Disseminated *Aspergillus fumigatus* Infection with Consecutive Mitral Valve Endocarditis in a Lung Transplant Recipient

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*Aspergillus* infection is a known complication of lung transplantation and remains associated with high mortality rates. The manifestation of the infection varies from simple colonization of the lung to disseminated complicated infections. Early *Aspergillus* infection has been rarely observed in a small number of lung transplant recipients; most cases occur during the late post-operative period. The pulmonary involvement has often been described as the first clinical localization of the disease. Although other various forms of *Aspergillus* infection are not uncommonly encountered after lung transplantation, *Aspergillus* mitral valve endocarditis is rare. We present a case of disseminated *Aspergillus fumigatus* infection with consecutive mitral valve endocarditis having developed 78 days after double-lung transplantation for cystic fibrosis. J Heart Lung Transplant 2005;24:2297-300. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Invasive aspergillosis is a serious complication after solid organ transplantation, with mortality approaching 100% in patients with disseminated disease.1,2 A recent review of invasive aspergillosis in solid organ recipients found the highest infection rate among lung recipients (8.4%).3 The diagnosis is frequently delayed or made post-mortem.

The increased risk for lung transplant recipients compared with other solid organ transplant recipients may be explained by both host and environmental factors. The lung is the most common site for invasive aspergillosis, and from the lung, it may disseminate to other organs. *Aspergillus* endocarditis, though, remains very rare. This report describes a case of mitral valve endocarditis as the first clinical manifestation of disseminated aspergillosis observed after double-lung transplantation for cystic fibrosis.

**CASE REPORT**

A 28-year-old woman underwent double-lung transplantation for cystic fibrosis. The patient and her donor were seropositive for antibodies to cytomegalovirus (CMV) at the time of transplantation. One year before transplantation, no fungal colonies were cultured from sputum or bronchioalveolar lavage (BAL). Post-transplant immunosuppression consisted of cyclosporine (to maintain whole blood levels of 250–300 ng/dl in the first 2 months and then 150–200 ng/dl), mycophenolate (3 g/day), and prednisone (0.5 mg/kg daily, tapering to 10 mg/day after 1 month). CMV prophylaxis was with valganciclovir (450 mg/day), and fungal infection prophylaxis with itraconazole (200 mg/day). For *Pneumocystis jiroveci* prophylaxis, the patient received co-trimoxazole (1.92 g twice weekly).

During the post-operative period, routine bronchoscopic examinations with transbronchial biopsy and BAL were performed. There was no evidence of rejection or tracheobronchial disease. No fungal colonies were cultured from BAL.

The patient was discharged from the hospital 47 days after transplantation without any complications during the post-operative period.

One month later, the patient was readmitted to our hospital with lip infection and reversible paralysis of the left body. From a computed tomography (CT) scan of the brain, a basal ganglia stroke in a small area on the right side was diagnosed (Figure 1). Transthoracic echocardiography did not show any source of embolization. The reason for the stroke could not be clarified at that time. Routine bronchoscopy with BAL demonstrated no evidence of infection or visible tracheobronchial disease.

After 2 weeks of hospital stay, the patient showed signs of cardiac failure. After intubation, a transesophageal echocardiography (TEE) was performed, which revealed a 20 mm × 9 mm posterior mitral valve leaflet vegetation with severe regurgitation (Figure 2). No clinical signs of infection were seen, and the chest X-ray was normal. In laboratory data, only the C-reactive protein value (7.8 mg/dl) was out of range. The results
Figure 1. A computed tomography scan shows a basal ganglia stroke (arrow).

of 2 sets of blood cultures obtained on admission were negative.

Mitral valve surgery was performed, and the patient underwent mechanical mitral valve replacement. Large perforations of both mitral valve leaflets were found. The excised mitral valve leaflets were sent for microbiologic and histopathologic examination.

One day after the operation, the patient was extubated and moved to our intermediate care unit. The microbiologic and histopathologic examination of the excised mitral valve leaflets showed colonies of Aspergillus fumigatus. Therefore, we started an intravenous anti-fungal therapy with caspofungin (50 mg/day). BAL fluid and sputum cultures failed to reveal any evidence of Aspergillus. The peripheral blood culture was also negative. A chest X-ray and CT scan showed interstitial infiltrations of both lungs, but these findings were not typical for an Aspergillus infection.

A few days later, the patient developed headache and a sudden blurred vision of both eyes. A bedside ocular examination showed massive retinal white infiltration of both eyes. A clinical diagnosis of Aspergillus endophthalmitis was made.

After 3 days of systemic anti-fungal therapy, the patient lost consciousness and had to be intubated. A brain CT scan showed multiple stroke and hemorrhagic areas. These findings were attributed to a brain fungal dissemination. Despite maximal support therapy, the patient died 78 days after bilateral lung transplantation.

DISCUSSION

Fungal infection remains a significant cause of post-operative morbidity and mortality after lung transplantation. Most fungal infections in lung transplant recipients involve Aspergillus species. The reported incidence of Aspergillus isolation after lung transplantation is 22% to 48%. It is controversial as to whether patients who are colonized before transplantation are at higher risk after transplantation for Aspergillus infections. Patients are pre-disposed to this through immunosuppression and the organism having direct access to the allograft.

The portal of entry for the Aspergillus is usually the respiratory tract, and from the lung it can disseminate to the other organs with a predilection of the central nervous system. The diagnosis of invasive aspergillosis is frequently delayed or made post-mortem, with mortality approaching 100% in patients with disseminated disease.

Endocarditis is among the unusual presentations of Aspergillus infections. There is 1 other previous report of lung transplant recipient who presented with Aspergillus mitral valve endocarditis. In this case, the disseminated Aspergillus infection diagnosis was made before the endocarditis had developed. The patient chose palliative care over aggressive medical or surgical intervention and died after discharge.

In our report, Aspergillus mitral valve endocarditis occurred 78 days after lung transplantation. It was the first evidence of any fungal infection. The basal ganglia small stroke area diagnosed after the second admission to our hospital may have been the first clinical manifestation of the invasive aspergillosis, but the diagnosis could not be clarified at that time.

In this case, we lost 2 weeks between the transthoracic echocardiography, where no pathologic findings on the mitral valve were seen, and the TEE, where the

Figure 2. A transesophageal echocardiogram shows posterior mitral valve leaflet vegetation with severe regurgitation.
itraconazole concentrations of more than 250 ng/ml could be rich in 50% of cystic fibrosis patients older than 16 years.

Acute invasive aspergillosis is a rapidly progressive infection, and its outcome is determined early in the course of therapy. Herbrecht et al13 found that initial therapy with voriconazole led to better responses and improved survival compared with amphotericin B therapy. Koss et al10 described a patient with amphotericin B-resistant aspergillosis successfully treated with caspofungin. Caspofungin also improved survival and reduced pulmonary injury in experimental pulmonary aspergillosis in persistently neutropenic rabbits.17 We chose to initiate caspofungin treatment in our patient.

One might be speculating that itraconazole prophylaxis was unsuccessful in eradicating the fungus before invasion. It remains to be demonstrated whether more effective post-transplant prophylaxis directed against Aspergillus fumigatus may decrease the incidence of serious Aspergillus infections in lung transplant recipients. Therefore, fungal infections should be considered in transplant recipients who display any signs of neurologic deficits. Furthermore, this case report shows that negative findings in bronchoscopy and BAL do not exclude the possibility of Aspergillus infection.

REFERENCES


