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A Rare Presentation of Cryptococcal Meningitis and Cerebellitis in an Asplenic Patient, Seronegative for Human Immunodeficiency Virus (HIV)

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Data Interpretation D
Manuscript Preparation E
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Patient: Male, 65
Final Diagnosis: Cryptococcal meningitis
Symptoms: Fever
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare co-existance of disease or pathology

Background: Cryptococcal meningitis in patients who are seronegative for the human immunodeficiency virus (HIV) and in patients who are splenectomized is rare. This report is an unusual case of meningeal and cerebellar infection due to the encapsulated yeast, *Cryptococcus neoformans*, which has not previously been associated with asplenia.

Case Report: A 65-year-old HIV-negative patient with a previous splenectomy, presented with a three-day history of fever, vomiting, and headache. His symptoms progressed to generalized body aches, persistent fever, and neck stiffness. A lumbar puncture was performed, and cerebrospinal fluid (CSF) culture grew *Cryptococcus neoformans*. Treatment commenced with intravenous amphotericin B and flucytosine. The patient required serial lumbar punctures due to persistent raised intracranial pressure (ICP). Magnetic resonance imaging (MRI) of the brain showed acute meningitis and cerebellitis. Antimicrobial therapy and CSF drainage resulted in clinical improvement.

Conclusions: The occurrence of meningeal and cerebellar cryptococcosis in an asplenic patient is rare, and few cases have been previously reported. This case report highlights the possibility of invasive cryptococcal infection, or cryptococcosis, in asplenic individuals in the absence of HIV infection.

MeSH Keywords: Cerebellar Diseases • HIV Seronegativity • Meningitis, Cryptococcal • Splenectomy

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Background

Infection with *Cryptococcus neoformans*, an encapsulated yeast, results in cryptococcosis, which is most commonly seen in individuals with severe immunodeficiency secondary to infection with human immunodeficiency virus (HIV). However, *Cryptococcus neoformans* may cause infection in individuals who are seronegative for HIV, but who may be immunocompromised for other reasons, including following long-term glucocorticoid therapy, solid-organ transplantation, or malignancy [1]. The occurrence of cryptococcosis in post-splenectomy patients is extremely rare. Only one case of cryptococcal meningitis has been reported in a patient following splenectomy [2]. This report is a case of cryptococcal meningitis in a patient who was seronegative for HIV infection and with a history of splenectomy.

Case Report

A 65-year-old Hispanic man from the Dominican Republic presented to the emergency room with a three-day history of fever, vomiting, and headache. His symptoms progressed to generalized body aches, persistent fever, and neck stiffness. The patient had a history of hypertension, dyslipidemia, and had a previous acute cerebrovascular accident (CVA) resulting in right-sided weakness, three years previously, which had improved over the following six months. He had undergone splenectomy 20 years previously following a road traffic accident. He had a history of laparoscopic cholecystectomy for symptomatic gallstones. The patient had quit smoking and alcohol use ten years prior to admission and denied illicit drug use.

On physical examination his temperature was 100.4°F (37.8°C), his pulse rate was 88 beats per minute, and his blood pressure was 104/58 mmHg. The patient appeared ill and had neck stiffness on examination. He had no focal motor or sensory deficits, and his cranial nerve examination was normal. There was no dysdiadokokinesia, dysmetria, ataxia, nystagmus, or intention tremor. The rest of the physical examination was unremarkable.

Laboratory tests showed an elevated leukocyte count of 13.6×10^3/ml (reference range, 4.8–10.8×10^3/ml), hemoglobin 12 g/dl (reference range, 12–16 g/dl) and platelets 308×10^3/ml (reference range, 150–400×10^3/ml). Liver function tests, renal functions tests, and electrolytes were within normal limits. Blood culture and urine cultures collected on admission showed no growth. The rapid plasma reagin (RPR) test for syphilis was non-reactive. Computed tomography (CT) of the brain, without contrast, showed atrophic changes, an old left basal ganglia infarct, and a posterior fossa arachnoid cyst. A lumbar puncture was performed that showed an opening pressure of 12 cm of cerebrospinal fluid (CSF) and a closing pressure of 8 cm. Analysis of the CSF showed a white blood cell count of 640 cells/µL, with a lymphocytosis (85%), a glucose level of 53 mg/dl, and a protein level of 87 mg/dl (normal range 15–45 mg/dl). Cryptococcal antigen was detected with a titer of 1: 512, but histochemical staining for Cryptococcus with Indian ink was not performed. No bacterial antigens were detected in the CSF. A heavy growth of *Cryptococcus neoformans* was found on culture of the CSF. The patient was seronegative for human immunodeficiency virus (HIV), and the CD4 cell count was noted to be 945/mm^3.

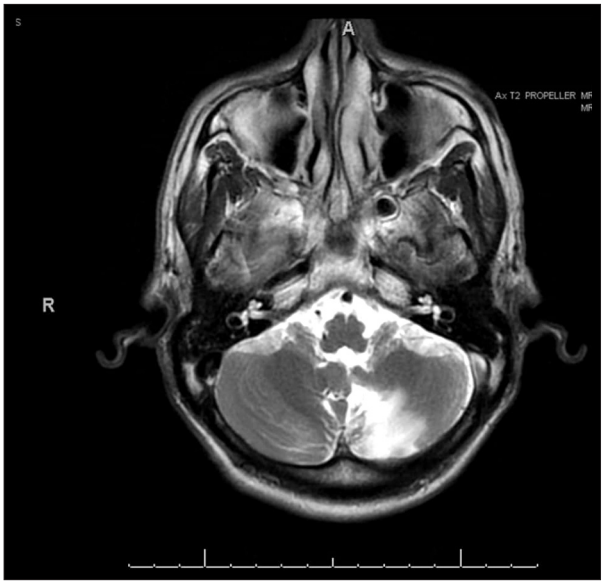

Figure 1. Magnetic resonance imaging (MRI) of the brain of the patient showing acute cryptococcal meningitis and cerebellitis.

The patient was treated with liposomal amphotericin B and flucytosine (5-fluorocytosine) as induction therapy but developed a worsening headache three days later. On repeat lumbar puncture, an opening pressure of 32 cm of H_2O was noted. Following the lumbar puncture, the patient reported improvement in symptoms. Magnetic resonance imaging (MRI) of the brain, performed with intravenous contrast showed mild leptomeningeal enhancement involving the cerebellum on the right side, indicating acute cerebellitis (Figure 1). Contrast-enhanced MRI also showed age-related cerebral atrophy and chronic cerebral infarcts of the left basal ganglia and cerebellum. However, there were no neurologic signs suggestive of cerebellar involvement. Multiple therapeutic spinal taps were performed, which resulted in clinical improvement. Following completion of two weeks of induction therapy, a repeat lumbar puncture was performed, with an opening pressure of 30 cm of H_2O. An Ommaya reservoir, or intraventricular catheter to allow for the aspiration of CSF, was sited at that time, for persistently elevated intracranial pressure (ICP). The patient's clinical

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course was complicated by herpes zoster of the right thigh, which was treated with valacyclovir. An episode of acute renal impairment subsequently resolved.

After four weeks of therapy with antifungal agents, CSF tap from the Ommaya reservoir showed a cryptococcal antigen titer of 1: 64, and fungal culture was negative. After completion of the induction therapy, the patient was discharged on a maintenance dose of treatment with fluconazole for three months. At 15-month follow-up, there were no neurological symptoms to suspect a recurrence of cyptococcal meningitis, and there were no clinical sequelae.

Discussion

Before the development of antiretroviral therapy (ART), cryptococcal meningitis was a common opportunistic infection in patients with human immunodeficiency virus (HIV) infection in the setting of a low CD4 cell count. *Cryptococcus neoformans* infection is one of the commonest invasive fungal infections in immunocompromised patients. The portal of entry for *Cryptococcus neoformans* is the respiratory tract, followed by hematogenous dissemination that has a predilection for the central nervous system (CNS) [3].

Clinical manifestations of cryptococcal infection can vary, from asymptomatic colonization of the respiratory tract to disseminated infection with rapid deterioration in clinical status, if untreated. Worldwide, about 957,900 cases of cryptococcal meningoencephalitis occur each year, resulting in more than 600,000 deaths [4,5]. Cryptococcal meningitis is also an important opportunistic infection in HIV-negative individuals with immunosuppression following organ transplantation, malignancy, chronic corticosteroid therapy, and chronic hepatitis C virus (HCV) infection being clinical associations [6]. Reports of cryptococcal meningitis in patients with splenectomy, or abnormalities of the function of the spleen, are largely lacking with only one detailed case report in the literature. [1,2]

The spleen is the largest lymphoid organ of the body and produces opsonins that promote phagocytosis to remove encapsulated organisms from the bloodstream. Asplenic individuals are at an increased risk for overwhelming sepsis due to encapsulated organisms that include *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neisseria meningitidis*, and certain other organisms such as *Capnocytophaga canimorsus* [7–9]. Two cases of cryptococcal meningitis causing cerebellitis have previously been reported, but cryptococcal meningitis has not previously been reported in asplenic individuals [10,11]. Clinical findings in cryptococcal cerebellitis are nonspecific, and radiology plays an essential role in diagnosis. Acute cerebellitis can resolve following treatment with antifungal agents, but occasionally it can result in localized brain edema, herniation, and death [10]. However, the consequences of the chronic healing process can include cerebral atrophy, calcification, and gliosis. In 2009, Fickweiler et al. described a case of cryptococcal meningitis and cerebellitis that occurred following chemotherapy for multiple myeloma. [11]. The risk factors for the development of cryptococcal cerebellitis, its prognosis, and its response to treatment remain poorly understood [11].

The Infectious Disease Society of America (IDSA) recommends lumbar puncture for diagnostic and therapeutic purposes if the patient has symptoms or signs of an elevated ICP and the CSF pressure is >25 cm H_2O, with the aim of reducing the opening pressure by 50% and the CSF pressure to normal levels of <20 cm H_2O [12]. Ventriculostomy, or the use of a percutaneous lumbar drain, may be required if the patient needs daily lumbar puncture. A permanent ventriculoperitoneal (VP) shunt can be sited during active infection and without complete sterilization of the CSF, if clinically necessary, provided that the patient is receiving the appropriate antifungal therapy [12]. Mannitol and acetazolamide are considered to have a limited role in the management of cryptococcal meningitis and cerebellitis, while steroids have no proven value in controlling raised ICP in this clinical setting [13].

In this case report, the patient received lumbar puncture, and the siting of an Ommaya reservoir for therapeutic drainage of CSF and a short course of steroids was administered for the management of acute cerebellitis. An HIV test should be done in all patients with disseminated cryptococcosis or cryptococcal meningitis and cerebellitis [12]. Although this patient was seronegative for HIV and had no other conditions associated with an immunocompromised state, a previous history of splenectomy was likely to be relevant. Of note in this case, the placement of an Ommaya reservoir has been previously reported to be beneficial in the management of raised ICP in cases of cryptococcal meningitis [14–16]. In this case, intrathecal antimicrobial agents were not used because clinical improvement was observed with intravenous antifungal agents. In this patient, an Ommaya reservoir was used only for therapeutic drainage of the CSF and was not removed after the completion of treatment.

Conclusions

Although classically reported in the setting of human immunodeficiency virus (HIV) infection, cryptococcal meningitis and cerebellitis can be associated with morbidity and mortality in HIV-negative patients. This case illustrates the infection risk posed by a history of splenectomy and supports the possible role of the spleen in fighting infection from *Cryptococcus neoformans*. Cryptococcal meningitis and cerebellitis should be

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considered in patients with asplenia or impaired splenic function, and lumbar puncture should be part of the diagnostic workup when neurological symptoms are present. Acute cerebellitis due to cryptococcal infection is an uncommon phenomenon that can lead to edema, a mass effect, and cerebral herniation. The combination of acute cryptococcal meningitis and cerebellitis in the setting of asplenia is very rare and, so far, only a few cases have been reported [17–19].

Conflict of interest

None.

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