Successful Treatment of Invasive Pulmonary Aspergillosis in Heart Transplantation

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ALTHOUGH posttransplantation immunosuppressive regimen has greatly improved, infection remains one of the leading causes of death in heart transplant recipients. Fungal infections are extremely serious because they are often disseminated at the time of diagnosis and respond poorly to conventional antifungal therapy. Pulmonary aspergillosis in heart transplant recipients often culminates in death despite aggressive treatment. Optimal management of this difficult problem remains undefined. We report a successfully treated invasive pulmonary aspergillosis in a cardiac transplant patient.

CASE REPORT

This 37-year-old male patient received heart transplantation for dilated cardiomyopathy with heart failure on November 24, 1992. After transplantation, triple therapy with cyclosporine (CyA) 200 mg/d, azathioprine 100 mg/d, and prednisolone 80 mg/d was given to prevent rejection successfully. Oral ketoconazole 200 mg/d and nystatin gargles were prescribed to prevent fungal infection. Pulmonary lesion (Fig 1) was first detected on routine chest radiological examination on 17th postoperative day (POD). Fungal cultures of blood and sputum were negative. Vital signs were stable with normal body temperature. On 21st POD, because of a rapid progressing 3 x 4 cm ill-defined hypoechoic heterogeneous lesion with central cavitation, echo-guide aspiration was performed and revealed Aspergillus infection (Fig 2A). Steroids and ketoconazole were discontinued, and amphotericin B (AmB) was given with rapid escalation of the daily dose to 1 mg/kg per day within 2 days. The dose of azathioprine was reduced to 50 mg/d, and CyA was reduced to keep the Abbott monoclonal whole blood CyA level around 250 ng/mL. Because the pulmonary nodules kept on growing rapidly (from nearly invisible small nodule to about 8 cm in diameter in 10 days) (Fig 3A), and because the patient began to suffer from systemic symptoms such as fever, cough, and general malaise, surgical intervention was decided, although chest computed tomography (Fig 3B) revealed another 2-cm nodule lesion in right middle lobe and suspicious lesions in the left lung in addition to the large nodule in the lower lobe.

After right posterolateral thoracotomy, wedge resection of the 2-cm nodule in the right middle lobe and cavernotomy with irrigation and drainage of another 8-cm nodule in the right lower lobe were performed on 28th POD. The cavity was irrigated with AmB solution and aqueous povidone-iodine solution thoroughly and then drained with chest tubes. The pathology of the small nodule showed an abscess containing Aspergillus. The content in the large nodule was aspirated and sent for fungal culture, which revealed Aspergillus infection. Surgical treatment was completed successfully. The patient was discharged from hospital with a normal chest x-ray on 77th POD, and he is now doing well 30 months after transplantation.

Fig 1. Chest x-ray revealed rapidly growing nodular lesion in the right lower lung field. (A) Nodule first detected on 17th posttransplant day. (B) Nodule with cavitation, 9 days later.
showed aspergillosis evidenced by septate branching hyphae with suppurative inflammation and foreign-body reaction (Fig 2B). The tissue around the large nodule also revealed cytomegalovirus. The chest tubes were removed within 1 week. Patient was kept on AmB infusion with a dose between 0.5 and 1.0 mg/kg per day until nephrotoxicity occurred at total dose of 1.5 g. The patient was then shifted to oral ketoconazole 200 mg/d. He was discharged in good condition and returned to work. Full resolution of the radiologic patch occurred 6 months after thoracotomy drainage. During the past year of outpatient follow-up, the chest lesion completely disappeared and patient was well without recurrence.

DISCUSSION

Pulmonary aspergillosis is a frequent complication in immunosuppressed high-risk patients, with liver transplant recipients and patients with hematological malignancies being at significantly greater risk of acquiring aspergillosis.
than others. Irrespective of current treatment, the mortality is very high, exceeding 94% in bone marrow transplant, and 100% in liver transplant. Delay of treatment beyond 2 weeks may be uniformly fatal. However, Aspergillus remains difficult to diagnose early. The characteristic rounded infiltrates on chest roentgenogram are not specific for aspergillosis, but should arouse the suspicion of aspergillosis. Rapid progression of the nodular lesion is another characteristic. Sputum or blood cultures may be negative for Aspergillus despite established infection like our case, but positive Aspergillus culture could frequently be obtained by multiple sputum culture. Echo-guide aspiration is an effective and safe method to establish the diagnosis. Our experience and that of others suggests that isolation of pulmonary Aspergillus from immunologically compromised patients must be considered as an indication for percutaneous lung aspiration, transbronchial aspiration, or even open lung biopsy to confirm the diagnosis.

Successful treatment with liposomal AmB was reported in one patient with mild pulmonary Aspergillus infiltrate.
lesion after heart transplantation.\textsuperscript{10} In our case, wedge resection of one small nodule and cavernostomy and drainage of another large nodule were performed in addition to AmB administration. At present, AmB is still the mainstay of therapy for invasive pulmonary aspergillosis.\textsuperscript{4,11} Pulmonary aspergillosis represents a serious infection because it is difficult to eradicate and requires high doses of AmB and also because immunosuppressive therapy often cannot be altered for fear of allograft rejection. Rapid progression of the pulmonary lesions in our case was noted despite AmB infusion. To control the dissemination, surgical intervention was performed. Wedge resection of the small nodule and cavernostomy with chest tube drainage were performed. Because the patient was in critically ill condition, the surgical procedure should be performed carefully with minimal surgical manipulation. As recommended in other transplantations,\textsuperscript{5,12} we also recommend aggressive operative treatment of fungal lesions with minimal destruction of the lungs combined with effective antifungal chemotherapy in heart transplantation.

Prevention of fungal infection with antifungal chemotherapy alone is not always successful, just like this case. Nystatin is not well absorbed from the gastrointestinal tract, and therefore does not protect the airway. Ketoconazole is not effective against *Aspergillus*. In fact, ketoconazole has an antagonist effect on the antifungal activity of AmB\textsuperscript{13} and should not be used during AmB treatment. Yet itraconazole, a drug related to ketoconazole, has been reported to be effective in treating aspergillosis.\textsuperscript{5,14,16} In our case itraconazole was used when the patient suffered AmB-induced nephrotoxicity. The pulmonary nodule disappeared completely 6 months after surgery under itraconazole treatment.

In patients after heart transplantation, invasive pulmonary aspergillosis can be treated successfully with AmB, itraconazole, and adequate drainage without lobectomy or pneumonectomy.

REFERENCES