Cryptococcal Meningitis in an Immunocompetent Male: Case Report

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Introduction

Cryptococcal meningitis is a life-threatening condition caused by an invasive, opportunistic, encapsulated saprophytic fungus, either *Cryptococcus neoformans* or *Cryptococcus gattii*. Cryptococcal meningitis is commonly seen in immunocompromised patients, especially those with human immunodeficiency virus (HIV). Overwhelming invasive infection of immunocompetent patients is rather uncommon, and diagnosis is often challenging. We present a case of cryptococcal meningitis (CM) in an immunocompetent male following a recent motor vehicle accident.

Case Presentation

A72-year-old immunocompetent male presented to the emergency department with a 7-day history of persistent headache, intermittent fever, progressive generalized weakness, upper airway congestion, and lower back pain. Of note, this patient sustained a complete T12 burst fracture following a motor vehicle accident one month prior for which he was treated conservatively and doing well at follow-up. Additionally, the patient's medical history was significant for congestive heart failure (CHF) with permanent pacemaker placed in 2009, hypertension (HTN), and peripheral neuropathy. The severity of the patient's CHF was unable to be obtained via the medical record. He did not endorse any current or past alcohol use. Upon presentation, he was tachycardic and hypotensive with positive upper neuron motor signs on physical exam including hyperreflexia of the bilateral lower extremities, positive Babinski sign and positive Hoffman's sign.

Initial lab studies revealed a normocytic normochromic anemia with a hemoglobin of 9.6 g/dL (normal reference range: 13.5 – 17.5 g/dL), decreased platelet count of 109,000 platelets/μL (normal reference range: 150 – 450 platelets/μL), elevated total bilirubin of 1.66 mg/dL (normal reference range: 0 – 1.60 mg/dL) and alkaline phosphatase of 131 units/L (normal reference range: 40 – 129 units/L). Both the serum total white blood cell (WBC) count and absolute neutrophil count (ANC) were within normal range at 8.64 cells/μL (normal reference range: 3.50 – 10.50 cells/μL) and 4.66 cells/μL (normal reference range: 1.70 – 7.00 cells/μL), respectively. Additionally, other liver function tests included the following: normal aspartate aminotransferase (AST) of 34 units/L (normal reference range: ≤ 40 units/L), normal alanine transaminase (ALT) of 24 units/L (normal reference range: 10 – 50 units/L), and mildly decreased albumin of 3.4 g/dL (normal reference rang: 3.5 – 5.2 g/dL). The remainder of the initial lab tests were within normal limits. Of note, the patient was prescribed spironolactone (25 mg, twice daily) as a diuretic, which may have influenced the observed thrombocytopenia as well provided some baseline immunomodulatory effect.

Computed tomography (CT) of the head revealed no abnormalities. Magnetic resonance imaging (MRI) studies were unable to be obtained as the patient had a pacemaker. CT imaging of the chest, abdomen, and pelvis revealed progressive vertebral body height loss of the T12 burst fracture with intraosseous gas compatible with interval osteonecrosis of the T12 vertebral body. There was also surrounding prevertebral soft tissue thickening concerning for an organizing hematoma; however, a superimposed infection could not be excluded.

The patient was admitted and the cerebrospinal fluid (CSF) analysis revealed colorless, clear fluid with a normal opening pressure; however, the protein level was critically high (194 mg/dL) and the glucose level was critically low (3 mg/dL). There were 16 white blood cells/μL, of which 6% were neutrophils, 21% lymphocytes, 71% monocytes, and 2% eosinophils. Histopathological examination of the CSF with gram staining revealed budding yeast forms consistent with *Cryptococcus* (Figure 1). Cytopathology of the CSF redemonstrated the presence of *Cryptococcus* and no evidence of malignant cells were identified. The CSF culture was positive for *Cryptococcus neoformans/gattii* and negative for both bacteria and mycobacterium species. Repeated blood cultures were also positive for *Cryptococcus neoformans*. Additionally, the patient's CSF was positive for Cryptococcus antigen with a titer of greater than 1:2560. The remainder of the workup was negative including testing for mycobacterium species, HIV, influenza, COVID-19, other fungal species, as well as a comprehensive viral and bacterial panel.

Subsequently, empiric bacterial coverage was discontinued, and the patient was treated with a 14-day course of intravenous liposomal amphotericin B (5 mg/kg/day) and flucytosine (800 mg/day) with improvement of symptoms. He was then discharged and completed an 8-week course of fluconazole (800 mg/day) for

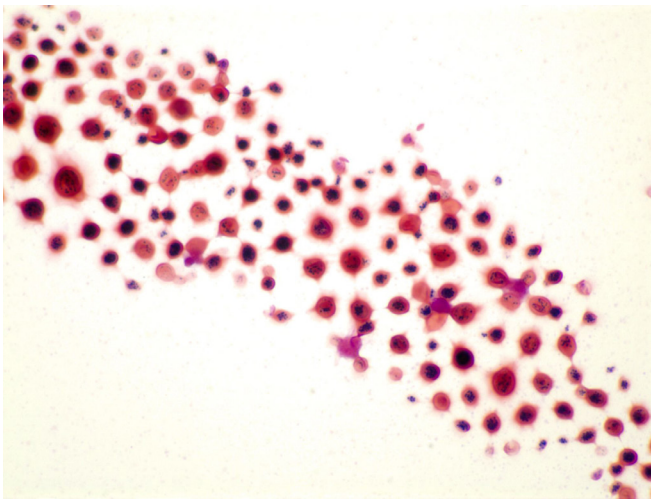

Figure 1. Gram staining of the cerebrospinal fluid reveals clusters of thin-walled, encapsulated yeast forms of various sizes with narrow-based budding consistent with Cryptococcus (Gram stain, 6000x magnification).

consolidation therapy. Today he is healthy with no residual neurological or serological evidence of disease.

Discussion

Cryptococcal infection is a life-threatening condition caused by invasive, opportunistic fungal pathogens, the most common of which include *Cryptococcus neoformans* and *Cryptococcus gattii*. Two serotypes of *C. neoformans* are currently identified, serotype A and serotype D, the former of which is more virulent. Additionally, two serotypes of *C. gattii* are currently identified, serotype B and serotype D, although no difference in virulence has been noted.[1] Both species grow as budding yeast and are often found in tree hollows and pigeon droppings.

Infection in immunocompromised patients often presents as overwhelming meningitis or meningoencephalitis with a high mortality rate; however, cryptococcal meningitis (CM) in immunocompetent patients is less common although cases have been reported.[1] Immunocompromised states that typically confer a more severe disease course include patients with hematologic malignancies, organ transplant recipients, and those receiving disease-modifying agents. Patients particularly at risk of contracting this disease are HIV positive individuals especially those with a CD4 count less than 100 cells/μL. In fact, the most common cause of adult meningitis in areas with high HIV rates is CM.[2]

The most common symptom of CM upon initial presentation is headache and may be accompanied by some degree of altered level of consciousness. Classic features of meningitis such as neck stiffness are present in less than 20% of cases.[3] To further complicate the matter, infection in immunocompetent patients can also prove to be quite difficult due to a more indolent course which may delay appropriate treatment and hasten neurological sequelae.

According to a retrospective cohort study conducted by Brizendine et al.,[4] significant risk factors of mortality from cryptococcosis include cryptococcemia, high intracranial pressure, HIV-status, and transplant status. Furthermore, a study conducted by Henao-Martinez et al.[5] demonstrated that a diagnosis of HIV infection or a positive serum cryptococcal antigen test were both significant predictors of CM. Amongst healthy patients several etiologies for possible immunosuppression are suggested including diabetes mellitus, alcoholism, and cirrhosis, which are thought to induce some level of immunosuppression.[6]

Although CM largely remains a disease of immunodeficient individuals, several case reports have been published describing CM affecting immunocompetent patients. Garcia-Villa et al.[7] described a 23-year-old Latino female with no significant medical history who presented with a one-month history of intermittent abrupt onset severe headaches. She received appropriate antifungal treatment and improved with no residual symptoms. Shokouhi et al.[2] described the case of a 55-year-old immunocompetent Iranian man with a 20-day history of gradual onset of headache that was treated and fully recovered. Newson et al.[8] reported the case of a previously healthy 22-year-old active-duty soldier that was admitted for a 2-month history of persistent headache, nausea, vomiting, weight loss, and nocturnal fevers. He was diagnosed with CM and experienced a full recovery after receiving appropriate antifungal therapy.

In this report, we present the case of a Caucasian man who was admitted with a one-week history of headache, intermittent fevers, and weakness in the setting of a recent traumatic burst fracture. It is important to consider the patient's recent history of a vertebral burst fracture as a potential etiology of an immunocompromised state which may have made him more susceptible to infection. Although the exact mechanism is not clearly delineated in the literature, it is possible that a cellular immune response to inflammation via release of interleukin-10 (IL-10) may lead to immunosuppression. Additionally, immunosenescence may be an additional risk factor in a patient over 70 years of age.

While diagnosis of CM in immunocompetent patients is less common, it is important to consider this diagnosis in patients presenting with headache and CSF specimens with high protein and low glucose levels. This case demonstrates the importance of broadening the differential in immunocompetent patients present with otherwise nonspecific symptoms, so appropriate and timely treatment can be initiated and effectively reduce the possibility of permanent neurological sequela.

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References

1. Kozubowski L, Heitman J. Profiling a killer, the development of Cryptococcus neoformans. FEMS Microbiol Rev. 2012 Jan;36(1):78-94. doi: 10.1111/j.1574-6976.2011.00286.x. Epub 2011 Jul 4. PMID: 21658085; PMCID: PMC3318972.

2. Shokouhi S, Hakamifard A. Meningitis Caused by *Cryptococcus neoformans* in an Apparently Immunocompetent Patient. J Investig Med High Impact Case Rep. 2022 Jan-Dec;10:23247096221111779. doi: 10.1177/23247096221111779. PMID: 35848079; PMCID: PMC9290167.

3. Mwaba P, Mwansa J, Chintu C, et al. Clinical presentation, natural history, and cumulative death rates of 230 adults with primary cryptococcal meningitis in Zambian AIDS patients treated under local conditions. *Postgrad Med J*. 2001;77(914):769-773.

4. Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with Cryptococcosis according to immune status. PLoS One. 2013;8(3):e60431. doi: 10.1371/journal.pone.0060431. Epub 2013 Mar 26. PMID: 23555970; PMCID: PMC3608592.

5. Henao-Martínez AF, Gross L, Mcnair B, McCollister B, DeSanto K, Montoya JG, Shapiro L, Beckham JD. Risk Factors for Cryptococcal Meningitis: A Single United States Center Experience. Mycopathologia. 2016 Dec;181(11-12):807-814. doi: 10.1007/s11046-016-0048-x. Epub 2016 Aug 8. PMID: 27502502; PMCID: PMC5121069.

6. Poley M, Koubek R, Walsh L, McGillen B. Cryptococcal meningitis in an apparent immunocompetent patient. *J Investig Med High Impact Case Rep*. 2019;7:2324709619834578.

7. Garcia-Villa M, Gonzalez-Lara A, Rodriguez-Leyva I. Cryptococcal meningitis due to Cryptococcus gattii in an immunocompetent patient: uncommon presentation of a thunderclap headache. BMJ Case Rep. 2022 Apr 4;15(4):e246158. doi: 10.1136/bcr-2021-246158. PMID: 35379676; PMCID: PMC8981403.

8. Jelaun Newsome, MC USA, Dana Nguyen, MC USA, Cryptococcal Meningitis Caused by Cryptococcus neoformans in an Immunocompetent Soldier, Military Medicine, Volume 179, Issue 9, September 2014, Pages e1059–e1061, https://doi.org/10.7205/MILMED-D-14-00020