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Treatment of a Pulmonary Aspergilloma in a Lung Transplant Recipient Using Catheter-directed Intracavitary Instillation of Liposomal Amphotericin B

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INTRODUCTION

Lung transplant recipients are at high risk for aspergillus infections because of transplant-related immunosuppression and ischemia-reperfusion injury impacting airway healing.[1] Single lung transplant recipients with structural changes related to advanced lung disease may develop aspergillomas or invasive aspergillus in their native lung. When patients with posttransplant aspergillomas present with hemoptysis, treatment options must take into consideration the impaired delivery of systemic antifungal agents into the relatively avascular mycetoma space, as well as the potential complications associated with surgical resection. We report a case of a native lung aspergilloma presenting with life-threatening hemoptysis in a lung transplant recipient who was successfully treated with percutaneous catheter-directed intracavitary liposomal amphotericin B.

CASE REPORT

A 68-y-old man with a history of coronary and carotid artery disease, recurrent venous thromboembolism, and combined idiopathic pulmonary fibrosis with emphysema underwent left lung transplant in March 2020. Chest computed tomography (CT) obtained 5 d before transplant showed bullous upper lobe predominant emphysema and fibrotic interstitial lung disease (Figure 1A). Serum beta-D-glucan and aspergillus galactomannan antigen by enzyme immunoassay were negative 4 d before transplant.

The donor was 16 y old with a traumatic brain injury related to a motor vehicle collision. He progressed to brain death after 2 d of mechanical ventilation. He smoked leaf marijuana weekly and had an extensive travel history, including China, Western Europe, and Anguilla. Chest CT 2 d before procurement showed dense consolidations in the right upper lobe (RUL) and right middle lobe consistent with pulmonary contusions. There was also a small consolidation in the left lower lobe consistent with aspiration or atelectasis. There were no nodular opacities. Bronchoscopy on the day of procurement demonstrated nonpurulent thick secretions in the RUL and right middle lobe. Bronchoalveolar lavage (BAL) cultures grew methicillin-sensitive *Staphylococcus aureus*.

Bronchoscopy on postoperative day 1 showed no airway ischemia, and BAL was negative for pathogenic fungal or bacterial organisms. Explant pathology showed advanced emphysema with interstitial fibrosis and superimposed acute lung injury. Acid-fast bacilli, Fite, and Grocott stains were negative for microorganisms. He was discharged home on postoperative day 12 on therapeutic anticoagulation. He was maintained on prednisone, mycophenolate mofetil, and tacrolimus. He presented in August 2020 with a fever. Chest CT showed left lung groundglass opacities and consolidations in the native lung (Figure 1B). Respiratory viral pathogen profile was negative. BAL bacterial and fungal cultures were negative. Serum and BAL aspergillus galactomannan antigens were negative. He underwent bilateral thoracentesis, which was notable for lymphocytic predominant exudative effusions with negative cytology, flow cytometry, bacterial, fungal, and acid-fast bacilli cultures. Serum Epstein-Barr virus PCR was negative. He improved with broad spectrum antibiotic therapy.

Follow-up chest CT in November 2020 showed a RUL thick-walled cavity consistent with a developing mycetoma (Figure 1C). Posaconazole was initiated, and mycophenolate mofetil was stopped. Posaconazole trough drawn 5 d after

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initial loading dose was 1.5 μg/mL. He was admitted to the hospital in March 2021 with approximately 20 mL of hemoptysis. A CT angiogram showed tortuous bronchial arteries in the vicinity of the cavity without a clear target for embolization. Apixaban was held and hemoptysis resolved without further intervention. Repeat posaconazole trough level was 2.8 μg/mL. Because of his venous thromboembolism history, anticoagulation was resumed. A multidisciplinary discussion was held with transplant and interventional pulmonology, thoracic surgery, and interventional radiology (IR) regarding treatment strategies. The cavity was felt to be resectable from a technical perspective, and he had adequate pulmonary reserve (forced expiratory volume in the first second of 4.45 L [129% predicted] and forced vital capacity of 5.58 L [122% predicted]). Coronary angiography, however, showed multivessel nonobstructive coronary artery disease, and carotid ultrasounds demonstrated >70% right carotid stenosis and 75% right subclavian artery stenosis. He was a poor surgical candidate for RUL lobectomy because of his cardiovascular disease, and he was offered intracavitary antifungal treatment.

In May 2021, IR placed a 14 French pigtail drainage catheter into the mycetoma under CT guidance with the patient in the right lateral decubitus position (Figure 1D). A 30-mL suspension of liposomal amphotericin mixed 5 to 1 with ethiodized oil (Lipiodol) was prepared (Figure 2A). Under fluoroscopic guidance, the cavity was lavaged with 20 mL of 1% lidocaine, followed by 10 mL of the amphotericin suspension, followed by 20-mL aliquots of normal saline to wash out the greater mass of the mycetoma (Figure 2B). The remaining 20 mL of the amphotericin suspension was mixed with Gelfoam sponge to form a slurry. This was administered through the catheter and left to dwell. A serum amphotericin level drawn a day later was 0.26 μg/mL.

Cultures from the aspirated material grew *Aspergillus fumigatus*, as identified by large subunit ribosome sequencing (analysis of 28S rDNA D1/D2 region). He underwent 2 additional fluoroscopically guided washouts and intracavitary administrations of amphotericin slurry 2 wks apart. Repeat chest CT in August 2021 showed resolution of the aspergilloma (Figure 1E). Susceptibility testing by the Clinical and Laboratory Standards Institute broth method demonstrated a minimum inhibitory concentration (MIC) of 2 μg/mL for posaconazole. The MIC for isavuconazole was 0.125 μg/mL and for voriconazole was 0.125 μg/mL. Itraconazole, isavuconazole, echinocandins, and amphotericin testing was not preformed, nor was genetic sequencing for resistance testing available. He was switched to voriconazole in September 2021. Trough level obtained 8 d after loading dose was 2.2 μg/mL. He has been maintained on voriconazole and has had no additional episodes of hemoptysis as of 4 mo following the procedure.

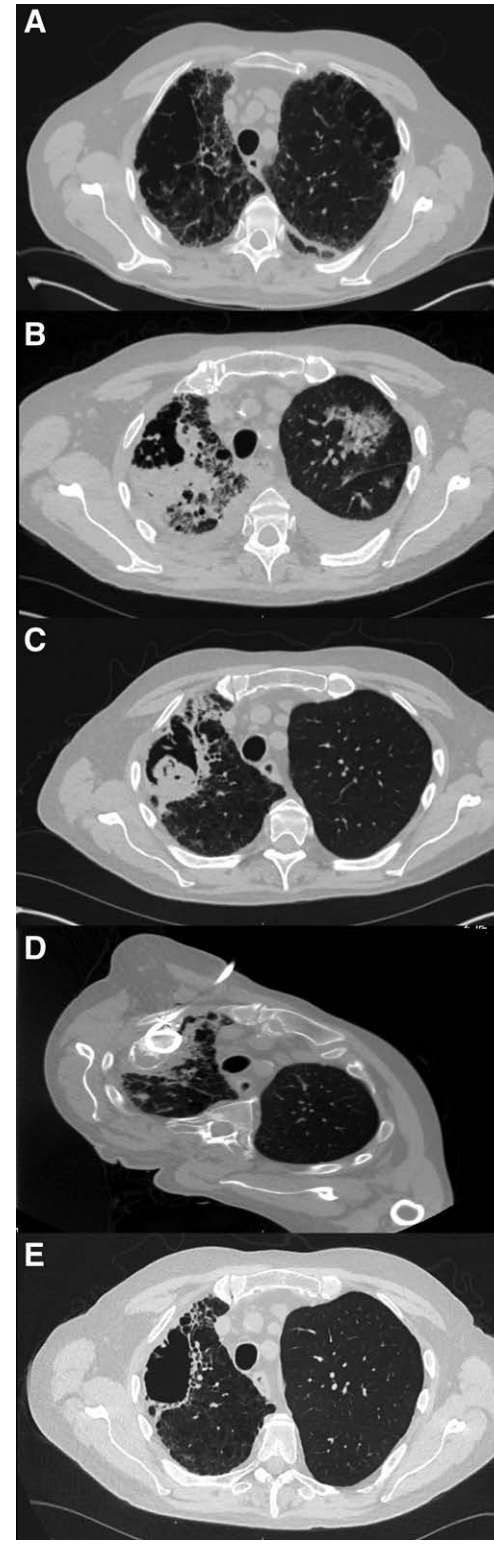

FIGURE 1. A, Chest CT before transplant demonstrates bullous interstitial lung disease without evidence of cavity formation. B, Chest CT 5 mo posttransplant demonstrates patchy left lung groundglass and consolidative opacities, increased consolidation with air-fluid levels in areas of advanced emphysema in the native lung, and new bilateral pleural effusions. C, Chest CT 8 mo posttransplant demonstrates a new right upper lobe thick-walled cavitary lesion with an internal air-fluid level consistent with a developing mycetoma. D, Chest CT 14 mo after transplant at the time of 14 French catheter placement. E, Chest CT 17 mo after transplant and 3 mo after initiation of intracavitary amphotericin treatment demonstrates resolution of the aspergilloma. CT, computed tomography.

DISCUSSION

We present a case report of successful percutaneous catheter-directed intracavitary liposomal amphotericin B therapy for the treatment of a pulmonary aspergilloma in a lung transplant recipient. Because serum markers of fungal infection, such as beta-glucan and aspergillus antigen, are less reliable in transplant patients, the time course and etiology of pulmonary aspergillosis remains unclear in this case. There was no

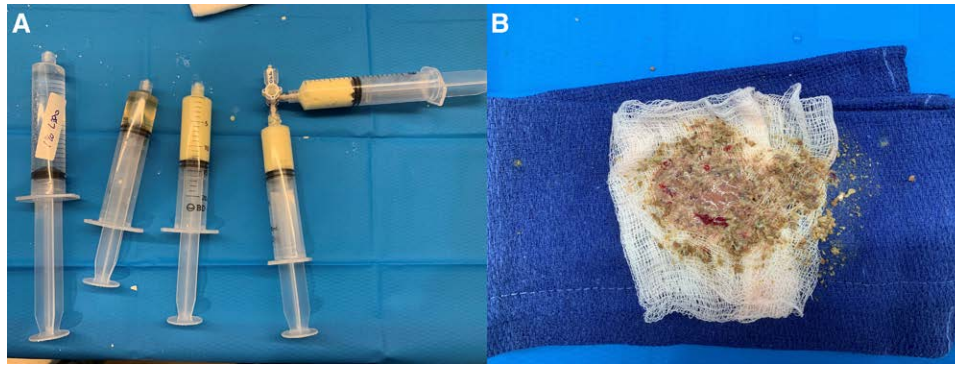

FIGURE 2. A, From left to right: lidocaine, Lipiodol, Lipiodol-amphotericin suspension, and Lipiodol-amphotericin-Gelfoam slurry are demonstrated. B, Necrotic debris and fungal elements evacuated during initial cavity washout.

definitive evidence of aspergillus colonization in the recipient based on explant and serial bronchial cultures. Other than being a single lung transplant recipient, he did not have other risk factors for aspergillus infection, such as airway necrosis, prolonged corticosteroid use, or significant neutropenia.[1] Although donor marijuana smoking may be a source, the time course makes this unlikely.[2] We hypothesize that his August 2020 bacterial pneumonia worsened underlying native lung structural changes, facilitating aspergilloma development.[3]

There are several explanations for the failure of systemic posaconazole. First, although posaconazole exhibits similar concentrations in alveolar cells as in serums, penetration into a relatively avascular mycetoma may be limited.[4] Second, transplant immunosuppression may have contributed to impaired neutrophilic response. Third, the cultured aspergillus demonstrated a significantly higher posaconazole MIC (2 μg/mL) than the cutoff value threshold for susceptibility (≤0.25 μg/mL).[5] There are several mechanisms for posaconazole resistance, primarily related to CYP51A gene mutations.[6,7] Because posaconazole resistance remains rare, however, a high index of suspicion is necessary to consider the rotation of antifungal agents.

Surgical resection, the recommended treatment for aspergillomas at risk for life-threatening hemoptysis, was unappealing. In addition to the patient's cardiovascular comorbidities, lobectomy in idiopathic pulmonary fibrosis on immunosuppression carries a substantial risk for complications, including bronchopleural fistula.[8] Although reports have demonstrated the efficacy of ultrasound-guided transbronchial amphotericin instillation, the caliber of the aspergilloma-adjacent airways was too small to allow transbronchial intervention in this case.[9]

Although the use of transthoracic intracavitary aspergilloma treatment has been described since the early 1990s, there are several unique aspects to this case. First, concerns about pleural seeding or pneumothorax, particularly for patients on high-dose immunosuppression or with severe structural abnormalities, may make this approach less appealing for transplant recipients.[10] To minimize the number of pleural passes, we placed an indwelling catheter to allow serial amphotericin instillations.[11] We saw no evidence of seeding or significant pneumothorax on subsequent imaging. In addition, the use of Lipiodol, which is radiopaque, allowed direct visualization of the cavity. Lipiodol also has intrinsic inflammatory, cytolytic, and sclerosant properties that may improve cavity sterilization.

The addition of absorbable gelatin sponge to the amphotericin slurry has several advantages. It increases contact dwell time with the remaining fungal elements, occupies more overall volume in the cavity, counteracts the effects of gravity, and delays expectoration of the antifungal agent. The use of intracavitary lidocaine decreases coughing during intracavitary amphotericin treatment.[12] The lateral decubitus position reduces exposure of the noninvolved lung to potential aspiration and increases cavity wall apposition. The dosing frequency was based on our institution's standard protocols in IR for cavitary sclerosis. The optimal interval for dosing requires further study. According to the manufacture's labeling, Gelfoam sponge dissolves over a period of 4 to 6 wks, although this process may be accelerated in the slurry process.[13]

Interestingly, we detected amphotericin systemically based on serum levels drawn within 24 h of his initial treatment. There was not, however, any evidence of toxicity—his serum creatinine remained stable, and he did not experience any systemic amphotericin infusion-related reactions, such as urticaria, nausea, or chills.

In summary, this case illustrates the efficacy of percutaneous catheter-directed intracavitary liposomal amphotericin treatment of an aspergilloma in a lung transplant recipient. Given the risks for surgical complications in this population, catheter-directed therapy should be considered as a treatment modality.

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