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CASE REPORT

Cryptococcemia in an HIV-negative patient with decompensated liver cirrhosis

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Background: Cryptococcal infections have been mostly associated with immunocompromised individuals, 80–90% of whom have been HIV-positive patients. Increasingly, cryptococcal infections are being reported in cirrhotic patients who are HIV-negative. The underlying immunologic defects in cirrhotic patients seem to play an important role in predisposing them to cryptococcosis and affecting their morbidity and mortality.
Case presentation: We present a case of disseminated cryptococcosis in an HIV-negative patient with underlying cirrhosis, who had rapid worsening of his hyponatremia with renal failure and was unable to recover, despite aggressive measures.
Conclusion: Cryptococcus is a more common culprit of infections seen in cirrhotic patients than what it was previously known, and a high index of suspicion is required to diagnose these patients. Identification of poor prognostic factors, early diagnosis and intervention is crucial in the management of these patients.

Keywords: *cirrhosis*; *disseminated cryptococcosis*; *Cryptococcus*; *fungal infections*; *decompensated liver cirrhosis*; *cryptococcemia*; *HIV-negative*

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Cryptococcal infections have been mostly associated with immunocompromised individuals, most of whom are HIV-positive patients. In recent times, cryptococcal infections are increasingly being reported in cirrhotic patients, with an estimated 6–21% of the systemic fungal infections being cryptococcosis (1).

Cryptococcosis can present in various ways depending on the site of infection. The common sites that are involved are lung, CNS, skin, prostate, and medullary cavity of bones. Rarely, disseminated cryptococcosis can occur when two or more organ systems are involved. Cryptococcal peritonitis is another rare manifestation of cryptococcosis seen even less frequently than disseminated cryptococcosis, although it is one of the most common manifestations seen in those with liver disease (1–9).

Various defects in the immune system that are specific for liver disease have been known to predispose cirrhotic patients to cryptococcosis. These include phagocytic dysfunction, complement and immunoglobulin deficiencies, and impaired cell-mediated immunity. Outcomes vary depending on the underlying conditions. Cryptococcal infections in this population have been associated with substantial morbidity and mortality, with some sources citing a mortality rate of 81% (1). We present a case of disseminated cryptococcosis in an HIV-negative patient with decompensated liver cirrhosis, whose condition deteriorated rapidly despite aggressive measures.

Case presentation

A 54-year-old male with a past medical history (PMH) of chronic hepatitis C and alcohol abuse with cirrhosis, stage III chronic kidney disease, and chronic hyponatremia was admitted to the hospital for acute on chronic hyponatremia, recurrence of ascites, and acute on chronic kidney disease. He was recently admitted for spontaneous bacterial peritonitis (SBP) and had been discharged with a peripherally inserted central catheter (PICC) line for 10 days of antibiotic therapy with ceftriaxone. Unfortunately, the patient returned 4 days after discharge when he was found to have acute on chronic hyponatremia on routine outpatient lab work.

At the time of readmission, ceftriaxone was resumed, and blood cultures were sent. Ascitic fluid analysis revealed total nucleated cells of 156, with 77% lymphocytes. Nephrology was consulted for his acute on chronic hyponatremia (sodium of 117 on admission with baseline

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being around 127), and he was placed on albumin and octreotide for possible hepatorenal syndrome. Due to frustration over his readmission, the patient left the hospital against medical advice. Within hours of discharge, the patient returned with worsening fatigue, and the initial blood cultures taken the day prior had resulted positive for yeast in both tubes, with speciation pending. With those results, the patient was started on micafungin for the fungemia.

Physical exam at this time was significant for ongoing ascites and an erythematous, macular, non-blanchable, non-pruritic, painful rash over the thighs. The combination of fungemia and rash raised concerns for disseminated candida. However, within 2 days, both tube cultures and the repeat blood cultures grew *Cryptococcus neoformans* and the patient's antibiotic regimen was switched to amphotericin B and flucytosine. There were also ongoing concerns of a related intracranial infection as the patient was more lethargic and complained of a headache. However, a lumbar puncture was not performed due to concurrent coagulopathy. There was a suspicion for disseminated intravascular coagulation as the patient had persistently low fibrinogen levels despite multiple units of fresh frozen plasma. Confirmatory testing for the serum cryptococcal antigen was also sent at this time, which reaffirmed the diagnosis of cryptococcemia. The peritoneal fluid with a lymphocytic predominance eventually grew cryptococcus confirming disseminated cryptococcosis.

During the hospital stay, the patient's kidney function progressively worsened. He was initially managed for hepatorenal syndrome with octreotide, midodrine, and albumin. After initiation of amphotericin B and flucytosine, the creatinine level rapidly worsened from 2.71 to 5.75. In the context of oliguria and worsening respiratory status, the patient was intubated, transferred to the intensive care unit, and urgent hemodialysis was initiated. Despite these changes, the patient continued to decline. The decision was made to transition the patient to comfort care measures based on his previously verbalized wishes in the context of worsening renal failure and underlying cirrhosis.

Discussion

Cirrhotic patients have been shown to have an increased frequency of immunodeficiency-associated infections, one in particular being *C. neoformans*, which was seen in the presented patient, as well as several other cases in the past few years (1, 8, 10–15. It can present as cryptococcemia, cryptococcal meningitis, disseminated cryptococcosis, cryptococcal pneumonia, or even cryptococcal peritonitis. These infections contribute to substantial morbidity and mortality in cirrhotic patients, making it essential for us to promptly identify and treat them.

Although the source of infection in our patient is unclear, Gastrointestinal (GI) tract has been proposed as a potential site of inoculation in cirrhotics, given the possibility of direct inoculation of *Cryptococcus* into the bloodstream following a GI bleed or fungal overgrowth with antibiotic use (2, 4, 11). The most common port of entry of the pathogen is through the respiratory tract. A markedly reduced immune response in cirrhotic patients predisposes them to cryptococcal dissemination by hematogenous spread from a subclinical focus of infection. The systemic failure of innate and adaptive immunity in these patients has been termed 'cirrhosis-associated immune dysfunction syndrome (CAIDS)' in recent years, with many proposed biochemical mechanisms to explain it (16–18). There are two main interlinked processes that are described. One is intracellular signaling alterations leading to damage to the gut-associated lymphoid tissue and circulating immune cells. The other one is persistent systemic inflammation as evidenced by the increased serum levels of pro-inflammatory cytokines and acute phase reactants. There is a hypothesized spectrum of CAIDS ranging from the pro-inflammatory phenotype in stable cirrhosis to the immune-deficient phenotype in decompensated cirrhosis, and this case describes a patient on the latter end (17).

With recent history of SBP and recurrent ascites requiring paracentesis, the patient was at a high risk of infection. His recurrent hospitalizations for these conditions as well as antibiotic use only served to increase his risk of fungal infection. There were a few other concerning factors that may have predicted a poor prognosis. These include acute on chronic hyponatremia, which has been reported as an early warning sign of cryptococcal meningitis (19), as well as the patient's hepatorenal syndrome which portends a poor outcome in cirrhotic patients with SBP. Our patient also had hepatitis C, which in itself downregulates the immune system to persist in the human tissue for years. Both cryptococcus and hepatitis C virus also have long incubation periods, and there have been reported co-infections of these two organisms previously (20–23). However, it is not yet known whether hepatitis C virus promotes cryptococcal infections, although it may predict a poor prognosis.

Diagnosis of disseminated cryptococcosis is based on positive cultures from any two organ sites (skin, CNS, peritoneum, and synovial fluid) or positive blood cultures (24). Our patient had positive blood cultures as well as positive ascitic fluid cultures. He also had a maculopapular skin rash and some CNS symptoms although we did not have a skin biopsy or cerebrospinal fluid (CSF) cultures to confirm infection in these organs. Cryptococcal antigen test performed on body fluids (blood, CSF, and ascitic fluid) is useful for diagnostic purposes. Diagnosis of cryptococcal peritonitis has been one of the biggest challenges due to the time needed to grow cultures and the lack of clear warning signs for empiric treatment.

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One study cited the mean time of detection in the ascites as 6 days (1). Bedsides inoculation of culture, mediums and India ink preparations may improve evaluation of ascitic fluid (6). Ascitic fluid analysis usually demonstrates a low protein level and a moderately elevated WBC count. Our case and a few previous cases have demonstrated a lymphocytic predominance in the ascitic fluid, and this may be a clue to fungal peritonitis (16).

Cryptococcal infections in cirrhotic patients are associated with a high mortality, ranging from 70 to 81% (1, 16). Disseminated cryptococcosis in HIV-negative patients is treated with amphotericin B (0.7–1 mg/kg/day) alone for 6–10 weeks or in conjunction with flucytosine (100 mg/kg/day in four divided doses) for 2 weeks followed by fluconazole 400 mg/day for a minimum of 10 weeks (25). In many cases, patients never survived long enough to complete a full course of therapy, regardless of the chosen method (26). Our patient was started on a combination of amphotericin B and flucytosine; however, this led to a deterioration in his renal function requiring hemodialysis, and eventually all care was withdrawn as per the patient's wishes. In patients like ours with renal dysfunction, fluconazole alone may be used as a second-line agent for initial therapy (10, 27). There is no guideline delineating a treatment plan specifically for patients with cryptococcal peritonitis. The closest thing to a guideline found was in the infectious diseases society of america (IDSA) guidelines for non-meningeal, non-pulmonary cryptococcosis, which recommended managing multisite cryptococcal infections as meningocryptococcal infections until proven otherwise. If a patient responds to initial therapy, it is recommended that CSF studies and blood cultures are repeated until negative and then initiate maintenance therapy with fluconazole 200 mg/day orally for 6 to 12 months.

Cirrhosis of liver and advanced liver disease are strong independent risk factors of increased mortality in patients with disseminated cryptococcemia (1, 16), with one study showing a 30-day mortality of 100% (28). Delayed diagnosis and treatment and progression to disseminated infections have been cited as possible causes for the poor outcomes in these patients. Factors responsible for a delay in diagnosis may be the variation in presentation and ascitic fluid findings that may not be classically suggestive of infection or peritonitis, longer time period for positive fungal cultures, and a low index of suspicion due to the above findings (11).

This case illustrates the importance of considering cryptococcal infections in cirrhotic patients, as this fungal organism may be a more common culprit of infections in these patients than what it was previously known. Rapid progression to death is common in these patients. An understanding of the immune defects in cirrhosis, which lead to variable presentations and a very high index of suspicion, will help in the timely diagnosis of cryptococcal infections in this population. Early identification of risk factors and poor prognostic factors should direct the physician toward prompt aggressive interventions to improve outcomes in cirrhotic patients.

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