


## CASE REPORT

# *Rhizopus microsporus* typhlitis in a patient with acute myelogenous leukemia

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## Abstract

While patients undergoing treatment for hematologic malignancies are at risk for a variety of infections, gastrointestinal mucormycosis is a rare and feared complication. Diagnosis requires a high index of suspicion and timely evaluation. Prompt treatment improves patient outcomes.

## KEYWORDS

AML, mucormycosis, neutropenic enterocolitis, rhizopus, typhlitis

## 1 | INTRODUCTION

Invasive fungal infections are an important cause of mortality and morbidity in patients with hematologic malignancies undergoing hematopoietic stem cell transplantation. While the majority of these infections are due to *Candida* or *Aspergillus* species, those caused by fungi of the order *Mucorales*, termed mucormycosis, are rare and often deadly.<sup>1-5</sup> While they are classically associated with rhino-orbital-cerebral infections, mucormycosis can affect any organ system. Gastrointestinal mucormycosis infections are uncommon, difficult to diagnose, and management is complicated by their aggressive nature and dearth of robust clinical guidelines.<sup>4-7</sup> We present an uncommon cause of typhlitis due to *Rhizopus* mucormycosis in a patient undergoing chemotherapy for acute myelogenous leukemia.

## 2 | CASE PRESENTATION

A 36-year-old man without significant past medical history presented to the hospital with 1 week of fatigue, fever, and cough. He was found to have anemia, thrombocytopenia, and a white blood cell count of 137.2 K/ $\mu$ L. Bone marrow biopsy confirmed the diagnosis of acute myelogenous leukemia with monocytic differentiation. Intensive induction chemotherapy with cytarabine and daunorubicin along with prophylactic cefepime, micafungin, and acyclovir was initiated.

On day 4 of induction, he developed right lower quadrant abdominal pain. On evaluation, he had a blood pressure of 98/67, regular heart rate at 74 beats per minute (bpm), and a respiratory rate of 18 per minute. Physical examination was notable for dry mucous membranes and right lower quadrant tenderness to palpation without rebound tenderness.

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Laboratory evaluation revealed a white blood cell count of 0.6 K/ $\mu$ L with an absolute neutrophil count of 80 cells/ $\mu$ L, hemoglobin 8.5 g/dL, and platelet count 16 K/ $\mu$ L. Basic metabolic panel, liver function studies, and blood cultures were unrevealing. Subsequent computerized tomography (CT) of the abdomen and pelvis demonstrated typhlitis of the cecum. Oral intake was restricted and antimicrobials were broadened to meropenem plus isavuconazole (later switched to amphotericin secondary to hyperbilirubinemia).

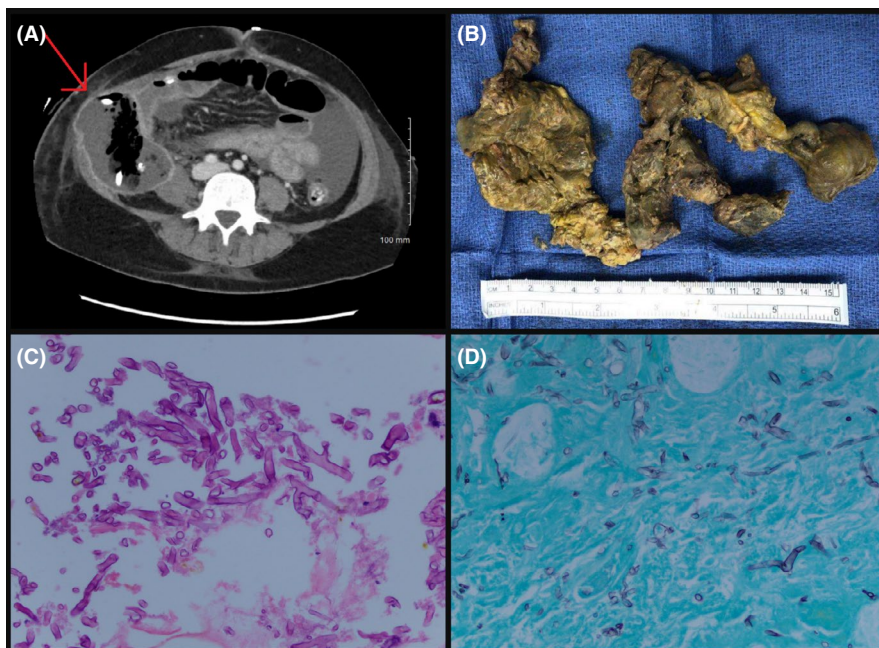
Despite this, the patient continued to experience worsening abdominal pain. On day 15, the patient had developed a fever to 102.6°F, tachycardia to 115 bpm, exquisite abdominal pain, abdominal distension, and rebound tenderness. Repeat CT was concerning for cecal necrosis with extension into the abdominal wall. The patient was thus brought urgently to the operating room which revealed cecal necrosis and perforation treated with hemicolectomy and end ileostomy. Surgical tissue culture grew nonseptate hyphae identified as *Rhizopus microsporus* and mixed anaerobic flora. Unfortunately, the patient was noted to have significant retroperitoneal contamination during the procedure. Following this, the patient was transferred to the surgical ICU where he continued to receive broad spectrum antimicrobial therapy. Due to persistent spiking fevers, repeat CT noted a large abdominal abscess.

Source control could not be achieved despite drainage catheters and both intravenous and intraperitoneal amphotericin (Figure 1A). On hospital day 42, he underwent incision and drainage of complex retroperitoneal abscess and evacuation of 15 cm of semisolid necrotic tissue with superimposed fungal infection (Figure 1B). Microscopy confirmed the presence of broad non-septate hyphae

consistent with *Rhizopus microsporus* (Figure 1C,D). Following definitive surgical source control, the patient began a long recovery process and achieved a complete remission of his AML. On day 77, the patient discharged home. He is currently receiving consolidative therapy with Azacitidine and remains on a prolonged course of antifungals.

### 3 | DISCUSSION

Typhlitis, also known neutropenic enterocolitis, is a life-threatening condition affecting immunocompromised patients, such as those with hematologic malignancies, solid organ or stem cell transplantation, and acquired immunodeficiency syndrome (AIDS).<sup>8</sup> The most common symptoms are abdominal pain, fever, and diarrhea.<sup>8</sup> The pathogenesis appears to be related to intestinal mucosal injury and neutropenia, leading to disrupted mucosal surfaces and vulnerability to intramural invasion by bacteria and fungi.<sup>8</sup> Chemotherapy can cause direct mucosal injury, intestinal distention, and altered intestinal motility.<sup>1,8</sup> The cecum, due to its distensibility and limited blood supply, is usually affected; the ileum, ascending and transverse colon may also be involved.<sup>8</sup> The incidence of typhlitis among hospitalized adults with hematological malignancies is estimated to be 5.3%.<sup>9</sup> Various organisms, alone or in combination, have been identified, including gram-negative rods, gram-positive cocci, enterococci, *Clostridium septicum*, and *Candida spp.*<sup>10</sup> While fungal etiology accounts for up to 16% of infections, typhlitis due to *Rhizopus microsporus* mucormycosis is exceeding



**FIGURE 1** *Rhizopus* Typhlitis. A, Axial computed tomography image of the abdomen. Typhlitis with superimposed right abdominal wall abscess/necrotic collection (red arrow) B, Necrotic tissue with superimposed fungal infection C, 400x H&E stain of tissue show broad-based, ribbonlike, nonseptate hyphae consistent with *Rhizopus microsporus*. D, 400x GMS stain highlighting presence of *Rhizopus microsporus*

rare.<sup>1-3</sup> Indeed, the 2010 Infectious Disease Society of America guidelines for neutropenic enterocolitis do not uniformly suggest antifungal therapy.<sup>11</sup>

Mucormycosis is a rare, often fatal, fungal infection caused by fungi of the order Mucorales. Risk factors for mucormycosis include solid organ or stem cell transplantation, hematologic malignancies, uncontrolled diabetes mellitus, treatment with corticosteroids, neutropenia, trauma, and burns.<sup>12</sup> The most common site of mucormycosis is rhinocerebral, followed by pulmonary, cutaneous, and lastly, gastrointestinal. While GI mucormycosis only accounts for up to 2%-11% of all mucormycosis infections, mortality ranges from 54% to 95%.<sup>4,5</sup>

The diagnosis of gastrointestinal mucormycosis is challenging. Clinical findings are nonspecific and include nausea, vomiting, abdominal pain, obstruction, perforation, and sepsis. Currently, there are no validated blood antigen tests to detect mucormycosis.<sup>6</sup> Notably, the 1,3 beta-D-glucan detection test is generally found to be negative.<sup>6</sup> Due to lack of biomarkers, definite diagnosis of mucormycosis relies on tissue biopsy for histology and culture. This is often difficult in patients with hematologic malignancies due to severe thrombocytopenia and other comorbidities.

Treatment should start as soon as possible to decrease mortality.<sup>6,7</sup> Amphotericin B, posaconazole, and isavuconazole show the greatest potency in vitro.<sup>7</sup> While high quality evidence regarding optimal therapy for mucormycosis is limited, the European conference on Infections in Leukemia (ECIL), European Society for Clinical Microbiology (ESCMID), and Infectious Diseases and European Confederation of Medical Mycology (ECMM) all recommended amphotericin B at 5 mg/kg/day as first line therapy.<sup>6,7</sup> ESCMID and ECMM recommended surgery whenever possible in combination with medical management; ECIL recommends considering surgery on a case-by-case basis. Salvage therapy options include posaconazole.<sup>6,7</sup> There are limited data regarding use of combination therapy as well as the role of caspofungin, echinocandins, and isavuconazole in treatment of mucormycosis.<sup>6,7</sup>

## 4 | CONCLUSION

In summary, while typhlitis due to *Rhizopus* mucormycosis is rare, it can be exceedingly deadly. This case emphasizes the importance of empiric mold-active therapy in leukemia patients with neutropenic enterocolitis. Moreover, for patients failing to improve with systemic therapy and percutaneous drainage catheters, surgical source control may be the only avenue providing a chance for survival in select patients.

## ACKNOWLEDGMENTS

Published with written consent of the patient.

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

MT and BCH: drafted the initial manuscript and revised the manuscript. DW: obtained and interpreted microscopy images. LB and TAP: obtained surgical image and gave surgical insights into case discussion. All authors reviewed and approved the final manuscript as submitted.

## ETHICAL APPROVAL

The patient has given his written informed consent to publish his case.

## PATIENT CONSENT STATEMENT

The patient provided written consent.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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