Pulmonary Mucormycosis: What Is the Best Strategy for Therapy?

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Introduction

Pulmonary mucormycosis is an uncommon but life-threatening opportunistic fungal infection.[1,2] It typically affects immunocompromised patients, such as recipients of stem cell or organ transplant, and has worse outcomes in those with hematologic malignancy or neutropenia.[1,3] In other immunosuppressed states, such as diabetes mellitus, it is less frequent.[2,4] In some series the incidence of pulmonary mucormycosis has been reported to be up to 24% among all cases of mucormycosis, but it may be underestimated due to the difficulties in diagnosis.[1,2] This infection has a high mortality (40–76%), and carries substantial morbidity in some cases, due to a rapid local progression and prominent angioinvasion.[2,4,5] Its clinical presentation ranges from acute to subacute, depending on the immune status of the host.

Case Summary

A 29-year-old male with uncontrolled type I diabetes mellitus of 10 years duration, presented with an 8-week history of progressive shortness of breath, left sided pleuritic chest pain, weight loss, and hemoptysis (3–5 tablespoons daily). He denied fever, chills, or night sweats. No intravenous drug use or close contacts with persons with tuberculosis were reported. He did not have any pets, recent travel, or substantial smoking history.

The patient was afebrile, with normal blood pressure, heart rate, and breathing frequency. Oxygen saturation was 99% on room air. He had egophony and decreased breath sounds in the middle and lower left lung fields. The remainder of the patient's physical examination was unremarkable. Complete blood cell count, liver function tests, urinalysis, and chemistry were normal, except for a glucose of 587 mg/dL and carbon dioxide total serum of 34 mmol/L. Serum ketones were negative, hemoglobin A1C was 10.2%, and arterial serum pH was 7.46. A chest x-ray revealed an extensive opacification involving the left upper lobe, along with multiple air/fluid levels (Fig. 1). Coccidiomycosis and aspergillus serologies were negative, including galactomannan. Both serum antibodies and urine antigens for histoplasmosis were negative. Cryptococcus serum antigen was negative. There was no evidence of acid-fast bacilli in the sputum. HIV and anti-neutrophil serologies were negative. Computed tomography of the chest revealed a large, multi-loculated, air and fluid filled cavity within the left upper lobe, and a left lower lobe consolidation (Fig. 2).

Bronchoscopy revealed a normal endobronchial examination, but the gross specimen from transbronchial biopsies revealed several fragments of black tissue. The left upper lobe bronchial alveolar lavage and transbronchial biopsies revealed non-septated hyphae (Fig. 3). Cultures were positive for a *Rhizopus* species. Computed tomography scan of the head and sinuses was normal, and the patient was started on liposomal amphotericin B (400 mg every 24 h, 5 mg/kg) and micafungin (100 mg every 24 h) intravenously on day 2. On day 4 he underwent left upper lobe lobectomy plus left lower lobe wedge resection (Fig. 4). Cultures from the left upper lobe were positive for a *Rhizopus* species. He completed 3 weeks of amphotericin B and micafungin, but developed renal failure, possibly from amphotericin B, and was changed to posaconazole. He recovered well, and his therapy was continued with posaconazole alone to complete 4 additional weeks of oral

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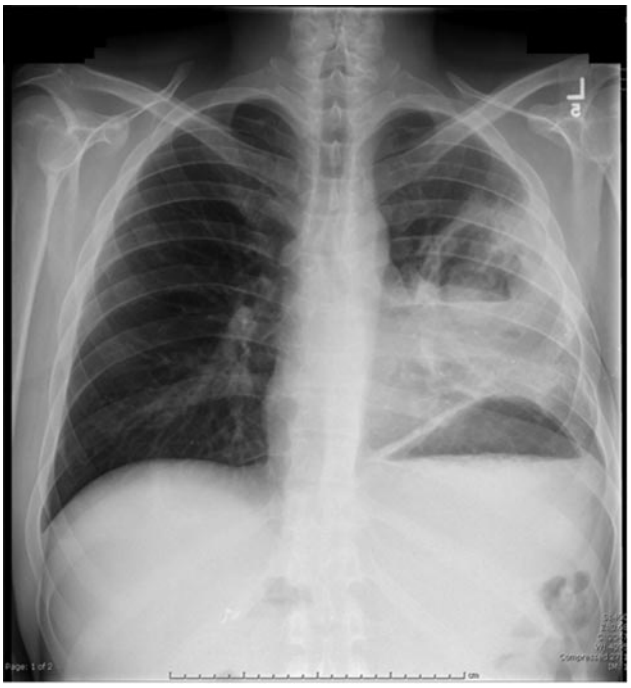

Fig. 1. Chest x-ray shows opacification of the left upper lobe, multiple air/fluid levels, and a 4 cm round mass-like lesion projecting over one of the air/fluid levels.

antifungal therapy as an out-patient. Levels of posaconazole were above 1.25 mg/mL but *Rhizopus* species susceptibilities were not available. When last evaluated, 6 months following the initial presentation, the patient was asymptomatic, with a stable chest radiograph (Fig. 5).

Discussion

The high mortality observed in pulmonary mucormycosis may be related to delays in the diagnosis, poor host response (eg, neutropenia), and limited available therapy.[3,5] Fever, hemoptysis, and tissue infarction are characteristic

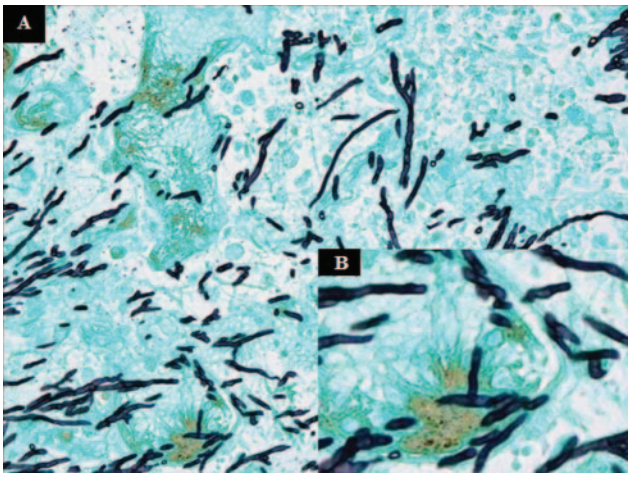

Fig. 3. Transbronchial biopsy with Grocott methenamine silver stain shows non-septate hyphae of *Rhizopus* species. A: Magnification 20. B: Magnification 40 shows a branching angle of 90°.

of pulmonary mucormycosis.[2,4] Radiographic findings include focal consolidation, pulmonary nodules, and rarely the "halo" and "reversed-halo" signs. Cavitary lesions with the "air crescent sign" have been described, but are rare.[1,4]

The diagnosis of mucormycosis is based on both histopathological findings of tissue invasion by hyphae and cultures isolating pathogens of the order *Mucorales*, most commonly *Rhizopus*, *Mucor*, and *Rhizomuc*or species.[1] The use of bronchoscopy in obtaining tissue for histological examination and culture appears to be safe in cavitary lung disease, despite its potential risk factors (eg, pneumothorax).[6]

The prognosis and outcomes of this infection have improved over the last several years as a result of early diagnosis, surgical debridement, and newer antifungal agents.[5] The recommended antifungal agent is liposomal amphotericin B, but there are concerns about the limited penetration of antifungals to the affected tissues, due to the substantial necrosis that accompanies this infection.[7] For this reason, surgical debridement has been advocated. Sev-

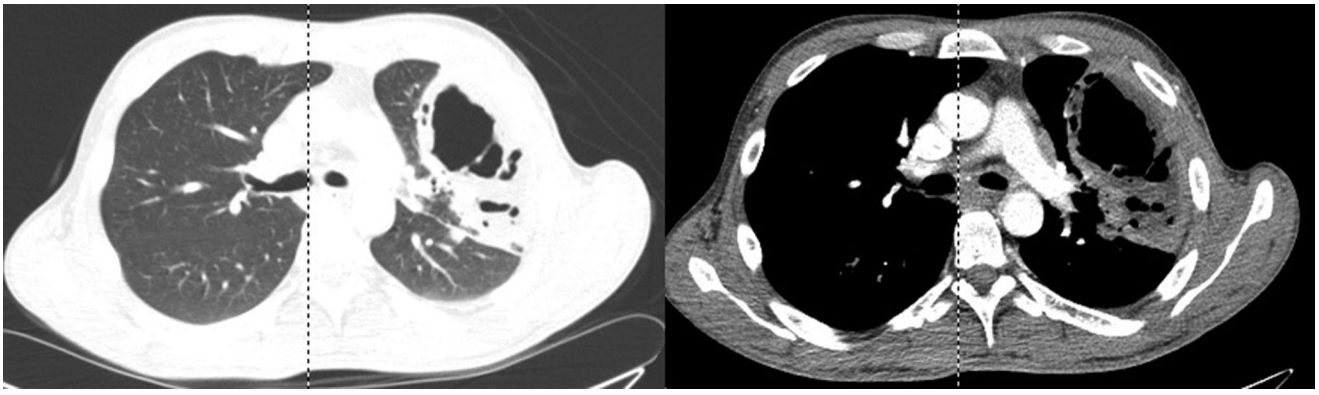

Fig. 2. Computed tomography shows a 10 × 12 × 7 cm multiloculated air and fluid filled cavity with a heterogeneously enhancing wall in the left upper lobe, and atelectasis and consolidation in the surrounding lung parenchyma.

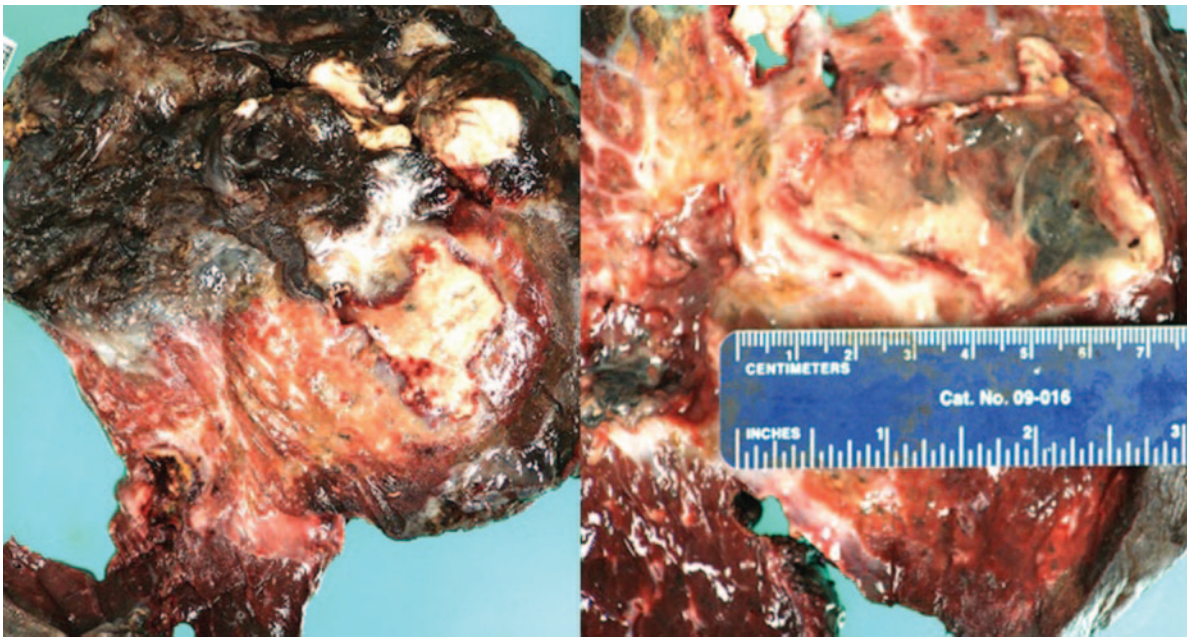

Fig. 4. Gross specimen from the left upper lobectomy shows a 7 cm cavitary lesion surrounded by congestive and necrotic lung tissue.

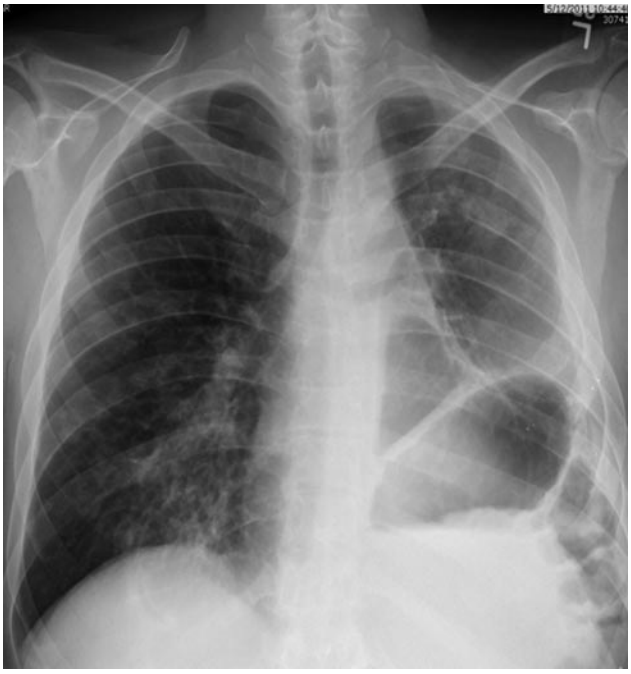

Fig. 5. Chest x-ray 6 months following initial presentation shows postsurgical changes of the left lung associated with pleural thickening/effusion.

eral studies have shown that the combination of early surgical resection and antifungal therapy has a significant improvement in survival, when compared to antifungal therapy alone.[1,4,8] This early aggressive approach is critical, since the delay of effective systemic antifungal treatment after the diagnosis of mucormycosis may increase mortality.[9] Therefore, unless surgery is contraindicated, the recommended therapy for pulmonary mucormycosis is early surgical debridement in conjunction with early amphotericin B therapy (< 6 d after diagnosis).[4,7] The duration of therapy is individualized to the patient, but the near normalization of radiographic abnormalities, negativity of cultures, or resolution of the immunosuppressed state can be used as surrogates to stop therapy.

Other antifungal agents have been used for the treatment of mucormycosis. Posaconazole has a potent activity against *Mucorales* species, but limited activity against *Rhizopus* species, and may be considered for patients who need long-term therapy.[1] Voriconazole has not been shown to be effective against the *Mucorales* species.[9] The role of some adjunctive therapies to amphotericin B has been proposed. The combination of amphotericin B with echinocandins for the treatment of mucormycosis has been suggested, based on animal studies.[7] *Rhizopus* species are the most common forms found in humans, and express the target enzyme for echinocandins.[7] A recent retrospective study of patients with rhino-orbital mucormycosis treated with a combination of amphotericin B and caspofungin showed a superior success and survival time, when compared to amphotericin B alone.[10] Because these studies suggest an improvement in survival with dual antifungal therapy, we chose to use amphotericin B in combination with micafungin. Nevertheless, no human data or case

reports are available investigating the role of surgical resection and combined medical therapy using amphotericin B and an echinocandin in pulmonary mucormycosis.

The use of cytokine therapy (interferon gamma and/or granulocyte macrophage colony stimulating factor) as adjunctive treatment is promising, but more clinical data are needed.[11,12] Similarly, there are few data regarding hyperbaric oxygen in pulmonary mucormycosis.[13]

This case evidences a positive clinical outcome in a poorly controlled diabetic with a non-ketoacidotic state, treated with early surgical resection and a combination of 2 antifungal agents (amphotericin B and echinocandin). It highlights the importance of the early diagnosis, treatment, and timely surgical debridement for the therapy of mucormycosis.

Teaching Points

- Pulmonary mucormycosis has high morbidity and mortality.
- Mucormycosis should be considered in the differential diagnosis of cavitary lung lesions in patients with poorly controlled diabetes or other immunosuppressed states.
- To prevent delays in treatment and improve the likelihood of survival, early diagnosis is imperative.
- Early surgical resection and amphotericin antifungal therapy are considered the standard treatment.
- Future prospective studies are needed to evaluate outcomes in pulmonary mucormycosis treated with early surgical resection and combination of amphotericin B and echinocandins.

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