Late *Aspergillus fumigatus* Endomyocarditis With Brain Abscess As a Lethal Complication After Heart Transplantation

Florian Rueter, MD, a Hans H. Hirsch, MD, MSc, b Franziska Kunz, MD, c Peter Buser, MD, d James M. Habicht, MD, a Holger Moch, MD, c Ursula Fluckiger, MD, b and Hans-Reinhard Zerkowski, MD a

We report the case of a 65-year-old male patient who died from lethal *Aspergillus fumigatus* endomyocarditis and multiple cerebral septic emboli 6 months after cardiac transplantation. This complication developed 4 weeks after diagnosis of bilateral pulmonary aspergillosis, which was immediately treated by surgical removal and intravenous amphotericin B. Preceding colonization with *Aspergillus* spp was not identified. Primary cytomegalovirus infection (donor+/recipient−) and toxoplasmosis reactivation (donor−/recipient+) occurring at 1 and 2 months post-transplantation were successfully treated. J Heart Lung Transplant 2002;21:1242–1245.

Infections remain a leading cause of morbidity and mortality after organ transplantation.1 Bacterial pathogens are typically encountered in the first month followed by infections with cytomegalovirus (CMV), *Pneumocystis carinii*, toxoplasmosis or fungi.2 The diagnostic procedures for CMV and toxoplasmosis are well defined and in part anticipated by serologic pre-transplant screening of donor and recipient. In contrast, invasive fungal infections such as aspergillosis are of insidious onset. Consequently, diagnosis and treatment of invasive aspergillosis often occur at a stage of significant organ involvement.3,4

CASE REPORT

A 65-year-old male patient suffering from severe ischemic cardiomyopathy after multiple myocardial infarctions (clinical status New York Heart Association [NYHA] Grade IV) underwent orthotopic heart transplantation. The donor was a 57-year-old man without known cardiac disease who died from spontaneous intracerebral hemorrhage. Left ventricular hypertrophy was the only finding upon echocardiographic and coronary angiographic investigation.

The initial immunosuppressive regimen consisted of an intravenous bolus of 1 g methylprednisolone given intra-operatively followed by three courses anti-thymocyte globulin (5 mg/kg body weight) from Days 1 to 3. Oral prednisolone was started at a dose of 30 mg on Day 5 and tapered until Day 11. Maintenance immunosuppression consisted of cyclosporine (target blood trough level 200 to 250 ng/ml; Abbott TDX) and azathioprine (target leukocyte count 3 to 6 × 10⁹/liter). Anti-herpesvirus prophylaxis consisted of oral acyclovir (4 × 400 mg/day, adjusted for renal function). Because of CMV mismatch (donor seropositive, recipient seronegative), six doses of CMV-specific human immunoglobulin were administered. Ganciclovir prophylaxis was not given because of moderately impaired renal function.
Endomyocardial biopsy on Day 15 showed histologic evidence of International Society for Heart and Lung Transplantation (ISHLT) Grade IIIa rejection, which was treated with intravenous methylprednisolone (1 g daily) for 3 days. On Day 21, sepsis was diagnosed with Enterobacter cloacae detected in blood cultures and urine, which was successfully treated with intravenous meropenem for 14 days. On Day 27, the patient was again febrile (39.4°C) and confused. Biopsy revealed resolving rejection to ISHLT Grade I, but intramyocardial Toxoplasma pseudocysts were found. Toxoplasma gondii DNA could be detected in the peripheral blood by polymerase chain reaction. Bacterial cultures and CMV antigenemia were negative at this point. Treatment for toxoplasmosis was initiated (pyrimethamine 75 mg/day and sulfadiazine 4000 mg/day) for 6 weeks before switching to secondary prophylaxis. An increase in Toxoplasma gondii-specific IgG from 4 IU/ml (high avidity) to over 10,000 IU/ml and the appearance of IgM was observed within 7 days. The patient improved and was transferred to the normal ward.

On Day 48, primary CMV infection was diagnosed by CMV pp65 antigenemia (41 positive cells per 250,000 leukocytes) without evidence of CMV disease. Pre-emptive therapy with intravenous ganciclovir was given for 4 weeks (5 mg/kg twice daily). CMV antigenemia returned to levels below 5 per 250,000 leukocytes after an initial increase to 146 in the first week of treatment. Ganciclovir was stopped after 4 weeks. A rebound antigenemia to a maximum of 19 per 250,000 leukocytes resolved spontaneously. CMV-specific IgM and IgG were first detected after 10 weeks (Day 117).

Three months after transplantation the patient was referred for rehabilitation. Echocardiography showed only slightly reduced left ventricular function. Maintenance immunosuppression consisted of cyclosporine (target blood trough level 180 to 200 ng/ml) and azathioprine (2 mg/kg per day). He was re-admitted on Day 198 with fever (38.5°C), tachyypnea and dry cough. The clinical examination revealed no pathologic findings of the heart and lungs. The leukocyte count was 4.4 × 10⁹/liter with 90% neutrophils, a thrombocytopenia of 60 × 10⁹/liter. The C-reactive protein measured 245 mg/liter. Empiric antibiotic treatment with tazobactam–piperacillin was started after blood cultures were drawn. Echocardiography findings were unremarkable. Thoracic computed tomography (CT) scans showed two pulmonary masses of 2-cm diameter in the left upper and the right middle lobe that strongly suggested invasive aspergillosis.

Bronchoscopy revealed an intra-bronchial mass at the orifice of the left upper bronchus. Intravenous liposomal amphotericin B was started and the affected lobes were resected by bilateral thoracotomy. Histologically, multiple dichotomous mycelia were found (Figure 1). Aspergillus fumigatus was identified by culture. Complex cognitive deficits and motoric tetraparesis became apparent. Cerebral CT scans showed multiple areas compatible with ischemic lesions. Repeat cerebral CT scans were performed after 2 weeks, which revealed multiple hypodense lesions compatible with abscess formations. The patient died on Day 205 post-transplantation. On autopsy, an ulcerato-thrombotic fungal vegetation of 3-cm diameter was identified on the posterior leaflet of the mitral valve (Figure 2A). The vegetation infiltrated the atrial wall, the anterior papillary muscle and the left ventricular anterior wall, consistent with endo-/myocarditis (Figure 2B). No residual aspergillosis was found in the lung. Multiple septic–embolic abscesses were found in the brain, revealing invasive Aspergillus hyphae (Figure 2C).

**DISCUSSION**

Invasive aspergillosis represents one of the most severe complications after organ transplantation, which is hardly altered by anti-fungal treatment. Pulmonary aspergillosis is associated with a mean mortality rate of around 50% (range 11% to 78%) in heart transplantation. The mortality rate is highest with cerebral aspergillosis (mean of 99%, range 86% to 100%), irrespective of the underlying condition. Aggressive diagnostic and therapeutic approaches
are indicated when suggestive lesions are found in a patient at risk.5–7 In our patient, intravenous amphotericin B was administered and both lesions were removed by bilateral open lung surgery within 24 hours as a diagnostic and therapeutic procedure.

The poor clinical outcome was not determined by pulmonary aspergillosis, but rather by endomyocarditis and subsequent septic–embolic abscesses in the brain. Although Aspergillus spp have a known propensity to invade blood vessels, the large fungal endomyocardial vegetation found on autopsy was unexpected (Figure 2A). The vegetation was not present in the echocardiography performed before the surgical resection of the affected pulmonary lobes and the patient was under continuous intravenous anti-fungal medication. In vitro testing of the isolated Aspergillus fumigatus cultures indicated no resistance (minimal inhibitory concentration 0.5 mg/liter). However, intravenous amphotericin B may not be sufficient to treat established fungal foci. Together, the data suggest that the endomyocardial seeding had already taken place at the time of diagnosis of pulmonary aspergillosis, but that the lesion was too small to be detected by echocardiography. Surgical removal including valve replacement is the treatment of choice for Aspergillus endomyocarditis but would not have been possible in our patient in his poor clinical condition.

The major risk factor for invasive aspergillosis in organ transplant recipients is respiratory exposure and colonization. Aspergillus spores are ubiquitous and often set free in large amounts by building reconstruction or gardening. Most infections occur within 1 to 3 months post-transplantation.2,8 Screening for galactomannan or Aspergillus-specific nucleic acids has been suggested.8 In our patient, there was no evidence of prior colonization. However, negative results do not exclude infection upon later exposure post-transplantation. We suspect that this scenario most likely explains the insidious and late onset in our patient at >6 months post-transplantation.

Early reactivation of Toxoplasma gondii at Week 3 post-transplantation was diagnosed by myocardial biopsy and by polymerase chain reaction in the peripheral blood.9 Consistent with mounting a memory response, rising IgG and IgM titers were noted in <7 days. In contrast, primary CMV infection treated pre-emptively with intravenous ganciclovir required >10 weeks for mounting an IgG and IgM response in this immunosuppressed patient. When ganciclovir was stopped after 28 days, a transient rebound CMV antigenemia to <50 infected cells per 250,000 leukocytes resolved spontaneously, indicating some degree of immunologic control. However, the frequent association of CMV infection with invasive aspergillosis has been inter-

FIGURE 2  Aspergillus fumigatus endomyocarditis in the transplanted heart. (A) Large polyp on the mitral valve and anterior papillary muscle. (B) Aspergillus hyphae infiltrating the heart muscle (Grocott stain; original magnification ×200). (C) Cerebral aspergillosis in septic infarctions (original magnification ×4).
interpreted as CMV being a risk factor for invasive fungal disease.²

In conclusion, this case represents a sequence of all classes of infectious disease complications following organ transplantation. Whereas the bacterial, viral and protozoan infections can be diagnosed and treated successfully, the respective armamentarium seems insufficient with respect to fungal infections, especially when occurring late after transplantation. Although an aggressive and prompt approach is paramount for optimal management of invasive pulmonary aspergillosis, our case shows that the success can be jeopardized by unsuspected secondary complications of high mortality such as endomyocarditis and embolic cerebral abscess.

REFERENCES