

Cryptococcus neoformans Meningoencephalitis in a Young Immunocompetent Patient

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Abstract

Cryptococcal meningitis is mainly seen in immunocompromised patients, but in recent years, there has been an increase in cases involving patients with no known immunodeficiencies. These patients have symptomatic presentations that range from indolent and mild to typical and severe. We present a case of cryptococcal meningitis in an immunocompetent young patient with a chronic headache. The patient underwent imaging which showed diffuse leptomeningeal enhancement and a lumbar puncture which confirmed *Cryptococcus neoformans*. She underwent guideline-based treatment for cryptococcal meningitis and improved clinically. Cryptococcal meningitis should be considered in immunocompetent patients who present with typical signs of symptoms of meningitis, particularly chronic headaches and altered mental status.

Keywords

cryptococcal meningitis, meningoencephalitis, immunocompetent, diffuse leptomeningeal enhancement

Introduction

Cryptococcosis is an invasive fungal infection due to *Cryptococcus neoformans*, with clinical manifestations ranging from asymptomatic pulmonary colonization to disseminated disease and life-threatening meningoencephalitis. While immunocompromised individuals comprise the vast majority of cases, a recent trend has been recognized in cases with patients in an apparent immunocompetent state. This low-incidence yet high-mortality infection can yield even higher mortality rates if the diagnosis is delayed due to subacute presentations and nonimmunocompromised patients.¹ We present a case of *C. neoformans* meningoencephalitis in an immunocompetent young individual with subacute manifestations.

Case Description

A 26-year-old female with a history of migraine headaches and bipolar disorder on medications was presented with progressively worsening headaches for about a month and was unresponsive to home migraine medications. On arrival to the emergency department, the initial workup was notable for a complete blood count with mild leukocytosis (white blood cell [WBC] count of 14.8; normal range 3.74–10.9) and an otherwise unremarkable complete metabolic panel. The head computed tomography (CT) scan obtained was negative for

acute intracranial pathology causing the patient to be admitted for further evaluation and workup. Further imaging with a neck magnetic resonance angiography was nonrevealing, and the head magnetic resonance imaging (MRI) did not show any significant intracranial stenosis, proximal occlusion or aneurysm. It also did not show evidence of hemodynamically significant cervical stenosis or dissection. Magnetic resonance venography of the head with and without contrast was negative for dural vein or deep cerebral vein thrombosis. The patient tested negative for HIV and does not use glucocorticoids or other immunosuppressants.

However, a brain MRI with and without contrast showed a subcentimeter focus of restricted diffusion in the right caudate head, possibly representing a small acute infarction—associated mild T2 flair hyperintensity. Diffused leptomeningeal enhancement throughout the visualized brain, particularly bilateral cerebellar hemispheres. This was nonspecific and may

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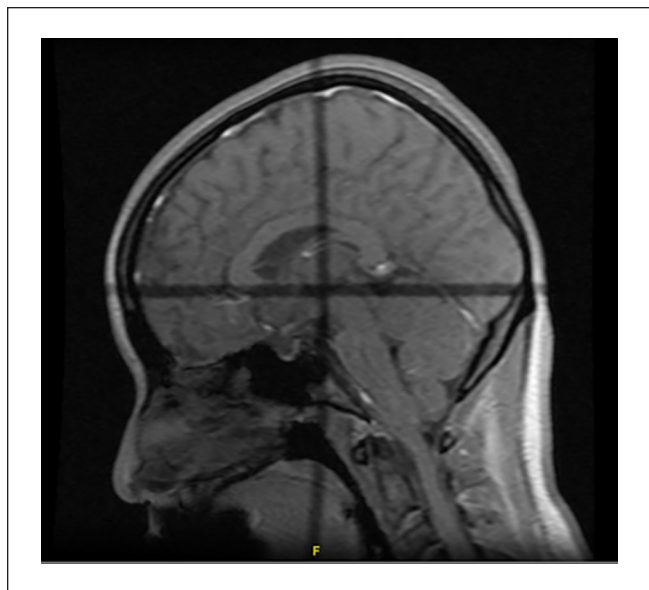


Figure 1. Leptomeningeal enhancement on brain MRI, a finding which may be seen in cryptococcal meningitis.

relate to meningitis or other etiology. The patient had low-lying cerebellar tonsils. Teleneurology was consulted and recommended antiplatelet therapy with aspirin 81 mg daily with a blood pressure goal in the normotensive range. Lumbar puncture was performed, and the cerebral spinal fluid (CSF) analysis showed WBC of 96 (normal range 0-5), red blood cell count of 2 (normal is 0), lymphocyte of 96 (normal range 40-80), monocytes of 4 (normal range 15-45), glucose of 43 (normal range 40-70), and total protein of 86 (normal range 15-45). The HIV test was negative. Cryptococcal antigen serum titer was 1:2560, and cryptococcal antigen in the serum was positive. CSF biofire was significant for *C. neoformans* and was negative for all other pathogens. CSF cultures grew presumptive identification of 3+ *C. neoformans*. EEG was done and did not show any epileptiform activities.

Infectious disease was consulted, and the patient was started on liposomal amphotericin B 5 mg/kg daily plus flucytosine 6 g daily divided into 4 doses for 2 weeks. The patient developed acute kidney injury likely due to amphotericin administration; nephrology was consulted, and recommended continued fluid management with subsequent improvement in creatinine. She had 2 serial lumbar punctures with significant improvement of the headaches and was discharged with fluconazole 800 mg daily for 8 weeks and then 400 mg daily for 1 year and was told to follow-up with infectious disease (Figure 1).

Discussion

The majority of patients with *C. neoformans* meningitis are immunocompromised. The most common sources of immunosuppression are HIV, chronic glucocorticoid use, solid

organ transplantation, cancer, organ failure, and hematologic malignancies.¹ However, there is a significant minority of patients with *C. neoformans* meningitis who have no risk factors; in one study of 15 medical centers in the United States between 1990 and 1996, 30% of all HIV-negative patients with central nervous system cryptococcosis had no risk factors.² In recent years, there has been a trend toward more cases involving HIV-negative and nontransplant patients.³

In immunocompetent patients, *C. neoformans* meningitis is more likely to present with subacute manifestations. A fever is observed in only approximately 50% of cases, and many patients have symptoms up to several months before the diagnosis. In one case report, a 37-year-old male with a history of alcohol abuse presented with persistent worsening headaches, dysarthria, and visual and tactile hallucinations after a recent 3-week hospitalization for alcohol withdrawal, which had required intubation. After a negative drug screen and CT of the head, he underwent a lumbar puncture which showed lymphocyte predominance, low CSF glucose, and slightly elevated opening pressure. Subsequent CSF analysis showed that encapsulated yeast identified as *C. neoformans* and cryptococcal antigen titer were positive. As this patient had no risk factors associated with the disease, his medical team suspected that he had occult cryptococcosis, which may have been activated by the stress of his recent hospitalization.¹

Cryptococcal meningitis should be considered in immunocompetent patients presenting with symptoms suggestive of subacute to chronic meningitis, such as headaches and altered mental status, in which more common causes, such as drug intoxication, have been ruled out. On CSF testing, patients often have low glucose levels and elevated protein levels with lymphocytic predominance. However, there have been cases in patients with normal protein and glucose values.⁴ India ink stain is only positive in approximately 50% of non-HIV cases, while CSF cultures are positive in approximately 90%.^{5,6}

Treatment of *C. neoformans* meningitis for immunocompetent patients is similar to its treatment for immunocompromised patients. In both cases, induction therapy is performed with amphotericin B and flucytosine followed by repeat lumbar puncture in 2 weeks to assess response to therapy. In immunocompetent patients with no severe symptoms at presentation, no new symptom development and clinical response to therapy, no repeat lumbar puncture is indicated at the 2-week mark, and the patient can be transitioned to consolidation therapy with high-dose fluconazole (usually 800 mg daily) for 8 weeks.⁷ Lumbar punctures may also be used therapeutically in the case of increased intracranial pressure that is not responsive to medication, as it is typically associated with poor prognosis.⁸ In the case of our patient, her headaches did not improve until after multiple lumbar punctures were performed.

Prognosis in immunocompetent patients depends on multiple factors. In a 2017 multicentered retrospective analysis,

higher Glasgow coma score, CSF leukocyte count >20 , and higher CSF glucose levels were associated with better prognosis.⁹ Our patient had all of the previously mentioned findings and was successfully transitioned to fluconazole after 15 days with no re-admission.

Conclusion

While cryptococcal meningitis is chiefly associated with immunocompromised individuals, a rare subset of infections has been recognized in apparently immunocompetent patients, leading to delays in diagnosis and treatments. Clinicians should consider this diagnosis in any patient with chronic headache with signs and symptoms of meningitis and characteristic findings on imaging.

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Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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