Segmental Meningomyelitis in 2 Cats Caused by *Toxoplasma gondii*

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Segmental myelitis in cats caused by agents belonging to the phylum Apicomplexa is a rare condition. Previously only 2 cases have been reported, focusing on the pathology and characterization of the causative agents.[1,2] We describe 2 cases of segmental myelitis caused by *Toxoplasma gondii* in cats from Europe. This report presents clinical, serological, pathological, and immunocytochemical results as well as magnetic resonance imaging (MRI) findings, which, to our knowledge, have not been described before.

Abbreviations:

CSF	cerebrospinal fluid
FeLV	feline leukemia virus
FIV	feline immunodeficiency virus
HIV	human immunodeficiency virus
IFAT	immunofluorescence antibody titer
IHC	immunohistochemistry
MRI	magnetic resonance imaging
PCR	polymerase chain reaction

Case 1

A 4-year-old neutered female domestic shorthair cat was presented with a 1-month history of progressive gait abnormalities. The cat had been obtained from an animal shelter 6 months previously. At that time, the cat had been vaccinated and dewormed. ELISA[a] tests for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) were negative. The cat was kept indoors in a single-pet home and was fed commercial cat food. Over the last month, the cat developed gait abnormalities, beginning with slight weakness progressing to nonambulatory paraparesis. Treatment with marbofloxacin (5 mg/kg/d) and prednisolone (1 mg/kg/d) for 10 days by the referring veterinarian did not lead to improvement.

On general physical examination, the cat was lethargic with unkempt matted hair due of failure to groom and was reluctant to move. The neurologic examination confirmed nonambulatory paraparesis, worse on the right side. Postural reactions were decreased in both pelvic limbs. The segmental spinal reflexes of all 4 limbs were normal as were anal tone, defecation, and urination. The cutaneous trunci response was absent bilaterally and severe pain was detected in the thoracic spine. The lesion was localized to T3-L3. Differential diagnoses included neoplastic, inflammatory, infectious, and degenerative diseases. Results of hematology, serum biochemistry, and urinalysis were unremarkable. Thoracic radiographs
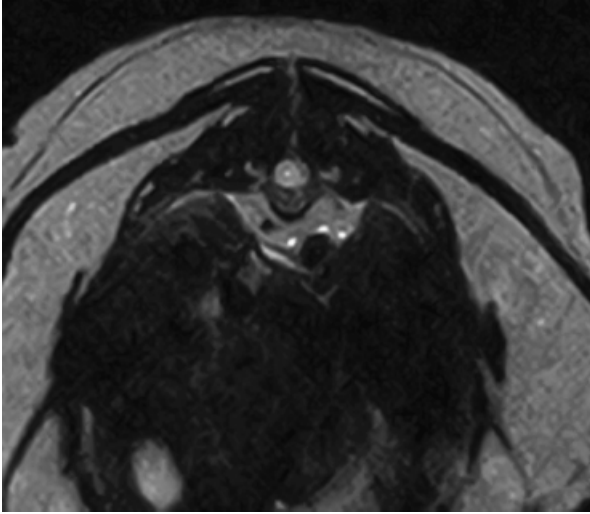
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indicated a mild interstitial lung pattern. Analysis of cerebrospinal fluid (CSF) taken from the cisterna magna disclosed 96 white blood cells/μL (reference range, 0–5/μL), a 1+ positive Pandy test (reference range, negative), and 30 mg/dL albumin (reference range, <30 mg/dL). Differential cell count on a cytospin preparation was 51% lymphocytes, 38% neutrophils, 7% monocytes, and 4% macrophages.

An MRI examination was performed with the cat in dorsal recumbency with a 0.3 T magnet[b] and a human knee coil. The protocol included T2-weighted sequences in transverse and sagittal planes (TR: 6.620 ms, TE: 125 ms, slice thickness 3 mm, interslice gap 0.5 mm), fluid-attenuated inversion recovery (FLAIR) in dorsal plane (TR: 7.500 ms, TE: 125 ms, TI: 1.900 ms, slice thickness 3.5 mm, interslice gap 1 mm), short tau inversion recovery (STIR) in dorsal plane (TR: 5.000 ms, TE: 25 ms, TI: 110 ms, slice thickness 3.5 mm, interslice gap 0.5 mm), balanced steady acquisition gradient echo (BASG) in dorsal plane (TR: 13 ms, TE: 6.5 ms, slice thickness 3 mm), and T1-weighted images pre- and post-IV contrast (0.1 mmol/kg gadopentetate dimeglumine[c]) in transverse (TR: 450 ms, TE: 20 ms, slice thickness 3 mm, interslice gap 0.5 mm) and dorsal planes (TR: 30 ms, TE: 15 ms, flip angle 30°, slice thickness 3.5 mm, no interslice gap).

A focal intramedullary lesion at the level of T6–T9 was identified. At this level, the spinal cord was slightly enlarged with decreased fluid and fat signal intensity in T2-weighted images (Fig 1). Lack of definition between gray and white matter was evident on the T1-weighted images. The lesion appeared irregularly hyperintense on T2-weighted and FLAIR images and irregularly hypointense on T1-weighted images (Figs 2 and 3). There was strong contrast uptake on T1-weighted postcontrast images (Figs 2 and 3). Cranial and caudal to the lesion the central canal was enlarged with preserved anatomic definition. Based on MRI and CSF findings, an inflammatory, infectious, or neoplastic disease was suspected.

Serum immunofluorescence antibody titer (IFAT)[d] for *T. gondii* was mildly positive for IgG at 1:64 (reference

Fig 1. T2-weighted transverse magnetic resonance image: Hyperintense signal within the spinal cord in the white and gray matter. Enlargement of the spinal cord with loss of the hyperintense signal around the spinal cord.

range, <1:32) and negative for IgM (<1:32). Because of the extensive lesion, prognosis was considered poor and the cat was euthanized and submitted for necropsy.

Case 2

A 6-year-old intact male domestic shorthair cat was presented with a 3-month history of progressive gait abnormalities in the pelvic limbs. There was temporary improvement after steroid therapy (prednisolone, 1 mg/kg/d). Seven days before presentation, there was rapid progression of clinical signs with severe tetraparesis and ataxia, and generalized hyperesthesia. The general physical examination was unremarkable. On neurological examination, the cat was lethargic and disoriented and remained in lateral recumbency. When supported, nonambulatory tetraparesis was noted with decreased postural reactions in all 4 limbs. The segmental spinal reflexes showed an absent withdrawal reflex on both thoracic limbs, and the cat had a pronounced hyperesthesia during the assessment of cutaneous trunci response, which was normal. Menace response was decreased bilaterally as was sensitivity of the face. The palpebral reflexes were normal. The cat had anisocoria with miosis of the right eye.
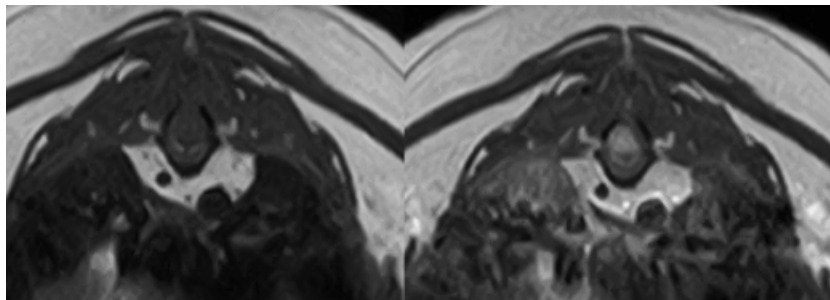
A multifocal localization in the central nervous system including spinal cord C6-T2 and forebrain was suspected. Differential diagnoses included inflammatory and infectious diseases and, less likely, neoplastic disease.

Results of hematology, serum biochemistry, and urinalysis were unremarkable. Serology (ELISA)[a] tests for FIV and FeLV were negative. Serum IFAT for *T. gondii* was moderately positive for IgG at 1:320 (reference range, <1:32) and mildly positive for IgG at 1:40 for *Neospora caninum* (reference range, <1:32). IgM titers were not performed.

Analysis of CSF taken from the cisterna magna disclosed 295 white blood cells/μL (reference range, 0–5 /μL) and total protein concentration of 156 mg/dL (reference range, <30 mg/dL). Differential cell count after sedimentation with cytospin was 64% neutrophils and 36% mononuclear cells.
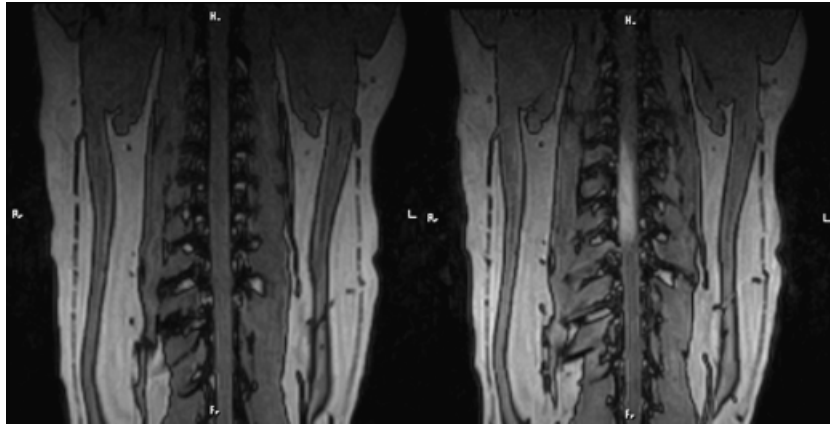
On suspicion of toxoplasmosis, the cat was treated with clindamycin (20 mg/kg PO q12h) but showed no improvement and died spontaneously after 1 week of therapy. Brain and spinal cord were sent for neuropathological investigation.

Neuropathology

General necropsy was unremarkable. Brain and spinal cord of both cats were fixed in 10% neutral buffered formalin. Representative blocks were embedded in paraffin, sectioned at 5 μm and stained with hematoxylin and eosin (H/E). Immunohistochemistry (IHC) was performed with specific antisera against *T. gondii* (1:800, rabbit polyclonal[e]). The labeled streptavidin biotin method was used with 3-amino-9-ethylcarbazole as chromogen, resulting in a red immunopositive reaction product at the side of the reaction.

Macroscopically, the spinal cord of cat 1 appeared slightly swollen and exhibited a grayish discoloration at the level of vertebral bodies T6–T7. On transverse sections of the fixed spinal cord, the normal structure of the spinal cord parenchyma was lost. A similar lesion was detected in the cervical intumescence of the spinal cord of cat 2.

Histologically, lesions in both cats consisted of marked inflammation with necrosis of large areas within gray and white matter. Lesions were lateralized in both cases with more pronounced involvement of the cord bordering the meninges on 1 side (Fig 4). Severe mononuclear meningitis, prominent perivascular cuffs with lymphocytes and

Fig 2. T1-weighted transverse section of the spinal cord pre- and postcontrast in the same region as seen in Figure 1. Spinal cord appears irregularly hypointense on precontrast images, with strong contrast uptake postcontrast.

Fig 3. T1-weighted dorsal section of the spinal cord pre- and postcontrast. Extension of the intramedullary lesion between T5 and T9 with strong contrast uptake.

plasma cells, parenchymal infiltration of the necrotic areas with lymphocytes and macrophages, and diffuse astrogliosis were present (Fig 5). Within the lesions, protozoal cysts were detected in both cases (Fig 5). On IHC for *T. gondii*, the latter were positively stained in both cases (inset Fig 5). No clinically relevant lesions were found in other CNS areas in either cat.

Discussion

This report describes segmental myelitis caused by *T. gondii* in 2 cats. The diagnosis was based on pathological findings, including detection of protozoal organisms and IHC.

Although *T. gondii* can be frequently isolated from the CNS of experimentally infected cats, CNS lesions caused by *T. gondii* are very rare in this species.[3,4] Dubey and Carpenter[5] analyzed 100 cases of histologically con-

firmed natural cases of feline toxoplasmosis and found only 7 cats with lesions in the brain. In our own neuropathological accessions, exceedingly small numbers of protozoal CNS infections were recorded in cats for the past 70 years.

A specifically spinal localization of protozoal infection in cats has only been reported twice in the United States. One was a 10-year-old cat with progressive paraparesis. The diagnosis of toxoplasmosis was achieved by postmortem visualization of tachyzoites in the spinal cord that were positive on IHC for *T. gondii* and ultrastructural analysis.[2] The other reported case was a 3-year-old cat with segmental myelitis at the level of the cervical intumescence (C6-T2). The diagnosis was based on intralesional identification of protozoal cysts and positive IHC for *T. gondii*. However, ultrastructural examination identified morphologic differences from *T. gondii* in the micronemes and rhoptries as well as in the size of the
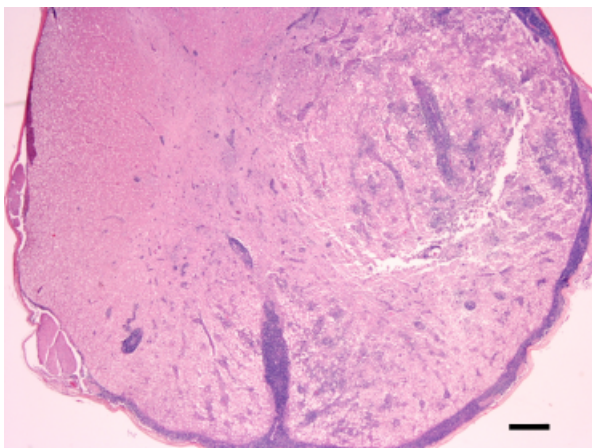
Fig 4. Histological transverse section of the spinal cord in the region of the lesion. Severe lateralized malacia of gray and white matter, and severe mononuclear meningitis. Prominent perivascular cuffs and infiltration of the parenchyma with inflammatory cells. Hematoxylin/eosin, bar = 1 mm.
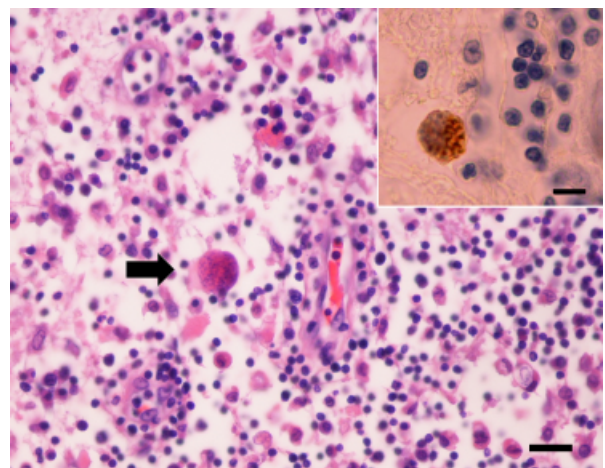
Fig 5. Prominent perivascular cuffs with lymphocytes and plasma cells, parenchymal infiltration of the necrotic areas with lymphocytes and macrophages, and diffuse astrogliosis. Protozoal cyst within the lesions (arrow). Hematoxylin/eosin, bar = 100 μm. **Inset**: Positively stained protozoal cyst. Immunohistochemistry for *Toxoplasma gondii*, bar = 20 μm.

bradyzoites, leading to a suspicion of a different species that could not be further identified.[1] This observation is consistent with other reports. Although serological assays and immunohistochemical staining are powerful diagnostic methods, there are important limitations such as antibody cross-reactivity and false-negative or false-positive results.[6–8] This is because of the morphology and biology of the Apicomplexa, which is highly preserved and makes speciation very difficult.[9–12] Over the years, it has been shown in the United States that protozoal encephalitis in cats also can be caused, albeit rarely, by *Sarcocystis* spp., notably *Sarcocystis neurona*.[12–14] Because antibodies to *T. gondii* do not cross react with *Sarcocystis* spp.,[6–8] it is unlikely that the latter were the cause of the lesions in our cats. Furthermore, the geographic origin of both of our cats does not support the possibility of *S. neurona* infection, because 1 cat came from a shelter in Switzerland and the other from Italy. Equine protozoal encephalomyelitis, the most frequent disease caused by *S. neurona*, does not occur in Europe.[15,16] Although *Neospora caninum* can cause encephalomyelitis in cats after experimental infection, there naturally occurring neosporosis has not been described in this species.[17] Thus, we conclude that our cases were indeed most likely caused by *T. gondii*.

T. gondii is an ubiquitous protozoan parasite belonging to the Apicomplexa phylum. The development of cysts with bradyzoites and their tissue tropism is not fully understood. The age of the cat, route of infection, infectious stage and strain of *T. gondii*, concurrent infections, and the immune status of the host all are important factors that affect the clinical outcome of feline toxoplasmosis.[3,5,18] Humans infected with human immunodeficiency virus (HIV) are most susceptible to toxoplasmosis. It is postulated that up to 30% of humans with acquired immune deficiency syndrome will develop toxoplasmosis encephalitis, which often is lethal.[11,19,20]

Despite the biological similarities of HIV and FIV, an association between symptomatic toxoplasmosis and FIV coinfection remains controversial.[2,21] The latest studies do not show a clinical correlation between *T. gondii* and coinfection with FIV,[22] but further investigations are needed. Both of our cats were tested for FIV and FeLV and were negative. At necropsy no other diseases were detected that could explain an immune-compromised status, and the diagnostic evaluation was unremarkable. In *T. gondii* infection, IgM antibodies precede IgG antibodies and generally do not last longer than 3 months after infection. In contrast, IgG antibodies can be detected for at least 6 years after infection.[11,23] IgM titers, which are considered to be indicative of an acute ongoing infection,[19] were only determined in 1 of our 2 cases, and were negative. This may suggest a nonrecent infection, and it remains obscure why an initially asymptomatic *T. gondii* infection became symptomatic. Stress associated with change of owner may have played a contributory role in case 1. It is also puzzling why the infectious agent can selectively target the spinal cord. The resulting clinical presentation as a focal spinal cord lesion makes a specific diagnosis particularly challenging.

To our knowledge, our study represents the first report of the MRI appearance of segmental protozoal myelitis. The MR study in cat 1 disclosed features of a segmental myelopathy with enlargement of the spinal cord at the level of T6–T9, with a mass effect that was hyperintense in T2-weighted images, and hypointense in T1-weighted images with strong contrast enhancement (Figs 1–3). These findings are consistent with those observed in human cases of myelitis because of toxoplasmosis,[24] which, however, are usually associated with CNS lesions at other localizations.

In cats, however, such focal destructive space-occupying intramedullary lesions are strongly suggestive of neoplasia, most often lymphosarcoma. Only the combination of the MRI findings with inflammatory CSF cytology led to a diagnosis of myelitis. Substantial numbers of CSF neutrophils were consistent with a bacterial, fungal, or protozoal etiology. The positive serology for toxoplasmosis allowed a definitive diagnosis in our cases. Serologic results in feline toxoplasmosis, however, do not always correlate with clinical disease.[8] Polymerase chain reaction (PCR) assay for *T. gondii* would theoretically be able to provide a definitive diagnosis.[8,9] Dupon et al[25] found a sensitivity of 76.9% and a specificity of 100 % for PCR done on CSF from HIV seropositive patients with cerebral toxoplasmosis. In veterinary medicine, frequent false positive and negative results render PCR insufficient as a diagnostic test by itself.[8,10] PCR for *T. gondii* may have the best clinical correlation when done on CSF or tissue samples.[8] In conclusion, although rare, toxoplasmosis should be considered in the differential diagnosis of focal spinal cord lesions in cats. A definitive antemortem diagnosis may be difficult, but MRI examination of the spinal cord helps narrow down the differential diagnosis. The latter, in conjunction with CSF examination, serology and, if reliable, PCR for the infectious agent should allow a definitive diagnosis and targeted treatment.

Footnotes

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