Cryptococcus neoformans Peritonitis in Two Patients with Liver Cirrhosis

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Abstract: *Cryptococcus neoformans* is an important pathogen in immunocompromised patients. We report 2 cases of spontaneous *C. neoformans* peritonitis in patients with liver cirrhosis, a condition not previously reported in Taiwan. Patient 1, a 59-year-old man with alcoholic liver cirrhosis, had primary *C. neoformans* peritonitis with fungemia. The patient recovered completely after prolonged fluconazole therapy without relapse. Patient 2, a 51-year-old woman with liver cirrhosis due to Budd-Chiari syndrome, had *C. neoformans* isolated from ascites, cerebrospinal fluid, and blood culture. In spite of adequate antifungal treatment, the patient died of fulminant sepsis. Information about the interaction and relation between liver cirrhosis and cryptococcal peritonitis is rare in the literature. The experience of these cases may help facilitate the diagnosis and treatment of cryptococcal peritonitis.

Key words: Cryptococcosis; *Cryptococcus neoformans*; Liver cirrhosis; Peritonitis

J Formos Med Assoc 2005;**104**:39-42

Cryptococcus neoformans is an important pathogen in immunocompromised hosts.[1–3] Although chronic meningitis and pneumonia are the 2 most common presentations, *C. neoformans* can invade virtually any organ.[4,5] There are a few reports mentioning cryptococcal peritonitis, especially in patients undergoing peritoneal dialysis.

Our search of *MEDLINE* in March 2004 found only 12 cases of cryptococcal peritonitis reported in patients undergoing continuous ambulatory peritoneal dialysis (CAPD).[6–14] Notably, some limited studies described the association between liver cirrhosis and cryptococcal peritonitis with emphasis on its unique pathogenesis and poor outcome.[12,15–19] Taiwan is an endemic area for liver cirrhosis. However, cryptococcal peritonitis in cirrhotic patients has not yet been reported in Taiwan. Herein, we describe 2 patients, both with liver cirrhosis, who developed peritonitis due to *C. neoformans*. We analyze the portals of entry and discuss their clinical presentation and the impact of underlying systemic illnesses upon this clinical entity.

Case Report

Case 1

A 59-year-old man, with an 8-year history of liver cirrhosis (alcohol-related, Child B) was admitted to the medical ward of National Taiwan University Hospital (NTUH) in late April 2000 due to fever, mild abdominal pain and poor appetite for 4 days. He experienced 1 episode of peptic ulcer on March 1, 2000, and received complete therapy then. Two days before this admission, he underwent a panendoscopic study, which disclosed esophageal varices, duodenitis (second portion) and a gastric ulcer. The nature of his abdominal pain was dull and the location was poorly defined. He reported no prominent headache, accompaying nausea/vomiting, concomitant constipation or diarrhea. On admission, physical examinations showed clear consciousness, blood pressure of 108/60 mm Hg, body temperature of 38.6°C, pulse rate of 102 beats per minute, respiratory rate of 24 times per minute, no nuchal rigidity and

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Received: 12 April 2004 Revised: 12 May 2004 Accepted: 1 June 2004
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clear chest breath sounds, no audible heart murmur, but diffuse whole abdominal tenderness and shifting dullness without rebounding pain, no joint swelling and no skin eruptions.

Abdominal ultrasonography performed in April 2000 suggested liver cirrhosis, mild splenomegaly, a gallbladder polyp and massive ascites. The laboratory investigations were as follows: initial hemogram consisted of white blood cells (WBCs) 5.88 x 10^9/L (WBC classification: neutrophil 78%, lymphocyte 9%, monocyte 11%, and eosinophil 2%), hemoglobin 10.4 g/dL, and platelet count 74 x 10^9/L. Blood biochemistry profile revealed the following: albumin 2.9 g/dL (normal range, 3.5-5.0 g/dL), globulin 3.3 g/dL (normal range, 2.3-3.5 g/dL), total bilirubin 2.0 mg/dL (normal range, 0.2~1.0 mg/dL) direct bilirubin 0.8 mg/dL (normal range, 0~0.4 mg/dL), alkaline phosphatase 232 U/L (normal range, 66-220 U/L); gamma-glutamyl transferase 71 U/L (normal range, 0-52 mg/dL), aspartate aminotransferase 26 U/L (normal range, 5-31 U/L); alanine aminotransferase 18 U/L (normal range, 0-41 U/dL), blood urea nitrogen 24.1 mg/dL (normal range, 4.5-24 mg/dL), and creatinine 1.0 mg/dL (normal range, 0.6-1.2 mg/dL). Chest roentgenogram at admission did not disclose significant lesion. After admission, ascites examination was done several times. The first ascites examination showed remarkable pleocytosis, with predominance of neutrophils (all sequential biochemistry results of ascitic fluids are listed in the Table. Spontaneous bacterial peritonitis in this cirrhotic patient was suspected and he was given intravenous cefotiam since April 29. However, intermittent low-grade fever persisted in the following 5 days.

Initial bacterial culture result of ascitic fluid was negative. After repeated paracenteses and septic work-up, the antibiotic regimen was subsequently changed to full-dose parenteral ciprofloxacin. Fever did not resolve. Follow-up chest X-ray (on May 11) revealed increased infiltrates over the right lower lung field. Later, ascites culture grew *C. neoformans*. The India ink preparation of ascites showed a positive result. The cryptococcal antigen titer of ascites (on May 12) was 1:128, and his serum cryptococcal antigen titer (on May 12) was also 1:128. Chest computed tomography (CT) disclosed 1 well-defined nodule 1.5 cm in diameter over the left lower lobe, and ascites. Serological test for human immunodeficiency virus (HIV) antibody was negative. Cerebrospinal fluid (CSF) was obtained on May 19th and revealed the following: WBC count of 0 x 11/9 per μL, glucose level of 52 mg/dL, total protein level of 42 mg/dL, cryptococcal antigen titer of 1:2, and culture yielded *C. neoformans*. He had not received any immunosuppressive agent previously. Thereafter, amphotericin B (at a dosage of 0.8 mg/kg/day) was given for 1 day, then intravenous fluconazole 400 mg per day for 2 consecutive weeks. His body temperature gradually returned to normal, and abdominal pain improved. Later, fluconazole was changed to the oral form (600 mg per day). None of the ascitic fluid cultures yielded common bacteria or *Mycobacterium tuberculosis*. After discharge, he continued oral fluconazole therapy for a total duration of 98 days. No relapse of clinical cryptococcosis was noted at 1-year outpatient follow-up.

Table. Sequential ascites profile during admission in case 1 (in 2000).

Characteristics	April 29	May 3	May 8	May 12
Total protein (mg/dL)	0.7	0.7	1.0	1.1
LDH (U/L)	56	51	54	65
Glucose (mg/dL)	134	-	138	124
WBC (per μL)	2400	1000	200	100
L:N:M&H (%)	2:67:31	61:1:38	43:19:38	47:8:45
Blood WBC x 10^9/L	5.88	4.91	4.57	-
Seg (%)	90	86.8	82.7	-

LDH = lactate dehydrogenase; WBC = white blood cells; L:N:M&H = lymphocytes: neutrophils:mesothelia and histiocytes; Seg = segmented neutrophils.

Case 2

A 51-year-old woman, with a past history of Budd-Chiari syndrome and complicated liver cirrhosis (Child B), was admitted to NTUH on October 7, 2000 because of fever and intermittent chills for 3 days. Physical examination at admission disclosed the following: clear consciousness, blood pressure of 100/62 mm Hg, body temperature of 38.2°C, pulse rate of 112 beats per minute, respiratory rate of 24 times per minute, no oral thrush or hairy leukoplakia, supple neck without lymphadenopathy, bilateral basal crackles over lung fields, no audible heart murmur, distended abdomen with shifting dullness without definite tenderness and rebounding pain, and pedal edema. Her initial laboratory values revealed the following: hemogram, WBC count of 23.47 x 10^9/L (WBC classification: band 4%, neutrophil 91%, lymphocyte 3%, atypical lymphocyte 1%, and eosinophil 1%), hemoglobin of 11.8 g/dL, and platelet count of 69 x 10^9/L. Blood biochemistry profile revealed albumin 3.2 g/dL, bilirubin 13.3/8.1 mg/dL (total form/direct form), alkaline phosphatase 194 U/L; gamma-glutamyl transferase 71 U/L, aspartate aminotransferase 16 U/L, blood urea nitrogen 43.3 mg/dL, and creatinine 2.1 mg/dL.

Chest roentgenogram showed mild bilateral pleural effusion only. After admission, massive ascites was detected by abdominal ultrasonography. Ascites examination revealed: WBC count of 100/μL (WBC classification: lymphocyte 56%, neutrophil 38%, mesothelial cells and histiocytes 6%), total protein

level of 1.0 g/dL, glucose level of 94 mg/dL (blood glucose of 121 mg/dL), lactate dehydrogenase of 880 U/L, a negative cytological result, and India ink preparation of ascites was also negative. Her stool test for occult blood was 4+. Under the impression of severe sepsis with undetermined source, parenteral broad-spectrum antibiotics were initiated immediately after septic work-up. No definite deferverence was noted then.

Subsequently, *C. neoformans* grew from both the blood and ascites. Parenteral fluconazole with the dosage of 400 mg per day was administered thereafter. However, her clinical condition exacerbated gradually. Her serum cryptococcal antigen titer was 1:32,768. The CSF examination revealed a WBC count of < 5 x 11/9 per μL, total protein of 51 mg/dL, glucose of 5 mg/dL, cryptococcal antigen titer of 1:32,768, and positive culture result for *C. neoformans*. Fluconazole was replaced by amphotericin B infusion at a dosage of 0.8 mg/kg/day. Unfortunately, she died due to severe sepsis on the fourth day of admission. Her HIV serological status was not checked.

Discussion

C. neoformans, an encapsulated soil fungus distributed world-wide, is an important pathogen causing chronic meningitis and pneumonia in both immunocompromised[1,20] and immunocompetent[5,21] hosts. This well-known yeast was gradually recognized as the common etiology of deep-invading infections, including endophthalmitis, endocarditis, pericarditis, and prostatitis.[22]

Ordinarily, humans, especially those who have had various underlying immunocompromising conditions, could acquire cryptococcosis mostly through inhalation of airborne fungi.[4,23] However, in some instances, including patients with chronic liver disease and recent gastrointestinal bleeding or disruption of the gastrointestinal mucosal integrity (via administration of corticosteroid or non-steroidal anti-inflammatory agent, or prolonged broad-spectrum antibiotic therapy, etc.), cryptococci could invade the human host through the gastrointestinal tract.[15,18,24] Neither peritoneal dialysis nor ventriculoperitoneal shunt implantation was performed in both of our patients. With regards to their entry portal of cryptococcal peritonitis, precedent upper gastrointestinal tract bleeding of case 1 was an important predisposing event, although respiratory tract origin was still suspected because of the pulmonary nodule proved by chest CT scan. For case 2, because of the strongly positive result of fecal occult blood test, and absence of significant lung parenchymal lesions, cryptococcosis originating from the gastrointestinal tract could not be completely excluded.

Fungal peritonitis (mostly from *Candida* species) was reported to account for 3.5% to 15% of CAPD peritonitis episodes.[14] Among these fungal peritonitis cases, cryptococcal peritonitis accounted for a very low percentage of all cryptococcal infection and was also found in patients with end-stage renal disease and those receiving CAPD.[12–14] Yinnon et al suggested that the entry portal of cryptococci in this patient population might be the catheter indwelling for peritoneal dialysis, which was evidenced by negative microbiological results of blood, CSF, and urine samples in more than half of the total cases.[12] Biologically, cryptococci use creatinine as a nitrogen source, assimilate glucose and hydrolyze urea. The high levels of glucose, creatinine and urea in peritoneal dialysate were proposed to promote cryptococcal infections.[22] Another patient group that had been reportedly predisposed to peritoneal cryptococcosis was patients with acquired immunodeficiency syndrome.[12,20,22,25,26] However, peritoneal cryptococcosis seemed to reflect systemic rather than local disease in these patients.[12,22] Liver cirrhosis had also been proposed as a risk factor for cryptococcal infection.[5,15–19,24,27] Patients with decompensated liver cirrhosis have impaired host defenses in several important areas, including deficiency of serum complement,[28] defects in chemotaxis,[29] and lymphocyte hyporesponsiveness.[30] Portal-systemic shunting of blood flow, which bypasses hepatic Küppfer cell scavenging, also facilitates the entry of bowel organisms into the systemic circulation in these patients. The impaired host defense and portal-systemic shunting are likely to predispose patients with liver cirrhosis to the invasion of *C. neoformans* from either the respiratory or gastrointestinal tract into the bloodstream.[5]

In addition, cryptococcal peritonitis in cirrhotic patients usually did not lead to obvious peritoneal signs or inflammatory reaction demonstrated by analysis of ascitic fluid.[15,18] According to the literature,[11,17–19,27] the characteristics in ascites analysis of cryptococcal peritonitis were variable. Many patients had lymphocyte predominance, but some presented with ascitic cell counts similar to those found in patients with bacterial peritonitis (polymorphonuclear neutrophils > 250 per μL), while others had scanty cellular counts in their ascites (total white cell count < 100 per μL). Additionally, the protein level and serum-ascites albumin gradient were similarly variable. Antemortem diagnosis of peritoneal cryptococcosis might therefore be too late, as our case 2, to initiate effective treatment in time. Cirrhotic patients who developed new sepsis episodes, or fever of

unknown causes after gastrointestinal bleeding or use of antibacterial agents, should consider the differential diagnosis of cryptococcal peritonitis even if the symptoms or signs of peritonitis are lacking.

Previous researchers also observed that patients with clinically disseminated cryptococcal infections usually have central nervous system (CNS) involvement but lack signs and symptoms related to CNS infection, as was seen in case 2. Therefore, it might be reasonable to suggest that a diagnostic approach to exclude CNS involvement is indicated in patients with peritoneal cryptococcosis.

In conclusion, cryptococcal peritonitis is an infrequent disease, and early diagnosis of this unusual entity has always challenged clinicians. According to the literature, a high mortality rate is predicted if patients have severe underlying illnesses. Above all, the paucity of remarkable clinical symptoms and signs in cirrhotic patients has led us to search for any evidence of serosal inflammation, and to initiate adequate antibiotics if indicated.

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