

Myelopathy: An Unusual Presentation of Toxoplasmosis

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ABSTRACT: Central nervous system toxoplasmosis is a well known disease of immunocompromised patients. Neuropathologic examinations have only rarely demonstrated spinal cord involvement. This report describes a fatal case of toxoplasmosis that presented with a subacute myelopathy. Toxoplasmosis should be considered in immunocompromised patients, including patients with the acquired immune deficiency syndrome, that develop intramedullary lesions of the spinal cord.

RÉSUMÉ: La myélopathie: un mode de présentation inusité de la toxoplasmosis La toxoplasmosis du système nerveux central est une maladie bien connue chez les patients immunocompromis. L'atteinte de la moëlle épinière a rarement été démontrée à l'examen neuropathologique chez ces patients. Nous rapportons un cas de toxoplasmosis fatale dont le mode de présentation a été une myélopathie subaiguë. La toxoplasmosis doit être envisagée chez les patients immunocompromis, incluant les patients atteints du syndrome d'immunodéficience acquise, qui développent des lésions intramédullaires de la moëlle épinière.

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There are many reports in the literature of central nervous system (CNS) toxoplasmosis in patients with impaired immunologic defense mechanisms due to immunosuppressive therapy or the acquired immune deficiency syndrome (AIDS).¹⁻⁸ The spinal cord is not usually involved in this disease. Cases of CNS toxoplasmosis presenting with a myelopathy have rarely been recognized.⁹⁻¹¹ This case report describes a patient treated with cyclophosphamide for an idiopathic autoimmune hemolytic anemia who presented with a myelopathy, and was found to have a toxoplasmic myelitis at autopsy.

CASE REPORT

A 58-year-old female presented with left-sided weakness and sensory loss. An idiopathic autoimmune hemolytic anemia was diagnosed five years earlier. She was initially treated with prednisone, and one year later she was switched to cyclophosphamide 150 mg/day.

Two months prior to admission she developed burning discomfort inferior to her left breast that involved her left lower trunk and left leg. The discomfort persisted and became associated with mild left leg weakness which progressed until she was unable to walk. She also had a 30 pound weight loss over six months prior to admission. She had a domestic cat.

On examination she had mild proximal weakness of the right leg and severe left leg weakness that was more marked proximally. There was sensory loss to pinprick below T5 level with greater involvement on the right side, and a loss of light touch below T6 level on the left.

Position sense was impaired in the left leg. Abdominal reflexes were absent and deep tendon reflexes were brisk in the legs. The left toe was upgoing.

On admission a pancytopenia was present with a leukocyte count of $1.8 \times 10^9/L$ and a platelet count of $66 \times 10^9/L$. The hemoglobin level was 101 g/L. A bone marrow aspiration showed moderate marrow hypoplasia and dyserythropoiesis. A CT myelogram revealed mild enlargement of the spinal cord at T5. A CSF examination revealed $8 \times 10^6/L$ mononuclear cells, and the protein and glucose levels were 0.76 g/L and 3.1 mmol/L, respectively. No atypical cells were present and cultures were negative.

She was treated with corticosteroids (initially prednisone 100 mg/day), which did not result in significant improvement in her weakness or sensory loss. On her 11th hospital day she became irritable and developed flaccid paraplegia with urinary and fecal incontinence. She had fever (39°C, rectal) on the following day that persisted despite intravenous antibiotics. She also developed persistent hematuria, and cyclophosphamide was discontinued.

She became comatose on her 16th hospital day and developed left arm weakness and nuchal rigidity. A CT head scan revealed low density lesions bilaterally in the frontal lobes with minimal enhancement, and a low density lesion in the right basal ganglia (Figure 1). A repeat CSF examination revealed $20 \times 10^6/L$ white cells (58% polys, 42% mononuclear cells), protein was 1.16 g/L, glucose was 2.1 mmol/L, and cultures were negative. The platelet count dropped to $33 \times 10^9/L$. A brain biopsy was not performed because of the high risk of a hemorrhagic complication. She was given broad antimicrobial coverage with intravenous penicillin, ceftazidime, metronidazole, and amphotericin B for a suspected CNS infection. She died on her 22nd hospital day.

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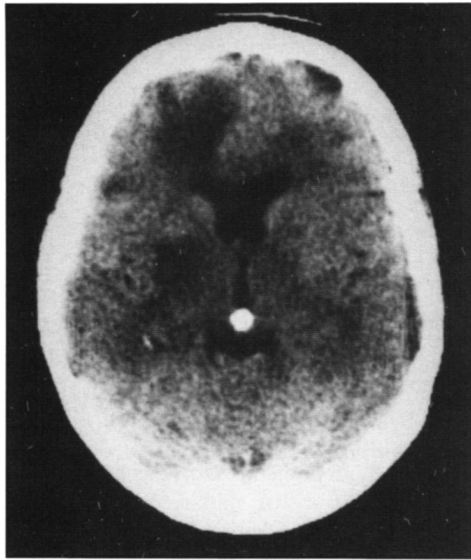


Figure 1 — Non-contrast C.T. scan of head showing hypodensities in both frontal lobes and in the basal ganglia region on the right side.

AUTOPSY FINDINGS

The spinal cord showed swelling and greyish discoloration extending from T5-T8 levels. Microscopic examination of the cord at these levels revealed coagulative necrosis involving the cross-sectional area with some sparing of the peripheral rim on the right side. At the periphery of the necrotic zone, ghost outlines of necrotic macrophages were evident. The vessels in this region showed endothelial swelling and thickening of their walls with eosinophilic material which likely represented protein exudation. However, because the reaction was a few weeks old, the material no longer gave a positive reaction for fibrin using the phosphotungstic acid hematoxylin stain. Axonal swellings and some remaining myelinated fibers were present at the periphery of the cord on the right side.

The area rostral and caudal to the T5-T8 levels showed evidence of ongoing active inflammation with necrosis of the neuropil associated with an inflammatory reaction consisting mainly of polymorphonuclear leukocytes (Figure 2A). The microvessels in this area showed fibrin in their lumen, and walls, with extravasation into the surrounding neuropil. Free tachyzoites of *Toxoplasma* were identified in these areas by light and electron microscopy (Figures 2B).

More rostral sections taken at C8 level revealed Wallerian degeneration of the posterior columns. Multiple microglial nodules were observed in the grey matter at this level. In addition, cysts of *Toxoplasma gondii* were identified (Figure 2C).

The brain was diffusely swollen and showed flattening of gyri. Both frontal lobes showed yellow-brown depressed areas measuring about 2 cms in diameter in a parasagittal location. On microscopy, the cellular and vascular changes were few weeks old and resembled the changes observed in the T5-T8 spinal cord levels. In addition, thrombosed arterioles with recanalisation of the lumina were present, suggesting that the tissue necrosis was secondary to vascular occlusion. Perivascular collections of lymphocytes were present in the brain and the subarachnoid space.

Horizontal sections of the brain showed additional areas of necrosis in the occipital lobes, both basal ganglia, cerebellum, right side of the midbrain, and the right side of the basis pontis (Figure 3). On microscopy, these areas showed active ongoing inflammation, similar to that seen in the spinal cord.

Examination of other body organs did not reveal evidence of toxoplasmosis. The heart showed a few areas of interstitial inflammation which were consistent with toxoplasma myocarditis, however, no organisms were identified on special stains. Examination of the hematopoietic system showed pancytopenia and mild hypoplasia and dyserythropoiesis of the bone marrow and lymphoid atrophy of the spleen and lymph nodes. These findings are related to the immunosuppressive effect of chemotherapy. The liver and spleen showed mild hemosiderosis consistent with autoimmune hemolytic anemia.

Postmortem serum had an antibody titre of 1/4096 to *Toxoplasma* (immunofluorescent antibody test). Human immuno-deficiency virus serology was negative.

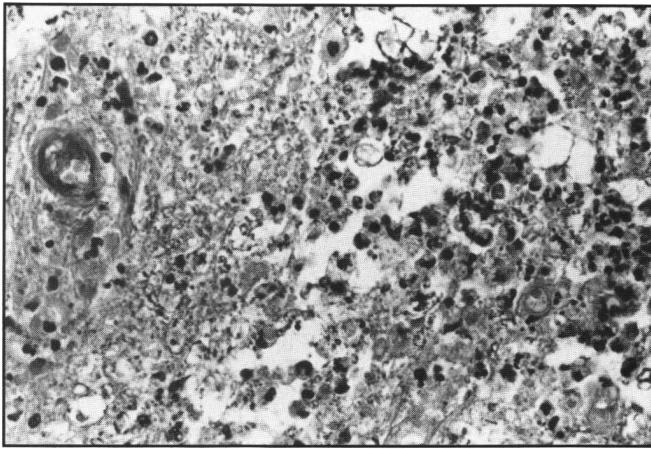
DISCUSSION

This patient with fatal CNS toxoplasmosis was immunosuppressed from treatment of an autoimmune hemolytic anemia with cyclophosphamide. She developed a left-sided intramedullary thoracic cord lesion that subsequently became bilateral. After initiation of corticosteroids, there was extension of the spinal cord lesion and the development of symptomatic multifocal brain lesions. It was clinically uncertain whether the spinal cord and brain lesions were part of the same pathologic process. The development of thrombocytopenia prevented a specific diagnosis of the cerebral lesions with a brain biopsy, and the patient died despite treatment with multiple antimicrobial agents for a suspected CNS infection. Neuropathologic examination showed that the spinal cord and brain lesions were due to *Toxoplasma* infection.

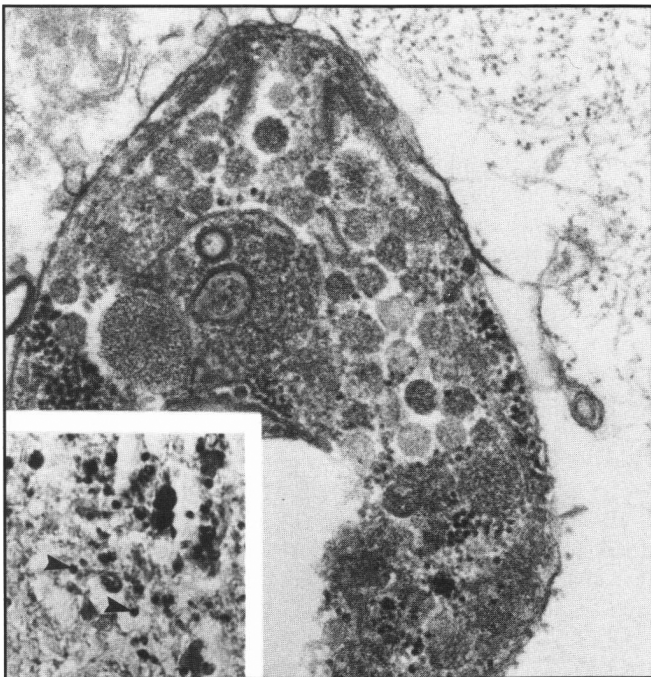
Patients with impaired immunologic defense mechanisms are at risk of developing CNS toxoplasmosis. These patients often have underlying systemic diseases and are treated with immunosuppressive therapy. Autoimmune hemolytic anemia has been reported as an underlying condition in toxoplasmosis in one other case.² Toxoplasmosis has been frequently observed in patients with AIDS.^{3,4,5,7,12,13} In fact, toxoplasmosis has been recognized as the most common cause of focal brain lesions in patients with AIDS.¹²

Pathologic evidence of spinal cord involvement in CNS toxoplasmosis has been recognized infrequently. At autopsy, spinal cord involvement was observed in only one of 16 patients with CNS toxoplasmosis and AIDS.⁵ Townsend et al⁸ found spinal cord involvement in one of 6 cases of CNS toxoplasmosis without AIDS. It is unclear whether spinal cord lesions were recognized clinically in these two cases.

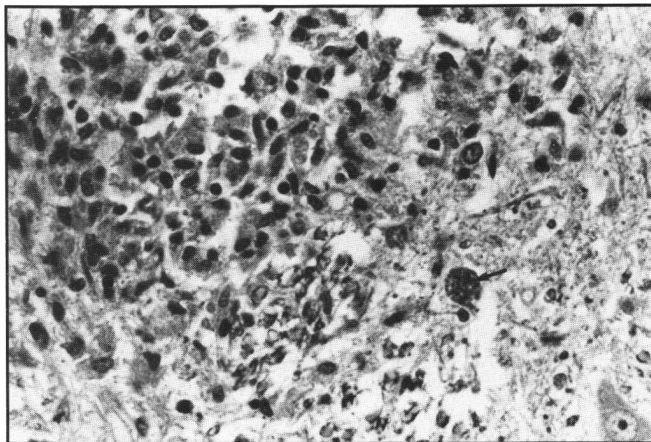
There have been three previous reports of patients presenting with a myelopathy associated with *Toxoplasma* infection. Mehren et al¹⁰ reported an AIDS patient who presented with a cervical myelopathy. This patient also had localized enlargement of the spinal cord on myelography and a CSF pleocytosis. At autopsy, *Toxoplasma* tachyzoites and cysts were found in the cervical spinal cord and brain. This is the only other well documented case of *Toxoplasma* myelitis. Mishra et al¹¹ described a patient with a myelopathy and myelographic blocks at T7 and



A



B



C

Figure 2 — (A) An area of active inflammation showing necrosis of the neuropil and a severe polymorphonuclear response. Fibrin is present in the lumen and wall of a microvessel. Tachyzoites of *Toxoplasma* were easily identified in areas of necrosis (B). The grey matter of the cord at C8 level showing a microglial nodule at the periphery of which a *Toxoplasma* cyst (arrow) is present. (A) x 300; (B) x 57,000; inset x 400, Geimsa stain; (C) x 400.

L2. A biopsy of granulation tissue in the epidural and subarachnoid space showed toxoplasmosis. Koh et al⁹ reported a patient with an acute transverse myelopathy, mild CSF pleocytosis, and serologic evidence of *Toxoplasma* infection. However, there was no pathologic confirmation that this was a toxoplasmic myelitis.

Although toxoplasmic myelitis is uncommon, it should be suspected in immunocompromised patients presenting with intramedullary lesions of the spinal cord. Determinations of serum and CSF titers of *Toxoplasma* antibodies may be helpful in making an antemortem diagnosis of CNS toxoplasmosis.^{4,14} Cerebral toxoplasmosis can respond to therapy with the combination of sulfadiazine and pyrimethamine,^{4,13,15} and it would be expected that this therapy might also be beneficial in cases of toxoplasmic myelitis.

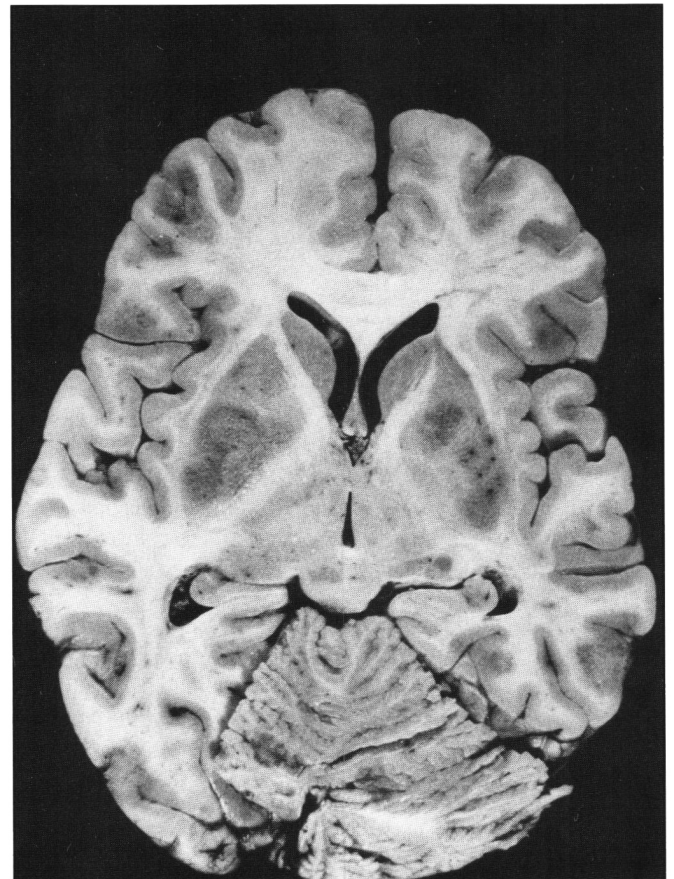


Figure 3 — Horizontal section of brain showing areas of necrosis in both frontal lobes and basal ganglia and in multifocal areas of the cortex and cerebellum. The centrum semiovale is enlarged due to cerebral edema associated with the frontal lobe lesions.

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