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CASE REPORT

Companion or pet animals

Clinical signs, diagnostic imaging and histopathology in a dog with granulomatous meningoencephalitis manifested as a polyneuropathy

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Abstract

An 11-year-old, female, neutered labrador retriever with a history of chronic and progressive right hindlimb lameness and facial asymmetry was referred for brain and lumbosacral magnetic resonance imaging and cerebrospinal fluid analysis. Multifocal non-enhancing T2-weighted images of hyperintense lesions were observed in the caudate nuclei and medulla oblongata. The right oculomotor nerve was markedly enlarged and showed marked enhancement on T1-weighted images after contrast injection, and there was diffuse enlargement of the sciatic and femoral nerves in the right hindlimb. Cerebrospinal fluid analysis showed a mixed pleocytosis. Histopathology revealed granulomatous inflammation affecting the brain, oculomotor and pelvic limb nerves, consistent with a diagnosis of granulomatous meningoencephalomyelitis.

BACKGROUND

Meningoencephalitis of unknown origin (MUO) in dogs encompasses a group of noninfectious inflammatory conditions of the central nervous system (CNS),[1–3] which include granulomatous meningoencephalitis (GME), necrotising meningoencephalitis (NME) and necrotising leukomeningoencephalitis (NLE),[4] among others. These diseases occur most commonly in small breeds like Yorkshire terrier,[5–7] Maltese, Chihuahua[8] and brachycephalic breeds like pugs[9,10] and French bulldog,[11,12] but any breed can be affected. There is a plethora of different clinical presentations depending on the neuroanatomic localisation and on the rapidity of onset of the clinical signs.

GME is the most frequently described form of MUO, with three well-defined presentations recognised[13–16]: focal, multifocal, and optic neuritis.[17] There are two reports of MUO in which there is peripheral nerve involvement and another with a cranial polyneuritis accompanying the CNS lesions.[18] In the first of these reports,[19] the diagnosis was based on electromyography and postmortem histopathological findings. The second one is a case series of three cases,[20] and the diagnosis was based on magnetic resonance images (MRI) and cerebrospinal fluid (CSF) findings. The present case report is the first one to correlate the MRI, CSF, gross postmortem and microscopic findings in a dog with an MUO accompanied by granulomatous polyneuritis.

CASE PRESENTATION

An 11-year-old, female, neutered labrador retriever was admitted with a 1-month history of progressive right hindlimb lameness and left facial paralysis. The dog was overweight (8/9 body condition) and exhibited xeromycteria, but there were no other abnormalities on general examination. The neurological examination revealed an obtunded mental status, right hindlimb monoplegia with negative proprioception and absence of withdrawal, patellar, sciatic and cranial tibial reflexes.

The left eye was miotic, with a negative menace response with negative palpebral reflex. The right eye was mydriatic, and the pupillary light reflex (PLR) and oculocephalic reflex were absent. The neurological examination findings were consistent with a multifocal lesion involving the brainstem and the right L4–S3 spinal segments and/or associated nerve roots.

INVESTIGATIONS

A complete blood cell count and biochemistry analysis were performed, revealing only a mild leukocytosis (19.7×10^3 cells/μl). Assays for antibodies to *Leishmania infantum* and *Ehrlichia canis* antibodies, using indirect immunofluorescence antibody testing (IFAT), were negative.

An MRI scan of the brain and the lumbosacral vertebral column (L4–S3) was carried out using a low-field magnet 0.23 T (Panorama, Philips Medical Systems) with knee and head coils. The imaging protocol of the brain included sagittal plane T2-weighted (T2W) images in TR: 4800 TE: 96, with transverse plane T2W (TR 5600 TE 90), T1 fast field echo 3D (FFE3D) (TR 30 TE 10), T2W fluid attenuated inversion recovery (T2-FLAIR) (TR 5676.56 TE 100) and T2*-weighted (T2*W) images (TR 60 TE 16). We also obtained dorsal plane T1W (TR 590 TE18) images, T1W and T1 FFE3D images were also obtained immediately after intravenous injection of contrast (0.1 mmol/kg of gadoteridol, ProHance, Bracco Diagnostics, Germany) in sagittal (TR 590 TE 18), transverse (TR 30 TE 10) and dorsal (TR 590 TE 18) planes. The vertebral column was studied using T2W images in sagittal plane (TR 3714.74 TE 176), T1W images in sagittal (TR 498 TE 16) with transverse planes in balanced fast field echo (B-FFE3D) (TR 10 TE 5) and T1 FFE3D (TR 30 TE 10); all the sequences of the vertebral column were obtained postcontrast.

There were multifocal, ill-defined T2W hyperintense lesions in the caudate nuclei and medulla oblongata (Figure 1a–c); no contrast enhancement was identified in postcontrast T1W images. The right oculomotor nerve was markedly enlarged compared to the left and showed mild homogeneous enhancement on T1W images after contrast injection (Figure 2a,b). In the lumbar region, there was a diffuse enlargement of the sciatic and femoral nerves, with marked atrophy of the pelvic limb musculature (Figure 3a,b).

Analysis of CSF collected from the cerebellomedullary cistern revealed hyperproteinorrachia (17.03 g/L), a mixed pleocyotsis (130 cells/μl, with 56% lymphocytes, 30% neutrophils and 14% monocytes) and erythrophagocytosis. No microorganisms were seen on cytological examination.

DIFFERENTIAL DIAGNOSIS

An inflammatory/infectious disease or neoplasia (lymphoma) was considered the main differential diagnoses. The coexistence of two different problems was also considered, such as a right L4–S3 nerve sheath tumour with a combination of intracranial neoplasia or inflammatory/infectious disease.

TREATMENT

Based on the clinical history, clinical signs, MRI findings and CSF analysis, a diagnosis of MUO with peripheral nerve involvement appeared most likely.

Treatment with oral prednisone 1 mg/kg twice a day (BID) was initiated, with subcutaneous cytosine arabinoside (50 mg/m^2 BID for 48 hours) after the investigation was initiated.

OUTCOME AND FOLLOW-UP

One week later, the patient deteriorated, developing non-ambulatory paraparesis. General examination revealed hyperaemia of the left conjunctiva, with a mild green discharge in the medial canthus, opaque cornea and Schirmer tear test of 10 mm in 1 minute. Euthanasia was performed due to the poor clinical status of the patient.

A new CSF tap was performed immediately after euthanasia, revealing hyperproteinorrachia (0.712g/L) and a mild mixed pleocytosis (10 cells/μl, with 82% macrophage, 14% lymphocytes, 2 neutrophils and 2% lymphoblasts).

Postmortem gross examination identified moderate enlargement of the right femoral and sciatic nerves. At the opening of the skull, the meninges were congested and attached to the brain surface. The brain surface was bright and the sulci were atrophied. A haemorrhagic area, which extended from the level of the pons to the caudal medulla oblongata, was identified in the ventral aspect of the brainstem. The extracranial section of the right oculomotor nerve was enlarged compared with the contralateral nerve.

The brain, the extracranial portion of the oculomotor nerve, the cranial portion of the cervical spinal cord and the right sciatic and femoral nerves were fixed in 10% formalin solution for histopathological examination. This revealed multiple perivascular cuffs comprising lymphocytes, plasma cells and macrophages. These were spread throughout the meninges, cortical hemispheres and brainstem, predominantly in the grey matter (Figure 1b). The neuropil showed a strong diffuse gliosis and dilated axons with occasional spheroids. There were sporadic haemorrhagic foci in the ventral of the brainstem.

The first segments of the spinal cord and medulla oblongata (Figure 1d) were severely affected, with multifocal perivascular cuffs mainly affecting the white matter. There was axonal degeneration in the sciatic, femoral and oculomotor nerves (Figure 2c and Figure 3b–d), with perivascular inflammatory cells, mainly lymphocytes and plasmatic cells, scattered throughout; there were also macrophages and neutrophils present between the nerve fibres.

The definitive diagnosis was GME with peripheral nerves involvement.

DISCUSSION

The present report describes the MRI findings in a case of GME with peripheral nerve involvement. There was a good

LEARNING POINTS/TAKE HOME MESSAGES

- Peripheral nerve involvement is rare in granulomatous meningoencephalitis.
- Granulomatous meningoencephalitis should be considered as a rare differential diagnosis in dogs with peripheral nerve involvement in the clinical exam.
- Granulomatous meningoencephalitis should be considered in the differential diagnosis for dogs with multifocal neuropathy accompanying central nervous system lesions with multiple distant nerve root enlargement detected on magnetic resonance imaging, especially when other lesions are detected in the central nervous system and there is an inflammatory cerebrospinal fluid analysis.

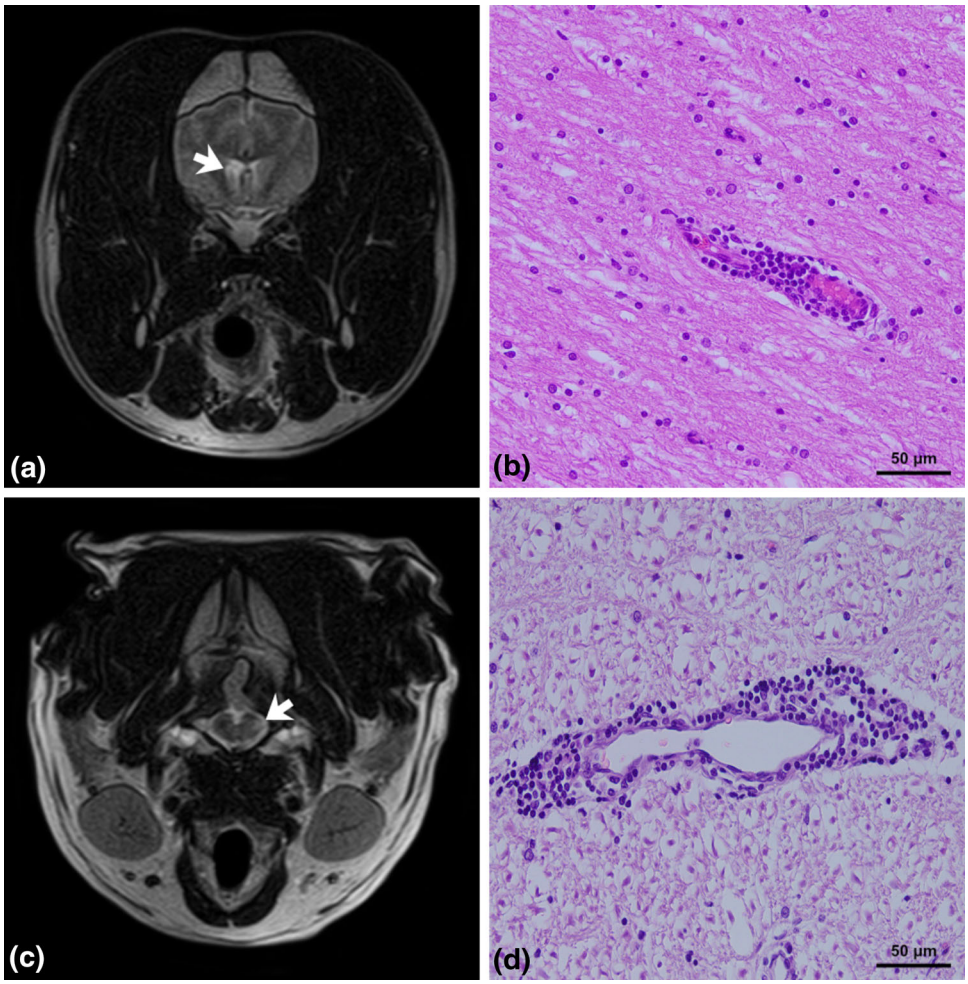
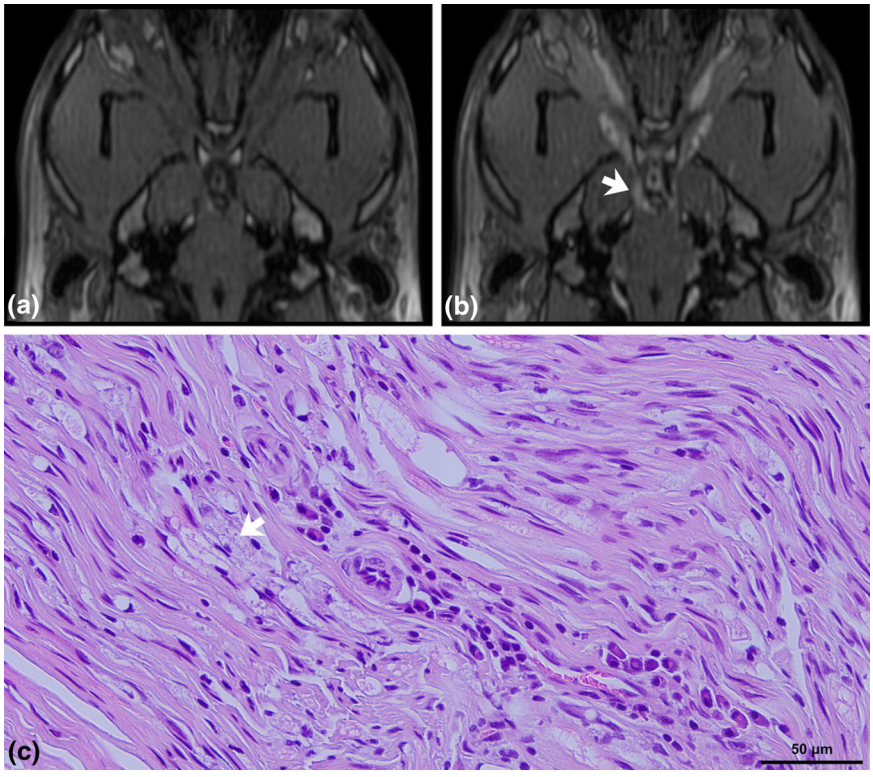


FIGURE 1 T2-weighted transverse sequences at the level of (a) caudate nuclei and medulla oblongata (c): notice the hyperintense lesions in the right caudate nuclei (arrow) and the left side of the medulla oblongata (arrow). Brain (b) and medulla oblonga (d) with granulomatous perivascular infiltrate compounds by lymphocytes, plasma cells and macrophages. Haematoxylin–eosin; bar = 50 μm

FIGURE 2 T1 fast field echo 3D (FFE3D) dorsal multiplanar reformation (MPR) reconstructions precontrast (a) and postcontrast (b): notice the contrast enhancement of the oculomotor nerve (arrow). (c) Oculomotor nerve infiltration with plasma cells, macrophages, lymphocytes and neutrophils between the nerve fibres. Haematoxylin–eosin; bar = 50 μm



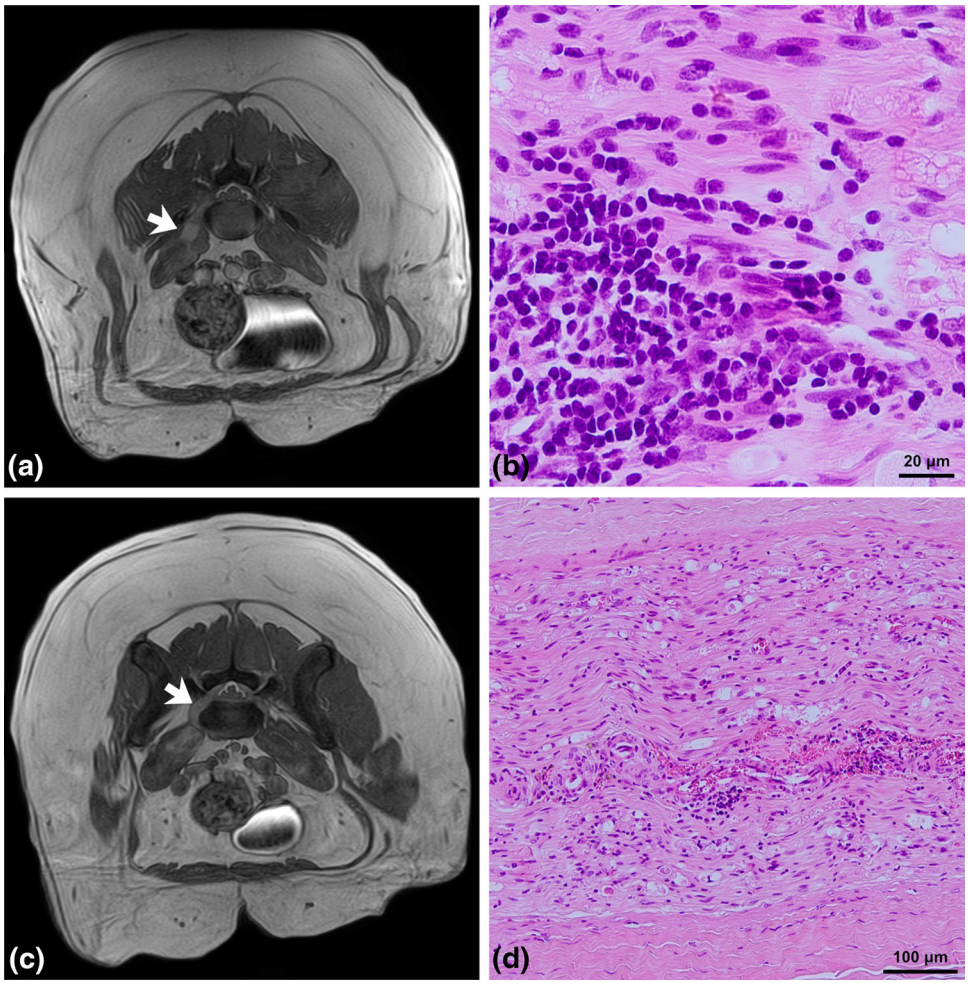


FIGURE 3 T1 fast field echo 3D (FFE3D) transverse postcontrast sequences at the level of L6–L7 (a) and L7–S1 (b), showing an enlargement of the right sciatic nerve (arrow). Right sciatic nerve infiltration with plasma cells, macrophages, lymphocytes and neutrophils between the never fibres. Haematoxylin–eosin (H&E); bar = 100 μm (c), and H & E; bar = 20 μm (d)

correlation between MRI findings and both gross postmortem and histopathological findings.

The clinical signs showed impairment of several cranial nerves: nerve III (negative PLR with the absence of oculocephalic reflex in the right site) and nerve VII (negative menace response with normal visual function) and its parasympathetic branch (xeromycteria).

Despite the neurological examination showing an impairment of the facial nerve, it was not clearly evident in the MRI. A potential explanation could be the severe compromise of the brainstem in the pathological examination that could have involved the facial nuclei.

In a previous case report documenting GME with peripheral nerve involvement,[19] several lesions in different segments of the spinal cord were found. In our case, the first spinal cord segment was severely affected, but we found no evidence of other spinal cord lesions elsewhere on neurological and MRI examination. Samples were not taken from the thoracic, lumbar and sacral segments, and it is possible that subclinical lesions might have been seen, had we done so.

Similar MRI findings have been described in the human literature in cases of multiple sclerosis[21,22] and Sjögren's syndrome[23,24]; both are immune-mediated diseases and are well-described causes of aseptic meningitis and radiculomyelopathies. Furthermore, the Sjögren's syndrome is an autoimmune disorder characterised by xerophthalmia and xerostomia; this was seen in our case and has been reported as a neurological complication of aseptic meningitis and other multiple neuropathies. The clinical presentation is rather similar to our case. However, in humans, ocular signs usually appear before neurological signs, whereas, in our case, no previous eye issues were reported.

The first CSF analysis revealed erythrophagocytosis. This finding supported active bleeding in the CNS, which was confirmed in the histopathological study. The presence of haemorrhagic lesions in MUO is an infrequent finding (prevalence of 12%[16]), with different MRI appearances depending on the age of the haemorrhage and changing concentrations of different by-products of degradation of haemoglobin over time. In our case, no MRI evidence of haemorrhage was detected, though this might be due to the use of a low-field MRI scanner.

The second CSF tap showed a notable improvement, despite the clinical deterioration of the patient. The patient may not have shown clinical improvement, because in chronic immune-mediated diseases as GME, the clinical recovery takes longer than the improvement of the inflammatory response in the CSF.

In conclusion, while the combination of CNS and peripheral nerve involvement is unusual in GME, the current case

confirms that it can occur. GME should therefore be considered as a possible cause of multiple nerve root enlargement detected on MRI, particularly when other CNS lesions are detected on the MRI and an inflammatory CSF analysis is present.

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The authors received no specific funding for this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ETHICS STATEMENT

The present study does not need ethical approval due to the nature of the case presented.

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