Hepatic mucormycosis with abscess formation

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Abstract

We describe a case of hepatic mucormycosis with abscess, an uncommon presentation of mucormycetes infection. Our patient was initially treated with transcutaneous pigtail catheter placement, liposomal amphotericin B, and micafungin without improvement. The patient subsequently improved after hepatic segmentectomy and hemidiaphragm resection.

1. Introduction

Mucormycosis is an uncommon infection that may exhibit a variety of manifestations, particularly in immunocompromised patients and those with diabetes mellitus. Here we present a case of hepatic mucormycosis which was treated with medical and surgical intervention. We also review the literature regarding mucormycetes infections, hepatic involvement, and hepatic abscesses.

2. Case

A 58-year-old Vietnamese man with a history of acute myeloid leukemia (AML), chronic hepatitis B infection, and diabetes mellitus presented with a 4-month history of worsening left upper quadrant pain, fevers, and nausea. He was diagnosed with AML in late 2009 after a history of myelodysplasia and was evaluated for unmatched stem cell transplant from an unrelated donor. He initially had an excellent response to azacitidine, but stopped chemotherapy while he returned to Vietnam for several months. When he returned to the USA, he was restarted on azacitidine with the addition of valproic acid, supplemented by monthly blood transfusions. He was previously treated with entecavir for hepatitis B, which was stopped 1 month prior to admission due to lactic acidosis.

Five months before admission, the patient developed worsening abdominal pain. An abdominal computed tomography (CT) showed hepatosplenomegaly. He was started on dexamethasone 4 mg twice daily for treatment of splenomegaly, with improvement in his symptoms. His dexamethasone dose was subsequently tapered to 4 mg once daily. Two days before admission, he presented to his primary care physician complaining of worsening left upper quadrant pain, fevers, nausea, constipation, and difficulty sleeping. Computed tomographic imaging of the abdomen and pelvis with contrast showed a localized left-sided subdiaphragmatic abscess measuring 4.9 × 2.8 × 5.2 cm (Fig. 1).

On admission, the patient had a temperature of 97.2 °F, pulse of 98 beats per minute, blood pressure of 117/71 mmHg, respiratory rate of 16 per minute, and oxygen saturation of 97% on room air. He was in no distress. Cardiac and pulmonary exam results were unremarkable. His abdomen was mildly tender to palpation in the left upper quadrant. His admission laboratory values included the following: white blood cell count, 9600 cells/μL; hemoglobin, 10.6 g/dL; hematocrit, 33.9%; platelet count, 120,000 cells/μL; bicarbonate, 24 mEq/L; creatinine, 1.58 mg/dL; serum glucose, 1033 mg/dL; hemoglobin A1c, 8.2%; total protein, 7.1 g/dL; albumin, 2.5 g/dL; alkaline phosphatase, 83 U/L; aspartate aminotransferase, 14 U/L; alanine aminotransferase, 19 U/L; and total bilirubin, 1.1 mg/dL. There were no periods of neutropenia prior to this admission.

Broad-spectrum antibacterials were started including ciprofloxacin 400 mg iv q12 h, vancomycin 1 g q12 h, and metronidazole 500 mg iv q12 h. On hospital day 2, the patient underwent ultrasound-guided percutaneous pigtail catheter placement with aspiration of 45 mL of blood-tinged pus. Gram-stain showed

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numerous white blood cells, but no organisms. Cultures from the aspirate grew Mucor species.

Antifungal treatment was started with liposomal amphotericin B 5 mg/kg every 24 h and micafungin 150 mg iv daily. Broad-spectrum antibiotics were discontinued.Repeat abdominal CT 1 week later showed no resolution of his abscess, and he subsequently underwent left lateral hepatic segmentectomy and resection of a portion of the left hemidiaphragm. No pleural involvement was observed. Intraoperative cultures also confirmed the presence of a mucormycetes infection, and surgical margins returned positive for fungal etiology. Intraoperative tissue samples were negative for the presence of any well-organized abscess. A repeat abdominal ultrasound several days later confirmed the absence of any well-organized abscess.

The patient clinically improved and was discharged on postoperative day 8. He was continued on daily liposomal amphotericin B for a planned 6-week course. Micafungin was discontinued, and he was started on oral posaconazole 400 mg bid. His dexamethasone was switched to prednisone, and he was discharged on a prednisone taper. Five days after discharge he returned to the emergency department with abdominal pain and was found to have abdominal bleeding requiring emergent exploratory laparotomy which revealed a large hematoma and diffuse bleeding from the omentum and diaphragmatic surface. Intraoperative tissue samples were negative for the presence of fungal organisms by both histopathology and culture. He subsequently had a lengthy hospital stay complicated by Klebsiella pneumoniae and mexitel-in-resistant Staphylococcus aureus bacteremia and septic shock requiring intensive care unit admission. The patient died approximately 2 months after his initial admission.

3. Discussion

Mucormycetes (formerly Zygomycetes) responsible for human disease (in decreasing frequency) include the genera Rhizopus, Lichtheimia (formerly Absidia), Apophysomyces, Cunninghamamella, Sakaguchia, Rhizomucor, and Mucor (Alvarez et al., 2009). These pathogens are distributed worldwide and can be acquired through inhalation, ingestion, cutaneous exposure, contamination of wounds, trauma, or injection (Chayakulkeeree et al., 2006). Mucormycosis is commonly seen in immunocompromised individuals, such as patients with hematologic malignancy, corticosteroid use, solid organ transplantation, injection drug use, AIDS, diabetes mellitus, deeroxamine therapy, and metabolic acidosis (Chayakulkeeree et al., 2006; Roden et al., 2005). The most frequent sites of infection are rhinocerebral, followed by pulmonary, disseminated, gastrointestinal, or cutaneous (Ribes et al., 2000). Our patient had several risk factors for mucormycosis, including diabetes mellitus, leukemia, corticosteroid use, and chemotherapy treatment. The mechanism of transmission in this case is unknown, although it is most likely that the source was gastrointestinal with local extension into the liver, since there was no evidence of a pulmonary source of infection on surgical intervention or radiographic imaging.

The development of improved chemotherapies for hematologic malignancies has led to an increase in the number of hepatic abscesses caused by all fungi. Aggressive chemotherapy for hematologic malignancies, aggressive treatment of malignant hematopoietic disease, long-term indwelling catheters, prolonged use of broad-spectrum antibiotics, long hospitalizations, and use of parenteral nutritional support have all been associated with fungal abscesses (Lipsett et al., 1997). The most common species responsible for fungal abscess formation is Candida albicans, while Aspergillus and Cryptococcus are less commonly identified (Marcus et al., 1993).

Hepatic involvement of mucormycosis is rare and is usually thought to arise from gastrointestinal disease, although dissemination uncommonly occurs from other sources (Chayakulkeeree et al., 2006). Hepatic mucormycosis has also been associated with direct ingestion of naturopathic medicine containing Mucor spp. and is well documented among neonatal patients (Al-Asiri et al., 1996; Luer et al., 2009; Oliver et al., 1996). No clear risk factor for hepatic involvement has been seen, with documented infection observed among patients with diabetes (Tsaioussis et al., 2000), those receiving chemotherapy for leukemia (Suh et al., 2000), those undergoing bone marrow transplantation (Oliver et al., 1996; Padmanabhuni et al., 2007), or those with immunosuppression following solid organ transplantation (Mazza et al., 1999). While most cases occur in immunocompromised patients, there is 1 documented case of a patient with both adrenal and hepatic mucormycosis who was immunocompetent (Li et al., 2010).

Fungal liver abscesses present in similar fashion to bacterial abscesses, with diffuse abdominal tenderness, jaundice, hepatomegaly, and liver function test abnormalities being the most commonly observed findings (Marcus et al., 1993).

Of note, fungal hepatic abscesses may occur as mixed fungal/bacterial abscesses, although these are more commonly seen in biliary or pancreatic malignancy, whereas pure fungal abscesses are almost always seen in patients being treated for hematologic malignancy. The presence of fungemia in the setting of fungal hepatic abscess is a poor prognostic factor with overall mortality approaching 80% in 1 case series (Lipsett et al., 1997). Regardless of the microbiologic cause, management of hepatic abscess involves drainage and appropriate antifungal therapy.

Hepatic mucormycosis is readily seen on abdominal imaging. Typical CT findings include the presence of hypodense hepatic lesions surrounding vessels without a mass effect, representing areas of liver necrosis due to fungal thrombosis. These findings are not specific but suggest the presence of an angioinvasive organism (Hagspiel et al., 1995). The presence of a discrete abscess on imaging differs substantially from radiographic findings of hepatic mucormycosis previously reported.

The management of mucormycosis consists of 3 key strategies: 1) rapid initiation of effective antifungal therapy, 2) surgical debridement, and 3) attempts to control predisposing factors, when feasible (Kontoyiannis and Lewis, 2011). Initial medical therapy for mucormycosis consists of either amphotericin B deoxycholate or lipid formulations of amphotericin B. The lipid formulations are less nephrotoxic than amphotericin B deoxycholate and can be safely administered at higher doses for longer periods (Spellberg et al., 2005). Echinocandins, such as caspofungin, meanwhile, are not used as a monotherapy. However, in 1 retrospective study, the combination of amphotericin B lipid complex plus caspofungin was associated with improved outcomes compared to treatment with amphotericin B lipid complex alone, suggesting that echinocandins

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may have a synergistic effect with amphotericin B potentially through an indirect mechanism (Reed et al., 2008). This indirect immunopharmacologic effect is believed secondary to the unmasking of cell-wall β-D-glucan with subsequent enhanced immune recognition. This synergistic effect with amphotericin B has also been observed with the other echinocandins, micafungin and anidulafungin, as well (Ibrahim et al., 2008a).

The link between iron availability and the risk of mucormycosis is well known. The predisposition of patients with diabetic ketoacidosis to mucormycosis is caused in part by the increased availability of iron during periods of acidemia (Boelaert et al., 1993; Ibrahim et al., 2008b). Additionally, deferoxamine acts as a siderophore delivering available iron directly to the fungus (Boelaert et al., 1993). These findings have prompted interest in the use of other iron chelators such as deferasirox and deferiprone, neither of which supplies iron to the Mucorales and which are fungicidal in vitro (Ibrahim et al., 2007). Chelation therapy was considered in our patient; however, limited data regarding the efficacy of these agents exist—and a recently completed randomized, double-blind, placebo-controlled trial demonstrated a higher mortality in patients treated with deferasirox (Spellberg et al., 2012).

Azole therapy with oral posaconazole has been shown effective in patients who have failed or cannot tolerate amphotericin B (Greenberg et al., 2006; van Burik et al., 2006). Some authors recommend amphotericin B and echinocandins in combination for the first 3 weeks of therapy, followed by transition to oral posaconazole as maintenance/secondary prophylaxis with serial monitoring of posaconazole serial drug concentrations to monitor compliance and absorption (Kontoyiannis and Lewis, 2011). Voriconazole prophylaxis in stem cell transplantation has been associated with an increased incidence of invasive mucormycosis (Spellberg et al., 2005). Our patient had never received antifungal prophylaxis with voriconazole during his courses of chemotherapy.

In conclusion, hepatic mucormycosis is rare and typically seen in disseminated disease in immunocompromised individuals. Management involves appropriate surgical intervention and medical treatment with intravenous amphotericin B in combination with an echinocandin, followed by long-term oral posaconazole.

References


