

Tuberculosis complicated by spinal cord cryptococcosis: a case report and literature review

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Abstract. – BACKGROUND: Spinal cord involvement by *Cryptococcus neoformans* infection is extremely rare, with most cases occurring in immunosuppressed patients.

CASE PRESENTATION: A young male patient presented with a 10-day history of progressive lower limb weakness culminating in paralysis, urinary incontinence, and constipation. The patient had no known immunodeficiency induced by the human immunodeficiency virus (HIV), malignancy, or organ transplantation.

Laboratory investigations showed elevated C-reactive protein (CRP) levels; however, all other immune indicators were normal. Magnetic resonance imaging (MRI) revealed oval-shaped extradural masses (1.3-3.5 cm) with iso-intense T1-weighted signal and heterogeneous T2-weighted signal in the spinal canal at the level of the 9th thoracic vertebra. The lesions spread along the intervertebral foramen and involved both sides, showing significant enhancement in contrast-enhanced MRI.

The patient was managed surgically, in combination with antifungal and anti-tuberculous therapy and could walk independently 3 months after the treatment. Cryptococcosis was confirmed by histopathology and fungal culture.

CONCLUSIONS: The results suggest that for lesions that affect spinal stability or cause severe nerve damage, surgical treatment should be considered along with medical management.

Key Words:

Spinal cord, *Cryptococcus*, Surgery, Outcome.

Introduction

Cryptococcus neoformans is a non-mycelium-forming, unicellular, budding yeast fungus widely distributed in air, soil, trees, and pigeon droppings^{1,2}. *Cryptococcus* accounts for approximately 1 million infections worldwide and approximately 630,000 deaths annually³⁻⁶. Although

immunocompetent individuals can be infected by *Cryptococcus*, 80-90% of cases occur in patients with cellular immunodeficiency, usually human immunodeficiency virus (HIV)-infected patients with CD4 lymphocyte counts below 100 cells/ μ L^{7,8}. Primary infection is typically acquired by inhaling spores in aerosols released from bird droppings. The most frequently involved organs are the central nervous system and lungs, and most cases commonly present in the central nervous system as meningitis or meningoencephalitis. In contrast, a space-occupying cryptococcal lesion is rare and characterized by a localized, solid, tumor-like mass usually found in the cerebral hemispheres or cerebellum and is extremely rare in the spinal cord⁹⁻¹². The patient has provided informed consent for publication of the case. Here, we report the case of a spinal, extradural cryptococcal granuloma on the background of pulmonary tuberculosis with lymphadenitis. The diagnosis was based on histopathological and culture findings rather than on imaging or laboratory tests. The patient was successfully treated with surgical excision of the lesion and postoperative antifungal (and anti-tuberculous) therapy.

Case Presentation

A 40-year-old man, who was known to have hypertension, presented to our hospital with a 10-day history of abnormal sensation in both lower limbs and a sudden onset of lower limb weakness 3 days prior to presentation. The weakness was progressive and resulted in paralysis (October 14, 2021), urinary incontinence, and constipation. The patient denied any history of trauma to the head or lower back. Physical examination showed grade 0/5 power in both lower extremities, hyperalgesia below the level of the T8 dermatome, and

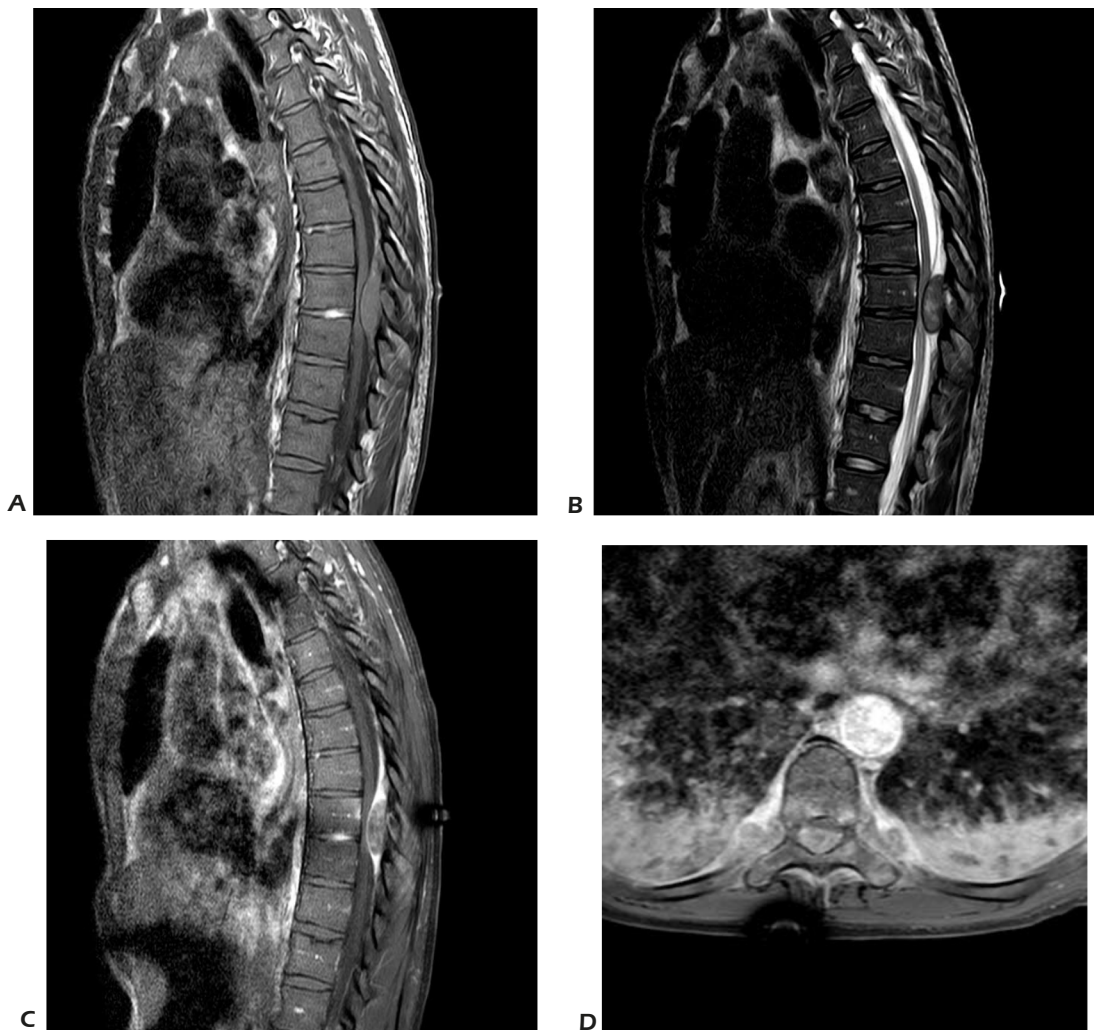


Figure 1. An isointense oval shape, was noted in the extradural spinal canal at the T9 level on (A) T1, mixed (B) T2 signal mass opacity. The lesion seemed to invade bilaterally along the intervertebral foramen, with unclear margins. C-D, After enhancement, there was evident partial enhancement of the lesion, adjacent dural thickening, enhancement, long T2 signal in the adjacent T9 vertebral body and accessories, enhancement.

positive Babinski sign bilaterally. The rest of the physical examination was unremarkable.

Upon admission, the patient had a high-sensitivity C-reactive protein (CRP) level of 71.19 mg/L and a normal white blood cell count. He tested negative for HIV antibodies, *Treponema pallidum*, and serum hepatitis A, B, C, and E. Enhanced magnetic resonance imaging (MRI) revealed an isointense oval shaped mass, approximately 1.3-3.5 cm in size, in the extradural spinal canal at the T9 level on T1 images and mixed T2 signal mass opacity. The lesion seemed to invade bilaterally along the intervertebral foramen with indistinct margins. After enhancement, there was obvious partial enhancement of the lesion, adja-

cent dural thickening, and a long T2 signal in the adjacent T9 vertebral body and accessories (Figure 1). The patient was treated with methylprednisolone and mannitol, but the symptoms did not improve, and the patient remained paralyzed.

On further questioning, it was revealed that the patient had had a productive cough for 7 months, without fever, but had not been concerned and had not sought immediate medical attention. On April 25, 2021, a mass was discovered in his neck, and ultrasound examination showed features of reactive lymphadenopathy. The patient was examined at a local hospital, and antibiotics were prescribed but there was no change in the patient's symptoms. A lymph node biopsy was performed,



Figure 2. Fibrous tissue hyperplasia with multicentric diffuse lesions. There is central necrosis within the mass and there are many encapsulated fungi between fibroblasts, inside and outside the cytoplasm of phagocytes, and in the necrotic tissue. Magnification: 200 ×.

which showed hyperplastic fibrous tissue with a small number of inflammatory cells but no lymphatic tissue. A computed tomography (CT) scan was then done, which showed pulmonary changes in keeping with tuberculosis. Purulent material from the cervical lymph node was then collected and tested for the *rpoB* gene, and rifampicin resistance rapid testing was performed. There was amplification of *M. tuberculosis* with sensitivity to rifampicin; probe tests A to E were all positive. Mixed lymphocyte culture showed the following results: $58 \times 10^6/\text{mL}$, an antigen stimulation + γ -interferon 94 spot forming cells (SFC)/ 2.5×10^5 peripheral blood mononuclear cell (PBMC) and B antigen stimulation + γ -interferon 66 SFCs/ 2.5×10^5 PBMC. This indicated a positive result. Fluorometric acid-fast staining of pus in the cervical lymph nodes, *M. tuberculosis* polymerase chain reaction (PCR), and the purified protein derivative (PPD) test showed positive results. The patient was, therefore, diagnosed with pulmonary tuberculosis and tuberculous lymphadenitis, and anti-tuberculosis treatment was administered for 5.5 months. Repeat lung CT did not reveal any significant change in the lung lesions.

The patient was administered anti-tuberculosis treatment for 5.5 months, but the intrapulmonary lesions were not absorbed. Enhanced MRI of the thoracic spine suggested an extradural space-occupying lesion in the spinal canal at the T9 level with inhomogeneous enhancement and significant compression of the corresponding region of the spinal cord resulting in bilateral lower limb paralysis. To relieve spinal cord compression and

to further confirm the diagnosis, the patient underwent surgery and complete excision of the lesion. The macroscopic view of the excised lesion indicated an approximately $3.0 \times 2.5 \times 0.7$ cm with a gray-red and gray-yellow excision surface and local regions of necrosis. Light microscopy indicated fibrous tissue hyperplasia, within which multicentric diffuse lesions were observed, and necrosis was observed in the center of the lesion. Many fungi with capsules were found between fibroblasts, inside and outside the cytoplasm of phagocytes, and in the necrotic tissue, and lymphocytic infiltration was found in the lesion (Figure 2). *Cryptococcus neoformans* was detected by tissue culture. Rapid *M. tuberculosis* culture and manual *M. tuberculosis* culture showed negative results. Tests for serum fungal (1-3)- β -glucan and *Aspergillus* galactomannan were also negative. Total T cells (CD3+/CD45+) were $342/\mu\text{L}$, helper T cells (CD4) were $136/\mu\text{L}$, suppressor T cells (CD8) were $190/\mu\text{L}$, and total lymphocytes (CD45+) were $513/\mu\text{L}$. Therefore, the patient was diagnosed with spinal cord cryptococcosis.

Post-surgery, the patient received oral voriconazole (0.2 g three times per day) combined with anti-tuberculous therapy and rehabilitation training. One and a half months later, MRI revealed no obvious protrusion and bulging of the intervertebral discs at the T8/9 and T9/10 levels and no narrowing of the subdural space (Figure 3). Two months later, chest CT revealed obvious shrinkage of the diffuse lesions in both lungs. Three months later, the numbness of both lower limbs disappeared, and the patient could walk independently.

Discussion

C. neoformans is a yeast-like mold that is considered a conditional pathogen. Pigeons are the intermediate hosts of human *C. neoformans* infection and are the primary source of infection. *C. neoformans* infection usually occurs in patients with immune suppression such as those with tuberculosis, diabetes, leukemia, lymphoma, organ transplantation, acquired immunodeficiency syndrome (AIDS), or histoplasmosis¹³. In this instance, nifedipine controlled-release tablets are being used to treat a medical intern with hypertension who has had the condition for a year. May 2021 treatment for tuberculosis and lymphadenopathy included isoniazid, rifampicin, and ethambutol. He had no history of drug allergies and



Figure 3. One and a half months later, MRI revealed no obvious protrusion and bulging of the intervertebral discs at the T8/9 and T9/10 levels and no narrowing of the subdural space (A). Slight long T2 signal visible in T9. No significant protrusion or bulging of the intervertebral disc, no stenosis and deformation of the subdural space, and long T2 signal visible in the spinal cord at the T9-10 level (B-C).

tested negative for *Treponema pallidum*, serum hepatitis A, B, C, and E, as well as HIV antibodies. However, at 136 cells/L, CD4 levels were substantially lower; therefore, the patient was considered immunocompromised and susceptible to opportunistic cryptococcosis. *Cryptococcus* has a relatively high affinity for the central nervous system, with most cases involving the meninges, brain, and basal ganglia but invasion of the spinal cord is rare¹⁴. The incidence of cryptococcosis in the spinal cord is estimated at 5%-10% of all cases. Isolated cryptococcosis of the spinal cord as the only manifestation of disease is extremely rare¹⁵⁻²², and only one case of spinal cord cryptococcosis has been reported in China^{23,24}. The symptoms of spinal cord cryptococcosis are atypical, with elevated erythrocyte sedimentation

rate (ESR; sensitivity 76-81%) and CRP (sensitivity 100%). The accuracy of serum cryptococcal antigen testing has been reported to be 66% in immunocompetent patients with cryptococcosis^{25,26}. Therefore, spinal cord cryptococcosis is difficult to diagnose through a simple physical examination, and biopsy and microbiological culture are required for a definitive diagnosis. In the present case, the patient presented with bilateral lower limb weakness progressing to paralysis as the primary clinical symptom. At the time of consultation, only ESR and CRP were elevated, and serum cryptococcal antigen testing was negative. An MRI of the thoracolumbar spine revealed an oval mass in the extradural spinal canal at the T9 level. Based on previous studies, the imaging presentation of thoracic spine cryptococcosis may

lack specificity and further examination is needed to distinguish it from tuberculosis²⁷⁻²⁹. The patient in the present case has pulmonary tuberculosis and tuberculous lymphadenitis, which further complicated clinical diagnosis. To confirm the diagnosis and relieve the symptoms of spinal cord compression, the patient underwent surgery. Post-operative histopathology and culture suggested cryptococcosis. After postoperative antifungal and anti-tuberculosis treatment and rehabilitation training, the patient regained the ability to walk. In addition, the patient's productive cough and pulmonary radiological changes resolved. An MRI of the thoracic spine indicated no protrusion of the T9 intervertebral disc and no stenosis or deformation of the corresponding subdural space.

Conclusions

The patient had pulmonary tuberculosis in addition to being immunocompromised, both of which predisposed him to cryptococcal infection. However, cryptococcosis of the spinal cord is still rare. Furthermore, the patient presented with sudden paralysis. Because the MRI features of spinal cord cryptococcosis have not been well described, the possibility of cancer could not be ruled out preoperatively. To provide rapid relief of spinal cord compression symptoms, the patient underwent surgical treatment, and the diagnosis was confirmed by postoperative pathology and culture. The paralysis caused by spinal cord compression was also rapidly relieved, and the patient could walk independently after 3 months. The findings in this case provide good evidence for surgical management of spinal cord cryptococcosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

The patient has provided informed consent for publication of the case.

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