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Letter to the Editor: New Observation

Cryptococcus neoformans Cerebellitis: A Rare Presentation of Cryptococcal Central Nervous System Infection

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Cryptococcal infection is a well-established cause of chronic meningitis, usually affecting immunocompromised individuals[1] Most patients with central nervous system (CNS) cryptococcal infection develop meningitis with correlating leptomeningeal enhancement on imaging.[1] To our knowledge, only seven cases of cryptococcal cerebellitis have been reported in the literature.[1,2]

A middle-aged otherwise healthy man presented to our emergency department with a two-week history of gradual onset bifrontal and temporal headache with associated photophobia and phonophobia. Initial assessment revealed sore throat, otalgia and a temperature of 41°C. He also endorsed drenching night sweats and six pounds of weight loss over the last two weeks. In the last two days, he developed difficulty ambulating and was veering to the left side when walking. The patient's spouse also noted apathy in the absence of past psychiatric history. He had no recent travel, sick contacts, consumption of raw meats, recent vaccinations or insect bites. The patient had not suffered recurrent fevers or infections in the past, and systemic review was unremarkable for rashes, ulcers or joint pain. Family history was unrevealing.

Neurological examination revealed gaze-evoked nystagmus, impaired smooth pursuit and large amplitude hypermetric saccades in the vertical and horizontal planes. He had scanning dysarthria and bradyphonia. He had no sensorimotor deficits. There was appendicular dysmetria on finger-to-nose testing bilaterally, although worse on the left, as well as rebound phenomena. Heel-to-shin testing was normal bilaterally. His gait was severely wide-based and unsteady, with left lateral veering.

His initial CT head showed left cerebellar edema with effacement of the fourth ventricle and early signs of hydrocephalus. This was followed up with an MRI of the brain with gadolinium, which showed extensive leptomeningeal enhancement along the bilateral cerebellar hemispheres (Figure 1) and associated left cerebellar edema with mass effect on the fourth ventricle resulting in moderate obstructive hydrocephalus (Figure 2). CT of the chest, abdomen and pelvis demonstrated diffuse lymphadenopathy. The differential diagnosis was broad and included an atypical infectious process, tuberculosis, sarcoidosis and a malignant process.

A lumbar puncture could not be safely performed due to the degree of obstructive hydrocephalus and risk for herniation. Cerebrospinal fluid (CSF) was therefore obtained neurosurgically via an Ommaya reservoir. CSF analysis revealed the following: White blood cells, 4 × 10E6/L; glucose, 3.7 mmol/L; protein, 116 mg/L; and RBC, 99 × 10E6/L. Herpes simplex virus, Epstein-Barr virus, cytomegalovirus and Varicella zoster virus polymerase chain reaction were negative. Syphilis and HIV serology were negative. West Nile virus and Lyme serology were negative. CSF cryptococcal antigen was positive, and CSF culture grew *Cryptococcus (C.) neoformans*. CSF flow cytometry revealed reduced B-cell cellularity, and cytology was negative for malignant cells. Serial blood cultures were negative. Right axillary core biopsy and right temporal bone and dural biopsies all revealed non-necrotizing granulomas, and stains for micro-organisms including acid-fast bacilli, periodic acid-Shiff with diastase and Grocott–Gömöri's methenamine silver stains for fungus were negative. Serum CD4 count was normal, and CD4/CD8 ratio was 1.7. Serum IgA was minimally elevated at 4.55 g/L, IgG normal at 14.4 g/L and IgM normal at 1.24 g/L.

The patient was started on the appropriate antifungal therapy for *C. neoformans*, which involved induction with L-amphotericin 400 mg intravenously daily and flucytosine 2000 mg orally q6 hours. He showed significant improvement in gait, ataxia and headache. His follow-up imaging showed improvement in cerebellar swelling, leptomeningeal enhancement and obstructive hydrocephalus. He was subsequently discharged in stable condition with outpatient neurology, respirology and infectious disease follow-up. In follow-up, he continued to improve clinically with antifungal therapy alone.

Cryptococcus is an encapsulated yeast commonly found in soil contaminated with bird droppings.[3] Infection occurs following inhalation of spores, resulting in primary pulmonary infection with potential hematogenous dissemination to the CNS.[3,4] Established risk factors for cryptococcal infection include HIV/AIDS, solid organ or hematopoietic stem cell transplantation, immuno-suppressive therapy and hematologic malignancies such as lymphoma and leukemia.[4,5] Sarcoidosis has also been associated with cryptococcal infection, although the underlying mechanism remains incompletely understood.[6] There have been reports of cryptococcal CNS infection in patients with pre-existing and new

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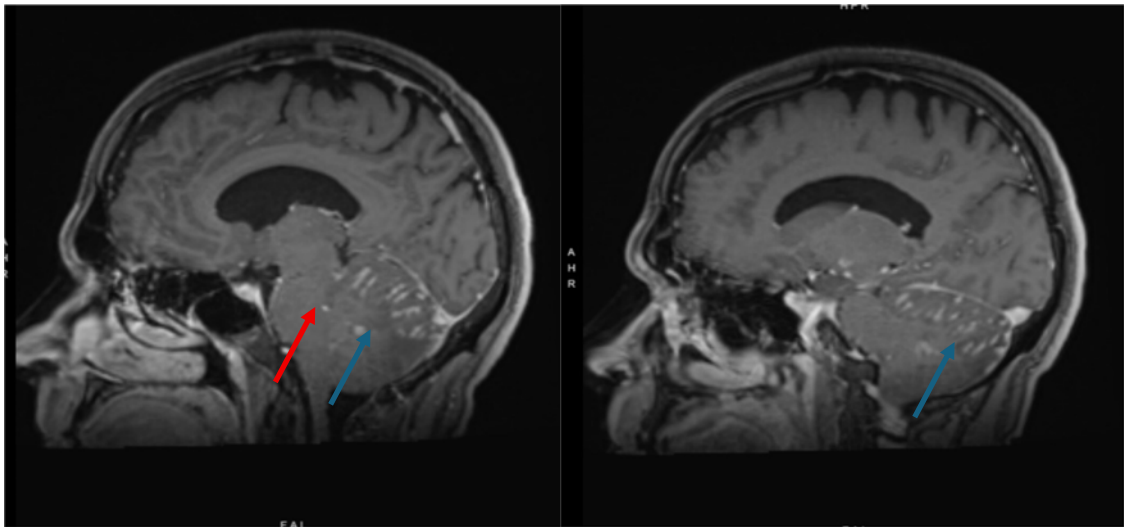


Figure 1. Sagittal T1 post-gadolinium brain MRI showing diffuse cerebellar swelling and leptomeningeal enhancement (blue arrows) resulting in compression of the fourth ventricle (red arrow) and obstructive hydrocephalus.

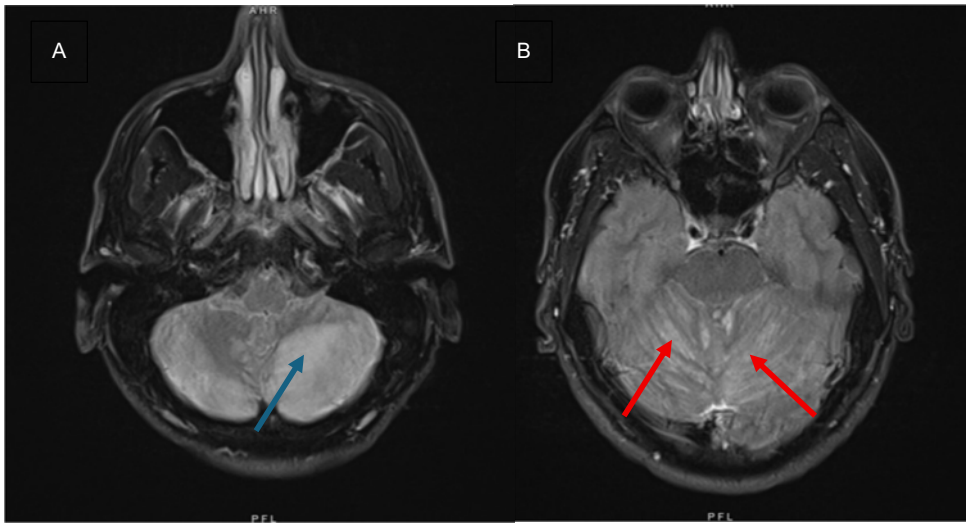


Figure 2. Axial T2 fluid-attentuated inversion recovery (FLAIR) post-gadolinium brain MRI showing asymmetric pan-cerebellar swelling with associated edema (blue arrow) and leptomeningeal enhancement (red arrows).

diagnoses of sarcoidosis.[5,6] Previous studies have demonstrated reduced numbers of circulating peripheral CD4+ T lymphocytes and impaired cell-mediated immune responses, or anergy, in some patients with sarcoidosis.[6,7] This is thought to be a result of sequestration of T lymphocytes at sites of granulomatous inflammation and does not appear to confer immune compromise in such patients[6,7] Additionally, there have been reports of sarcoid-like reactions occurring in patients with CNS cryptococcal infection, which makes the diagnosis more nuanced, especially in patients without a history of pre-existing sarcoidosis, such as ours.[8] Our patient was not started on immunotherapy since he continued to improve neurologically and remained otherwise asymptomatic without symptoms of other organ involvement. His chest radiographic findings remained the same despite antifungal therapy. This, together with negative biopsy staining, is suggestive of sarcoidosis rather than a sarcoid-like reaction.

In most cases of CNS cryptococcosis, neuroimaging demonstrates leptomeningeal enhancement, nodular enhancement or cryptococcomas, most commonly involving the basal ganglia, thalami and cerebral hemispheres.[3,4] In contrast to pathogens such as Varicella zoster virus, which have a well-recognized association with cerebellitis, cerebellar-predominant involvement is rarely described in cryptococcal infection.[9] Cryptococcal cerebellitis typically presents as a subacute headache and ataxia.[1,2] Cerebellar swelling, increased signal and leptomeningeal enhancement are common findings on imaging[2,10] Due to the anatomy, obstructive hydrocephalus due to compression of the fourth ventricle is not uncommon, and this makes CSF sampling challenging due to the risk of herniation.[2,11] While cerebellar involvement tends to be bilateral, it is often asymmetrical both radiologically and clinically.[1,2]

This report describes cryptococcal cerebellitis caused by *C. neoformans* in a patient with non-necrotizing granulomas. Although CNS cryptococcal infection has been reported in association with sarcoidosis, the nature of this relationship remains incompletely understood as highlighted above. There have also been reports of sarcoid-like reactions in patients with CNS cryptococcal infection, which makes diagnosis and

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management more nuanced in such patients. The novelty of this case lies in its striking cerebellar phenotype, with prominent cerebellar dysfunction dominating the clinical presentation.

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Consent. Written informed consent was obtained from the patient.

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