Native Valve *Aspergillus* Endocarditis Complicating Lung Transplantation

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We present 2 cases of *Aspergillus* endocarditis occurring in lung transplant recipients, both of whom were treated with early surgical intervention and triazole anti-fungal agents. Neither had evidence of airway colonization/infection with *Aspergillus* post-transplant, suggesting hematogenous spread of fungi at the time of surgery as a possible mechanism of infection. One case was successfully treated and discharged from the hospital, but, despite initial recovery, death occurred 10 months later due to a recurrence of *Aspergillus* endocarditis. *Aspergillus* endocarditis should be considered a relapsing disease and survivors of the condition should receive ongoing anti-fungal therapy. J Heart Lung Transplant 2008;27:910–3. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Fungal infections, particularly those involving *Aspergillus* sp, are a frequent cause of morbidity and mortality after solid-organ transplantation. Lung transplant recipients especially are at increased risk of fungal disease, with *Aspergillus* infection occurring in 6.2% to 31% of these patients.1–5 The most common manifestations of *Aspergillus* infection are tracheobronchitis, bronchial anastomotic infection and invasive pulmonary aspergillosis.5 Mortality from tissue-invasive *Aspergillus* infection exceeds 60%.4 Native valve, fungal endocarditis is an infrequent but lethal manifestation of disseminated *Aspergillus* disease.5,6

**CASE 1**

A 19-year-old woman underwent bilateral sequential lung transplantation for cystic fibrosis (CF), complicated by allergic bronchopulmonary aspergillosis (ABPA). Surgery was performed on cardiopulmonary bypass. Induction of immunosuppression consisted of pre-operative cyclosporine (Neoral; Novartis) 4.5 mg/kg orally and azathioprine 6 mg/kg orally. The doses given reflect the patient’s known malabsorption due to having CF. Peri-operatively, 1 g of intravenous methylprednisolone was administered. Maintenance immunosuppression included cyclosporine, azathioprine and prednisolone. Anti-microbial prophylaxis after transplant consisted of 10 days of intravenous gentamycin, ceftazidime and teicoplanin (Targocid; Aventis). Pre-transplant the patient was taking itraconazole (Sporonox; Janssen-Cilag). Post-transplant nebulized amphotericin (Fungizone; Squibb) was given for 3 months together with itraconazole. Multiple sputum and bronchoalveolar lavage specimens were negative for fungi. Pathologic assessment of the explanted lungs disclosed a previously undiagnosed left upper lobe aspergilloma.

Five months post-operatively an episode of acute rejection (Grade A2) was treated with three daily doses of intravenous methylprednisolone followed by a tapering course of oral prednisolone. Nine months post-operatively the patient was re-admitted with a fall in forced expiratory volume in 1 second (FEV1), a new diastolic murmur, ankle swelling and bilateral pleural effusions. She was afebrile but had a raised C-reactive protein (CRP). Multiple blood and sputum cultures were negative for both fungi and bacteria. A transthoracic echocardiogram (TTE) demonstrated minimal aortic regurgitation but no vegetations. Night sweats developed and CRP remained elevated despite broad-spectrum antibacterial treatment. A repeat TTE 2 weeks later demonstrated an aortic valve vegetation. Urgent surgery was undertaken. At operation, multiple vegetations on the aortic valve and a large aortic root abscess were found. The aortic valve was replaced with a tissue homograft. *Aspergillus fumigatus*, sensitive to both itraconazole and voriconazole, was cultured from the vegetations and abscess. Intravenous voriconazole (Vfend; Pfizer) was administered for 6 weeks.

The patient remained well until 18 months post-transplant when symptoms of malaise, nausea and loss of appetite developed. There were no fevers, spirometry was stable, and inflammatory markers were normal. Clinical examination was unremarkable. A transesophageal echocardiogram (TOE) showed mild regurgitation.
through the prosthetic aortic valve but no vegetations. Multiple blood cultures were negative for both bacteria and fungi. Empirical treatment with caspofungin (Cancidas; MSD) was commenced. Twice-weekly TOEs consistently demonstrated aortic incompetence but no valve lesions or abscess. Five weeks after admission acute pulmonary edema developed. Emergency aortic valve replacement was undertaken. At operation, an aortic root abscess and multiple vegetations on the replacement aortic valve were found; these subsequently cultured *Aspergillus fumigatus*. Post-operatively the patient remained septic and hypotensive. Three days after surgery she suffered cardiac arrest and died. Galactomannan antigen was negative throughout the illness. Post-mortem examination did not demonstrate any evidence of extra-cardiac *Aspergillus* infection.

**CASE 2**

A 24-year-old woman underwent bilateral lung transplantation for CF, complicated by ABPA and a left apical aspergilloma. Transplantation was performed on cardiopulmonary bypass. Intra-operative red cell salvage was utilized so as to minimize transfusion requirements. Induction and maintenance of immunosuppression followed the regimen outlined in Case 1. Anti-staphylococcal and anti-pseudomonal antibiotics were administered intravenously for 10 days post-operatively. Nebulized amphotericin and oral itraconazole were administered pre-lung transplantation and continued for 6 weeks post-operatively. Post-transplant sputum samples were consistently negative for fungi on microscopy and culture.

Eleven weeks after transplantation the patient developed a painful, red right eye with reduced visual acuity. Ophthalmologic assessment disclosed endophthalmitis (later confirmed to be due to *Aspergillus fumigatus*). Treatment with intra-ocular vancomycin, amikacin and amphotericin as well as intravenous voriconazole, septrin and ciprofloxacin was commenced empirically. Over the next 12 hours progressive dyspnea developed. Examination revealed a new pan-systolic murmur. TTE demonstrated a 1.8 × 1.3-cm mass on the anterior mitral valve leaflet associated with severe mitral regurgitation (Figure 1a and b). At emergency surgery, vegetations were found to be destroying the anterior mitral valve leaflet and extending into the outflow tract of the left ventricle (Figure 2). The mitral valve was repaired with a pericardial patch. *Aspergillus fumigatus* was cultured from the vegetations.

Post-operative treatment was maintained with intravenous voriconazole. Initial response to treatment was good, but 5 days post-operatively the patient developed acute abdominal pain. Emergency laparotomy demonstrated extensive bowel infarction. The patient died later that day after cardiovascular collapse due to sepsis. Post-mortem assessment confirmed mesenteric infarction secondary to a mycotic embolus. There was no evidence of residual fungal disease in the thoracic cavity.

**Figure 1.** (a) Long-axis views from a transthoracic echocardiogram of Case 2, demonstrating a large vegetation adherent to the anterior mitral valve leaflet. (b) Color-flow Doppler image of Case 2 demonstrating severe regurgitation through the mitral valve.

**Figure 2.** Intra-operative photograph of Case 2 demonstrating a large aspergilloma located on the anterior mitral valve leaflet.
or heart and no sign of *Aspergillus* within the transplanted lungs. Galactomannan antigen was negative throughout the illness.

**DISCUSSION**

In the non-transplant population fungal endocarditis is unusual, accounting for only 1.3% to 6% of all cases of endocarditis. Aspergillus sp account for only 20% of these infections. Fourteen previous cases of *Aspergillus* endocarditis occurring in non-cardiac, solid-organ transplant recipients have been reported in the literature. Of these patients, 10 were diagnosed post-mortem and 3 died shortly after valve replacement surgery. Three of the reported cases occurred in lung transplant recipients. Two of these patients were transplanted for CF and neither was identified to have pre-existing fungal disease. The first of these patients was diagnosed with mitral endocarditis 20 months post-transplant and received palliative treatment only. The second patient developed mitral endocarditis diagnosed 78 days post-transplant. The patient died from disseminated aspergillosis 3 days after undergoing mitral valve replacement and having received 48 hours of treatment with caspofungin. The third reported patient, a 57-year-old man, underwent bilateral lung transplantation for pulmonary fibrosis complicated by bilateral aspergillomas and post-transplantation by *Aspergillus* empyema. He underwent mitral valve replacement with a Carpentier–Edwards valve and received 6 weeks of treatment with intravenous amphoterin and caspofungin. The patient remained alive at 3 months after diagnosis.

*Aspergillus* endocarditis is often difficult to diagnose. As in our cases, patients may have non-specific symptoms and signs. Blood cultures are frequently negative. Embolic infection, such as the *Aspergillus* endophthalmitis seen in our second case, may be the primary manifestation of valvular disease and should prompt further detailed cardiac investigation. Similarly, mycotic emboli, resulting in ischemic phenomena, are a frequent manifestation of *Aspergillus* endocarditis. In one series of *Aspergillus* endocarditis in non-transplant patients, embolism affected 61% of the patients. At the time of disease relapse our first case underwent multiple TOEs. Despite a high index of clinical suspicion we were unable to identify vegetations until 5 weeks into the illness. This case suggests that for patients in whom a high likelihood of fungal endocarditis exists, the absence of visible vegetations on TOE, particularly in the presence of valvular incompetence, cannot exclude early disease. Serial measurements of serum galactomannan were similarly unhelpful in these cases.

Both cases presented herein had CF, had been chronically colonized with *Aspergillus* prior to transplant, and had pulmonary aspergillomas. Retrospective, single-center analyses suggest that both nebulized amphoterin B and oral itraconazole can reduce the incidence of *Aspergillus* infection in lung transplant recipients. Eighty-six percent of U.S. transplant centers give pre-transplant anti-fungal agents, usually itraconazole, to patients culturing *Aspergillus*. Post-transplant, 76% of centers give prophylactic anti-fungal agents, most commonly nebulized amphoterin. In both of our cases, itraconazole was administered prior to transplantation and continued, in combination with nebulized amphoterin, after transplantation. *Aspergillus* endocarditis developed despite prophylaxis. Perhaps surprisingly, we did not find evidence (either pre- or post-mortem) of *Aspergillus* colonization or infection in the transplanted lungs in either case. This suggests that hematogenous dissemination of *Aspergillus* may have occurred at the time of transplantation. Thus, patients known to be colonized with *Aspergillus* prior to transplantation may benefit from prophylactic intra-operative treatment with either caspofungin or voriconazole at the time of transplant surgery.

*Aspergillus* endocarditis is difficult to treat and carries a mortality of >50%, even in immunocompetent patients. Furthermore, it is a condition that may relapse; of 36 successfully treated patients in one series, 5 later suffered disease recurrence. Because of the risk of emboli and because drug penetration of vegetations is poor, we favored an early surgical approach. As Case 1 has demonstrated, voriconazole, after initial surgical debridement, is an effective therapy for *Aspergillus fumigatus* endocarditis. The echinocandin, caspofungin, is an alternative to voriconazole for the treatment of invasive *Aspergillus* disease. Caspofungin was used to treat the recurrence of *Aspergillus* infection in Case 1, because, in the absence of culture results, we were concerned about the possibility of voriconazole resistance. Given that our patient relapsed 10 months after initial successful treatment, and in view of the frequency of relapse of fungal endocarditis in non-transplant patients, we now suggest long-term anti-fungal therapy in survivors of fungal endocarditis.

In conclusion, native valve *Aspergillus* endocarditis is a rare but devastating complication of solid-organ transplantation. Many lung transplant recipients are colonized with *Aspergillus* prior to transplant. Careful attention needs to be paid to prophylaxis with anti-fungal agents in these individuals. The absence of fungal colonization or infection in the transplanted lungs of either of the cases we report here suggests that *Aspergillus* may have spread hematogenously to the heart valves at the time of transplant surgery. The initial success of a combination of early surgery and intravenous voriconazole in one of our patients demonstrates that effective treatment of *Aspergillus* endocarditis is possible. However, the unfortunate relapse and death...
of this same patient with a recurrence of Aspergillus endocarditis suggests that lifelong anti-fungal treatment for survivors of this disease should be mandatory.

REFERENCES