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Therapeutic Challenges of Hepatic Mucormycosis in Hematologic Malignancy: A Case Report and Review of the Literature

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Manuscript Preparation E
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Patient: Female, 58
Final Diagnosis: Hepatic mucormycosis
Symptoms: Abdominal pain • fever
Medication: Amphotericin • posaconazole
Clinical Procedure: IR-guided aspiration
Specialty: Infectious Diseases

Objective: Rare disease
Background: The clinical presentation of mucormycosis can vary widely based on various host factors. Among malignancy- and bone marrow transplant-associated infections, the lungs are the most common site of infection. Involvement of the gastrointestinal tract is less frequently encountered. The clinical presentation is often nonspecific, and cultures typically yield no growth, making the diagnosis challenging.

Case Report: We present a case of isolated hepatic mucormycosis in the setting of neutropenic fever and abdominal pain following induction chemotherapy for the treatment of acute myeloid leukemia. The patient was treated with combination antifungal therapy with amphotericin and posaconazole without surgical resection, given the presence of multiple liver lesions. After a prolonged course of dual antifungal therapy, the size of her liver lesions improved. Unfortunately, her lymphoproliferative disorder proved fatal, following approximately 13 months of antifungal therapy.

Conclusions: Among patient with mucormycosis, mortality remains high, especially in the setting of gastrointestinal involvement. Although surgical resection along with dual antifungal therapy can improve outcomes, the high mortality rate necessitates further investigation into improved diagnostic and treatment strategies including optimal antifungal therapy.

MeSH Keywords: Amphotericin B • Antifungal Agents • Leukemia, Myeloid, Acute • Liver Abscess • Mucorales • Mucormycosis

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Background

The initial presentation of mucormycosis varies widely based on various host factors [1]. Although infection can be seen in patients with a relatively intact immune system, malignancy, especially hematologic malignancy, poses a particular risk for infection [1]. Pulmonary infections comprise more than 50% of all cases of malignancy- and bone marrow transplant-associated infections, whereas gastrointestinal tract infections comprise a much smaller percentage [1]. Isolated hepatic mucormycosis is an even less frequently encountered entity. Presentation is often nonspecific; however, patients with liver involvement frequently present with abdominal tenderness and liver function abnormalities [2]. Often, negative culture results further confound the diagnosis. We present a case of isolated hepatic mucormycosis in a woman following induction chemotherapy for the treatment of acute myeloid leukemia (AML) whose liver lesions improved following several months of dual antifungal therapy.

Case Report

A 58-year-old woman with AML was admitted to our hospital for evaluation of persistent hepatic abscesses despite broad-spectrum antibiotics. Upon presentation, she felt well and denied fever, anorexia, abdominal pain, nausea, or vomiting. She had been earlier diagnosed with a myelodysplastic syndrome, underwent chemotherapy with azacitadine, and was maintained on prophylaxis with moxifloxacin, valacyclovir, and voriconazole. Despite two cycles of chemotherapy, disease progressed to AML. Induction chemotherapy was initiated with idarubicin and cytarabine. Her course, however, was complicated by an idarubicin-associated cardiomyopathy and neutropenic fever.

One week following completion of her induction chemotherapy, the patient developed neutropenic fever and abdominal tenderness. A computed tomography (CT) scan of the abdomen was performed, demonstrating neutropenic enterocolitis. Additionally, a 2.8-cm subcapsular hepatic cyst and several additional hepatic hypodensities were noted. Because of persistent fever, she underwent a noncontrast CT scan of the chest 4 days later that revealed 3 new hypodense lesions within the liver (2.2 cm in the right lobe, 1.7 cm within the lateral segment of the left lobe, and 1.3 cm at the dome of the liver) that were not appreciated on earlier CT (Figure 1). A dedicated contrast CT of the abdomen revealed at least 9 new low-attenuation lesions throughout the liver including 1 measuring 2.6 cm with a halo of enhancement (Figure 2A, 2B).

After a failed attempt at a technically difficult aspiration by interventional radiology (IR) and resolution of her neutropenia, she was discharged home on levofloxacin and metronidazole

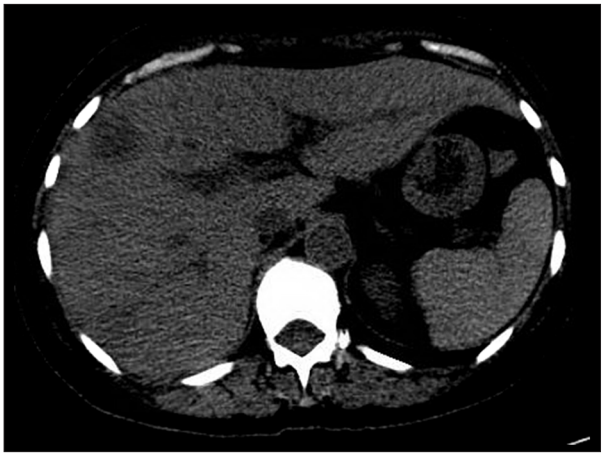


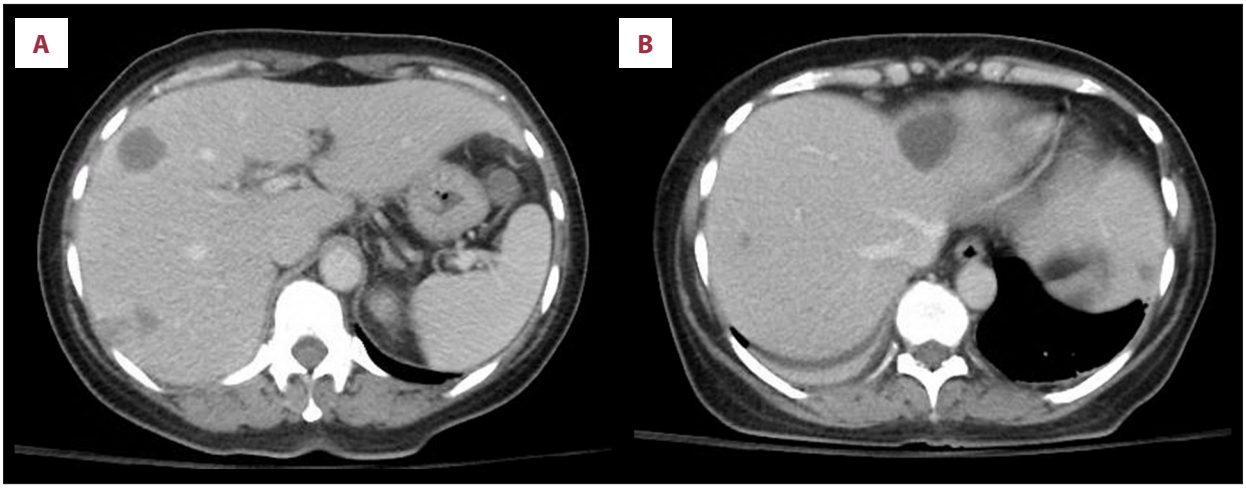
Figure 1. Noncontrast CT scan demonstrating several hepatic lesions.

with the presumptive diagnosis of bacterial hepatic abscesses. Several weeks following her discharge, she underwent follow-up CT imaging, again demonstrating multiple lesions throughout the liver, most with interval enlargement. A positron emission tomography (PET) CT scan found several of these lesions to be hypermetabolic, some with central necrosis (Figures 3A, 3B).

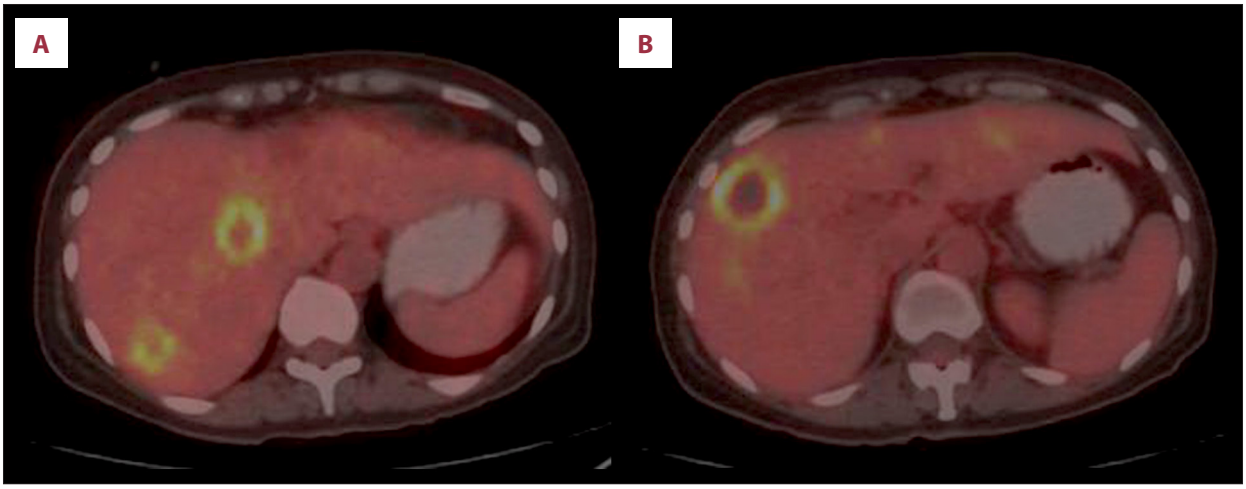
A liver biopsy performed 1 week following her PET CT scan revealed extensively infarcted liver parenchyma with numerous fungal hyphae (Figures 4, 5). The hyphae, which were highlighted with Periodic acid-Schiff (Figure 4) and Grocott (Figure 5) stains, appeared broad with occasional septa and branching (both acute and right angle) and raised a differential diagnosis of aspergillosis versus mucormycosis. Immunochemical testing using antibodies against *Aspergillus* and *Mucor* confirmed the fungus to represent *Mucor*. Because no growth was observed on culture, susceptibility testing could not be performed. Amphotericin B was started at 5 mg/kg every 24 hours.

Following approximately 10 days of therapy, her course was complicated by amphotericin-related nephrotoxicity. The amphotericin B dose was reduced to 3 mg/kg, and posaconazole was added. Despite 4 weeks of combination therapy and therapeutic posaconazole levels, hepatic lesions remained unchanged on PET CT scan. She underwent IR-guided drainage of the biggest lesion measuring 2.7 cm and placement of a catheter with subsequent drainage. The aspirate demonstrated an acute inflammatory exudate with fungal forms consistent with mucormycosis. Hepatectomy was considered; however, given the presence of multiple lesions, the decision was made to proceed with medical management.

After 2 months of dual antifungal therapy, the patient developed diarrhea, which was presumed to be posaconazole related. Her therapy was switched to anidulafungin and amphotericin with resolution of her diarrhea. Unfortunately, pancytopenia



Figures 2. (**A, B**) Contrast CT scan demonstrating several hepatic lesions.



Figures 3. (**A, B**) PET CT scan demonstrating several hypermetabolic lesions, some with central necrosis.

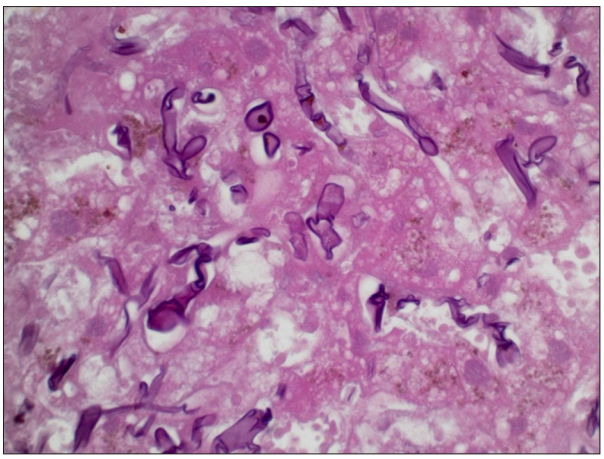


Figure 4. Periodic acid-Schiff stain, 400×.

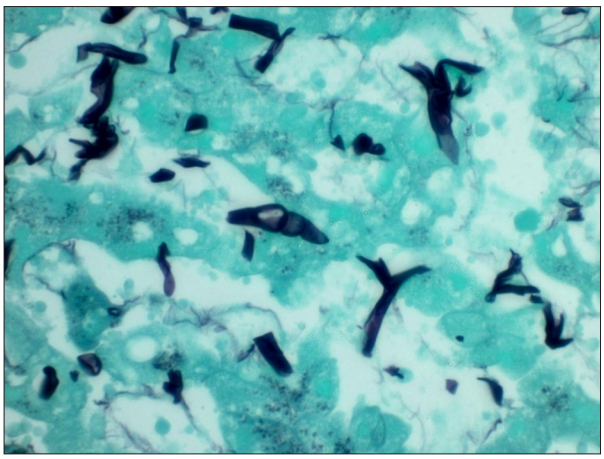


Figure 5. Grocott methenamine silver stain, 400×.

developed in the setting of AML progression, complicated by neutropenic fever and *Escherichia coli* bacteremia, which was treated with 14 days of ciprofloxacin. She was readmitted and underwent treatment with high-dose cytarabine, complicated by neutropenic fever and viridans group *Streptococcus* and *Klebsiella* bacteremia. In addition to her antifungal therapy

Table 1. Reported cases of isolated hepatic mucormycosis with an underlying hematologic malignancy.

Patient	Age/ Sex	Leukemia	Presentation	Number of hepatic lesions	Diagnostic method	Treatment	Follow-up days	Status at last follow-up day	Reference
1	58/M	AML	LUQ pain, fever, and nausea	One (5 cm)	Culture	LAmB + micafungin Percutaneous drainage but eventually required surgical resection	60 days	Deceased due to *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* sepsis 60 days after resection	[2]
2	21/M	ALL	Neutropenic fever and failure to thrive	Multiple (small, not measured)	Histopathology	AmB Surgical resection	~2 months	Alive	[11]
3	9/M	ALL	Neutropenic fever and RUQ pain	One (4 cm)	Histopathology	LAmB + posaconazole Surgical resection	2 years and 6 months	Alive	[12]
4	58/F	AML	Neutropenic fever and abdominal pain	Nine (1.3–2.6 cm)	Histopathology	AmB then AmB + posaconazole; switched to AmB + anidulafungin Percutaneous drainage	14 months	Deceased likely from progression of malignancy	Current case

M – male; F – female; ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; LUQ – left upper quadrant; RUQ – right upper quadrant; LAmB – liposomal amphotericin B; AmB – amphotericin B deoxycholate.

for hepatic mucormycosis, she was discharged with levofloxacin for bacteremia.

A follow-up PET CT scan almost 10 months after her initial presentation demonstrated improvement in her liver lesions; however, in addition to a new large pericardial effusion, multiple new areas of airspace disease were noted bilaterally, some with cavitation, as well as an intense focus of increased uptake in the left femur. None of her lung lesions were safely amenable to biopsy. She underwent pericardiocentesis with removal of 250 mL of serosanguinous material; pathologic evaluation was consistent with involvement of a hematolymphoid malignancy. Her course was further complicated by recurrent neutropenic fever, occult gastrointestinal bleed, and persistent thrombocytopenia. Given her grim prognosis, approximately 14 months following the initial identification of liver abscesses, the patient elected for comfort care measures and expired shortly thereafter.

Discussion

Mucormycosis is caused by a group of filamentous fungi that can affect many individuals, from the most heavily immunosuppressed to those with apparently intact immune systems. The more common organisms include species of *Rhizopus, Mucor, Cunninghamella, Apophysomyces,* and *Absidia* [1,3]. Pulmonary mucormycosis comprises the vast majority of infections among patients with underlying malignancy as well as those who underwent bone marrow or solid organ transplantation [1,4]. The gastrointestinal tract is involved in fewer than 10% of these patients, and hepatic involvement is rare [1]. It has been postulated that fungal hepatic abscesses are secondary to translocation of organisms from the colonized gut following mucosal breakdown [5]. One reported case suggested that ingestion of naturopathic medicine could be linked to hepatic mucormycosis [6].

Although several other cases of isolated hepatic mucormycosis have been described [2,6–13], to the best of our knowledge, this is the fourth reported case of hepatic mucormycosis in the setting of leukemia (Table 1). The common clinical presentation of all four cases was abdominal pain and fever. Multiple hepatic lesions were found on radiographic imaging in two cases, while the remaining cases had a single lesion. Diagnosis in this cohort was achieved by histopathology in three of the four cases.

The Mucorales are typically difficult to grow in culture. The diagnosis is more often made by identification of the organism in histopathology by observing wide, thin-walled, and occasionally fragmented hyphae that contain few if any septae along with right-angle branching [14]. Immunohistochemical testing may have an advantage when distinguishing between aspergillosis and mucormycosis cannot be done morphologically [15]. Molecular diagnostic techniques, such as polymerase chain reaction, may provide a more rapid and sensitive result that can impact treatment decision [16,17]; however, such assays will require further standardization and validation.

As mucormycosis becomes increasingly recognized among those with hematological malignancies with or without bone marrow transplantation, the approach and treatment of disease will need to be studied further. Mortality remains high, approaching 85% among those with gastrointestinal involvement [1]. Among patients with leukemia (Table 1), all-cause mortality is estimated to be 50%, despite therapy. Treatment often requires a combined medical and surgical approach. In one review, 532 patient received amphotericin B deoxycholate with a 61% survival rate. Those who received both a surgical and medical approach had a 70% survival rate [1]. In addition to this approach, it has been suggested that dual antifungal therapy can also improve outcomes, typically utilizing a polyene as a backbone [18,19]. In one retrospective review of 41 cases of biopsy-proven rhino-orbital-cerebral mucormycosis, for example, outcomes of patients treated with polyene-caspofungin therapy plus surgical debridement were compared with those of patients who did not receive combination therapy. A 100% success rate was reported for all evaluable patients (n=6) at 30 days after hospital discharge, compared with 45% (n=45) with polyene monotherapy [20]. Successful treatment of rhino-cerebral mucormycosis with a combined approach utilizing surgical debridement and medical therapy with a polyene followed by posaconazole was previously reported [21]. Although surgical resection was not feasible in our patient, the use of dual antifungal therapy alone resulted in improvement of hepatic lesions, suggesting a role for this approach. Unfortunately, because none of her lung lesions were amenable to biopsy, it remains unclear whether these represented further *Mucor* dissemination or progression of her underlying lymphoproliferative disorder.

A new potential option for the treatment of invasive mold infections, including those secondary to *Mucor* species, is isavuconazole, a second-generation triazole antifungal with high oral bioavailability [22]; however, further investigation is needed, including its role and efficacy used alone or in combination with amphotericin.

Conclusions

Outcomes for invasive mucormycosis remain poor, especially in the setting of hematologic malignancy. Although early diagnosis and aggressive treatment that includes surgery whenever possible may potentially improve outcomes, optimal treatment strategies have not yet been defined. With the development of newer and safer antifungal agents, combination antifungal therapy will likely remain fundamental to any treatment approach; however, further investigation into this area is needed.

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