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Short segment myelitis as a dominant manifestation of cryptococcal infection: a case report

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Abstract
Cryptococcal infection of central nervous system commonly involves meningitis or meningoencephalitis, but rarely mimics inflammatory myelitis. We present short segment myelitis as a dominant manifestation caused by *Cryptococcus neoformans* in a patient with nephrotic syndrome under immunosuppressive therapy. This case report highlights *Cryptococcus neoformans* as a potential etiological factor for short segment myelitis in immunocompromised hosts.

Keywords *Cryptococcus neoformans*, Short segment myelitis, Rituximab, Tacrolimus, Nephrotic syndrome

Background

Cryptococcus neoformans, an encapsulated yeast fungus, causes fungal infections in both immunocompromised and immunocompetent hosts [1]. The most frequently affected sites of cryptococcal infection are meninges and lung [2]. Meningitis and meningoencephalitis are major manifestations of central nervous system cryptococcosis [3]. To our knowledge, eight cases of cryptococcal myelopathy have been reported in the available literature [4–11]. Among them, one patient with systemic lupus erythematosus had longitudinal myelitis secondary to *Cryptococcus laurentii* pneumonia [11]. Other seven patients were immunocompetent hosts [4–10]. Here, an immunocompromised patient mainly manifested with myelitis due to cryptococcal infection is reported.

Short segment myelitis (SSM), defined as spinal cord lesions extending fewer than 3 vertebral segments, was commonly regarded as clinical characteristics of central nervous system inflammatory demyelinating disorders, including multiple sclerosis, clinically isolated syndrome [12], and neuromyelitis optica spectrum disorders [13]. In this paper, we describe a nephrotic syndrome patient treated with immunosuppressants who developed cryptococcal SSM and meningitis. This report discloses *Cryptococcus neoformans* as a potential cause of SSM in immunocompromised hosts.

Case presentation

In November 2023, a 38-year-old male, with weakness of proximal lower limbs and numbness below the xiphoid level for 14 days, presented to our neurology department. Numbness initiated at bilateral sole and progressively extended to the xiphoid level. He also complained of

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hypoesthesia of the ulnar left hand, right hand, and right forearm for 3 days. No pain on eye movement or blurred vision were reported. Bladder and bowel functions were normal. In June 2021, the patient was diagnosed with nephrotic syndrome and his renal biopsy showed atypical membranous nephropathy with tubulointerstitial damage. Prednisone was administered for 2.5 years, initially at a dose of 40 mg daily, and subsequently tapered down to 10 mg daily. He received rituximab 1 mg twice on September 9, 2022 and September 22, 2022. Subsequently, tacrolimus was taken for the last 11 months, started at 2 mg daily for the first 6 months, and currently maintained at 1 mg daily. He had a 6-month history of diabetes mellitus secondary to oral prednisone treatment with unsatisfactory blood glucose control. No history of prodromal infection, infectious diseases, trauma, surgery, smoking, or drug misuse was documented.

His neurological examination showed symmetrical proximal lower extremities weakness (manual muscle testing score: 4/5), hypoesthesia below the xiphoid level, hypoesthesia of the ulnar left hand, right hand, and right forearm, and diminished deep sensibility on bilateral ankles, knees, and hip joints. Ankle reflex and knee jerk reflex were decreased. Bilateral Babinski's signs were positive. Examinations of cranial nerves and other deep reflexes were normal. Meningeal irritation sign was negative.

Laboratory tests showed that 24-hour urine protein quantification was 9.02 g/L (normal range 0–0.05 g/24 h). The glycosylated hemoglobin level was 12.2% (normal range 4.0–6.0%). Decreased serum immunoglobulin G (IgG) and immunoglobulin M (IgM) levels were identified (4.35 g/L, 0.30 g/L; normal range 7.00–16.00 g/L, 0.40–2.30 g/L). Decreased number of peripheral $CD3^{-}CD19^{+}$ B cells was observed (1.24/μL; normal range 118–642/μL). The numbers of $CD3^{+}CD4^{+}$ T cells, and $CD3^{+}CD8^{+}$ T cells were normal (415.52/μL, 452.93/μL; normal range 396–1309/μL, 224–1014/μL). Serum creatinine and urea levels, and estimated glomerular filtration rates were normal. Liver function, electrolyte, C-reactive protein, erythrocyte sedimentation rate, blood cell count, and urine and stool test results were normal. The patient was negative for HIV, hepatitis antibodies, and syphilis antibodies. Serum complement (C3 and C4) levels were normal. There was no signs of tuberculosis or autoimmune systemic disease. Serum and cerebrospinal fluid (CSF) myeline oligodendrocyte glycoprotein IgG, glial fibrillary acidic protein IgG, and anti-aquaporin 4 IgG were negative.

The CSF findings were shown in Table 1. The first lumbar puncture revealed an elevated intracranial pressure (220 mmH_2O). CSF analysis showed an increased protein level of 4.26 g/L (normal range 0.12–0.6 g/L) and hypercellularity of 116×10^6/L with 98% lymphocytes. A decreased CSF glucose level was observed (2.61 mmol/L) and the concurrent serum glucose level was 8.93 mmol/L (decreased ratio of CSF glucose to serum glucose: 0.29). Cryptococcus was detected by CSF smear. The serum cryptococcus capsular antigen was positive and the titer was 1:8. CSF was positive for cryptococcus capsular antigen. *Cryptococcus neoformans* was detected in CSF by next-generation sequencing with a species-specific read number of 2. Type 3 oligoclonal bands (OBs) were observed in CSF with additional bands in serum. Cytomegalovirus, EB virus, herpes simplex virus, varicella-zoster virus, human herpes virus 6, and tubercule bacilli, were not detected in CSF by polymerase chain reaction.

A spinal cord magnetic resonance imaging (MRI) revealed hyperintensity at the C4-5 level on T2-weighted images (Fig. 1A and B, and 1C). Gadolinium-enhanced MRI showed a slight enhancement of the posterior part of the lesion (Fig. 1D and E, and 1F). No significant abnormalities were observed on brain MRI and thoracic and lumbar medulla MRI.

These findings confirmed the diagnosis of cryptococcal SSM and meningitis. The patient underwent antifungal therapy with daily doses of 0.6 g fluconazole and 8 g fluorocytosine, accompanied by a decline of prednisone to 5 mg and cessation of tacrolimus. The patient had an improvement of lower limbs weakness (manual muscle testing score: 5/5) and resolution of hypoesthesia below the xiphoid level after two months. Numbness in the

Table 1 CSF and blood examinations of the patient before and after anti-fungal treatment

Items	November 2023	January 2024	April 2024
Intracranial pressure (mmHg)	220	141	148
CSF protein level (g/L)	4.26	2.46	1.22
CSF WBC count (*10^6/L)	116	42	27
CSF glucose level (mmol/L)	2.61	2.03	3.12
Blood glucose level (mmol/L)	8.93	5.16	11.17
Ratio of CSF glucose to serum glucose	0.29	0.39	0.28
CSF cryptococcal smear	Positive	Negative	Negative
CSF cryptococcus capsular antigen	Positive	Negative	Negative
Serum cryptococcus capsular antigen	Positive	Negative	Negative

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell

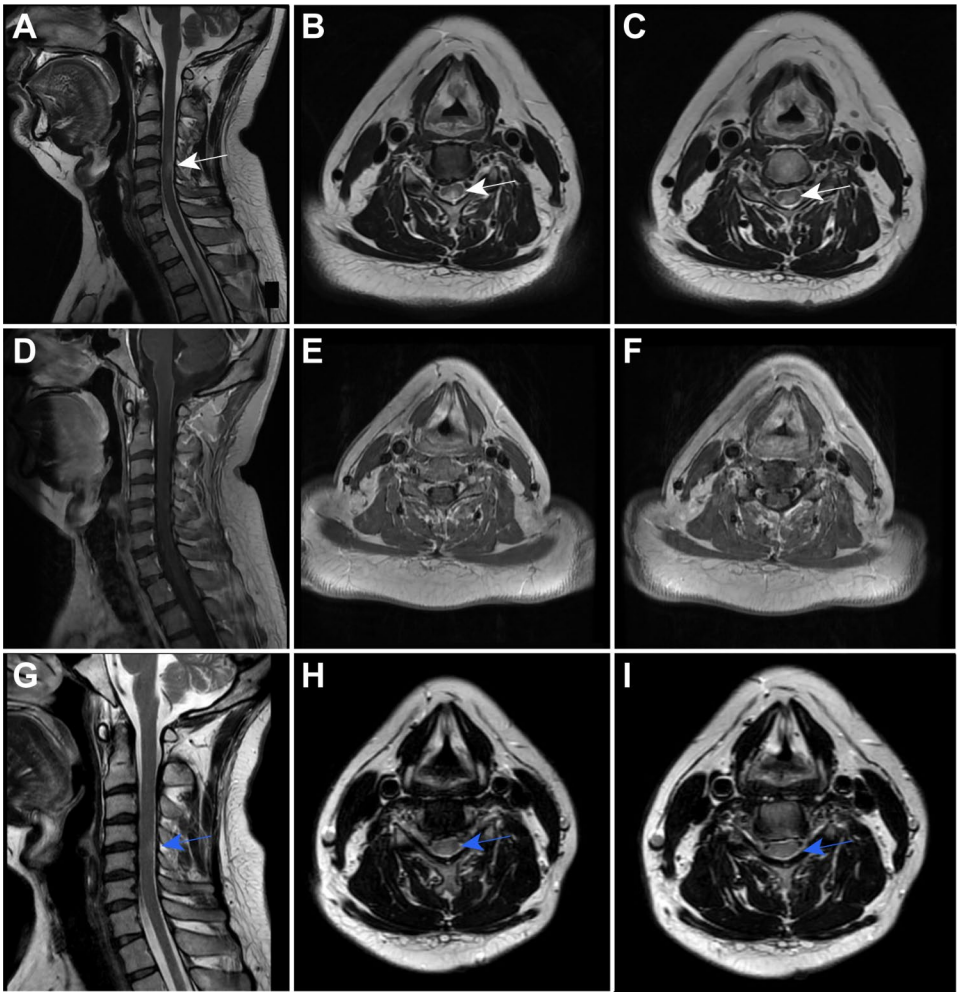

Fig. 1 Cervical spinal MRI findings of the patient. The hyperintensity extending along C4-5 in the sagittal T2-weighted image in November 2023 (white arrow, **A**). The lesion primarily located in the posterior part on axial T2-weighted images (white arrow, **B** and **C**). A slight contrast enhancement in the posterior part of the lesion in sagittal (**D**) and axial (**E** and **F**) views of spinal MRI with gadolinium enhancement in November 2023. After 5-month antifungal therapy, near-resolution of the lesion on the cervical spinal MRI in April 2024 (blue arrow, **G**, **H**, and **I**)

right hand and forearm still remained. In January 2024, repeated lumbar puncture revealed a normal intracranial pressure (141 mmH_2O). Both the CSF protein level and white blood cell count decreased (2.46 g/L; 42×10^6/L). The CSF glucose level was 2.03 mmol/L and the simultaneous blood glucose was 5.16 mmol/L (ratio: 0.39). Both CSF and serum samples were negative for cryptococcus capsular antigen. At the last follow-up visit in April 2024, the CSF test showed a reduction in the white blood cell count and protein level (27×10^6/L; 1.22 g/L). The glycosylated hemoglobin level decreased to 6.2%. The CSF glucose level was 3.12 mmol/L and the simultaneous blood glucose was 11.17 mmol/L (ratio: 0.28). The lesion significantly diminished on cervical spinal MRI (Fig. 1G and H, and 1I). His numbness of the ulnar left hand, right hand, and right forearm almost disappeared and the renal function was stable.

Discussion

Myelitis requires prompt and a broad-spectrum etiological screening for treatment. Fungal myelopathies are rare, especially in patients with nephrotic syndrome.

To the best of our knowledge, there have been eight reported patients of myelopathy caused by cryptococcus infection in the available literature [4–11]. Among them, seven patients were immunocompetent and one patient with systemic lupus erythematosus was under immunosuppressants. Our patient was an immunocompromised host. He was treated with corticosteroids, rituximab, and tacrolimus for nephrotic syndrome treatment. Immunotherapy potentially compromised the immune function and thus rendered him susceptible to opportunistic infections, which was revealed by the reduced levels of serum IgG and IgM. Two patients reported by Scullery [7] and Qu [9] had lung involvement apart from spinal cryptococcoma. There was no evidence of cryptococcal

infection in other areas of the body in our case. Of these reported patients with cryptococcal myelopathy, spinal MRI of five patients was documented [4, 8–11]: three cases presenting with longitudinally extensive myelitis (>3 vertebral segments) on T2-weighted images [9–11]; other two patients with tumor-like intense enhancement of the lesion on spinal MRI with gadolinium enhancement [4, 8]. By contrast, our patient had a mild enhancement on cervical spinal contrast-enhanced T1-weighted MR images. Five reported patients performed operation to excise spinal cryptococcoma [4–8]. Our patient did not undergo surgery because of the absence of spinal cryptococcoma and he responded well to antifungal treatment.

Cryptococcus neoformans is an opportunistic pathogenic fungus that preferentially affects HIV-infected patients, organ transplant recipients, and patients with immunomodulatory therapy [14–16], and occasionally appears in individuals with normal immunity [10, 17–19]. Rituximab, a human/mouse chimeric monoclonal antibody against CD20, has been widely used to prevent the recurrence of nephrotic syndrome [20, 21]. Cryptococcal osteomyelitis [22], cryptococcal meningitis [21, 23], cryptococcal meningoencephalitis [24], and disseminated *Cryptococcus neoformans* infection [25–28] were observed in several patients treated with rituximab. In our case, the reduced number of $CD3^+CD19^+$ B cells and decreased levels of serum IgG and IgM were largely attributed to rituximab. Calcineurin inhibitors (tacrolimus) has in vitro activity against fungi, including *C. neoformans* [29], but most studies implicated that the immunosuppression of tacrolimus exceeds its antifungal effect in vivo and tacrolimus is a risk factor for fungal infections [30, 31]. Several case reports and a pooled cases analysis showed that cryptococcal meningitis [32], pulmonary cryptococcosis [33], cutaneous cryptococcosis [34], and disseminated cryptococcosis [35, 36], occurred in patients with nephrotic syndrome, which implied a potential susceptibility to cryptococcosis in nephrotic syndrome. It is supposed that our patient suffered from cryptococcosis due to the combined effect of immunotherapy and nephrotic syndrome.

In conclusion, we reported a rare case of cryptococcal SSM and meningitis. We aimed to raise awareness regarding *Cryptococcus neoformans* as a potential cause for SSM in patients with nephrotic syndrome on immunotherapy. Early recognition of an etiological factor in myelitis is an initial step towards achieving a comprehensive cure.

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Data availability
All data generated or analyzed during this study are included in this article.

Declarations

Ethical statements
Our study did not require an ethical board approval because it is a case report.

Conflict of interest
The authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

Consent to participate
Written informed consent for participate was obtained from the patient.

Consent for publication
Written informed consent for publication was obtained from the patient.

Competing interests
The authors declare no competing interests.

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