Cryptococcal Peritonitis Complicating Hepatic Failure: Case Report and Review of the Literature

Muhammad Wasif Saif, MD, MBBS*
Mohan Raj, MD†

**Medical Oncology, Yale University School of Medicine, New Haven, Connecticut*
†Department of Medicine, New Britain General Hospital, New Britain, Connecticut

KEY WORDS: cryptococcal peritonitis, hepatic failure, *Cryptococcus neoformans*, ascites, disseminated cryptococcosis

ABSTRACT

Background: *Cryptococcus neoformans* is an encapsulated yeast that is an important cause of infection in patients with human immunodeficiency virus (HIV), lymphoid malignancies, and in those receiving corticosteroid therapy. The spectrum of diseases caused by *C neoformans* ranges from pulmonary infection to disseminated disease frequently involving the central nervous system, and occasionally skin and bone. Other extrapulmonary and extraneural sites of infection are less common. Cryptococcal peritonitis is an unusual entity, which is most often encountered in patients with end-stage renal disease undergoing ambulatory dialysis.

Case Report: We present a case of cryptococcal peritonitis which developed in a patient with hepatitis C-related cirrhosis. As little is know about the relationship between cirrhosis and cryptococcosis, we further reviewed the literature of this unusual but life-threatening relationship.

Discussion: Severe liver disease has not been fully recognized as a predisposing factor in the development of cryptococcal infection, particularly cryptococcal peritonitis, but the scattered case reports in the medical literature and our case report augment the association between the advanced liver disease and cryptococcal peritonitis. Therefore, cryptococcal infection should be considered in the evaluation of these patients with possible peritonitis.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a common complication in cirrhotic patients with ascites. Clinically, it manifests as fever, abdominal pain, and abdominal tenderness. The diagnosis is confirmed by presence of >250 neutrophils/mm^3 in the ascitic fluid and by demonstration of bacteria on Gram stained smear or peritoneal fluid culture.[1] *Cryptococcus neoformans* is an encapsulated yeast that is an important cause of infection in patients with human immunodeficiency virus (HIV) infection, lymphoid malignancies, and in those receiving corticosteroid therapy. The

Table 1. Case reports of patients with liver disease and crypotococcal peritonitis

Age/Sex/Race	Underlying disease	Risk/predisposing factors	Ascites fluid profile WBC/µ and protein g/L
60/F/C	Cirrhosis (hepatitis C)	Antibiotics	WBC: 150 P: 7
63/M/C	Cirrhosis (hepatitis B)	Upper GI bleeding, antibiotics	WBC: 220 P: 25
54/M/C	Fulminant hepatic failure	Corticosteroids, antibiotics	ND
63/M/C	Cirrhosis (hepatitis C)	Corticosteroids, antibiotics	WBC: 480 P: ND
56/M/C	Chronic active hepatitis	Corticosteroids	ND
NA	Ventriculoper intoneal shunt		ND
NA	Lupus nephritis	Upper GI bleeding, antibiotics, steroids	ND
57/M/C	Cirrhosis (hepatitis B)	Upper GI bleeding, antibiotics	WBC: 160 P:6
45/M/C	Cirrhosis (hepatitis C)	Upper GI bleeding, antibiotics	WBC: 220 P: 21
43/M	Cirrhosis; Hepatitis C AIDS	Upper GI bleeding, ascites	WBC: 0 P: 15.2
39/M	Hepatitis B and alcoholic cirrhosis	Ascites	WBC: 300 P: 2.4
42/F	Alcoholic cirrhosis; AIDS	Ascites, upper GI bleeding	WBC: 200 P: 1.7

F=female, M=Male, C=Caucasian, WBC=white blood cells, D=differential, P=protein, CSF= cerebrospinal fluid, BAL=broncho-aveolar lavage, GI=gastrointestinal, ND=not done, NA=not available.

continued

Other culture specimens showing C *neoformans*	Therapy	Outcome	Reference
CSF, blood, BAL	Amphotericin, flucytosine	Death	Mabee and Mabee[2]
CSF blood	Amphotericin, flucytosine	Death	Poblete[3]
Blood	None	Death	Sabesin and Tallen[4]
	Amphotericin, flucytosine	Death	Daly and Porter[5]
CSF blood, urine	Amphotericin	Death	Perfect and Durack[6]
CSF	Amphotericin	Death	Crum and Feldman[7]
ND	Amphotericin	Death	Watson and Johnson[8]
NA	Amphotericin	Death	Clift and Bradsher[9]
CSF, blood	Amphotericin, fluconazole (Discharged home on fluconazole)	Improved	Present Case
Blood, feces, sputum	Amphotericin B	Death	Stiefel et al [10]
Blood	Amphotericin B and fluconazole	Death	Cleophas et al[11]
Blood	_ _	Death	Sungkanuparph et al[12]

Table 1. Case reports of patients with liver disease and crypotococcal peritonitis (continued)

Age/Sex/Race	Underlying disease	Risk/predisposing factors	Ascites fluid profile WBC/μ and protein g/L
34/M	Alcoholic cirrhosis, lymphoma	Chemotherapy, upper GI bleeding	WBC: 450 P: 1.6
64/F	Cirrhosis, hepatitis B, breast cancer	Chemotherapy, ascites, jaundice	WBC: 340 P: 1.3
53/F	Cirrhosis, hepatitis C	Ascites	WBC: 470 P: ND
57/F	Hepatitis C	Corticosteroids	ND
39/M	Alcoholic cirrhosis	Ascites, esophageal varices	WBC: 50 P: 4
50/M	Hepatitis B, subacute hepatic failure	Ascites, jaundice	WBC: 3600 P: 3
44/F	Alcoholic cirrhosis	Ascites	WBC:60 P: 7
NA	Cirrhosis	Portal hypertension	ND
NA	Cirrhosis	Portal hypertension	ND

F=female, M=Male, C=Caucasian, WBC=white blood cells, D=differential, P=protein, CSF= cerebrospinal fluid, BAL=broncho-aveolar lavage, GI=gastrointestinal, ND=not done, NA=not available.

spectrum of diseases caused by *C neoformans* ranges from pulmonary infection to disseminated disease frequently involving the central nervous system, and occasionally skin and bone. Other extrapulmonary and extraneural sites of infection are less common. However, spontaneous peritonitis caused by *C neoformans* is rarely reported. Delayed diagnosis of cryptococcus peritonitis due to its rarity and the fact that its presentation is indistinguishable from SBP often results in fatal outcome. We present a case of cryptococcal peritonitis which developed in a patient with hepatitis C-related cirrhosis. We also reviewed the literature of this unusual association.

CASE REPORT

A 45-year-old male was admitted to the hospital complaining of progressive

Other culture specimens showing C *neoformans*	Therapy	Outcome	Reference
Urine	--	Death	Sungkanuparph et al[12]
Blood	Amphotericin B	Death	Sungkanuparph et al[12]
Blood, muscle biopsy	Amphotericin B, fluconazole	Alive	Flagg et al[21]
Blood	Amphotericin, flucytosine	Death	Singh et al[22]
ND	--	Death	Albert-Braun et al[23]
ND	--	Death	Cleophas et al[11]
ND	--	Death	Hoche-Delche et al[24]
Blood	--	Death	Jean et al[25]
Blood	--	Death	Jean et al[25]

weakness, fatigue, increased abdominal distension, and dyspnea. The patient was hospitalized 1 month prior to this admission for variceal bleeding and spontaneous bacterial peritonitis. During that hospitalization, he underwent diagnostic and therapeutic abdominal paracentesis, blood transfusion, and treatment with cefotaxime.

His past medical history was significant for end-stage liver disease secondary to hepatitis C–induced cirrhosis confirmed on biopsy and repeated interventions with abdominal paracentesis for his recurrent ascites during the previous 2 years. Review of systems revealed a history of mild confusion. His HIV status was known to be negative.

On physical examination, the patient, a hispanic male, was icteric and afebrile with normal vital signs. Further examination demonstrated spider

angiomas, mild nuchal rigidity, and scleral icterus. Abdominal examination revealed ascites with splenomegaly but no signs of guarding or rebound tenderness. Neurological examination showed only mild confusion, but no motor or sensory deficits. Chest radiograph showed no pulmonary infiltrates.

Abdominal paracentesis revealed ascitic fluid containing leukocytes 220/μL with 78% lymphocytes and 22% polymorphonuclear neutrophils; total protein was 2.1 g/dL. Gram stain and acid-fast bacilli stains were negative. Three days later, the patient's ascitic fluid culture grew *C neoformans*. Subsequent search for disseminated disease included microbiological studies of cerebrospinal fluid (CSF), blood, and urine. Blood and spinal fluid cultures also grew *C neoformans*. Serum cryptococcal antigen measured by indirect enzyme immunoassay (EIA) was 1:32 and CSF antigen was 1:640. Cryptococcal antigen titer by latex agglutination of the ascites fluid was 1:4. Abdominal ultrasound showed cholelithiasis. This was followed by a radionucleide scan which revealed cystic duct obstruction. Percutaneous drainage of the gall bladder under sonographic guidance was considered but not performed at that time.

The patient was initially treated with fluconazole 6 mg/kg intravenously (IV) and 3 days later was switched to amphotericin B 0.75 mg/kg IV for 9 days due to lack of change in the clinical picture. His condition improved and the repeated ascitic, blood, and CSF cultures were sterile 12 days later. He was discharged to home on oral fluconazole. Patient was alive at the follow up of 6 months.

DISCUSSION AND LITERATURE REVIEW

Cryptococcal peritonitis is an uncommon infection. The respiratory tract is considered to be the usual port of entry of *C neoformans*. However, the gastrointestinal (GI) tract has been proposed as a potential site either following ingestion or possible direct inoculation of *C neoformans* into the blood stream following upper GI bleeding or overgrowth of fungus after antibiotic use.[2,3]

Review of our case and of previously reported cases (Table 1) reveals a striking association between hepatic disease and cryptococcal peritonitis.[2-12,21-25] The spectrum of hepatobiliary and pancreatic diseases found in these cases include hepatocellular carcinoma, liver cirrhosis either due to alcohol abuse or hepatitis B or C fulminant hepatitis, polyarteritis nodosa, gall bladder cancer, and cystadenocarcinoma of the pancreas.[13,14]

Although *Candida spp.* and *Aspergillus spp.* are also known causes of proven fungal peritonitis, cases due to cryptococcal peritonitis appear to be more highly associated with hepatobiliary diseases.

Patients with liver disease have an increased predisposition to infections, often secondary to impaired phagocytic function, reduced complement levels, dysimmunoregulation, corticosteroids, the need for invasive procedures, use of antibacterial agents, and, possibly, GI bleeding associated with liver disease which may result in translocation of organisms from the GI tract to the blood.[1,2,15] Such qualitative or quantitative impairment of humoral immunity may also increase the risk of cryptococcosis.[10]

Proposed mechanisms underlying the pathogenesis of cryptococcal peritonitis include direct percutaneous inoculation of contaminating organisms during repeated paracentesis for management of ascites, hematogenous spread from a pulmonary site, and hematogenous spread from the alimentary tract facilitated by upper GI bleeding. In our patient, previous paracentesis, antibiotic exposure, and recent upper GI bleeding occurred within a relatively

short period of time before development of cryptococcal peritonitis. These events raise the possibility of direct percutaneous inoculation or the possibility of translocation of the *cryptococci* from the GI site into the blood stream. Casadaval and Perfect previously suggested the GI tract as a portal of entry in HIV-infected patients.[16]

In patients who have responded to an initial course of amphotericin, the use of oral fluconazole improves quality of life in the ambulatory setting. While careful monitoring of aspartate aminotransferase, alanine aminotransferase, and bilirubin in patients with liver impairment is warranted for this azole, the frequency of truly attributable hepatotoxicity due to fluconazole remains acceptably small. Moreover, as only approximately 15% of fluconazole is hepatically metabolized, no dosage adjustment is necessary in patients with liver disease.[17]

If not diagnosed and treated promptly, progressive disseminated cryptococcosis and ultimately death may ensue. The possible reasons for a delay in diagnosis and therapy include low degree of suspicion; lack of classic signs and symptoms of peritonitis (as in our case) or even other signs of infection (lack of fever, absence of signs of meningismus); absence of characteristic ascitic fluid examination findings—as seen in our case where the ascitic fluid total protein was <2.5 g/dL suggesting a transudative rather than an exudative process[2]; and longer time period for fungal culture to grow. Similarly, the microscopic evaluations and culture techniques are also sub-optimal. Clift and Bradsher demonstrated that india ink preparations may be beneficial.[9] Runyon suggested that inoculation of blood culture bottles containing fungal media with ascitic fluid at the bedside may provide an increased yield of ascitic fluid cultures for microorganisms.[18] Diagnostic sensitivity is further enhanced by performing serum cryptococcal antigen testing by latex agglutination or EIA of serum and CSF. The positivity of the test in our case supports the diagnostic utility for early detection of *C neoformans* in high-risk patients. A similar diagnostic suspicion also maybe warranted in patients receiving peritoneal dialysis, where cryptococcal peritonitis has been reported.[19]

Mortality rate in cirrhotic patients developing spontaneous cryptococcal peritonitis is high.[10,20] The advanced hepatic decomposition (cirrhosis), disseminated fungal infection, and delayed diagnosis may contribute to such high fatality rates. Clinical suspicion of this disease may lead to an earlier diagnosis and a better therapy and outcome.

Severe liver disease has not been fully recognized as a predisposing factor in the development of cryptococcal infection, particularly cryptococcal peritonitis, but the scattered case reports in the medical literature and our case report augment the association between the advanced disease and cryptococcal peritonitis. Therefore, cryptococcal infection should be considered in the evaluation of these patients with possible peritonitis. Abdominal paracentesis with bedside inoculation of culture medium, india ink preparations, and serum (CSF, ascitic fluid) cryptococcal antigen testing should be included in the evaluation of infected ascitic fluid in this group of patients. If discovered from ascitic fluid, prompt search for disseminated cryptococcal infection should be performed. Amphotericin B followed by oral fluconazole may result in successful therapy.

ACKNOWLEDGEMENT

The authors wish to acknowledge Meagan Johanson for assistance in publication editing and preparation.

REFERENCES

1. Such J, Runyon BA. Spontaneous bacterial peritonitis. *Clin Infect Dis.* 1998;27:669-674.
2. Mabee CL, Mabee SW. Cirrhosis: a risk factor for cryptococcal peritonitis. *Am J Gastroenterology*. 1995;90:2042-2045.
3. Poblete RB. Cryptococcal peritonitis. *Am J Med.* 1987;82:665-667.
4. Sabesin SM, Tallen HJ. Hepatic failure as a manifestation of cryptococcosis. *Arch Intern Med*. 1963;3:661-669.
5. Daly JS, Porter KA. Disseminated, non-meningeal gastrointestinal cryptococcal peritonitis in an HIV-negative patient. *Am J Gastroenterology*. 1990;85:1421-1424.
6. Perfect JR, Durack DT. Cryptococcemia. *Medicine.* 1983;62:98-109.
7. Crum CP, Feldman PS. Cryptococcal peritonitis complicating a ventriculoperitoneal shunt in unsuspected cryptococcal meningitis. *Hum Pathol.* 1981;12:660-663.
8. Watson NE, Johnson AH. Cryptococcal peritonitis. *South Med J.* 1973;66:387-388.
9. Clift SA, Bradsher RW. Peritonitis as an indicator of disseminated cryptococcal infection. *Am J Gastroenterology.* 1982;77:922-924.
10. Stiefel P, Pamies E, Miranda ML. Cryptococcal peritonitis: report of a case and review of the literature. *Hepatogastroenterology*. 1999;46:1618-1622.
11. Cleophas V, George V, Mathew M, et al. Spontaneous fungal peritonitis in patients with hepatitis B virus related liver disease. *J Clin Gastronenterology*. 2000;31:77-79.
12. Sungkanuparph S, Vibhagool A, Pracharktam R. Spontaneous cryptococcal peritonitis in cirrhotic patients. *J Postgrad Med.* 2002;48:201-202.
13. Diamond RD, Bennett JE. Disseminated cryptococcosis in man. *J Infect Dis.*1973;127:694-697.
14. Rolando N, Philpott-Howard J. Bacterial and fungal infection in acute liver failure. *Sem Liver Dis*. 1996;16:389-402.
15. Walsh TJ, Hamilton SR. Disseminated aspergillosis complicating hepatic failure. *Arch Intern Med.* 1983;143:1189-1191.
16. Casadaval A, Perfect JR. *Cryptococcus neoformans*. In: Cassadavell A, Perfect JR (eds), *Physical defenses and nonspecific immunity*. Washington, DC, American Society for Microbiology Press, 1998;177-222.
17. Groll A, Piscitelli, Walsh TJ. Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. *Adv Pharmacol.* 1998;44:343-500.
18. Runyon BA. Care of patients with ascites. *N Eng J Med.* 1994;330:337-342.
19. Mansoor GA. Cryptococcal peritonitis in peritoneal dialysis patients. *Clin Nephrol.* 1994;41:230-232.
20. Yinnon AM, Solages A, Treanot JJ. Cryptococcal peritonitis: report of a case developing during continuous ambulatory peritoneal dialysis and review of the literature. *Clin Infect Dis*. 1993;17:736-741.
21. Flagg SD, Chang YJ, Masuell CP, et al. Myositis resulting from disseminated cryptococcosis in a patient. *Clin Infect Dis* 2001;32:1106-1107.
22. Singh N, Hussain S, de Vera M, et al. Cryptococcus neoformans infection in patients with cirrhosis, including liver transplant candidates. *Medicine*. 2004;83:188-192.
23. Albert-Braun S, Venema F, Bausch J, et al. *Cryptococcus neoform* and peritonitis in a patient with alcoholic cirrohsis: Case report and review of the literature. *Infection*. 2005;33:282-288.
24. Hoche-Delche C, Kauffmann-Lacroix C, Beau P, et al. Cryptococcose disseminee au cours d une cirrhose alcoolique severe decompensee. *Presse Med*. 2003;32:1366.
25. Jean SS, Fang CT, Shau WY, et al. Cryptococcaemia: clinical features and prognostic factors. *QJM*. 2002;95:511-518.