Gastrointestinal Cryptococcosis Presenting as Spontaneous Jejunal Perforation in a Nonimmunocompromised Host

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CASE REPORT

At surgery he was found to have an extensively soiled peritoneal cavity with abundant fibrinous exudate. A single 2-cm x 2-cm perforation was found in the jejunum. This was debrided and repaired. Careful examination of other abdominal organs revealed no abnormality. Following surgery the patient required ventilatory and inotropic support and was admitted to an intensive care unit for further care. His condition remained hemodynamically unstable, and on day 4 after admission, due to evidence of persistent intraabdominal sepsis, a repeat laparotomy was performed, at which time more extensive debridement of purulent, necrotic material was required to be performed. Histological examination of the jejunal wound edge biopsied at the first laparotomy revealed the presence of edema, necrosis, and full-thickness invasion of the wall by encapsulated yeasts identified as Cryptococcus neoformans (Figures 1 and 2). Fungal organisms and inflammatory exudate were also seen on the serosal surface, consistent with the picture of a cryptococcal peritonitis. Antifungal therapy (fluconazole 400 mg intravenously daily) was added to the broad-spectrum empirical antibacterial therapy that had already been instituted.

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ELISA tests performed at that time for HIV 1 and 2 antibodies were negative. A lymphocyte subset analysis revealed a CD4 count of 419.1 cell/mm^3. The CD4/CD8 ratio was 2.23 (normal range: 1.0–3.5). Microscopic examination of endobronchial aspirate was negative for cryptococcus, as were fungal blood cultures. A lumbar puncture was not performed.

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Fig 1. Cross-sectional view of the jejunal wall. The gut lumen is oriented towards the upper left corner, and the serosa towards bottom-right. The intervening lamina propria is heavily infected with dark-staining, round cryptococci.

primarily on cell-mediated immunity, with the CD4+ T-lymphocyte playing a central role, a finding that substantiates its increased incidence in AIDS patients. Other identified conditions that predispose patients to primary infection with or without disseminated spread are intensive and prolonged corticosteroid use, chronic leukemias and lymphomas, cirrhosis, and diabetes (1). Cryptococcosis has also been reported in rare primary immunodeficiencies such as idiopathic CD4+ T-lymphopenia (5), interleukin-2 deficiency (6), Job’s syndrome (hyperimmunoglobulinemia E-recurrent infection (7), and severe combined immunodeficiency (8). Infection occurs via the respiratory route, and extrapulmonary...
manifestations occur as a result of hematogenous spread. While the central nervous system is the most commonly affected site in symptomatic cryptococcosis, infection with or without clinical manifestations has been reported in a wide variety of extraneurological sites, including various parts of the gastrointestinal tract.

Washington et al. (4) reviewed autopsy reports of 24 patients diagnosed with disseminated or pulmonary cryptococcosis and found that a third of these had evidence of gastrointestinal involvement, affecting, in order of frequency, the colon, esophagus, stomach, and the small bowel. In all 8 cases there was an underlying predisposing condition of immunosuppression and in 7 of the 8 cases there was involvement of multiple other extrapulmonary sites.

Despite the apparently high rate of gastrointestinal involvement reported in this series, the incidence of symptoms directly attributable to cryptococcal infection of the gastrointestinal tract seems to be exceedingly rare. In one study of a series of 68 patients with cryptococcosis and AIDS, no subjects with evidence of gastrointestinal involvement were found (9). Similarly, a more recent review of the 1013 cases of cryptococcosis documented in France in a 9-year period (1985–1993) did not report any clinical manifestations of gastrointestinal disease (10).

Three AIDS patients have been reported in whom antemortem endoscopic investigation for complaints of abdominal pain has revealed the presence of gastrointestinal involvement and four involving the colon and one the esophagus. In four of the five patients an underlying cause of immunocompromise was identified. Subsequent to this review, one other HIV-negative case has been reported (14), that of an 84-year-old woman who presented with rectal bleeding due to isolated cryptococcosis of the sigmoid colon mimicking an adenomatous polyp. No cause of immunocompromise was identified in this patient, but a history of significant exposure to pigeons was noted. One further case, not included in the above review, related to a 2-month-old infant with severe combined immunodeficiency syndrome who, at autopsy, was found to have disseminated cryptococcosis with a particularly heavy fungal load noted in the region of the terminal ileum (8).

Cryptococcal peritonitis as a disease entity has been documented and reviewed (15). Approximately half of the described cases have occurred in patients undergoing continuous peritoneal dialysis and the remainder in the setting of disseminated disease occurring in immunocompromised patients. In the latter group, liver dysfunction and cirrhosis have been shown to be special risk factors (16).

In our patient, no predisposing underlying cause for impaired immunity was identified. Although the patient’s measured CD4+ count was lower than normal, it is nevertheless still higher than the value of 300 cells/mm3 proposed for a diagnosis of idiopathic CD4+ T-lymphopenia (17) and well above the values shown to predispose patients to cryptococcal infection (18).

There was no evidence of disseminated cryptococcosis in our patient, the small intestine and peritoneum being the only sites of proven infection. Other cases of isolated intestinal cryptococcosis have led to speculation that the gastrointestinal tract represents an additional portal of entry for cryptococcal infection (13, 14), and several experiments have been performed to prove this hypothesis in animal models (19–21). In our patient, there was no clinical evidence to suggest the presence of cryptococcosis outside of the jejunum. Nevertheless, in the absence of either CSF examination or systematic histological examination, the diagnosis of true isolated gastrointestinal cryptococcosis cannot be made, and we therefore cannot cite this case as evidence adding strength to the viewpoint proposing the gastrointestinal tract as a portal of entry for Cryptococcus. The histological pattern of uniform, diffuse infection of the entire gut wall and serosa might be an indication of hematogenous spread, but might also be the result of contiguous spread through necrotic tissue and seeding of the serosa by way of the perforation.

Spontaneous perforation of the jejunum is exceedingly rare. Its causes include intestinal tuberculosis (22), small-bowel diverticula (23), various primary intestinal tumors (24), and Kaposi’s sarcoma (25). Conditions that primarily cause ulceration of the jejunum, such as inflammatory bowel disease, tropical sprue, isolated intestinal ulceration, and idiopathic diffuse ulcerative nongranulomatous enteritis, are also known as complications of perforation (26). To our knowledge, this is the first reported case of spontaneous jejunal perforation resulting from cryptococcal jejunitis and adds to the varied list of presentations of cryptococcosis in the literature.

The growing AIDS pandemic, especially in sub-Saharan Africa where cryptococcosis affects in excess of 15% of AIDS patients (1), can reasonably be expected to bring about a parallel increase in the incidence of this disease in its many manifestations. Our case demonstrates that spontaneous intestinal perforation is a possible manifestation of cryptococcosis. In cases of unexplained small-bowel perforation, this diagnosis
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should be considered, and histological and mycological examination of the lesion edges should performed so that, if appropriate, antifungal treatment might be instituted in a timely manner.

REFERENCES

1. Mitchell TG, Perfect JR: Cryptococcosis in the era of AIDS—100 years after the discovery of Cryptococcus neoformans. Clin Microbiol Rev 8:515–548, 1995
2. Lewis JL, Rubinstein S: The wide spectrum of cryptococcal infections. Am J Med 53:315–322, 1972
3. Zelman S, O’Neil RH, Plant A: Disseminated visceral tularaemia without nervous system involvement. Am J Med 1:658–664, 1951
4. Washington K, Gottfried MR, Wilson ML: Gastrointestinal cryptococcosis. Med Pediatr 4:707–711, 1991
5. Duncan RA, von Reyn CF, Alliegro GM, Toossi Z, Sugar AM, Levitz SM: Idiopathic CD4+ T-lymphocytopenia—four patients with opportunistic infections and no evidence of HIV infection. N Engl J Med 328:393–398, 1993
6. Sorenson RU, Boehm KD, Kaplan D, Berger M: Cryptococcal osteomyelitis and cellular immunodeficiency associated with interleukin-2 deficiency. J Pediatr 121:873–879, 1992
7. Stone BD, Wheeler JG: Disseminated cryptococcal infection in a patient with hyperimmunglobulinaemia E syndrome. J Pediatr 117:92–95, 1990
8. Smith JH, Nichols MM, Goldman AS, Schmalstieg FC, Goldblum RM: Disseminated cryptococcal meningitis in an infant with severe combined immunodeficiency. Hum Pathol 15:505–503, 1982
9. Clark RA, Goriz D, Atkinson W, Valainis GT, Hyslop N: Spectrum of Cryptococcus neoformans infection in 68 patients infected with human immunodeficiency virus. Rev Infect Dis 12:768–777, 1990
10. Dromer F, Mathoulin S, Dupont B, Laporte A: Epidemiology of cryptococcosis in France: a 9-year survey (1985–1993). French Cryptococcosis Study Group. Clin Infect Dis 23:82–90, 1996
11. Chalasani N, Wilcox CM, Hunter HT, Schwartz DA: Endoscopic features of gastrointestinal cryptococcosis in AIDS. Gastroenterol Endosc 45:115–118, 1997
12. Van Cäk M, Morte S, Rickard F, Stanton E, Adair M, Wyllie R: Gastrointestinal and cutaneous in a patient with AIDS. Am J Gastroenterol 81:1306–1308, 1988
13. Daly JS, Porter KA, Cheng FK, Robillard RJ: Disseminated non-meningeal gastrointestinal infection in an HIV-negative patient. Am J Gastroenterol 85:1421–1424, 1990
14. Melato M, G교 N: Primary intestinal cryptococcosis mimicking adenomatous polyp in an HIV-negative patient. Am J Gastroenterol 95:1592–1597, 1998
15. Yoon AM, Solages A, Tarasov J: Cryptococcal peritonitis: Report of a case developing during continuous ambulatory peritoneal dialysis and review of the literature. Clin Infect Dis 17:736–741, 1993
16. Makela CL, Mabey SW, Kithcart J, Keletar SL: Cryptococcosis: A risk factor for cryptococcal peritonitis. Am J Gastroenterol 90:2042–2045, 1995
17. Ramirez JA, Sinha L, Adker S, Huang AK, Raff MJ: HIV-negative “AIDS” in Kentucky: a case of idiopathic CD4+ lymphopenia and cryptococcal meningitis. South Med J 87:751–752, 1994
18. Aratid K, L’Age M, Fath O, Grosse G, Stäub F: CD4 lymphocyte count in HIV-positive persons exposed to Cryptococcus neoformans. Int J Med Microbiol 283:127–135, 1995
19. Takos MJ: Experimental cryptococcosis produced by the ingestion of virulent organisms. N Engl J Med 254:598, 1996
20. Sethi KK: Attempts to produce experimental intestinal cryptococcosis and sporotrichosis. Mycopathologia 31:245, 1967
21. Salkowski CA, Bartik KE, Bullock ME, Bullock E: Colonization and pathogenesis of Cryptococcus neoformans in gastrointestinal mice. Infect Immun 55:2000, 1987
22. George JM: Mycobacteria and Human Disease, 2nd ed. London, Edward Arnold, 1996
23. Choson DC, Baban H, Tumbull E: Immunological diverticula. Gastroenterolog 5:76–84, 1997
24. Dosa LA, Bridget J, Grace PA, Kreaser T, Spencer J: Primary jejunal tumors: a review of 45 cases. World J Surg 15:151–156, 1991
25. Yoshida EM, Chan H, Chan Y, Bani R: Perforation of the jejunum secondary to AIDS-related gastrointestinal Kaposi’s sarcoma. Can J Gastroenterol 11:38–40, 1997
26. Rai R, Bayless TM: Isolated and diffuse ulcers of the small intestine: In Feldman Sleisenger & Fordtran’s Gastrointestinal Disease: Pathophysiology/Diagnosis/Management. M Scharschmidt BF Sleisenger MH (eds). Philadelphia, WB Saunders, 1998, pp 1771–1778