

Case Report

Magnetic Resonance Imaging Lesions in the Central Nervous System of a Dog with Canine Monocytic Ehrlichiosis

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A ten-year-old neutered male dog was examined for tetraparesis, vestibular dysfunction, ataxia, and vertebral column hyperesthesia of 10 days duration. On magnetic resonance imaging (MRI), there were multifocal, punctate, T2-hyperintense lesions in the brain and cervical spinal cord and intracranial leptomeningeal contrast enhancement. Cerebrospinal fluid (CSF) analysis revealed a predominantly mononuclear pleocytosis and mildly elevated protein. *Ehrlichia canis* was diagnosed by serum immunofluorescent antibody (IFA) testing. The dog improved with administration of doxycycline. This report describes MRI central nervous system findings in a dog with ehrlichiosis.

1. Introduction

Canine monocytic ehrlichiosis (CME) is a disease often associated with varied and vague clinical signs. Neurologic manifestations of canine ehrlichiosis include seizures, ataxia, abnormal mentation, vestibular dysfunction, cranial nerve deficits, and hyperesthesia [1, 2]. This paper describes the magnetic resonance imaging (MRI) findings in a dog diagnosed with *Ehrlichia canis* meningoencephalitis. Diagnosis was based on clinical and neurologic examination findings, compatible clinicopathologic and cerebrospinal fluid (CSF) abnormalities, canine vector-borne infectious disease serologic testing, and MRI images.

2. Case Presentation

A ten-year-old neutered male mixed-breed dog was examined because of a ten-day history of tetraparesis. Treatment with prednisone, enrofloxacin, and low-dose aspirin was initiated by the referring veterinarian on the third day of illness. Five days prior to admission, cervical radiographs

and CSF analysis were unremarkable. The dog had reportedly been treated with two 14-day courses of doxycycline for ehrlichiosis eleven and seven months prior to development of tetraparesis.

Neurological examination identified gait abnormalities including general proprioceptive ataxia, vestibular ataxia, and ambulatory tetraparesis. Postural reactions were diminished in all limbs. There was a left-sided head tilt, right-sided Horner's syndrome, and hyperesthesia of the cervical and lumbar vertebral column. Neurological examination supported a multifocal neuroanatomical localization, with lesions involving the caudal brainstem and spinal cord.

Complete blood count abnormalities included polycythemia (62.3%; reference range 31–56%), lymphopenia (665/ μ L; reference range 1000–4800 μ L), and thrombocytopenia (144,000/ μ L; reference range 200,000–500,000/ μ L). Serum biochemistry abnormalities included hyperproteinemia (8.5 g/dL; reference range 5.7–7.8 g/dL) and hyperglobulinemia (5.5 g/dL; reference range 1.7–3.8 g/dL). Urinalysis revealed a specific gravity of 1.023 with proteinuria, bacteriuria, and pyuria. A *Bacillus* species was isolated by

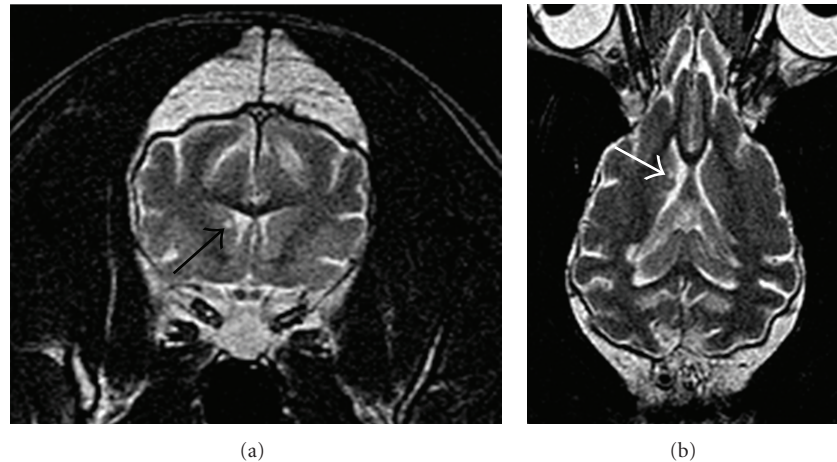


FIGURE 1: T2-weighted images at the level of the caudate nuclei in the transverse (a) TR = 3500, TE = 90 and dorsal plane (b) TR = 3500, TE = 99) in a dog with monocytic ehrlichial meningoencephalitis. There is a subtle, punctate, hyperintense lesion of the right caudate nucleus consistent with arterial infarction and/or perivascular inflammation (arrows).



FIGURE 2: T2-weighted (a) TR = 3500, TE = 90), T1-weighted precontrast (b) TR = 588, TE = 15), and T1-weighted postcontrast (c) TR = 588, TE = 15) transverse plane images at the level of the thalamus in a dog with monocytic ehrlichial meningoencephalitis. A punctate T2 hyperintense lesion in the left dorsal aspect of the thalamus corresponds to a small cavitated region seen on T1-weighted images (white arrows). There is very subtle T1 hyperintensity of brain surrounding the cavitated region. There is little or no contrast enhancement of this lesion.

urine culture. Coagulation findings included increased prothrombin (7.9 sec; reference range 6.0–7.5 sec) and partial thromboplastin times (11.2 sec; reference range 7.1–10.0 sec) with reduced antithrombin III levels (60.6% NHP; reference range >114% NHP).

A heart murmur was auscultated and an electrocardiogram revealed multiform ventricular premature complexes. Echocardiography identified a hypokinetic right ventricular free wall and mitral regurgitation. Hypochoic regions in the interventricular septum likely represented infarcts or myocardial infiltration.

Magnetic resonance imaging of the brain at 1 Tesla (Siemens, Magnetom Expert, NY, USA) included T2-weighted images in the transverse, sagittal, and dorsal planes, T2-weighted fluid-attenuated inversion recovery (FLAIR) images in the transverse plane, T2-weighted gradient echo

images (T2*) in the transverse plane, precontrast T1-weighted images in the transverse plane, and postcontrast T1-weighted images. Gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals) (0.1 mmol/kg) was given intravenously (IV) prior to obtaining postcontrast T1-weighted images. On T2-weighted transverse images, there were punctate hyperintensities of the right caudate nucleus (Figure 1) and left thalamus (Figure 2(a)). These were not associated with a signal void on T2* images. On T1-weighted precontrast images, part of the lesion in the thalamus was hypointense (small cavitated area) (Figure 2(b)). On postcontrast T1-weighted images, there was contrast enhancement of the leptomeninges and forebrain (Figure 3). There was no evidence of an intracranial mass effect.

Magnetic resonance imaging of the C1-T2 vertebral column was performed including short-tau inversion recovery

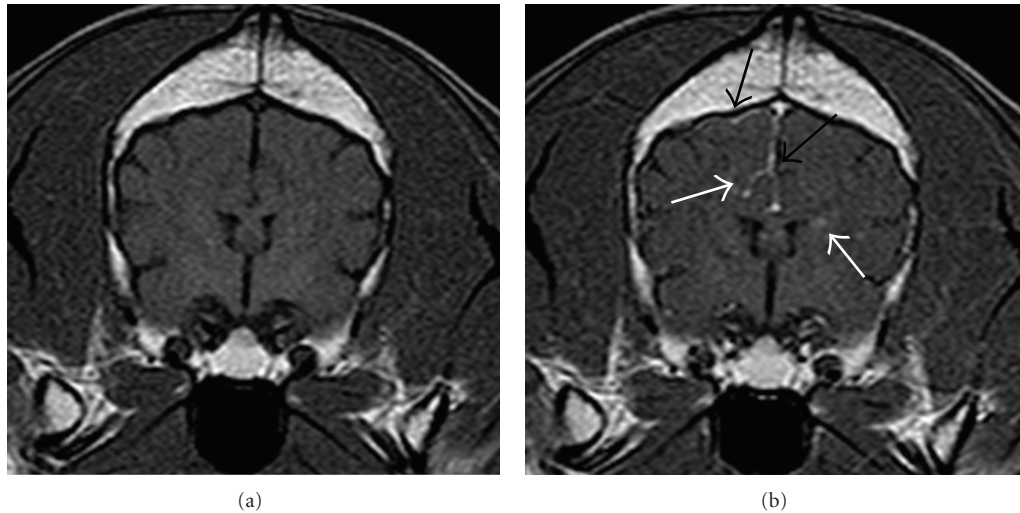


FIGURE 3: T1-weighted precontrast (a) TR = 588, TE = 15) and T1-weighted postcontrast (b) TR = 588, TE = 15) transverse plane images at the level of the rostral part of the 3rd ventricle in a dog with monocytic ehrlichial meningoencephalitis. There is contrast enhancement of the meninges (black arrows). There are a few subtle, poorly defined regions of contrast enhancing brain parenchyma (white arrows).

images (STIR) in the dorsal plane and T2-weighted images in the sagittal and transverse planes. The spinal cord overlying the caudal portion of the C2 vertebral body contained a small, spindle-shaped region of T2 hyperintensity in the left lateral funiculus.

The MRI diagnosis was multifocal inflammatory central nervous system disease. A small, partially cavitated lesion of the thalamus was thought to represent a chronic lacunar infarct.

CSF analysis revealed a mixed large mononuclear cell (54%) pleocytosis (26 nucleated cells/ μL ; reference range <5 cells/ μL) with elevated microprotein (28 mg/dL; reference range <25 mg/dL).

Tick-borne disease serology was submitted to the Vector Borne Disease Diagnostic Laboratory at North Carolina State University. The dog was seroreactive to *Ehrlichia canis* (titer 1:1024) by indirect immunofluorescent antibody (IFA) testing. IFA antibody reactivity to *Babesia canis*, *Bartonella henselae*, *Bartonella vinsonii* subsp. *Berkhoffii*, and *Rickettsia rickettsii* was not detected. An enzyme-linked immunosorbent assay (SNAP 4Dx; Idexx Laboratories, Westbrook, ME, USA) was only *Ehrlichia* spp. positive. A *Bartonella* alpha Proteobacteria (BAPGM) enrichment blood culture was negative. Polymerase chain reaction (PCR) on whole blood failed to amplify *Ehrlichia*, *Anaplasma*, or *Bartonella* species DNA.

The dog was transfused with fresh frozen plasma and treated with IV fluids, famotidine (Baxter Healthcare) (0.5 mg/kg IV twice daily), sucralfate (Nostrum Labs) (1 g orally twice daily), methadone (Methadose; Mallinckrodt) (0.2 mg/kg IV four times daily), clindamycin (Ranbaxy Pharmaceuticals) (10 mg/kg orally twice daily), doxycycline (West-Ward Pharmaceutical) (10 mg/kg orally twice daily), prednisone (Qualitest Pharmaceuticals) (0.5 mg/kg orally twice daily), clopidogrel bisulfate (Plavix; Bristol-Myers Squibb) (1.3 mg/kg orally once daily), and dalteparin sodium

(Fragmin; Pfizer) (100 U/kg subcutaneously three times daily). The dog was discharged two days after admission with marked improvement in ataxia, but was euthanized a month later for reported congestive heart failure. A postmortem examination was not performed.

3. Discussion

Canine monocytic ehrlichiosis (CME), caused primarily by *Ehrlichia canis*, is a tick-borne disease of worldwide distribution. *Ehrlichia canis*, an obligate intracellular Gram-negative coccobacillus that infects circulating mononuclear cells in dogs, is transmitted transtadially by the brown dog tick (*Rhipicephalus sanguineus*) [3]. Clinical signs associated with ehrlichiosis are vague, including fever, anorexia, depression, weight loss, ocular and nasal discharge, lymphadenomegaly, hepatomegaly, and splenomegaly [1, 4, 5]. Bleeding tendencies (petechia, ecchymoses, and epistaxis) may be present [2]. Neurologic manifestations are reported in about one-third of the cases of CME [6]. Neurologic signs can include seizures, ataxia, abnormal mentation, vestibular dysfunction, cranial nerve deficits, and hyperesthesia [1, 2, 7].

Neuropathological changes associated with CME include perivascular cuffing with plasma cells in the meninges or brain parenchyma [8, 9]. A smaller percentage of dogs have nonsuppurative encephalitis with a predilection for the brainstem, midbrain, and cerebral cortex. Gross meningeal hemorrhage has also been reported [8]. Neurological signs may arise as a direct consequence of central nervous system inflammation or due to vasculopathy [10].

MRI findings recognized in various meningoencephalitis in dogs include areas of abnormal brain signal intensity (T2 hyperintense \pm T1 hypointense), contrast enhancement of brain parenchyma and meninges, loss of cortical gray/white matter demarcation, mass effect, and space-occupying lesions [11, 12]. There are few MRI studies in

human patients with ehrlichiosis, and findings are often normal or nonspecific (e.g., meningeal enhancement) [13]. MRI findings in CME have not been reported to the authors' knowledge. The multifocal, punctate distribution of T2 hyperintense lesions in this case is unusual and almost identical to lesions described in people with meningoencephalitis caused by *R. rickettsii* [14]. In that report, 4 of 6 patients had focal or punctate T2-hyperintense lesions of the basal nuclei and frontal lobes, presumed to represent arterial infarction. Other MRI findings in humans with Rocky Mountain spotted fever (RMSF) included brain edema, meningeal contrast enhancement, and prominent perivascular spaces in the region of the basal nuclei. Others have attributed the perivascular distribution of T2 hyperintense lesions in *R. rickettsii* to perivascular inflammation [15]. Additional differential diagnoses for this pattern in dogs would include infections with *Borrelia burgdorferi* or *Cryptococcus neoformans* (perivascular inflammation is common) [15, 16], granulomatous meningoencephalitis or intravascular lymphoma (although these diseases often produce large, poorly marginated T2 hyperintense lesions) [17, 18], and bartonellosis, which has been associated with endocarditis, myocarditis, and neurologic disease in dogs and human patients [19–21].

We suspect that this dog was in the chronic phase of CME and had failed previous treatments with doxycycline. *E. canis* IgG titers greater than 1 : 80 by IFA testing indicate exposure to an *Ehrlichia* sp. and support the potential of infection [3]. When interpreted in conjunction with thrombocytopenia and hyperglobulinemia, the titer in our dog (1 : 1024) was consistent with a serological diagnosis of ehrlichiosis [22]. While high titers can persist for months to years after treatment [23], the persistent thrombocytopenia is suggestive of active infection [24, 25]. PCR can help distinguish infection from exposure and can be used to evaluate response to treatment [26]. The negative *E. canis* PCR result may be due to sequestration of the *E. canis* organisms in the spleen or central nervous system, doxycycline-induced suppression of blood infection below the level of PCR detection, or suppression of *E. canis* DNA copies in association with the recent administration of enrofloxacin, which experimentally elicits improvement in hematological abnormalities but is not curative for CME [27]. PCR from spleen samples has been reported to be more sensitive than blood sample PCR for detecting persistent infection, suggesting that the spleen harbors the organism longer than blood [28, 29]. *Ehrlichia morulae* have been found in the CSF of a dog without concurrent demonstration of morulae in blood, indicating the potential for localization of the infection in the central nervous system [7]. PCR from splenic aspirates or CSF may have helped to confirm the presence of active infection in this dog. Treatment failure in this dog may have been due to the short durations of drug administration. Treatment with 28 days of doxycycline has been recommended for canine ehrlichiosis [30], while subclinical and chronic infections may take 6 weeks or longer to clear [29]. Coinfection with organisms such as *B. canis* or *B. vinsonii* subsp. *berkhoffii* can contribute to an inadequate response to treatment with doxycycline [25], but infection with these organisms was not identified in this dog.

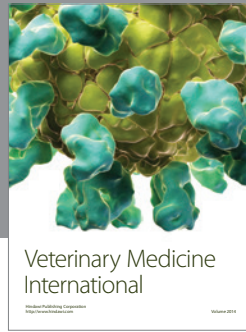
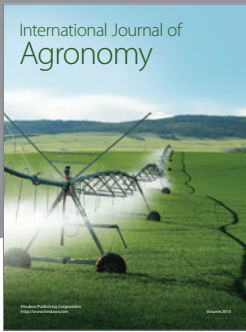
The cardiac arrhythmia noted in this case may have been associated with ehrlichiosis or may have been unrelated. Cardiac pathologic changes associated with CME have included hemorrhage and myocarditis [8]. Elevated serum cardiac troponin I concentrations in dogs infected with *E. canis* suggest that myocardial injury frequently accompanies CME [31].

In conclusion, canine monocytic ehrlichiosis should be considered as a differential diagnosis for dogs with multifocal, punctate, T2 hyperintense brain and spinal cord lesions on MRI. MRI findings in conjunction with clinicopathologic abnormalities, serology, and PCR testing can be helpful in confirming a diagnosis of canine ehrlichiosis and assist in ruling out coinfections with other vector-borne pathogens.

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