approximately 6% of all spinal disorders in dogs.

436

437 **Conclusion**

438

439 Presumptive MMUO can be diagnosed in every dog breed of every age that is
440 presented with signs of a mainly acute or chronic, possibly painful, myelopathy.
441 Although clinical signs can vary, affected animals most typically present with
442 ambulatory paraparesis and ataxia, localizing to T3-L3 spinal cord segments. MRI
443 typically reveals an extensive, ill-defined and intramedullary lesion that appears
444 hyperintense on T2W images and isointense on T1W images. Most lesions showed
445 parenchymal contrast enhancement and/or enhancement of the overlying meninges on
446 post-contrast T1W images which can possibly differentiate dogs with MMUO from
447 other more common spinal diseases. In 10% of cases, no lesion was visible on sagittal
448 T2W and T1W images. Almost 50% of dogs died or were euthanized because of
449 MMUO, with a MST of 669 days for all dogs. Future studies should be performed
450 looking into intracranial imaging in dogs diagnosed with presumptive MMUO and its
451 prognostic value, extensive infectious disease testing in all cases and outcome using a
452 standard treatment protocol to give more information about this condition.

453

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457 REFERENCES

- 458 Cardy, T. J. A., De Decker, S., Kenny, P. *et al.* (2015). Clinical reasoning in canine
459 spinal disease: what combination of clinical information is useful? *Veterinary*
460 *Record* 177, 171.
- 461 Coates, J. R. and Jeffery, N. D. (2014). Perspectives on meningoencephalomyelitis of
462 unknown origin. *Veterinary Clinics of North America Small Animal Practice*
463 44, 1157-1185.
- 464 Csebi, P., Jakab, C., Janoski, K., *et al.* (2010). Vertebral osteomyelitis and
465 meningomyelitis caused by *Pasteurella canis* in a dog – clinicopathological
466 case report. *Acta Veterinaria Hungarica* 58, 413-21.
- 467 Da Costa R. (2012). Spinal Pain. In: *Small Animal Neurological Emergencies*. 1st
468 edition. Eds S. Platt and L. Garosi. Manson Publishing, London. pp 219-228.
- 469 De Risio, L., Adams, V., Dennis, R., *et al.* (2007). Magnetic resonance imaging
470 findings and clinical associations in 52 dogs with suspected ischemic
471 myelopathy. *Journal of Veterinary Internal Medicine* 21, 1290-1298.
- 472 Dewey, C. W., da Costa, R. C., Ducoté, J. M. (2016) Neurodiagnostics. In: *Practical*
473 *Guide to Canine and Feline Neurology*. 3rd edition. Eds C. W. Dewey and R.
474 C. da Costa. Wiley Blackwell, West-Sussex, UK. pp 64-65.
- 475 Eminaga, S., Cherubini, G. B., Villiers, E. (2013) STIR muscle hyperintensity in the
476 cervical muscles associated with inflammatory spinal cord disease of unknown
477 origin. *Journal of Small Animal Practice* 54, 137-142.
- 478 Fenn, J., Drees, R., Holger, H. A., *et al.* (2016). Inter – and intraobserver agreement
479 for diagnosing presumptive ischemic myelopathy and acute noncompressive
480 nucleus pulposus extrusion in dogs using magnetic resonance imaging.
481 *Veterinary Radiology and Ultrasound* 57, 33-40.

- 482 Granger, N., Smith, P. M., Jeffery, N. D. (2010). Clinical findings and treatment of
483 non-infectious meningoencephalomyelitis in dogs: a systematic review of 457
484 published cases from 1962 – 2008. *The Veterinary Journal* 184, 290-297.
- 485 Griffin, J. F., Levine, J. M., Levine, G. J., *et al.* (2008). Meningomyelitis in dogs: a
486 retrospective review of 28 cases (1999 to 2007). *Journal of Small Animal*
487 *Practice* 49, 509-17.
- 488 Meric, S. M. (1988). Canine meningitis – a changing emphasis. *Journal of Veterinary*
489 *Internal Medicine* 2, 26-35.
- 490 Parry, A. T., Penning, V. A., Smith, K. C., *et al.* (2009). Imaging diagnosis –
491 necrotizing meningomyelitis and polyarthritis. *Veterinary Radiology and*
492 *Ultrasound* 50, 412-415.
- 493 Scott, H. W. (1997). Hemilaminectomy for the treatment of thoracolumbar disc
494 disease in the dog: a follow-up study of 40 cases. *Journal of Small Animal*
495 *Practice* 38, 488-494.
- 496 Tipold, A. and Stein, V. M. (2010). Inflammatory diseases of the spine in small
497 animals. *Veterinary Clinics of North America, Small Animal Practice* 40, 871-
498 879.
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504 FIGURE LEGENDS

505 **Figure 1**

506 Figure 1: T2W transverse (left image) MR image of the vertebral column and spinal
507 cord at the level of C3, and mid sagittal (right image) MR image of the cervical and
508 cranial thoracic vertebral column and spinal cord of a 56-month-old Jack Russell
509 Terrier. There is presence of a large, ill-defined, intramedullary hyperintensity
510 extending from cranial C2 until cranial C6.

511

512 **Figure 2**

513 Figure 2: T2W sagittal (top image) and transverse (bottom left image), and T1W
514 transverse (bottom right image) of the vertebral column and associated spinal cord of
515 a 13-month-old French Bulldog. There is presence of a large, ill-defined,
516 intramedullary lesion that is hyperintense on T2W images and isointense on T1W
517 images. The lesion is extending from mid T10 until caudal L1.

518

519 **Figure 3**

520 Figure 3: Kaplan-Meier survival curve for overall survival in dogs diagnosed with
521 MMUO. Results were censored for dogs that were still alive at time of data capture
522 and dogs that died because of unrelated causes (single little blocks).

523

524

525

526

527 TABLES

528 **Table 1**

529 Table 1: Clinical details of the 21 dogs diagnosed with MMUO. FE = female entire,
530 FN = female neutered, ME = male entire, MN = male neutered, CSF = cerebrospinal
531 fluid, TNCC = total nucleated cell count, SC = subcutaneous, CRI = constant rate
532 infusion, NA = not applicable, NP = not performed, GMEM = granulomatous
533 meningoencephalomyelitis, NMEM = necrotising meningoencephalomyelitis.
534

Case	Breed	Gender	Age (months) at presentation	Clinical presentation	Neuroanatomical localisation	Spinal hyperesthesia	CSF TNCC (cells/ μ l)	MRI lesion	Initial treatment	Cytosine arabinoside dose (mg/m ²), SC or CRI	Initial response to treatment	Long-term follow-up and treatment	Death or euthanasia because of MMUO	Overall ST 24 (days)	Post mortem findings
1	Akita	FE	36	Non ambul paraparesis	Multifocal	Yes	1740	Focal	Prednisolone 2mg/kg /day	50 mg/m ² SC	Improvement	Euthasia because of acute deterioration after discontinuation of prednisolone treatment	Yes	380	NP
2	Rottweiler	ME	123	Ataxia	T3-L3	No	209	Focal	Prednisolone 2mg/kg /day	50 mg/m ² SC	Deterioration	Euthanasia because of disease progression	Yes	20	NP
3	Bull Mastiff	ME	42	Ambulatory paraparesis	T3-L3	Yes	6	No lesion visible	Prednisolone 2mg/kg /day	No cytosine arabinoside	Deterioration	Euthanasia because of disease progression	Yes	6	NP
4	Labrador	MN	105	Ambulatory paraparesis	L4-S3	Yes	123	Focal	Dexamethasone 0,3mg/kg/day	50 mg/m ² SC	Improvement	Euthanasia because of acute deterioration, was still receiving 1mg/kg of prednisolone every day	Yes	30	NP
5	JRT	MN	89	Ambulatory paraparesis	T3-L3	No	200	Focal	Prednisolone 2mg/kg /day	No cytosine arabinoside	Improvement	Normal dog, still receiving 0,2 mg/kg/day prednisolone	No	237	NA
6	Lhasa Apso	FE	48	Ambulatory tetraparesis	C1-C5	Yes	900	Focal	Prednisolone 4mg/kg /day	50 mg/m ² SC	Improvement	Euthasia because of acute deterioration, was still receiving 0,5 mg/kg prednisolone per day	Yes	171	GMEM
7	Shih Tzu	MN	50	Ambulatory tetraparesis	C6-T2	Yes	5	Focal	Prednisolone 2mg/kg /day	50 mg/m ² SC	Improvement	Normal dog, receiving cyclosporine 5mg/kg/day	No	2250	NA
8	Giant Schnauzer	ME	32	Non ambul paraparesis	Multifocal	No	1345	Focal	Prednisolone 2mg/kg /day	50 mg/m ² SC	Improvement	Euthanasia because of aggression, was only receiving cytosine arabinoside every 5 weeks	No	752	NP
9	Yorkshire Terrier	FN	36	Ambulatory tetraparesis	C1-C5	Yes	7	Focal	Prednisolone 2mg/kg /day	No cytosine arabinoside	Improvement	Euthanasia because of acute deterioration, was still receiving 1mg/kg of prednisolone per day	Yes	202	NMEM
10	English Springer Spaniel	ME	85	Ataxia	Multifocal	No	455	Focal	Prednisolone 2mg/kg /day	No cytarabine	Improvement	Euthanasia because of post-operative infection after stifle surgery, dog normal and on no medication	No	304	NP
11	Rhodesian Ridgeback	FE	123	Normal gait	C1-C5	Yes	89	Focal*	Dexamethasone 0,3mg/kg/day	50 mg/m ² SC	Improvement	Euthanasia because development of seizures, was still receiving cytarabine 50mg/m ² SC every 7 weeks	Yes	669	NP
12	Bearded Collie	MN	136	Ambulatory paraparesis	Multifocal	Yes	162	No lesion visible	Prednisolone 2mg/kg /day	50 mg/m ² SC	Improvement	Normal dog, receiving no current treatment	No	1100	NA
13	Boxer	ME	26	Normal gait	Multifocal	Yes	6000	Focal	Prednisolone 2mg/kg /day	50 mg/m ² SC	Improvement	Normal dog, receiving cytarabine 50mg/m ² SC every 9 weeks	No	1460	NA
14	Lhasa Apso	MN	128	Ambulatory paraparesis	L4-S3	Yes	1540	Multifocal	Prednisolone 2mg/kg /day	50 mg/m ² SC	Stable	Euthanasia because of disease progression	Yes	33	NP
15	Chihuahua	ME	19	Ataxia	T3-L3	Yes	9	Multifocal	Dexamethasone 0,3mg/kg/day	No cytosine arabinoside	Improvement	Normal dog, receiving no current treatment	No	635	NA
16	Cross Breed	FN	83	Ambulatory paraparesis	Multifocal	No	1230	Multifocal	Dexamethasone 0,3mg/kg/day	200 mg/m ² CRI	Improvement	Euthanasia because of acute deterioration, was still receiving 2mg/kg of prednisolone every day, combined with 2mg/kg azathioprine	Yes	93	NP
17	French Bulldog	ME	13	Ambulatory paraparesis	T3-L3	No	250	Multifocal	Prednisolone 2mg/kg /day	No cytosine arabinoside	Improvement	Normal dog, receiving no current treatment	No	791	NA
18	Maltese Terrier	FN	104	Ataxia	Multifocal	Yes	95	Focal	Dexamethasone 0,3mg/kg/day	50 mg/m ² SC	Improvement	Normal dog, still receiving 1mg/kg of prednisolone per day, and cytarabine 50mg/m ² SC every 4 weeks	No	577	NA
19	Jack Russell Terrier	FN	56	Non ambulatory tetraparesis	C6-T2	Yes	2690	Focal*	Dexamethasone 0,5mg/kg/day	No cytosine arabinoside	Dog never recovered from general anaesthesia for MRI	Dog never recovered from GA	Yes	0	GMEM
20	French Bulldog	ME	10	Non ambulatory paraparesis	T3-L3	Yes	43	Focal	Dexamethasone 0,3mg/kg/day	50 mg/m ² SC	Improvement	Ataxia and ambulatory paraparesis, still receiving 0,5mg/kg of prednisolone every other day and cytarabine 50mg/m ² every 5 weeks	No	90	NP
21	West Highland White T.	FE	103	Non ambulatory tetraparesis	Multifocal	Yes	1980	Multifocal	Dexamethasone 0,3mg/kg/day	50 mg/m ² SC	Improvement	Normal dog, receiving cyclosporine 5mg/kg/day	No	210	NA

Table 2

Table 2: summary of the most important demographic, treatment and outcome data in dogs diagnosed with MMUO. IQR = interquartile range, CSF = cerebrospinal fluid, TNCC = total nucleated cell count, TP = total protein, IV = intravenous, CRI = constant rate infusion, SC = subcutaneous.

Variable	Number (%) or median (IQR)
Signalment	
Age (months)	56 (10 – 128)
Male / female	13 (62%) / 8 (38%)
Duration of clinical signs prior to diagnosis (days)	8 (1 – 90)
Onset of neurological signs	
Peracute	1 (5%)
Acute	9 (43%)
Chronic	11 (52%)
Neurological examination	
Focal / multifocal lesion	13 (62%) / 8 (38%)
Focal lesion localisation	
C1-C5	3 (23%)
C6-T2	2 (15%)
T3-L3	6 (47%)
L4-S3	2 (15%)
Neurological grade	
Grade 0	0
Grade 1	2 (10%)
Grade 2	14 (67%)
Grade 3	5 (24%)
Grade 4	0
Grade 5	0
Pain on spinal palpation	15 (71%)
Urinary retention	2 (10%)
Urinary and faecal incontinence	2 (10%)
CSF examination	
TNCC (cells/mm ³)	209 (6 – 6000)
TP concentration (g/l)	1.67 (0.21 – 16.3)
Treatment	
Glucocorticosteroids	21 (100%)
IV dexamethasone	9 (43%)
Oral prednisolone	12 (57%)
Cytosine arabinoside	14 (67%)
CRI	1 (7%)
SC injections	13 (93%)
Outcome	
Survival to discharge	20 (95%)
Alive at time of data capture	9 (45%)