Case Report

A Mimic of Hepatic Encephalopathy: Two Cases of Cryptococcal Meningitis in North America

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Abstract

In the non-human immunodeficiency virus infected population, cryptococcosis occurs primarily in people who are functionally immunosuppressed, including patients who have undergone solid organ transplantation requiring immunosuppressive medications, are on corticosteroids, or have renal failure or cirrhosis. Cryptococcal meningitis poses a particular challenge in the setting of cirrhosis because its clinical presentation can mimic hepatic encephalopathy. Here, we describe two patients with decompensated cirrhosis, both with a known history of hepatic encephalopathy who had lumbar punctures and were found to have cryptococcal meningitis. The first patient had a subacute fluctuating change in mental status, while the second patient had progressive subacute headaches, gait disturbance, and hearing loss. Both patients were treated with amphotericin B and flucytosine induction, but only the second survived to maintenance therapy. These cases demonstrate the importance of having a high index of suspicion for cryptococcal meningitis in cirrhosis and having a low threshold for performing a lumbar puncture when altered mental status or other neurologic complaints are not fully explained by hepatic encephalopathy. We also provide a brief review of the pathobiology of cryptococcal infection in cirrhosis and highlight the challenges in therapy.

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Introduction

In patients with cirrhosis, neurologic complaints are frequently seen in the setting of hepatic encephalopathy (HE), and clinicians are often reassured once patients show signs of improvement in mental status upon treatment for HE. Cryptococcal meningitis poses a particular challenge in the setting of cirrhosis because its clinical presentation can mimic HE. Most of the data for the description of and treatment for cryptococcosis has come from studies of the human immunodeficiency virus (HIV)-infected population, who accounted for more than 80% of incident cryptococcosis cases occurring prior to widespread availability of antiretroviral therapy. In the era of antiretroviral therapy, however, we are beginning to see a larger proportion of cryptococcal infections in non-HIV infected patients, and up to 36% of these patients have cirrhosis.[1–4]

In the non-HIV infected population, cryptococcal infection is commonly seen in functionally immunosuppressed patients, including patients who have undergone solid organ transplantation requiring immunosuppressive medications, are on corticosteroids, or have renal failure or cirrhosis.[5] Cryptococcal meningitis typically manifests as a subacute to chronic meningoencephalitis, with gradually worsening headaches and common symptoms such as nausea, vomiting, lethargy, personality changes, and confusion. Unlike in the population with acquired immune deficiency syndrome (commonly known as AIDS), wherein cryptococcal meningitis is often promptly suspected and disseminates to other organs if untreated, cryptococcal meningitis in cirrhotic patients often has a more insidious presentation.[5] The frequently observed lag time to diagnosis makes cryptococcal meningitis an often fatal disease in cirrhosis.[4,6] If the diagnosis is not made early or missed prior to liver transplantation, the outcome can be devastating.

Pathobiology

Cryptococcal infections in humans are due to *Cryptococcus neoformans* and, much less frequently, *Cryptococcus gatti*.[7] *Cryptococcus* species are ubiquitous in the environment and are easily aerosolized and inhaled.[8] Once in the lungs, the primary host responses are complement-mediated macrophage and neutrophil phagocytosis and intracellular killing and natural killer cell response. The ensuing T cell immunity ensures *Cryptococcus* is either eradicated or confined in walled-off granulomas. *Cryptococcus* species avoid phagocytosis and killing by a variety of mechanisms, most important among them being the polysaccharide capsule that resists opsonization and melanin production, ultimately thwarting intracellular killing by resisting oxidative stress.[9–11]

If the organism is permitted to replicate to a critical mass due to a deficiency in the aforementioned immunologic mechanisms, it can disseminate hematogenously to the central nervous system either by a "Trojan Horse" method (piggybacking in macrophages) or by direct transcellular entry through the cerebral capillaries.[12] In cirrhosis with synthetic dysfunction, there is a marked decrease in complement and immunoglobulin production, leading to a decrease in both innate and humoral immunity. Furthermore, the liver is a reservoir for both B and T cells and T cell immune deficiencies have also been described in cirrhosis.[13,14] Though no one specific immune deficiency in

Keywords: Cryptococcal meningitis; Decompensated cirrhosis; Liver transplant.
Abbreviations: CSF, cerebrospinal fluid; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; LP, lumbar puncture; MELD, model for end-stage liver disease.
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cirrhosis has been identified as predisposing to cryptococcal meningitis, the organism likely reactivates from the lung following worsened innate, complement-mediated, and T cell immune function with progressive liver disease.

Case 1

A 69 year-old woman presented with worsening confusion and agitation over the span of a month. She had a past medical history of decompensated cirrhosis due to hepatitis C virus complicated by HE, ascites, and untreated hepatocellular carcinoma. History regarding her illness was obtained primarily from her family and was limited, particularly regarding lactulose compliance, frequency of bowel movements, and symptoms of infection. Her daughter did report the patient had altered sleeping habits and exhibited bizarre behaviors, such as leaving the house not fully dressed. The patient's neurologic exam on admission was notable for being oriented only to self intermittently, without asterixis or any focal neurologic deficits. Laboratory values on admission were notable for a model for end-stage liver disease (commonly known as MELD) score of 17, total bilirubin of 4 mg/dL, international normalized ratio of 1.6, creatinine of 0.8, albumin of 2 g/dL, venous ammonia of 34 μmol/L (reference range: 0–32 μmol/L), venous blood gas with a pH of 7.39 and pCO_2 of 42, white blood cell count of 4,080/mm^3, hemoglobin of 8.8 g/dL, platelet count of 64,000/mm^3, negativity for pyuria on urinalysis and urine toxicology, and normal electrolytes and thyroid studies.

The patient's mental status did not improve after receiving treatment for HE with lactulose and rifaximin therapy following admission. MRI of the brain (Fig. 1) was suggestive of meningitis or cerebritis.

Lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) analysis showed white blood cell count of 99/mm^3 (61 monocytes, 38 neutrophils), glucose of 33 mg/dL, protein of 188.8 mg/dL, reactivity for cryptococcal antigen, and positivity for *Cryptococcus neoformans* in fungal culture. First opening pressure was 33 cmH_2O and subsequent opening pressures remained above 30 cmH_2O, necessitating the insertion of a lumbar drain during the patient's admission. Serum cryptococcal antigen test was also positive.

The patient was started on induction therapy with liposomal amphotericin B and flucytosine, which was challenging because of her agitation and the flucytosine availability only as an oral medication. Her CSF fungal culture was clear of *Cryptococcus* by day 4 of the induction therapy. She sustained a pre-renal acute kidney injury after 10 days of induction therapy, most likely due to amphotericin B, and was resuscitated with daily albumin, but the creatinine remained elevated above baseline throughout her admission. Her mental status would wax and wane with LPs and her hospital course was complicated by hospital-acquired pneumonia requiring intubation. Following goals of care discussion with family, she was terminally extubated and died 29 days after initiation of antifungal therapy.

Case 2

A 57 year-old man presented with shortness of breath due to left hepatic hydrothorax. He had a past medical history of decompensated hepatitis C virus cirrhosis complicated by refractory ascites status post-transjugular intrahepatic portosystemic shunt placement and HE, and he was listed on the liver transplant waiting list. He also had a history of treated neurosyphilis without documented cure by repeat LP. On review of systems, he described progressive headache, gait disturbance, and hearing loss over the span of months. On neurologic exam, he was alert and oriented with no signs of HE or focal neurologic deficits other than mild auditory deficits bilaterally.

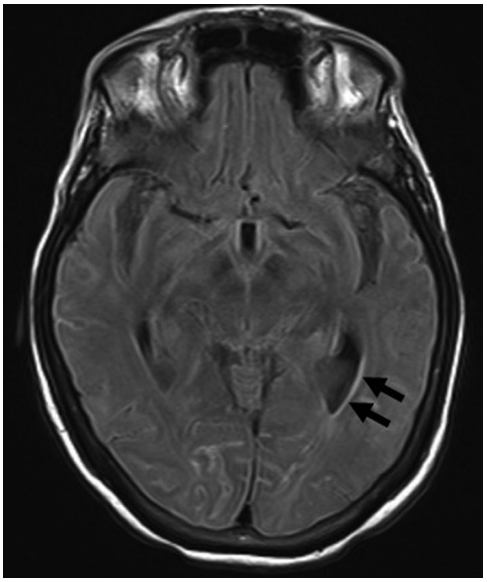

Fig. 1. MRI with and without contrast for Case 1. Curvilinear pial/subarachnoid enhancement and T2/FLAIR hyperintensity in the left temporal lobe is shown adjacent to the left posterior horn (black arrows).

The initial treatment focus was on addressing volume overload in the setting of transjugular intrahepatic portosystemic shunt occlusion, but an LP was performed to evaluate for neurosyphilis treatment response. CSF analysis showed white blood cell count of 128/mm^3 (105 monocytes, 23 neutrophils), glucose of 14 mg/dL, protein of 219.9 mg/dL, and venereal disease research laboratory titer being 1:1 reactive. Due to the increased white blood cell count with monocytic predominance, low glucose and elevated protein in the CSF, cryptococcal antigen stain was requested as an add-on test and returned reactive. *Cryptococcus neoformans* also grew in fungal culture.

Subsequent opening pressure was measured at 19 cmH_2O and serial LPs were deferred in the absence of new neurologic symptoms. Serum cryptococcal antigen was also positive. The patient was started on induction therapy with liposomal amphotericin B and flucytosine, in addition to repeat neurosyphilis treatment with IV penicillin G. He completed a 2-week course of each. He was then placed on continued flucytosine and fluconazole maintenance therapy, and his headache resolved on follow-up without any new neurologic complaints or deficits.

Discussion

The cases presented demonstrate the importance of having a high index of suspicion for cryptococcal meningitis in cirrhosis and the utility of LP when altered mental status or other neurologic complaints are not fully explained by HE. These cases illustrate the wide variety of complaints possible in cryptococcal meningitis, from headache, gait disturbance, and hearing loss to mimicking HE. The previous reports and studies of cryptococcal meningitis in non-HIV infected patients with cirrhosis have been based outside of North America primarily.[15–19] Our cases and review show that this is certainly not a geographically-limited problem and cryptococcal meningitis in

this patient population should remain an important differential in North America.

Even with timely diagnosis, adequate treatment remains a tremendous challenge, given the toxicity inherent in the current standard of care with amphotericin B and flucytosine induction. Namely, the nephrotoxicity and myelosuppression of this regimen exacerbates existing hepatorenal syndrome and pancytopenia often already present in patients with decompensated cirrhosis. Fluconazole induced hepatotoxicity can happen, but it is not common and should not prevent patients from being on the indicated lifesaving therapy even in the setting of cirrhosis.

Despite the challenges in treatment, a recent multicenter case series describing liver transplant outcomes in cryptococcosis showed that most patients who end up receiving the transplant survived, with the caveat that only 8 of 39 patients (20.5%) who were listed for transplant did eventually undergo liver transplantation. Survival rate was 87.5% (7/8) at 3.5 year follow-up among those transplanted, compared with a 90-day survival rate of 57.1% for all patients. Risk factors for mortality include more advanced liver disease (by Child-Pugh or MELD score), requirement for hemodialysis or mechanical ventilation, hypotension/shock, altered mental status and fungemia, whereas protective factors notably include headache. Of note, those pretransplant recipients who were ultimately transplanted underwent a median duration of 43 days on antifungal treatment prior to transplantation and a median of 272 days of antifungal therapy posttransplant.[20]

Selection bias in favor of healthier patients undergoing transplant may partly account for the observed trend towards good outcomes in transplant recipients, but it is important to emphasize that 4 out of the 8 patients transplanted in the aforementioned study had disseminated disease, including 3 with meningitis. These observations suggest cryptococcal infection should not be an absolute exclusion criteria and liver transplantation can remain an option in selected patients with decompensated cirrhosis with cryptococcosis who are able to tolerate antifungal therapy and show clinical improvement. According to the American Society of Transplantation guidelines for cryptococcosis, transplant can be considered in patients who completed induction therapy and all the sites that previously yielded positive cultures are no longer positive.[21] Fluconazole maintenance therapy should be continued for at least 12 months following induction therapy in transplanted patients, but can be extended based on the level of immunosuppression and any residual symptoms.[21]

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Participated in patient care as a resident physician, conducted the literature review and prepared the manuscript draft (PST), participated in patient care as a clinical gastroenterology and hepatology fellow, conducted the literature review and reviewed the manuscript draft (AA), and participated in patient care as the hepatology attending physician, corresponded with specialist consultants and reviewed the final manuscript (TAW).

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