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CASE REPORT

Gastrointestinal Cryptococcosis Presenting as Spontaneous Jejunal Perforation in a Nonimmunocompromised Host

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KEY WORDS: *Cryptococcus neoformans*; gastrointestinal infection; intestinal perforation.

Cryptococcus neoformans has been recognized as a human pathogen for over a century. Occurring primarily in immunocompromised patients, cryptococcosis has achieved new prominence in recent years with the emergence of the acquired immune deficiency syndrome pandemic (1). Although considered principally as a pathogen of the central nervous system, *Cryptococcus* is known to affect a wide variety of other organ systems (2). Involvement of the gastrointestinal tract was first described nearly 50 years ago (3) and probably occurs frequently in the setting of disseminated disease (4). Nevertheless, despite the recent dramatic increase in the incidence of this disease, the occurrence of overt gastrointestinal symptoms directly attributable to cryptococcal infection reported in the literature remains exceedingly rare. We report the case of a patient with gastrointestinal cryptococcosis presenting with intestinal perforation.

CASE REPORT

A 50-year-old South African Black male security guard presented to an outlying rural hospital following a short history of progressive abdominal pain culminating in him "collapsing" at his workplace. The patient had no significant medical or surgical history, did not smoke, and drank alcohol socially on weekends. He denied NSAID use. There was no history of significant exposure to birds or other animals. Features of an acute abdomen, together with the presence of free peritoneal gas seen on chest x-ray suggested the diagnosis of perforated peptic ulcer, and the patient was referred for an urgent exploratory laparotomy.

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At surgery he was found to have an extensively soiled peritoneal cavity with abundant fibrinous exudate. A single 2-cm × 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.

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.

The patient was weaned off ventilatory support on day 10, but within 48 hr, due to the development of a nosocomially acquired pneumonia, became severely dyspneic with hypoxemia, and required mechanical ventilation once again. His respiratory parameters continued to deteriorate, with a picture of the acute respiratory distress syndrome (ARDS) eventually emerging, and on day 19 after admission, despite intensive supportive therapy, the patient succumbed to intractable hypotension and died. Postmortem exam was not performed.

DISCUSSION

Cryptococcus neoformans is a ubiquitous, yeastlike organism that finds a natural reservoir in soil rich in avian droppings. Natural defense against this fungus depends

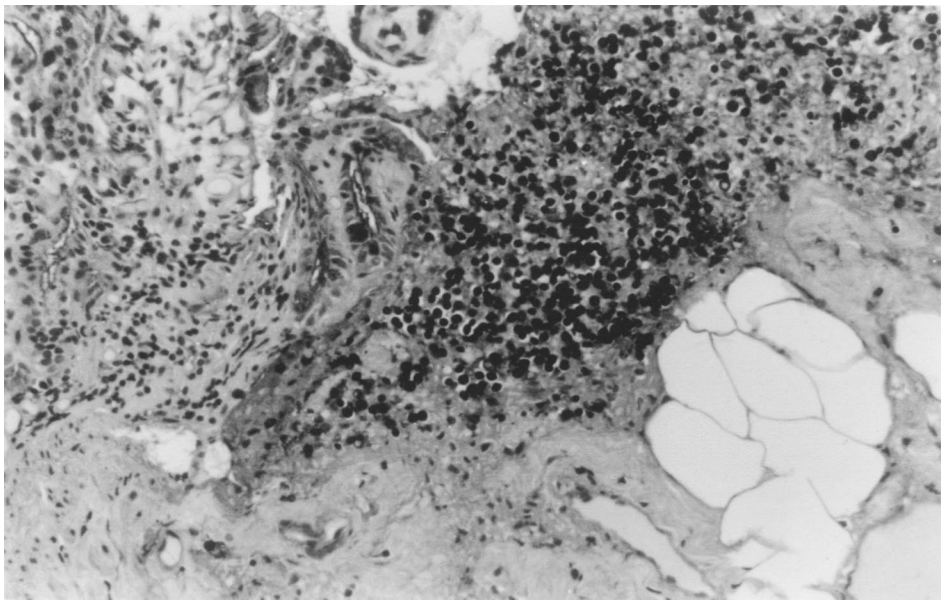

Fig 1. Cross-sectional view of the jejunal wall. The gut lumen is oriented towards the upper left corner, and the serosa towards bottom-right. The intervening lamina propria is heavily infested with dark-staining, round cryptococci.

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, Cushing's syndrome, organ transplantation with use of immunosuppressive drugs, 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

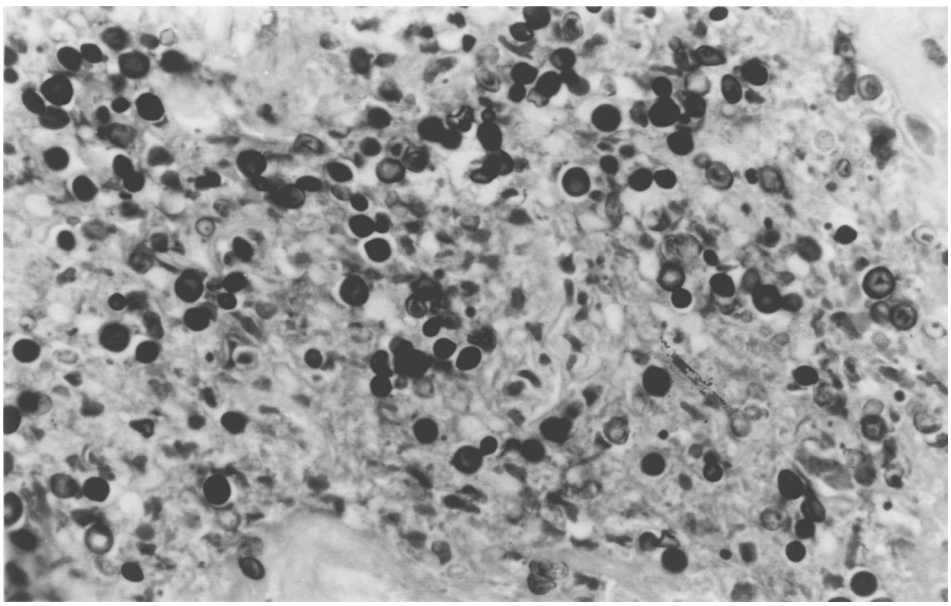

Fig 2. High-power view showing the characteristic clear, surrounding capsule of *Cryptococcus neoformans*.

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 gastroduodenal cryptococcosis (4, 11). In an African AIDS patient whose presenting complaints included hematochezia, a diagnosis of cryptococcal anal ulceration was made (12). In all the above AIDS-related cases there was documented evidence of disseminated disease.

In 1990, Daly and colleagues (13) reviewed reported symptomatic cases of gastrointestinal cryptococcosis in HIV-negative subjects. Five cases were documented, 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/mm^3 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

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.

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