Pulmonary Mucormycosis in a Patient With Recurrent Acute Lymphoblastic Leukemia

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Abstract: Mucormycosis infection is an often fatal complication of chronic immunosuppressive therapy in patients with hematological malignancies. This risk can be further heightened in patients who are on chronic suppressive therapy with voriconazole. We review a case of an immunocompromised patient on chronic suppressive voriconazole therapy who developed severe pulmonary mucormycosis infection.

Key Words: mucormycosis, pulmonary, voriconazole

Pulmonary mucormycosis is an aggressive, invasive zygomycosis that characteristically affects neutropenic patients with hematological malignancies, especially acute lymphoblastic leukemia (ALL). The angioinvasive nature of the disease leads to rapid progression and is associated with a high mortality. Therefore, a high index of suspicion in the appropriate clinical setting with prompt diagnosis and optimal treatment is recommended.

CASE REPORT

A 67-year-old female with history of pre-B cell ALL status-post Linker protocol presented for a routine follow-up appointment at the hematology clinic with complaints of fatigue and fever of 2 weeks’ duration. A bone marrow biopsy performed 10 days prior to presentation showed recurrence of acute pre-B cell ALL with greater than 90% blasts in the marrow. Medical history included hypertension, diabetes mellitus, hypertriglyceridemia, deep venous thrombosis, and right upper lobe pulmonary aspergillosis status-post thoracoscopic resection. The patient was being treated with voriconazole 200 mg orally daily for chronic fungal infection suppression.

On presentation, the patient had a temperature of 38°C (100.4°F), heart rate of 100 beats/min, blood pressure of 154/50 mm Hg, and respiratory rate of 20 breaths/min. The patient appeared fatigued, but otherwise had an unremarkable physical examination. Laboratory data were notable for white blood cell count, 2.5 × 10^9/L; absolute neutrophil count (ANC), 600; hemoglobin, 11.0 g/dL; and platelets, 17 × 10^9/L. Broad-spectrum antibiotic therapy was initiated for presumed infection in the setting of neutropenic fever in a patient with ALL.

No obvious source of infection was evident on initial presentation. Initial blood, respiratory, and urine cultures were negative. Initial chest radiograph showed bibasilar atelectasis, and thoracic CT showed dilated bronchi and linear scars involving the right middle lobe and lingular atelectasis, unchanged from previous scans. The patient was started on hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (hyperCVAD) on day 2 of admission. She subsequently became more neutropenic and was started on daily injections of granulocyte-colony stimulating factor (G-CSF).

The patient continued to experience intermittent neutropenic fevers. Vancomycin was added on day 15 of hospital admission and empiric gram-negative coverage was changed from cefepime to meropenem on day 16. A chest radiograph obtained at this time showed left lower lung opacity with blunting of the left costophrenic angle (Fig. 1). A repeat thoracic CT performed on day 17 showed an area of dense, rounded consolidation in the left upper lobe and lingula with minimal central lucency (Fig. 2).

During hospital day 19, the patient underwent fiberoptic bronchoscopy with transbronchial biopsies, endobronchial brushings, and bronchoalveolar lavage (BAL). Black necrotic debris and diffuse edema were noted on bronchoscopy in the lingula (Fig. 3). Given the patient’s prior history of pulmonary aspergillosis and chronic suppressive fungal therapy, she was empirically started on amphotericin for high suspicion of a fungal pneumonia. The following day, bronchoscopic brushing specimens revealed 90° branching hyphae consistent with mucormycosis (Fig. 4). This was later confirmed by tissue culture (Fig. 5).

The patient continued to deteriorate, developing acute respiratory failure requiring intubation and progressive septic shock requiring hemodynamic support. She progressively deteriorated despite the addition of mycafungin to liposomal...
amphotericin. In addition to the radiographic abnormalities noted on thoracic CT, abdominal CT showed a wedge-shaped infract in the left kidney as well as splenic microinfarcts consistent with disseminated mucormycosis. Despite all interventions, the patient’s condition continued to deteriorate, and she died shortly thereafter.

DISCUSSION

Mucormycosis is an invasive fungal infection caused by fungi of the order Mucorales (class Zygomycetous), which are ubiquitous in nature and can be found on decaying vegetation and in the soil. The genera most commonly found in human infections are *Rhizopus*, *Absidia*, *Mucor*, and *Rhizomucor*. Mucormycosis is the third leading cause of fungal infections following *Aspergillus* and *Candida* species. The fungi have broad hyphae (5–15 mm in diameter), irregular branching at right angles and rare septations. The histopathological hallmarks of mucormycosis are vascular invasion and tissue necrosis, which are due to the angioinvasive nature of the infection. The primary risk factors for developing mucormycosis include diabetes mellitus, metabolic acidosis, hematologic malignancies, solid organ transplantation, and renal insufficiency. Patients with these risk factors are immunocompromised, with defective neutrophil and macrophage function. Mucorales can cause rhinocerebral, pulmonary, gas-

FIGURE 1. Anterior–posterior chest radiograph shows left lower lung opacity with blunting of the left costophrenic angle.

FIGURE 2. Axial thoracic CT shows a rounded area of consolidation in the lingula associated with central lucency and ground-glass opacity.

FIGURE 3. Bronchoscopic image shows black, necrotic debris within the lingular bronchus.

FIGURE 4. Histopathological specimen obtained via transbronchial brushings shows fungal organisms with wide hyphae that show 90-degree branching, practically nonseptate morphology (H&E stain, de-stained and restained with Grocott’s methenamine-silver stain; ×600 magnification).
Since the initial report by Furbinger in 1876, several re-pulmonary aspergillosis 10 months prior to presentation. The literature on pulmonary mucormycosis is sparse. The initial report by Furbinger in 1876, several reviews of pulmonary mucormycosis have been published. Moreover, with the increasing use of voriconazole as initial treatment of acute invasive aspergillosis in immunocompromised patients and as prophylaxis for invasive fungal infections, an increased rate of zygomycosis is being observed. Voriconazole is known to be ineffective against Mucorales infections. In a report on 4 immunocompromised patients with hematologic disease on chronic voriconazole therapy ranging from 7 to 30 weeks who were diagnosed with zygomycosis, 3 died soon after diagnosis at 12, 13, and 45 days. The authors concluded that prolonged use of voriconazole in severely immunocompromised patients increases the risk of zygomycosis and disseminated infection. Our patient had profound neutropenia from both recurrent leukemic malignancy and chemotherapy and did not recover despite G-CSF. Favorable outcomes in patients with hematologic malignancy seem to correlate with lack of pulmonary involvement, surgical debridement, neutrophil recovery, and a cumulative total amphotericin B dose of 2000 mg.

Moreover, with the increasing use of voriconazole as initial treatment of acute invasive aspergillosis, a high level of suspicion is important in any patient in the appropriate clinical setting. Although no gold standard exists, conventional recommendations for establishing the diagnosis of mucormycosis require demonstration of mucor hyphae within the parenchyma. However, a recent case series of 5 patients suggests that waiting for demonstration of fungi in the tissues may not be possible given patients’ other comorbidities. Bronchoalveolar lavage was diagnostic in 3 of the 5 patients where transbronchial biopsy was not performed due to thrombocytopenia. The authors conclude that whenever mucormycosis is found in BAL cultures from neutropenic or immunocompromised patients, the diagnosis of invasive pulmonary mucormycosis is extremely likely and should be assumed until proven otherwise. Patients with pulmonary mucormycosis who were shown to have the best outcome have been treated with both amphotericin and surgical resection. Unfortunately, our patient’s comorbidities prevented her from undergoing surgery.

CONCLUSION

Pulmonary mucormycosis is an aggressive, invasive zygomycosis that characteristically affects neutropenic patients with hematological malignancies, especially acute lymphoblastic leukemia, in addition to certain other risk factors, mucormycosis and hematologic malignancy had a survival rate of only 25%. Among the survivors, only 1 (8%) of 13 patients with neutropenia survived, compared with 6 (40%) of 15 patients without neutropenia. None of the radiologic findings were characteristic, but the authors found a predilection for the upper lobes. The air-crescent sign is noteworthy and should increase the urgency of evaluation because massive hemoptysis and death were more common in this group of patients. Surgical resection is important in the treatment of pulmonary mucormycosis, especially since its angiocentric nature can lead to invasion of the pulmonary vasculature and subsequent massive hemoptysis.

Although in the most recent review by Lee et al, radiographic assessment in pulmonary mucormycosis was usually nondiagnostic, radiographic presentation of this disease has been well documented as reviewed by Bigby et al. Chest radiograph abnormalities include nodular, lobar, or wedge-shaped infiltrates; mediastinal widening; bronchopneumonia; solitary nodule; miliary pattern; cavitary; fungus ball; and pleural effusion. The typical thoracic imaging findings of pulmonary mucormycosis are the result of vascular invasion by the organism and include wedge-shaped opacities, pulmonary consolidation, cavitary, and, less commonly, pleural effusions. Thoracic CT may show the “halo” sign (a pulmonary nodule or focus of consolidation surrounded by ground-glass opacity) or the “air crescent” sign (a peripheral air lucency partially surrounding a nodule contained within a pulmonary cavity, produced by infarction and retraction of necrotic lung tissue within the cavity). The latter is most commonly seen in pulmonary infections with angio-invasive fungus. However, it is not nonspecific and may also be seen in lung abscesses, tuberculomas, hematomas, echnococcal cysts, and cavitary neoplasms.

Given the rapid progression and often fatal outcome of pulmonary mucormycosis, a high level of suspicion is important in any patient in the appropriate clinical setting. Although no gold standard exists, conventional recommendations for establishing the diagnosis of mucormycosis require demonstration of mucor hyphae within the parenchyma. However, a recent case series of 5 patients suggests that waiting for demonstration of fungi in the tissues may not be possible given patients’ other comorbidities. Bronchoalveolar lavage was diagnostic in 3 of the 5 patients where transbronchial biopsy was not performed due to thrombocytopenia. The authors conclude that whenever mucormycosis is found in BAL cultures from neutropenic or immunocompromised patients, the diagnosis of invasive pulmonary mucormycosis is extremely likely and should be assumed until proven otherwise. Patients with pulmonary mucormycosis who were shown to have the best outcome have been treated with both amphotericin and surgical resection. Unfortunately, our patient’s comorbidities prevented her from undergoing surgery.

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Pulmonary mucormycosis is an aggressive, invasive zygomycosis that characteristically affects neutropenic patients with hematological malignancies, especially acute lymphoblastic leukemia, in addition to certain other risk factors.
such as diabetes mellitus, renal insufficiency, and metabolic acidosis. Chronic fungal immunosuppressive therapy has also been associated with an increased incidence of mucormycosis in patients with hematological malignancy. Pulmonary mucormycosis is associated with a high mortality, and prompt diagnosis is essential for maximizing the possibility of survival. While not specific, the characteristic radiographic findings of mucormycosis include multifocal consolidation or solitary or multiple nodules or masses. Lymphadenopathy and pleural effusion may occur but are uncommon. The “halo” sign may be seen on thoracic CT studies earlier in the course of disease, whereas the “air crescent” sign is usually seen later in the disease course. The diagnosis of pulmonary mucormycosis traditionally rests on the demonstration of the characteristic fungal hyphae or the organism itself within the pulmonary parenchyma, although some authors suggest that the demonstration of Mucorales in broncholoalveolar lavage fluid in neutropenic or immunocompromised patients may be sufficient to establish the diagnosis. Optimal treatment of mucormycosis includes both amphotericin therapy and surgical resection.

REFERENCES