Breaking the mold: A case of pulmonary mucormycosis treated with
isavuconazole

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ABSTRACT

Pulmonary mucormycosis is a rare opportunistic invasive fungal infection that disproportionately affects immunocompromised hosts and carries high morbidity and mortality. It is traditionally treated with combined pharmacologic and surgical modalities. Here we present a case of pulmonary mucormycosis in a patient whose disease burden precluded surgical management, and in whom acute kidney injury necessitated therapy with an alternative to the recommended pharmacologic antifungal therapy.

1. Introduction

Pulmonary mucormycosis is a rare opportunistic invasive fungal infection of the immunocompromised host that although rare, is associated with high mortality [3]. Individuals with diabetes mellitus, hematologic malignancies, renal insufficiency, and solid organ transplant recipients are predisposed to infection [2]. Infection is classically associated with diabetic ketoacidosis and iron overload states [3]. Transmission occurs predominantly through inhalation of spores from the environment resulting in infection of the lungs and paranasal sinuses [2]. Pulmonary infection is more common in patients with malignancy and in recipients of bone marrow transplants [3]. A 1999 literature review of 87 cases reported in the literature identified 11 cases in immune-competent hosts [4].

Clinical manifestations include fever, cough, hemoptysis, and dyspnea [5]. Radiographic findings include infiltrates, consolidation, cavitary, focal masses, or nodules. A reverse halo sign is particularly suggestive of the diagnosis [2]. Direct microscopy of clinical specimens can provide rapid presumptive diagnosis of mucormycosis through visualization of the characteristic non-septate or pauci-septate hyphae with an irregular ribbon shape appearance and wide-angle bifurcations. In recent registries, histopathology has yielded diagnosis in between 63% and 66% of cases [6].

Pulmonary mucormycosis has been traditionally treated with combined pharmacologic and surgical modalities. Here we present a case of pulmonary mucormycosis in a patient whose disease burden precluded surgical management, and in whom acute kidney injury necessitated therapy with an alternative to the recommended pharmacologic antifungal therapy.

2. Case

The patient is a 62-year-old man with a history of sarcoidosis, non-alcoholic steatohepatitis-related (NASH-related) cirrhosis, and poorly-controlled type II diabetes mellitus who presented with productive cough and left-sided, pleuritic chest pain. The chest pain began one week prior to presentation, was non-exertional, and localized to the mid-axillary line on the left side without radiation. The patient also reported dyspnea on exertion, but no recent change in his exercise tolerance of two to three blocks.

The cough began five days prior to presentation and was productive of scant yellow sputum. He denied associated fevers and chills. He denied changes in his weight and denied hemoptysis.

The patient immigrated to the United States from Bangladesh in 1991. He traveled to Saudi Arabia four years prior to presentation, and to London two weeks prior to presentation. He had no history of tuberculosis, and denied exposure history. He was a former smoker, but denied active tobacco use. He had no relevant exposure history in his work as a food vendor.

His last HbA1c prior to admission was 10.6% and he was taking insulin glargine. Sarcoidosis was diagnosed on mediastinal lymph node biopsy three years prior to presentation, but he never had symptoms requiring steroid therapy. The NASH-related cirrhosis was complicated by large (grade F3) esophageal varices, which required banding several
The differential diagnosis for the patient's presentation with findings of cavitary lung lesions included infectious, rheumatologic and malignant etiologies [1]. Given the time course, infectious etiologies were thought to be most likely with the differential diagnosis including septic emboli, lung abscesses, mycobacterial infections (tuberculous and non-tuberculous), Nocardia and fungal infections (including Aspergillus and Mucor). Other considerations of rheumatologic (e.g. granulomatosis with polyangiitis) and malignant (e.g. squamous cell lung cancer) etiologies were considered less likely.

Upon admission, the patient was placed on airborne isolation and was initiated on empiric broad-spectrum antimicrobial therapy with vancomycin and aztreonam to cover for bacterial infection, while further diagnostic studies were performed. Aztreonam was used instead of piperacillin-tazobactam as the patient reported having a rash after exposure to penicillins in the past. The patient was also started on his home dose of insulin glargine and an insulin aspart pre-meal and bedtime sliding scale to control his hyperglycemia. On day 0, an interferon-gamma release assay (IGRA) was sent and collection of sputum samples for acid-fast bacilli was initiated. By day 3, the patient's symptoms still had not improved on empiric antibiotics. The IGRA returned positive on day 3 but active pulmonary tuberculosis was ruled out by three negative consecutive sputum smears for acid-fast bacilli.

The pulmonary service was consulted on day 3 for possible bronchoscopy with bronchoalveolar lavage and trans-bronchial biopsy, however given the peripheral location of the pulmonary nodules, transcatheter biopsy by interventional radiology was thought to be more appropriate.

Interventional radiology was consulted and a CT-guided biopsy of a left lower lobe nodule was performed on day 4. Vancomycin was discontinued given absence of evidence for methicillin-resistant Staphylococcus aureus (MRSA) infection but the aztreonam was continued pending the biopsy results. Microscopy results on day 7 revealed sparse non-septate fungal hyphae suggestive of zygomycoses species. Aztreonam was discontinued and he was initiated empirically on liposomal amphotericin B at 5 mg/kg daily immediately after the microscopy results were available. Cultures subsequently confirmed Rhizopus oryzae sensitive to amphotericin B on day 8. In addition to initiating anti-fungal therapy, the patient's hyperglycemia was managed aggressively with insulin glargine and aspart sliding scale.

Five days after the initiation of amphotericin B (day 12 of admission), the patient developed acute kidney injury with creatinine rising from 1.2 mg/dL on admission to 2.0 mg/dL. In consultation with the infectious disease service, the patient was transitioned to isavuconazole that day. Loading was performed over 6 days with a dose of 200 mg intravenously every eight hours. He was subsequently transitioned to a maintenance oral dose of 200 mg daily on day 19 to complete a six-week course.

The patient tolerated isavuconazole therapy well, and the presumed amphotericin B-induced acute kidney injury resolved following discontinuation of the medication. The patient was ultimately discharged to follow-up with an infectious disease specialist for repeat imaging and tailoring of his antifungal course. Imaging at six months revealed resolution of the previously described pulmonary nodules (Fig. 3).

3. Discussion

Pulmonary mucormycosis is a rare opportunistic invasive fungal infection of the immunocompromised host that predominantly affects individuals with diabetes mellitus, hematologic malignancy, renal insufficiency, and solid organ transplant recipients [2]. Patients typically present with fever, cough, hemoptysis, and dyspnea [5]. Chest imaging findings include infiltrates, cavitation, focal masses, or nodules [2]. Diagnosis is made by direct microscopy of tissue specimens showing the characteristic non-septate or pauci-septate hyphae with an irregular ribbon shape appearance and wide-angle bifurcations.

In terms of treatment, current guidelines recommend combined

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**Fig. 1.** Chest radiography showing a focal rounded opacity in the left lateral mid-lung zone measuring 3.2 cm in diameter.

**Fig. 2.** Computed tomography of the chest with iodinated contrast showing multiple bilateral, pre-dominantly subpleural cavitary pulmonary nodules.
pharmacologic and surgical management in addition to correction of any underlying predisposing disorder. There have been no well-designed randomized trials to establish efficacy of any particular treatment approach [6]. These recommendations are based in part on a retrospective study of 30 patients combined with a literature analysis of 225 patients that suggested that surgical debridement of involved lung was associated with a decline in mortality from 62% to 11% [7].

Mortality of pulmonary zygomycosis is high with a 2005 literature review reporting an overall mortality of 54%. Survival among patients who received no therapy has been reported as low as 3%. Among patients treated with antifungal therapy, survival is 62%. Among patients who received surgical therapy alone, survival was 57%. However, among patients who received combined surgical and pharmacologic treatment, survival increased to 70% [3]. Among patients undergoing therapy for hematologic malignancies or transplantation, mortality is particularly high (52–91%) [8,9].

Recently, the FDA granted approval for isavuconazole in the treatment of invasive mucormycosis infections [10]. Approval was granted in part based on a single-arm open-label trial comparing isavuconazole to amphotericin B in the treatment of mucormycosis. The study enrolled 37 patients, 21 of whom received isavuconazole as primary treatment, five received the drug after intolerance to other antifungals, and 11 had refractory disease. The primary study endpoint was overall response at day 42. Only one patient in the isavuconazole group had lung-limited disease (10 in the Amphotericin B group). At day 42, no patients had a complete response. Three patients in the primary treatment group and one patient in the treatment refractory group had a partial response at 42 days. By the end of therapy (day 180) three in the primary treatment group (of 19 remaining patients) had a complete response, compared to two in the refractory group [11].

The case presented here suggests viability of a non-surgical approach to management of invasive mucormycosis infection where surgery was prohibited by clinical circumstances. In addition, it serves as anecdotal evidence that isavuconazole is a safe and effective alternative to amphotericin B in the treatment of invasive mold infections. However, it is important to note that the patient described in this case report had several factors that may have contributed to a favorable outcome despite a non-surgical approach. These factors include aggressively managed hyperglycemia, not being on immunosuppressive agents and a normal absolute neutrophil count [12].

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