Spontaneous Fungal Peritonitis in Patients with Hepatitis B Virus-related Liver Disease


Abstract
Spontaneous bacterial peritoneal infections is recognized as a very common complication of cirrhotic ascites, but isolation of fungus in pure culture from ascitic fluid is relatively rare, even more so in the human immunodeficiency virus (HIV)-negative or nonimmunocompromised hosts. We describe two patients of spontaneous fungal peritonitis where the isolate was Cryptococcus neoformans. Both cases were infected with hepatitis B virus (HBV) infection. The clinical and laboratory profiles of both patients were similar to those of conventional spontaneous bacterial peritonitis. We suggest that it would be prudent to heighten clinical suspicion for fungal peritonitis in such cases. Key Words: Spontaneous bacterial peritonitis—Cryptococcus neoformans—Fungal peritonitis—Hepatitis B virus.

Spontaneous peritoneal infection is best defined as peritonitis without an evident gastrointestinal source. It is a serious problem with an incidence of 10–20% in patients admitted with ascites. It has been reported in association with cirrhosis, subacute hepatic failure, and acute hepatitis as well. Gram-negative bacilli are the most frequent isolates being present in ≤72% of cases. However, isolation of fungus from ascitic fluid is very rare except for in situations including secondary peritonitis or after prolonged treatment with broad spectrum antibiotics. In this report, we present two cases of spontaneous fungal peritonitis caused by Cryptococcus neoformans, both of which had underlying hepatitis B virus (HBV)-related decompensated liver disease without history of preceding use of broad spectrum antibiotics.

CASE 1
A 39-year-old man with alcoholism and diabetes was diagnosed to have alcohol-related micronodular cirrhosis and was reporting for follow-up. He was found to be positive for hepatitis B surface antigen, hepatitis B e, antigen and immunoglobulin M (IgM) anti-hepatitis B core (HBc) during his last visit to the hospital. He presented with a 20-day history of low grade fever, abdominal pain, and worsening ascites despite diuretic therapy. Physical examination revealed a febrile, well-built, conscious patient with significant pedal edema and moderate degree of ascites. Routine laboratory investigations were normal. The liver function tests were as follows: serum total bilirubin, 6.5 mg/dl with a direct, 2.7 mg/dl; serum protein, 6.5 g/dl; albumin, 2.6 g/dl; globulins, 4.3 g/dl; aspartate aminotransferase, 124 U/L; alanine aminotransferase, 88 U/L; and alkaline phosphatase, 137 U/L. His prothrombin time was grossly deranged (15 seconds prolonged over control). Biochemical workup for Wilson’s disease, autoimmune hepatitis, and hemosiderosis was negative. He tested negative for hepatitis C virus and human immunodeficiency virus (HIV) antibody. An ultrasonogram of the abdomen revealed a shrunken liver with evidence of portal hypertension and free fluid. Gastroscopy revealed candidal esophagitis without varices. Ascitic fluid analysis showed a total white cell count of 300/mm² with neutrophils, 75%; protein, 0.7 g/dl; albumin, 0.2 g/dl; and serum ascites albumin gradient, 2.4. He began a treatment of parenteral cefotaxime, pending the culture report. However, the fever persisted despite antibiotic therapy.

On the seventh day, the ascitic fluid culture grew gram-positive, spherical, yeast-like organisms suggestive of C. neoformans. An India ink preparation showed a similar structure, but the characteristic halo representing the capsule was absent. On sunflower seed agar it showed a brown colored effect typical of C. neoformans var neoformans. Subjecting the strain to further biochemical tests and a coagglutination test, the strain was finally identified as C. neoformans var neoformans. Because the isolate did not show a capsule, it was inoculated intraperitoneally into mice after a standard procedure. Impression smear from the brain of the mice showed cryptococci as shown in Figure 1. Subsequent ascitic fluid and blood cultures from this patient also grew the same organism, further confirming the significance of the isolate. Based on the culture report, he was treated with fluconazole and amphotericin B. Despite these measures he deteriorated rapidly and succumbed to multi-organ failure.

CASE 2
A 50-year-old man with asthma who had been exposed to multiple venipuncture during exacerbations was admitted with a 6-week history of jaundice, abdominal distention, and pedal edema. Examination revealed an elderly man who was deeply icteric with bilateral pedal edema. He had no stigmata of chronic liver disease. Abdominal examination revealed a normal liver span, minimal ascites, and no splenomegaly. Routine
laboratory tests were normal. Liver function tests were as follows: serum total bilirubin, 42 mg%; direct fraction, 33 mg%; serum total protein, 5.3 g%; and albumin, 3.3 g%. The aminotransferases were grossly elevated (aspartate aminotransferase, 1,100 U/L; alanine aminotransferase, 1,650 U/L). His alkaline phosphatase was 170 U/L. The prothrombin time was deranged (control, 14 seconds; patient, 25 seconds). He was positive for the hepatitis B surface antigen and anti-HBe IgM antibody. Hepatitis B e antigen was negative. Ultrasonography of the abdomen showed a normal liver size with minimal ascites and no splenomegaly. Gastroscopy was negative for varices. A diagnosis of HBV-related sub-acute hepatic failure was made. Ascitic fluid analysis showed total white blood cell count, 3,600/mm³ with 69% polymorphs and serum-ascites albumin gradient of 3.0. Ascitic fluid culture grew budding yeastlike organisms that were eventually identified as *C. neoformans*. Methods of culture and isolation of the organism were similar to the previous case. The enzyme-linked immunosorbent assay test for HIV was also negative in this patient. In view of the delay in obtaining the final culture report on the ascitic fluid, he was treated with parenteral cefotaxime for culture-negative neutrocytic spontaneous bacterial peritonitis. Despite these measures, he deteriorated over the next 2 weeks with worsening ascites, a rising creatinine, and encephalopathy.

**DISCUSSION**

The body of currently available evidence suggests that the spontaneous forms of ascitic fluid infection are the result of translocation of a specific organism in the gut, leading to spontaneous bacteremia and, finally, colonization of susceptible ascitic fluid.7,8 Impaired clearance of bacteria from the blood could result from hypocomplementemia,9 decreased serum opsonic activity,10 defective neutrophil chemotaxis,11 impaired IgM antibody activity,12 or decreased intracellular killing of phagocytized organisms.8,13 Besides these, the opsonic and bactericidal activity of ascitic fluid are also reduced.14,15 Gastrointestinal lesions due to *C. neoformans* are very rare and usually manifest as part of disseminated disease.1 Isolated peritoneal involvement has been reported earlier in a 13-year-old girl with underlying lupus nephritis and ascites.16 Disseminated cryptococcosis involving the gastrointestinal tract in patients with underlying chronic liver diseases have also been documented.17-19 It is noteworthy that nearly all cases of HIV-negative gastrointestinal cryptococcosis described thus far have had some form of underlying chronic debilitating diseases.15,19 In the present report, both cases had underlying decompensated liver disease resulting from HBV infection. In vitro as well as in vivo studies have demonstrated a depressed cell mediated immunity among cirrhotics.20,21 In addition, the immune response of lymphocytes and macrophages have also been seen to be blunted by HBV infection itself.22 Because of normal host defense against *Cryptococcus* is principally cell-mediated, we would expect enhanced susceptibility of patients with defective cellular immunity to invasive cryptococcosis. Other risk factors like intravenous drug use can act as a source of fungal infection in such cases. However, one of our patients has had history of exposure to repeated venipuncture during exacerbation of his bronchial asthma. Thus, due to limited evidence so far and a paucity of numbers, we do not presume to associate the presence of underlying chronic liver disease (especially due to HBV) with invasive cryptococcosis; but, we do suggest that further prospective studies in this area could prove such a relationship.

In daily clinical practice, that *Cryptococcus* is an uncommon cause of spontaneous peritoneal infection is usually overlooked as a cause of nonneutrocytic or neutrocytic ascites (as exemplified by our two cases). This underscores the need to increase clinical suspicion in cases presenting as conventional spontaneous bacterial peritonitis that are apparently culture-negative and this may promote early diagnosis and, thereby, early, appropriate treatment of this serious infection.

**REFERENCES**

SPONTANEOUS FUNGAL PERITONITIS AND HBV-RELATED LIVER DISEASE


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**Errata**

**March 2000**

In the March 2000 issue of *J Clin Gastroenterol*, in the article entitled “Hepatitis C: An Update on the Silent Epidemic” by Steedman A, Sarbah and Zobair M, Younossi (pp 125-143), the following clarifications/corrections should be noted:

In the first page, the third National Health and Nutrition Examination estimated that 1.8% of the U.S. population (3.9 million individuals) carry anti-HCV antibody, 74% of whom (2.7 million individuals) had detectable HCV RNA indicating chronic HCV infection. Given that certain populations were excluded from this survey (institutionalized individuals), these numbers may slightly underestimate the true prevalence of HCV in this area.

The first paragraph of the summary (last page) should read, “... by the year 2008 there will be more than 20,000 deaths per year...”