An Autopsy Case of Disseminated Cryptococcosis Manifesting as Acute Diarrhea in a Patient with Primary Biliary Cirrhosis

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Abstract

A 58-year-old woman with an 18-year history of primary biliary cirrhosis was admitted because of pneumococcal pneumonia. She was treated with antibiotics and mechanical ventilation. After the pneumonia improved, she developed severe watery diarrhea. Although vancomycin was administered enterally, the diarrhea persisted. She died of multiple organ failure within 16 days of the onset of diarrhea. An autopsy showed intracapillary cryptococci in the systemic organs, especially in the intestinal tract. The cause of diarrhea was considered to be extensive intestinal mucosal necrosis due to disseminated cryptococcosis. This is a rare case of cryptococcal infection manifesting as acute diarrhea.

Key words: disseminated cryptococcosis, gastrointestinal cryptococcosis, acute diarrhea, intracapillary cryptococci, primary biliary cirrhosis

(Inter Med 49: 1793-1796, 2010)
(DOI: 10.2169/internalmedicine.49.3785)

Introduction

Cryptococcosis is a fungal infection caused by Cryptococcus neoformans, an encapsulated yeast. This infection commonly occurs in immunocompromised patients, and is often disseminated (1, 2). Disseminated cryptococcosis generally manifests as pulmonary lesions or meningitis; gastrointestinal cryptococcosis is rare (3). In addition, acute severe diarrhea is an uncommon symptom of cryptococcal infection. Here, we report a case of disseminated cryptococcosis presenting with severe diarrhea and discuss the associated pathological findings.

Case Report

Our patient was a 58-year-old woman with primary biliary cirrhosis (PBC), which had been detected on a liver biopsy examination performed 18 years earlier. After the diagnosis, she had been treated with ursodeoxycholic acid, furosemide, spironolactone, and branched-chain amino acids. She had never been treated with corticosteroids or immunosuppressive agents. She had undergone endoscopic ligation of esophageal varices 2 years previously.

She had developed fever and dyspnea 1 day before admission to our hospital and had visited another hospital. A chest radiograph showed bilateral shadows, and she was therefore diagnosed with acute pneumonia and referred to our hospital. On admission, the patient was alert, and physical examination revealed high fever, tachypnea, oxygen desaturation, jaundice, bilateral pulmonary rales, and leg edema. Initial laboratory examination revealed a marked inflammatory response and findings associated with liver cirrhosis namely, liver dysfunction, thrombocytopenia, hyperbilirubinemia, hypoalbuminemia, and prolonged prothrombin time (Table 1). Her liver dysfunction was classified as grade B according to the Child-Pugh classification (4). We also diagnosed a severe pneumococcal infection on the basis of the results of a urinary antigen test, and sputum and blood cultures. Because a chest computed tomography (CT) scan showed bilateral
multiple consolidations (Fig. 1), we considered the possibility of co-infection with atypical organisms.

We therefore administered meropenem (MEPM, 0.5 g x 2/day) and ciprofloxacin (CPFX, 300 mg x 2/day); however, the respiratory failure progressed, and eventually resulted in acute respiratory distress syndrome (ARDS) on day 3 (5). Mechanical ventilation was therefore initiated as a lung-protective strategy (6), and 1,000 mg/day methylprednisolone was administered for 3 consecutive days. These therapies improved the respiratory status along with the other symptoms and laboratory findings. Therefore, we stopped CPFX on day 10. On day 12, fever and pulmonary infiltration were noted, and methicillin-resistant Staphylococcus aureus (MRSA) was detected on sputum culture. On the basis of these findings, we diagnosed ventilator-associated pneumonia caused by MRSA, and administered vancomycin (VCM, 0.5 g x 2/day) parenterally, which improved the pneumonia. However, the patient remained ventilator dependent. We continued MEPM and VCM until day 18.

On day 18, severe watery diarrhea occurred, resulting in a fluid loss of 5 L/day. The stools were not bloody, but the patient’s vital signs became unstable, and she required hydration and treatment with vasopressors. On stool culture, MRSA, but not Clostridium difficile, was identified. Further, C. difficile toxin assay and blood culture were also negative. Serum cryptococcal antigen test was not performed. Vancomycin was administered via the enteral route, but the watery diarrhea persisted. An abdominal CT scan on day 27 showed intestinal distension and fluid accumulation (Fig. 2A). A chest CT scan obtained on the same day did not show any new pulmonary lesions (Fig. 2B). Despite intensive care, the patient’s general condition worsened, and multiple organ failure developed. The patient died on day 33. The cause of the severe diarrhea remained unknown at that time.

**Autopsy findings**

An autopsy showed mucosal necrosis in both the small and large intestines, and partial pseudopolyposis (Fig. 3). Microscopic examinations revealed intracapillary cryptococci in the systemic organs such as the lung, intestine, lymph node, bone, thyroid, and kidney. The lungs (Fig. 4) and intestines (Fig. 5) were the most severely affected. Pseudomembranes in the colon and granulomas in the lungs were not detected. However, intrahepatic cholestasis was found, consistent with the diagnosis of PBC. The central nervous system was not examined.

**Discussion**

Here, we report a case of disseminated cryptococcosis, which developed after therapy for acute pneumonia in a patient with liver cirrhosis. The occurrence of acute fatal diarrhea makes this a rare case. In addition, the microscopic finding of intracapillary cryptococcal bodies in the intestinal mucosa was unusual.

Cryptococcosis is one of the most common fungal infections in immunocompromised patients. Although human immunodeficiency virus (HIV) infection is a well recognized risk factor for disseminated cryptococcosis (7), other causes of reduced immunity can also predispose to this infection, such as immunosuppressive medications, organ transplantation, chronic organ failure, or hematologic disorders (8). Liver cirrhosis is the most frequent predisposing factor for disseminated cryptococcosis, and is associated with a poor prognosis (9). Opsonic, complement, and leukocyte dysfunction has been reported to increase the risk of cryptococcosis in cirrhotic patients (10). Considering that our patient had PBC and had undergone steroid therapy for ARDS, we assumed that she was immunocompromised and at high risk for disseminated cryptococcosis.

Although disseminated cryptococcal disease may invade any organ, gastrointestinal involvement is rare, especially in an HIV-negative patient (11). In addition, gastrointestinal cryptococcosis is most often asymptomatic (12), and acute fatal diarrhea caused by gastrointestinal cryptococcosis, which occurred in this patient, has never been reported to our knowledge. In the present patient, the pathological find-
Figure 2. Computed tomography (CT) scans obtained on day 27. (A) A chest CT scan showed that the consolidations had become organized; no new lung lesions were detected. (B) An abdominal CT scan showed intestinal distension and fluid accumulation.

Figure 3. Macroscopic findings of the large intestine. The intestinal mucosa from the ascending colon to the transverse colon appeared gray due to dissection of the normal mucosa (arrows). In contrast, white intact mucosa was seen in the descending colon (arrowhead). Part of the transverse colon showed pseudopolyposis. Pseudomembranes were not detected.

Figure 4. Microscopic findings of the lung. (A) Hematoxylin and Eosin staining of the lung. Inflammatory cell infiltrate and pulmonary granuloma were not detected. (B) Alcian blue staining revealed blue cryptococcal bodies in the pulmonary capillaries (arrows) in both lungs.

Figure 5. Microscopic findings of the small intestine. (A) Hematoxylin and Eosin staining of small intestine. Mucosal capillaries containing the cryptococcal bodies were seen (arrow). (B) Grocott’s staining of the small intestinal mucosa showed black cryptococcal bodies (arrowhead).

ings suggested that cryptococcal bodies embolized to the intestinal capillaries, and resulted in mucosal necrosis and eventually acute diarrhea. Fulminant C. difficile colitis, which is characterized by life-threatening, medically refractory diarrhea, is considered in the differential diagnosis of severe nosocomial diarrhea (13). However, C. difficile infection was unlikely in our patient because of the absence of pseudomembranes in the colorectal mucosa. MRSA, which was detected on stool culture, can cause enterocolitis (14), but bacterial bodies of MRSA were not found on microscopic evaluation. Therefore, we think that stool culture was positive for MRSA because of intestinal colonization by this bacterium, but that MRSA was not the cause of the watery diarrhea.

Gastrointestinal cryptococcosis is difficult to diagnose because of its minimal symptoms, and usually the diagnosis is made postmortem (15). In the present case also, disseminated cryptococcosis was diagnosed on autopsy. Cryptococcal antigen testing is useful for the diagnosis of cryptococcal infection in asymptomatic patients (16), and can thus be used for the early diagnosis of gastrointestinal cryptococcosis. Unfortunately, we did not perform this test, because we did not suspect cryptococcal infection. The delay in diagnosis
Some authors have proposed a classification of pulmonary cryptococcal infections on the basis of histological findings. McDonnell and Hutchins reported 4 distinct histologic patterns of pulmonary cryptococcal infection: pulmonary peripheral granuloma, granulomatous pneumonia, intracapillary/interstitial infection, and massive pulmonary involvement (17). The microscopic findings in our patient corresponded to the intracapillary involvement described by McDonnell and Hutchins (17). The histologic features observed in our patient indicate hematogenous dissemination of the infection and poor prognosis. In fact, the autopsy findings in this case revealed systemic dissemination of cryptococcus, and the clinical outcome was poor.

Additionally, we did not observe pulmonary granuloma formation, which is commonly seen in disseminated cryptococcosis. Moreover, significant CT findings were absent in this patient, except for organizing inflammation following pneumococcal pneumonia. On the basis of these observations, we conclude that the patient had a cryptococcal infection, which did not have any pulmonary manifestations. However, cryptococcal bodies in the pulmonary capillaries, which resulted from hematogenous progression of cryptococcosis, were detected by autopsy. Because of the poor immune response against cryptococcal infection, which reflects the severe immunocompromised status of this patient, these bodies were undetectable by chest CT scan. We found few inflammatory cells in the alveolar area even by microscopic observation. On the other hand, embolism of the pulmonary capillaries can cause respiratory failure, such as septic pulmonary embolism (18). Therefore, in this case the intracapillary cryptococci might have contributed to the ventilator-dependent state after treatment of pneumonia.

References