

Bronchial-Pulmonary Artery Fistula With Fatal Massive Hemoptysis Caused by Anastomotic Bronchial Aspergillus Infection in a Lung Transplant Recipient

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Introduction

Invasive pulmonary aspergillus infection in immunosuppressed patients is associated with a 50–80% mortality rate, even in the setting of aggressive antifungal therapy.^{1,2} In lung transplant recipients, a less well known, yet highly morbid, complication of aspergillus infection is bronchial aspergillosis that involves the surgical anastomosis and the adjacent graft bronchus (termed necrotizing or ulcerative tracheo-bronchial aspergillosis or anastomotic aspergillosis).^{3,4} These anastomotic infections have been associated with anastomotic dehiscence, bronchial stenosis, bronchomalacia, and fatal hemorrhage.^{3,4} We report a case of fatal, massive hemoptysis in a lung transplant recipient secondary to a bronchial-pulmonary artery fistula caused by anastomotic aspergillosis.

Case Report

The patient was a 61-year-old man who had received a bilateral lung transplant for chronic obstructive pulmonary disease 3.5 months prior to his death. His immediate postoperative course was complicated by atrial fibrillation, re-

current bouts of *Clostridium difficile* colitis, and a *Candida albicans* and *Candida dubliniensis* empyema with sternal wound infection and chorioretinitis. He had a bronchoscopy performed because of increasing pulmonary infiltrates one month after transplant, which showed the anastomosis sites to be intact, and the lavage fluid grew *Streptococcus pneumoniae*, for which he was treated. He received several courses of metronidazole for *C. difficile* and a 6-week course of fluconazole, as well as empirical vancomycin, for the sternal wound infection.

Ten weeks after transplant, he was admitted with persistent diarrhea and fever, which was diagnosed as *C. difficile* colitis, and he underwent total colectomy for toxic megacolon and sepsis. Continued respiratory failure and ventilator dependence necessitated a protracted intensive care unit stay and tracheotomy. He developed a central-line-associated upper-extremity deep venous thrombosis, which was treated with unfractionated heparin.

A chest computed tomogram (CT) 12 weeks after transplant showed diffuse bilateral pulmonary parenchymal nodules, including 2 nodules that showed cavitation (Fig. 1). Intravenous amphotericin was begun empirically. A serum galactomannan test was negative, and culture of bronchoalveolar lavage fluid grew 30,000 colonies of pan-sensitive *Pseudomonas aeruginosa*, but no fungus. At bronchoscopy, the mucosal surface of the left bronchial anastomosis was white and heaped up with small black surface patches. Because the clinical picture was concerning for invasive aspergillosis, a CT-guided lung biopsy of one of the left-upper-lobe pulmonary nodules was performed, which showed acute and organizing pneumonitis with extensive necrosis and no identifiable fungal forms; however, a culture of the tissue biopsy grew *Aspergillus fumigatus*.

After the cultures grew aspergillus, amphotericin was stopped and combination therapy with caspofungin and voriconazole was started. A 2-week course of ciprofloxacin for the *P. aeruginosa* ventilator-associated pneumonia was completed. A chest CT obtained one week after initiation of antifungal therapy showed minimal progression of disease; the voriconazole dose was increased, and pred-

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The authors report no conflicts of interest related to the content of this paper.

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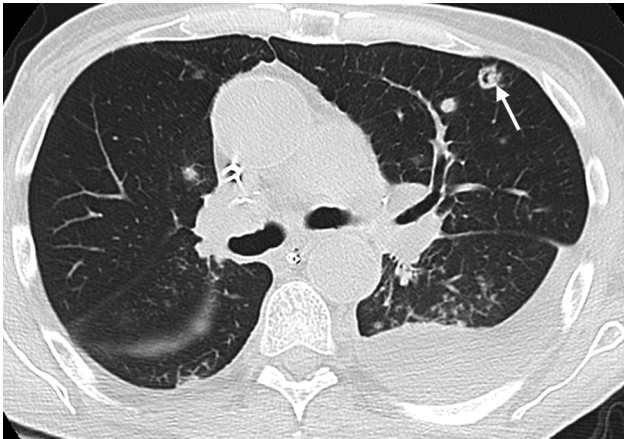


Fig. 1. Chest computed tomogram shows bilateral parenchymal nodules, including a cavitating nodule in the lingula (arrow) and a moderate left pleural effusion.

nisone and tacrolimus dosages were decreased (although tacrolimus blood concentrations were maintained at approximately 5 ng/mL). Acute renal failure developed but did not require hemodialysis. The patient continued to improve. After approximately 3 weeks of definitive therapy for aspergillus infection, he had a witnessed apneic arrest, which was followed by pulseless electrical activity. During endotracheal intubation a substantial amount of blood was seen in the oropharynx, emanating from the trachea.

At autopsy, there was massive recent airway hemorrhage, extending from the larynx, just below the vocal cords, into the secondary lobar bronchi of both lungs, with some associated intra-alveolar hemorrhage as well. There was bronchial aspergillus (Fig. 2) that involved the bilateral bronchial anastomoses, with deep ulcers that extended from just proximal to the bronchial anastomoses into the graft bronchi, which exposed the bronchial cartilage (Fig. 3). The pulmonary arterial, venous, and bronchial anastomoses were intact. However, a fistula extended from the left main bronchial ulcer, just proximal to the left-upper-lobe bronchus, into the left main pulmonary artery, just distal to the left pulmonary arterial anastomosis, where there was a 0.7-cm in diameter circular defect in the pulmonary artery (Fig. 4). In addition, both lungs contained multiple pulmonary and subpleural nodules of necrotizing granulomatous inflammation surrounding fungal hyphae of aspergillus; these nodules were centered on airways, and were likely a result of distal spread from the proximal bronchial ulcers. There was no significant vascular invasion by aspergillus fungal hyphae identified in the lung nodules. There was no histologic evidence of cellular rejection in the lungs, and there was no evidence of aspergillus involvement of any organ or tissue other than the lungs. Death was attributed to massive airway hemorrhage resulting from the left bronchial-left pulmonary artery fis-

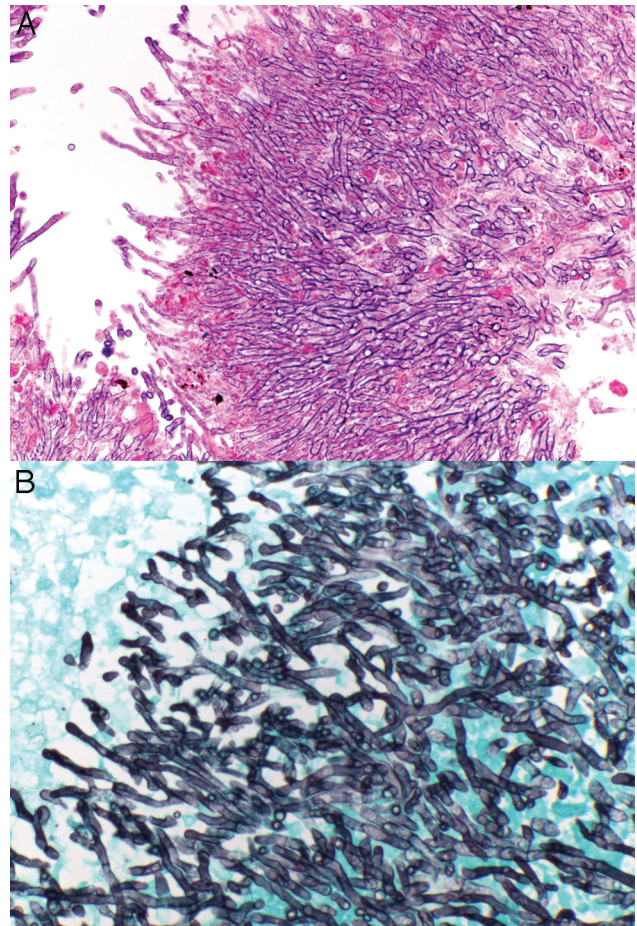


Fig. 2. Numerous fungal hyphae morphologically consistent with aspergillus species. Upper panel: hematoxylin and eosin stain. Lower panel: Gomori methenamine silver stain for fungus.

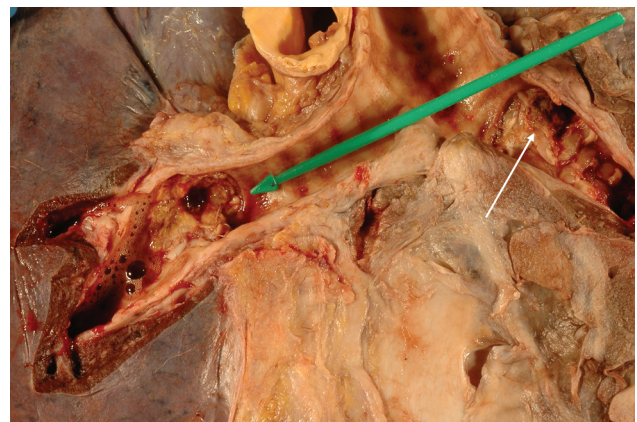


Fig. 3. Necrotizing ulcer at left bronchial anastomosis (green arrow); similar ulcer at right bronchial anastomosis (white arrow).

tula, due to ulcerative and necrotizing bronchial aspergillosis that involved the bilateral anastomotic regions of the transplanted lungs.

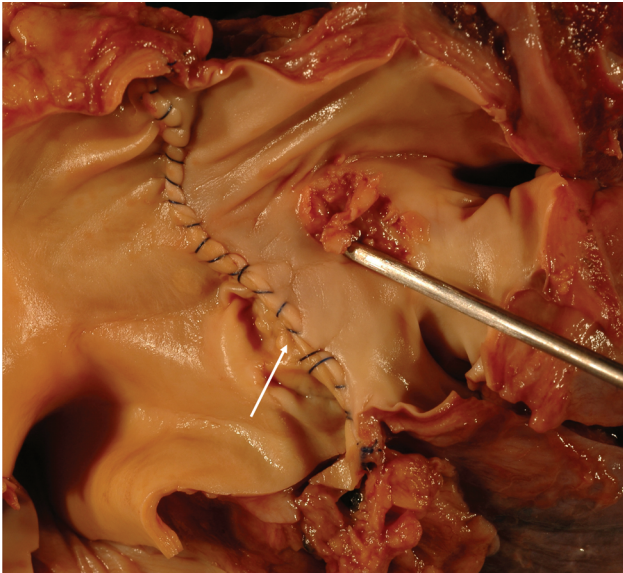


Fig. 4. Defect in donor left main pulmonary artery; the probe is extending into the left bronchial ulcer; intact anastomosis (small arrow).

Discussion

All hematopoietic and solid-organ transplant patients are at increased risk for invasive fungal infections, especially with aspergillus, because of immunosuppression. Lung transplant recipients are at highest risk because of the high degree of immunosuppression and because the lungs directly communicate with the environment and are thus a portal of entry for aspergillus.⁵ Prophylactic antifungal therapy has not prevented the morbidity and mortality associated with aspergillus infections. Aspergillus infection following lung transplantation continues to be a highly fatal disease.²

A unique manifestation of aspergillus infection in lung transplant recipients is anastomotic aspergillosis, termed ulcerative or necrotizing tracheo-bronchial aspergillosis. This condition develops in 5–13% of lung transplant recipients, despite the use of prophylactic oral and/or nebulized antifungal agents. It has had a case fatality rate of 14–30% in some case series. Patients with cystic fibrosis who have airway colonization with aspergillus prior to transplantation appear to be at highest risk.^{2,4,6} Of note in our case, aspergillus organisms had never been identified on any pretransplantation or posttransplantation specimens other than the specimen obtained at the time of diagnosis.

Anastomotic aspergillosis occurs within 1–6 months of transplantation, with the vast majority of cases diagnosed in the first 3 months.^{2,4,6} It manifests as dusky ulcerations of the bronchial walls, often bilateral, just distal to the surgical anastomosis. The pathogenesis of tracheo-bronchial aspergillosis is not well understood, but the charac-

teristic findings are theoretically explained by the unique nature of the anastomotic site.⁴ In the immediate post-transplantation period, the anastomotic site has relative ischemia, its vascular supply having been severed from the donor bronchial circulation. The ischemic, denuded tissue may provide a fertile terrain into which inhaled aspergillus can extend. Presumably, within several months of transplantation a new blood supply is firmly established to the anastomotic area, which reduces the risk of aspergillus invasion. Distal spread from the ulcerative bronchial aspergillus infection can result in bronchocentric pulmonary involvement, as in this case. The pulmonary nodules in this case did not show vascular invasion by aspergillus hyphal elements, but instead consisted of a necrotizing granulomatous inflammation surrounding the centrally located fungal organisms.

There are no clinical, serum, or radiographic markers that are diagnostic of anastomotic aspergillosis. For instance, even for the more widely studied phenomenon of invasive aspergillosis of the lung parenchyma, the usefulness of the serum galactomannan test has been questioned.⁷ This patient had a negative serum galactomannan despite extensive pulmonary disease. Some experts recommend serial bronchoscopy, including direct visualization and biopsy of the distal anastomotic margin, to look for emergence of anastomotic aspergillosis.^{4,6}

Experience with prophylaxis against invasive aspergillosis, which includes nebulized amphotericin, has been reported, but practice varies widely.⁸ Once clinical evaluation suggests the possibility of anastomotic aspergillosis, intravenous antifungal therapy should be started. The choice of antifungal agent is open to debate. Traditionally, some formulation of intravenous amphotericin B was considered the accepted standard for care of tissue-invasive aspergillosis. However, recent data from a randomized, unblinded trial in a diverse population of immunocompromised adults suggest that intravenous voriconazole may be better tolerated and more effective than amphotericin B.⁹ Caspofungin is another alternative, although data on its effectiveness in invasive aspergillosis appear limited to an open-label noncomparative study and a case report.^{10,11} A recent report showed improved survival by using a combination of caspofungin and voriconazole, compared to voriconazole alone, in patients with invasive aspergillosis.¹² However, none of these studies address the question of treatment of anastomotic aspergillosis.

Anastomotic aspergillosis can result in a number of complications, including anastomotic dehiscence, bronchial stenosis, bronchomalacia, and formation of bronchial-to-pulmonary-artery fistulas.^{3,4,6} In one series, 47% (7 of 15) of transplant recipients with saprophytic fungal infections of the anastomotic site (the majority due to aspergillus) developed bronchial complications, compared to only 9% (4 of 46) of those without such infections. The complications

required intravenous antifungal therapy along with invasive treatment, which included bronchial stenting, balloon dilation, laser debridement, and electrocautery. There were 3 deaths in the infected group (all of whom had anastomotic aspergillosis), but no deaths in the uninfected group.⁴ Another complication of anastomotic aspergillosis is fatal, massive hemoptysis secondary to a bronchial-to-pulmonary-artery fistula, which has been reported only rarely.^{3,13} The 2 cited cases had findings similar to ours; death resulted from massive hemoptysis from bronchial-to-artery fistulas caused by anastomotic aspergillosis.

In summary, anastomotic aspergillosis is not uncommon in the several months following lung transplantation. It carries a high burden of morbidity and mortality. The most catastrophic consequence is fatal, massive hemoptysis caused by formation of a bronchial-to-pulmonary-artery fistula. There is no current standard of care for prevention or surveillance. Thus, clinicians should have a high index of suspicion for diagnosis and a low threshold for treatment. Diagnosis is made via bronchoscopy, which allows for direct visualization, and biopsy of the bronchial-wall tissue just distal to the anastomotic surgical margin. Initial treatment includes intravenous antifungal agents. Despite optimal management, complications often occur and sometimes result in death.

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