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CASE REPORT

Successful treatment of gastrointestinal mucormycosis in an adult with acute leukemia: case report and literature review

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ABSTRACT

Mucormycosis has emerged as an important cause of invasive fungal infection in patients with hematologic malignancies. Gastrointestinal mucormycosis is an unusual presentation of this invasive fungal infection, and it causes considerable morbidity and mortality. Such outcomes are due in part to a nonspecific presentation that results in delays in diagnosis and treatment. Successful treatment of gastrointestinal mucormycosis involves surgical debridement and appropriate antifungal therapy.

Key Words Mucormycosis, gastrointestinal; hemicolectomy

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INTRODUCTION

Since the mid-1990s, treatment of acute leukemia and use of hematopoietic stem-cell transplantation have considerably advanced. However, the advances realized have resulted in enhanced immunosuppression, related to prolonged neutropenia produced by more-potent chemotherapeutic regimens, iron overload related to multiple transfusions, and the use of broad-spectrum azole therapy effective against aspergillosis. As a consequence, mucormycosis has emerged as an increasingly important invasive fungal pathogen in hematopoietic stem-cell transplantation (HSCT) recipients and in patients with hematologic malignancies[1,2]. Not only does mucormycosis cause considerable morbidity, but it is also associated with a high mortality rate[1,2]. Gastrointestinal mucormycosis, however, is rare. Not surprisingly, it is associated with significant mortality in patients with an underlying hematologic malignancy and neutropenia, a consequence of its nonspecific presentation, which causes delay in diagnosis and in turn predisposes patients to a high risk of perforation and exsanguination.

The successful management of gastrointestinal mucormycosis in neutropenic patients requires a careful assessment of symptoms, appropriate diagnostic imaging, subsequent adequate surgical debridement, and antifungal therapy. Here, we present a case of gastrointestinal mucormycosis that was managed successfully with surgical debridement and combination antifungal therapy.

CASE DESCRIPTION

A 58-year-old man diagnosed with acute myeloid leukemia received induction chemotherapy by continuous infusion of cytosine arabinoside (7 days) and daunorubicin (3 days), after which he went into remission. Thereafter, he received consolidation chemotherapy with high-dose cytosine arabinoside and daunorubicin. He was then discharged home in good condition on prophylactic ciprofloxacin 500 mg twice daily, amoxicillin 500 mg 3 times daily, and fluconazole 400 mg daily (all oral).

About 2 weeks after discharge, the patient presented to the emergency department with a febrile neutropenic episode (absolute neutrophil count $< 0.1\times10^9$/L), a platelet count of 17×10^9/L, and an acute abdomen. Intravenous piperacillin–tazobactam and vancomycin were initiated empirically. Computed tomography imaging of the abdomen revealed a thickened and inflamed appendix (cross-sectional diameter 1.3 cm), non-drainable fluid around the appendix, and a normal terminal ileum, findings consistent with acute uncomplicated appendicitis (Figure 1). The patient was taken for an urgent laparoscopic appendectomy, during which the appendix was noted to be perforated.

The patient's condition did not improve postoperatively. He continued to have abdominal pain, and he remained febrile and neutropenic. The final surgical pathology report was consistent with fungal appendicitis produced by mucormycosis, for which the patient was started on

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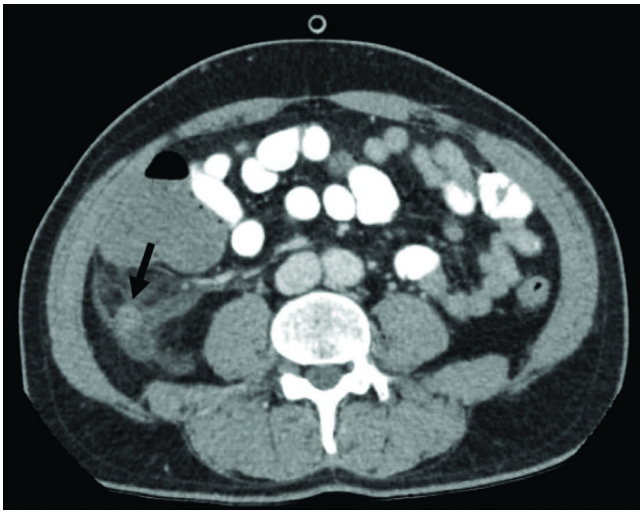

FIGURE 1 Computed tomography image of abdomen, showing inflamed appendix. The arrow points to the thickened appendix wall.

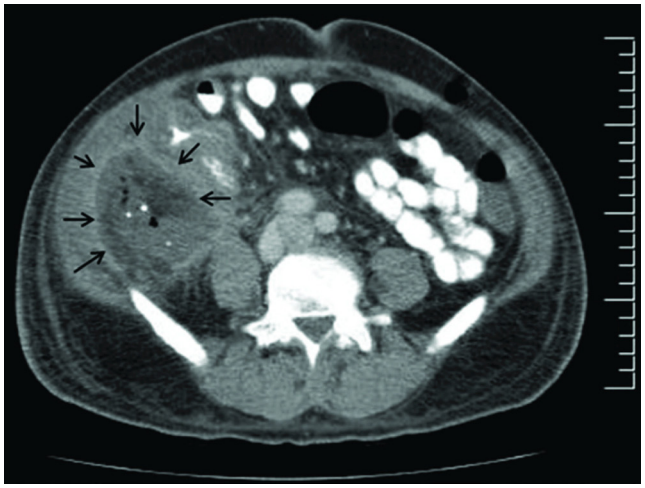

FIGURE 2 Computed tomography image of abdomen, showing large complex fluid collection (arrows).

intravenous liposomal amphotericin B 5 mg/kg daily (AmBisome: Astellas Pharma, Tokyo, Japan). However, he continued to be symptomatic, and repeat computed tomography imaging of the abdomen about a week after surgery showed interval worsening of colitis, which involved the entire right and transverse colon and was associated with a large complex fluid collection along the right flank, with invasion of the adjacent abdominal wall (Figure 2). The dose of liposomal amphotericin B was increased to 7 mg/kg daily, and a pigtail catheter was used in an attempt to drain the fluid. Fungal culture of the drainage fluid grew *Rhizopus microsporus*.

Because of ongoing symptoms and a lack of clinical improvement, the patient underwent exploratory laparotomy for debridement, with a right hemicolectomy (Figure 3). Maintenance therapy with oral posaconazole suspension 400 mg twice daily was added to the liposomal amphotericin therapy after an initial loading dose of 200 mg four times daily for 2 days.

The pathology report for the tissue obtained at the time of the exploratory laparotomy was consistent with mucormycosis involving the right resected hemicolectomy specimen, with viable margins. Postoperatively, the patient experienced marrow recovery from his consolidation chemotherapy–induced neutropenia. He remained on intravenous liposomal amphotericin B 7 mg/kg daily plus oral posaconazole suspension 400 mg twice daily until liposomal amphotericin B was discontinued because of renal impairment after 54 days of therapy. Therapy with oral posaconazole suspension was maintained, however. Subsequently repeated computed tomography imaging of the abdomen did not show any residual abscess. Posaconazole antifungal therapy was continued for 7 months, until the patient underwent allogeneic HSCT. He received antifungal prophylaxis with liposomal amphotericin B during the neutropenic phase of that procedure, which was successfully completed without recurrence of ileocolic mucormycosis.

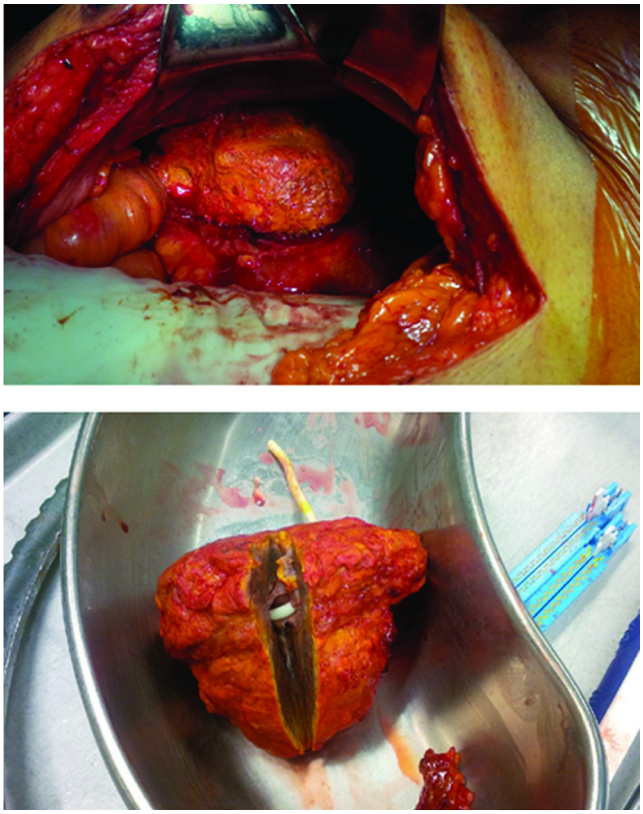

FIGURE 3 Intraoperative (top panel) and post-resection (bottom panel) images of the large fungus ball behind the cecum (pigtail catheter *in situ*).

DISCUSSION

Mucormycosis was first reported as a cause of human disease by Paultauf in 1885 (as described by Roden *et al.*[1]). Mucorales are ubiquitous in nature, often being found in decaying organic matter[2,3]. Since the mid-1990s, mucormycosis has emerged as an important

invasive fungal infection among HSCT recipients, solid-organ transplant recipients, and patients with hematologic malignancies, being associated with a substantial mortality rate[1,4]. *Rhizopus* species are the organisms that most commonly cause mucormycosis in humans. Other less frequently isolated species include *Mucor, Rhizomucor, Lichtheimia, Cunninghamella, Saksenaea,* and *Apophysomyces*[2,5]. In a large study of more than 900 reported cases, the major involved sites were rhinocerebral (21%), pulmonary (24%), cutaneous (19%), localized cerebral (9%), and gastrointestinal (7%)[1]. The sites commonly involved in gastrointestinal mucormycosis are the stomach, colon, and ileocecal region, resulting from possible ingestion of the fungus, with subsequent invasion[6,7].

Colonic and ileocecal infection represent a clinical challenge for surgeons, because typhlitis and early mucormycosis appear similar radiographically[7]. Gastrointestinal mucormycosis varies in its clinical presentation. Patients can present with fever, abdominal pain, hematochezia, or perforation leading to peritonitis[2,8]. The entity has a high rate of dissemination to other non-contiguous organs. Indeed, in one large study, dissemination occurred in 38% of patients (25 of 65), with a subsequent mortality rate as high as 85%, primarily related to bowel perforation[1]. The diagnosis is often delayed because of the nonspecific presentation, and only 25% of cases are diagnosed antemortem[2,5].

A definitive diagnosis requires histopathologic identification of characteristically broad, thin-walled, non-septate, irregularly branching hyphae with evidence of blood vessel invasion; however, Mucorales hyphae are delicate and easily damaged during processing of tissue samples[9]. Although fungal hyphae are seen in histopathology sections, fungal cultures are positive in only 50% of cases. Every effort should be made to obtain tissue biopsies for histopathology and culture[10]. Fungal markers such (1→3)-β-D-glucan and galactomannan tests do not detect the antigenic components of the Mucorales cell wall[11]. Polymerase chain reaction of formalin-fixed and paraffin-embedded tissue can be useful for confirmation of the diagnosis of mucormycosis and for further species identification[12].

All efforts should be undertaken to control comorbidities and to minimize immunosuppression. Corticosteroids should be avoided, and if avoidance is not feasible, the dose should be reduced. Optimization of blood glucose control and acid–base status are other therapeutic interventions that should be undertaken[13,14]. Amphotericin B deoxycholate—the only licensed antifungal for primary treatment of mucormycosis—has been used[1,11], but the formulation is nephrotoxic and has been replaced by the lipid formulations such as liposomal amphotericin B or amphotericin B lipid complex, which are much less so. In fact, the recently published joint clinical guidelines from the European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology strongly recommend the immediate initiation of treatment with liposomal amphotericin B as the drug of choice at a dose of at least 5 mg/kg daily; the use of amphotericin B deoxycholate is discouraged[15,16]. Salvage treatment might be required because of intolerance to prior antifungal therapy or because of disease refractoriness. The addition of oral posaconazole, a broad-spectrum azole, at a starting dose (for the suspension) of 200 mg four times daily and then 400 mg twice daily, or (for the tablets) of 300 mg twice daily on day 1 and then 300 mg daily as part of combination therapy, is recommended for salvage treatment of mucormycosis[15]. Continuation of antifungal treatment until complete clinical response as demonstrated by imaging and resolution of risk factors is also advised[15].

A combined approach of surgical and medical treatment is strongly recommended for patients with mucormycosis in general and with gastrointestinal mucormycosis in particular, because the infection is associated with high risk of perforation and exsanguination[1,15,17–20]. Furthermore, the hallmark of mucormycosis is angioinvasion by the fungus, resulting in thrombosis and tissue necrosis that limit the penetration of antifungal agents to the site of infection, making antifungal therapy ineffective *in vivo*[21]. For adult patients with an underlying hematologic malignancy who presented with gastrointestinal mucormycosis, survival was better among those who underwent surgical debridement than among those not treated with a combination of surgery and medical therapy[7].

The surgical team must be aware of gastrointestinal mucormycosis as a possible differential of acute abdomen in these susceptible patients, and they must be prepared to provide recommendations on surgical interventions and anticipated outcomes.

SUMMARY

Gastrointestinal mucormycosis is a rare invasive fungal infection associated with substantial mortality in patients with an underlying hematologic malignancy and neutropenia. Careful assessment of such patients with acute abdominal findings is therefore necessary to provide a timely diagnosis, adequate surgical debridement, and early initiation of antifungal therapy. Surgical debridement combined with appropriate antifungals is essential for the successful management of gastrointestinal mucormycosis.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare the following interests: CR has received speaker fees from Merck Canada, Pfizer Canada, and Teva Pharmaceutical Industries. CR has received fees as an advisory board member for Astellas Pharma Canada, Merck Canada, Pendopharm, and Pfizer Canada. CR's institution receives funding from Astellas Pharma Canada, Chimerix, Merck Canada, and Pfizer Canada for trials in which he is co-investigator.

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