Cirrhosis, gastrointestinal bleed, and cryptococcal peritonitis

Amy E. Barnett, DO^a, and Karen B. Brust, MD^b

^aDepartment of Internal Medicine, Baylor Scott & White Medical Center – Temple, Temple, Texas; ^bDivision of Infectious Diseases, Department of Internal Medicine, Baylor Scott & White Medical Center – Temple, Temple, Texas

ABSTRACT

Disseminated *Cryptococcus neoformans* infection rarely causes peritonitis in non-HIV-infected patients but does affect cirrhotic patients. Diagnostic challenges delay treatment, and mortality is high. We performed a literature search of proven cryptococcal peritonitis cases in HIV-negative adults with underlying cirrhosis, included our own case, and collected demographic, infection risk factor, diagnostic, treatment, and outcomes data. We identified 16 articles and 21 cases. Most patients were men. Alcohol abuse was the leading cause of underlying cirrhosis ($n = 10$, 48%). Eight (38%) patients experienced an upper gastrointestinal bleed (UGIB) within a month before peritonitis presentation. Peritoneal fluid analysis was abnormal and lymphocytic predominant. Half the patients were fungemic. When performed, peritoneal fluid cryptococcal antigen (CrAg) test results were positive. Amphotericin B was the primary treatment. Mortality was high at 76%. In conclusion, *C. neoformans* is an opportunistic pathogen that causes peritonitis in non-HIV, cirrhotic patients. People with recent UGIB seem to be at risk. *Cryptococcus* species infection should be suspected in patients with clinical signs and symptoms of spontaneous bacterial peritonitis whose lymphocytic-predominant peritoneal fluid and cultures are negative for bacterial growth. Peritoneal CrAg testing expedites diagnosis because growth on fungal media is slow. Mortality remains high, despite standard therapy with amphotericin B.

KEYWORDS Cirrhosis; cryptococcal antigen; *Cryptococcus*; peritonitis

Cryptococcus *neoformans*, a ubiquitous encapsulated yeast, is known to cause opportunistic infections of the respiratory and central nervous systems (CNS). HIV-seropositive patients are disproportionately affected at an estimated annual incidence of 17 to 66 per 1000 patients as compared to HIV-negative individuals, at 0.2 to 0.9 per 100,000 patients.^{1–3} Cryptococcal dissemination can affect most organs (lungs and meninges more than other sites), and risk factors for disseminated infection include lymphoid malignancies, chronic corticosteroid use, solid organ transplantation, sarcoid, and liver cirrhosis.^{4–9} *C. neoformans* causing spontaneous fungal peritonitis is a rare disease process associated with underlying end-stage liver disease and cirrhosis.^{1,8}

METHODS

We performed a literature review of all PubMed articles published after 1980. Search terms were

“Cryptococcus and peritonitis,” “cryptococcal peritonitis,” or a combination of these terms (*Figure 1*). The identification of studies was limited to English-language articles of human cryptococcal peritonitis cases. We excluded articles if infection was related to peritoneal dialysis or the patient was HIV positive. The articles reviewed included HIV-negative adults with underlying cirrhosis of any type and a diagnosis of cryptococcal peritonitis. Collected data included demographics, infection risk factors, diagnostics, treatment, and outcomes.

RESULTS

Our review resulted in 16 articles and 21 cases of cryptococcal peritonitis in HIV-negative patients (*Table 1*).^{1,5,6,8–20} Most patients were men ($n = 14$, 67%) with a median age of 54 years (range, 34–65). Alcohol abuse was the most common cause of underlying cirrhosis ($n = 10$, 48%), with or without

Corresponding author: Karen B. Brust, MD, Division of Infectious Diseases, Baylor Scott & White Medical Center – Temple, 2401 S. 31st Street, Temple, TX 76508 (e-mail: Karen.brust@bswhealth.org)

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Figure 1. Flow chart of the literature search and study selection.

concomitant viral hepatitis. Of the 21 cases, 8 (38%) involved patients who experienced upper gastrointestinal bleed (UGIB) within a month before presentation. Specific information regarding UGIB was not available for the other cases. Ascitic fluid analysis was universally abnormal and typically lymphocytic predominant. It took an average of 5 days from the time paracentesis was performed until culture results were available. About 50% of patients were concomitantly fungemic, and 8 patients had cryptococcal meningitis. Peritoneal fluid cryptococcal antigen (CrAg) testing was performed on only 4 patients, but all results were positive, ranging from 1:4 to 1:2048. Amphotericin B (with or without the use of flucytosine or fluconazole) was the primary treatment. Sixteen patients died. Mortality is estimated at 76%.

DISCUSSION

Our case series describes *C. neoformans* as the cause of spontaneous fungal peritonitis in HIV-negative cirrhotic

patients. Risk factors include end-stage liver disease and recent UGIB. Results of peritoneal fluid analysis suggest infection. However, unlike spontaneous bacterial peritonitis (SBP), the peritoneal fluid is lymphocytic predominant. Mortality is high.

Spontaneous fungal peritonitis is rare, accounting for <10% of peritonitis cases, and *Candida* species causes most, if not all, cases.^{21–23} Peritonitis in general occurs when an UGIB compromises the intestinal barrier.^{21,22} Some experts believe that cryptococcal peritonitis is a reflection of disseminated disease, but this case series suggests a link to UGIB, similar to *Candida* peritonitis. Unlike SBP, no recommendations exist regarding antifungal prophylaxis following UGIB. Spontaneous fungal peritonitis should be suspected when paracentesis reveals lymphocytic-predominant peritoneal fluid and is without growth of bacterial organisms. This case series suggests the utility of CrAg testing in peritoneal fluid because all four patients tested had detectable levels. Serum CrAg testing performs well in general but is best when CNS or disseminated disease is present or when the host is HIV positive.^{24,25} In the non-HIV, non-CNS, nonpulmonary patient, CrAg sensitivity is lower and is positive at a rate of only 67%.²⁵

Guidelines for treatment of severe and disseminated cryptococcal disease can be followed for peritonitis treatment. This includes use of a lipid formulation of amphotericin B and flucytosine for an induction period followed by fluconazole for either 8 weeks or until clinical cure is achieved.²⁶ In our case series, no one treatment regimen was suggestive of improved mortality. Diagnostic delay and not empirically starting antimycotic therapy contribute to high mortality for spontaneous fungal peritonitis, which is estimated at 50% to 90%.^{21–23} Mortality specifically for cryptococcal peritonitis is 76% according to our data and up to 100% in the cases described by Hwang et al.²²

C. neoformans is an opportunistic pathogen that causes disseminated infection and peritonitis in immunosuppressed patients. People with advanced underlying cirrhosis and recent UGIB seem to be at particular risk. Patients with clinical signs and symptoms of SBP in whom paracentesis reveals lymphocytic-predominant fluid but no bacteria should be suspected of being infected with *Cryptococcus* species. The time between paracentesis and growth of the organism in culture is substantial; therefore, CrAg testing of peritoneal fluid can help expedite the diagnosis. Mortality remains high, despite use of amphotericin B and flucytosine. Armed with the diagnosis and known mortality of 76% to 100%, clinicians can then address the poor prognosis of this disease process.

ORCID

Karen B. Brust <http://orcid.org/0000-0001-5853-2323>

Table 1. Cryptococcal peritonitis case descriptions

Reference	Cause of liver cirrhosis	UGIB a month prior	Ascites fluid analysis WBC count (mm ³) with differential	Culture		Antigen			Primary therapy	Outcome
				Blood	CSF	Ascites	Serum	CSF		
Albert-Braun et al ¹	Alcohol	ND	50 mm ³ , 46% PMN, 17.5% lymph, 27% mono	ND	ND	ND	1:8	ND	ND	Died
Bal et al ⁹	HBV	ND	900 mm ³ , predominant lymph	+	ND	ND	ND	ND	Amphotericin B	Died
	HCV	ND	800 mm ³ , predominant lymph	+	ND	ND	ND	ND	Fluconazole IV	Lived
Barnett ^a	Alcohol	Yes	97 mm ³ , 51% lymph, 45% mono, 4% PMN	+	+	ND	1:4096	1:256	Amphotericin B and flucytosine	Died
Cleophas et al ¹⁰	Alcohol	ND	300 mm ³ , 75% PMN	+	ND	ND	ND	ND	Amphotericin B and fluconazole	Died
Clift et al ¹¹	Alcohol HBV ¹	Yes	1148 mm ³ , 84% PMN	–	+	1:2048	ND	1:128	Amphotericin B	Died
Daly et al ¹²	Unknown	ND	480 mm ³ , 59% PMN	+	–	ND	1:4096	ND	Amphotericin B	Died
El-Kersh et al ¹³	HCV, HBV cirrhosis	Yes	1250 mm ³ , 90% PMN	ND	ND	ND	+ ^b	+ ^b	Amphotericin B and flucytosine	Died
Flagg et al ¹⁴	Alcohol, HCV	ND	470 mm ³ , 32% PMN, 25% macro, 17% mono, 9% lymph	+	ND	ND	ND	ND	Amphotericin B then fluconazole	Lived
Jean et al ¹⁵	Alcohol	Yes	2400 mm ³ , 90% PMN	ND	+	1:128	1:128	1:2	Fluconazole IV then oral fluconazole	Lived
	Budd-Chiari syndrome	ND	100 mm ³ , 56% lymph, 38% PMN	+	+	ND	1:32,768	1:32,768	Fluconazole IV then amphotericin B	Died
Kandula et al ⁶	Alcohol, HCV	Yes	156 mm ³ , 77% lymph	+	ND	ND	+ ^b	ND	Amphotericin B and flucytosine	Died
Mabee et al ⁸	Jejunioileal bypass surgery	ND	"Unremarkable"	–	–	ND	ND	ND	Amphotericin B and flucytosine	Lived
	HCV	ND	400 mm ³ , 51% lymph, 32% PMN	+	+	ND	1:3421	ND	Amphotericin B and flucytosine	Died
Poblete and Kirby ¹⁶	Alcohol, HBV	Yes	200 mm ³ , 12% PMN, 88% mono	+	+	1:4	1:64	ND	Amphotericin B and flucytosine	Died
Saif and Raj ¹⁷	HCV	Yes	220 mm ³ , 78% lymph, 22% PMN	+	+	1:4	1:32	1:640	Fluconazole then amphotericin B	Lived
Singh et al ¹⁸	HBV	ND	700 mm ³ , 87% lymph	ND	ND	ND	ND	ND	Amphotericin B	Died
Singh et al ¹⁹	HCV	ND	ND	+	–	ND	ND	ND	Amphotericin B and flucytosine	Died
Sungkanuparph et al ²⁰	Alcohol	Yes	450 mm ³ , 80% lymph	ND	ND	ND	ND	ND	ND	Died
	HBV	ND	340 mm ³ , 60% lymph	–	ND	ND	ND	ND	Amphotericin B	Died
Yehia et al ⁵	Alcohol	ND	797 mm ³ , 81% PMN	+	+	ND	ND	+ ^b	Amphotericin B and flucytosine	Died

HBV indicates hepatitis B virus; HCV, hepatitis C virus; IV, intravenous; lymph, lymphocytes; mono, monocytes; ND, not done/not reported; PMN, polymorphonuclear leukocytes; UGIB, upper gastrointestinal bleed; WBC, white blood cells.

^aAuthors' case.

^bTiter not specified.

1. Albert-Braun S, Venema F, Bausch J, Hunfeld KP, Schäfer V. *Cryptococcus neoformans* peritonitis in a patient with alcoholic cirrhosis: case report and review of the literature. *Infection*. 2005;33:282–288. doi:10.1007/s15010-005-4120-6.
2. Kokturk N, Ekim N, Kervan F, et al. Disseminated cryptococcosis in a human immunodeficiency virus-negative patient: a case report. *Mycoses*. 2005;48(4):270–274. doi:10.1111/j.1439-0507.2005.01136.x.
3. Hajjeh RA, Conn LA, Stephens DS, et al; the Cryptococcal Active Surveillance Group. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. *J Infect Dis*. 1999;179(2):449–454. doi:10.1086/314606.
4. Chuang YM, Ho YC, Chang HT, Yu CJ, Yang PC, Hsueh PR. Disseminated cryptococcosis in HIV-uninfected patients. *Eur J Clin Microbiol Infect Dis*. 2008;27(4):307–310. doi:10.1007/s10096-007-0430-1.
5. Yehia BR, Eberlein M, Sisson SD, Hager DN. Disseminated cryptococcosis with meningitis, peritonitis, and cryptococcemia in a HIV-negative patient with cirrhosis: a case report. *Cases J*. 2009;2:170. doi:10.1186/1757-1626-2-170.
6. Kandula M, Kelkar AH, Liberio N, Aiyer MK. Cryptococcemia in an HIV-negative patient with decompensated liver cirrhosis. *J Community Hosp Intern Med Perspect*. 2016;6(6):33383. doi:10.3402/jchimp.v6.33383.
7. Perfect JR. Cryptococcosis. *Infect Dis Clin North Am*. 1989;3(1):77–102.
8. Mabee CL, Mabee SW, Kirkpatrick RB, Koletar SL. Cirrhosis: a risk factor for cryptococcal peritonitis. *Am J Gastroenterol*. 1995;90(11):2042–2045.
9. Bal CK, Bhatia V, Khillan V, et al. Spontaneous cryptococcal peritonitis with fungemia in patients with decompensated cirrhosis: report of two cases. *Indian J Crit Care Med*. 2014;18:536–539. doi:10.4103/0972-5229.138161.
10. Cleophas V, George V, Mathew M, Samal SC, Chandy GM. Spontaneous fungal peritonitis in patients with hepatitis B virus-related liver disease. *J Clin Gastroenterol*. 2000;31(1):77–79. doi:10.1097/00004836-200007000-00018.
11. Clift SA, Bradsher RW, Chan CH. Peritonitis as an indicator of disseminated cryptococcal infection. *Am J Gastroenterol*. 1982;77(12):922–924.
12. Daly JS, Porter KA, Chong FK, Robillard RJ. Disseminated, nonmeningeal gastrointestinal cryptococcal infection in an HIV-negative patient. *Am J Gastroenterol*. 1990;85(10):1421–1424.
13. El-Kersh K, Rawasia WF, Chaddha U, Guardiola J. Rarity revisited: cryptococcal peritonitis. *BMJ Case Rep*. 2013;2013:bcr2013009099–bcr2013009099. doi:10.1136/bcr-2013-009099.
14. Flagg SD, Chang YJ, Masuell CP, Natarajan S, Hermann G, Mendelson MH. Myositis resulting from disseminated cryptococcosis in a patient with hepatitis C cirrhosis. *Clin Infect Dis*. 2001;32(7):1104–1107. doi:10.1086/319589.
15. Jean SS, Wang JL, Wang JT, Fang CT, Chen YC, Chang SC. *Cryptococcus neoformans* peritonitis in two patients with liver cirrhosis. *J Formos Med Assoc*. 2005;104(1):39–42.
16. Poble RB, Kirby BD. Cryptococcal peritonitis. Report of a case and review of the literature. *Am J Med*. 1987;82(3):665–667. doi:10.1016/0002-9343(87)90120-3.
17. Saif MW, Raj M. Cryptococcal peritonitis complicating hepatic failure: case report and review of the literature. *J Appl Res*. 2006;6(1):43–50.
18. Singh DK, Tyagi I, Saran RK, Gondal R. Fatal spontaneous Cryptococcal peritonitis in a woman with decompensated liver cirrhosis. *Acta Cytol*. 2010;54(5 Suppl):1087–1089.
19. Singh N, Husain S, De Vera M, Gayowski T, Cacciarelli TV. *Cryptococcus neoformans* infection in patients with cirrhosis, including liver transplant candidates. *Medicine (Baltimore)*. 2004;83(3):188–192. doi:10.1097/01.md.0000126760.45299.69.
20. Sungkanuparph S, Vibhagool A, Prachartam R. Spontaneous cryptococcal peritonitis in cirrhotic patients. *J Postgrad Med*. 2002;48(3):201–202.
21. Lahmer T, Brandl A, Rasch S, Schmid RM, Huber W. Fungal peritonitis: underestimated disease in critically ill patients with liver cirrhosis and spontaneous peritonitis. *PLoS One*. 2016;11(7):e0158389. doi:10.1371/journal.pone.0158389.
22. Hwang SY, Yu SJ, Lee JH, et al. Spontaneous fungal peritonitis: a severe complication in patients with advanced liver cirrhosis. *Eur J Clin Microbiol Infect Dis*. 2014;33(2):259–264. doi:10.1007/s10096-013-1953-2.
23. Bremmer DN, Garavaglia JM, Shields RK. Spontaneous fungal peritonitis: a devastating complication of cirrhosis. *Mycoses*. 2015;58(7):387–393. doi:10.1111/myc.12321.
24. Singh N, Alexander BD, Lortholary O, Cryptococcal Collaborative Transplant Study Group et al. *Cryptococcus neoformans* in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. *J Infect Dis*. 2007;195(5):756–764. doi:10.1086/511438.
25. Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis*. 2001;33(5):690–699. doi:10.1086/322597.
26. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(3):291–322. doi:10.1086/649858.