Successful Treatment of Invasive Aspergillosis in a Heart Transplant Patient


Infection continues to be a major cause of mortality in cardiac transplant patients, and even though there has been significant progress in diagnosing and treating many infectious disease problems, invasive aspergillosis in the transplant patient represents a serious and usually fatal complication. Even with successful early diagnosis, the use of free amphotericin B (a polyene antibiotic) has failed to cure disseminated infection. We report the case of a 46-year-old transplant patient who failed to respond to treatment with free amphotericin B after a 7-day period of treatment for biopsy-proven pulmonary aspergillosis. However, a subsequent substitution of a liposomal form of amphotericin B was used, and the patient responded well to a total dose of 1.5 mg. After 7 months, the patient continues free of infection. This experience suggests that the introduction of liposomal amphotericin B may give new hope for treating an otherwise lethal infection.

Infection is still a common cause of death after heart transplantation; also, there is a correlation between the increased use of corticosteroids in the treatment of acute episodes of rejection and infection caused by opportunistic pathogens. During recent years, cyclosporin A has become a more specific immunosuppressive agent, decreasing the overall rate of infection and rejection episodes, and generally extending survival time.

Pneumocystis carinii pulmonary infections continue to be the most commonly encountered during the post-transplant period. Because this infection is frequently anticipated, and the appropriate biopsy procedures can be performed to identify the pathogen, treatment may be instituted immediately, decreasing the mortality rate markedly. In contrast, however, pulmonary infection caused by Aspergillus species has continued to become more common, causing an increased mortality rate in patients with this infection.

CASE REPORT

A 46-year-old man underwent orthotopic heart transplantation because of end-stage ischemic heart disease. During the early postoperative period, he was successfully treated for severe graft rejection. On the tenth postoperative day, he developed right-sided empyema, and a chest tube was inserted. A month later, we performed decortication and wedge resection of the right lower lobe, and the patient gradually improved. He was discharged 2 months after heart transplantation.
Fig. 1 The chest X ray shows extensive bilateral spheric infiltrates before treatment.

Fig. 2 Histopathologic findings of invasive aspergillosis are shown.
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The treatment was changed to cefuroxime plus amikacin because of deteriorating renal function; however, his condition remained the same. Subsequently, a lung biopsy was performed at bronchoscopy, and the diagnosis of invasive aspergillosis was established (Fig. 2). Treatment was started with free amphotericin B, 25 mg intravenously, but after a total of 125 mg, the patient was no longer able to tolerate this preparation because of decreasing renal function. Subsequently, 75 mg of liposomal amphotericin B was given daily until a total dose of 1.03 gm had been reached.

With the onset of treatment for aspergillosis, immunosuppressive therapy was reduced; after 15 days, a heart biopsy showed severe rejection, and treatment with Anti-Thymocyte Globulin (ATG) was begun. Although the treatment with ATG was necessary for rejection, the patient’s pulmonary function improved, and the liposomal amphotericin B therapy was stopped. A lung biopsy was performed by bronchoscopy 16 days after onset of treatment, and there was no evidence of infection.

Seven months later, there are no pathologic
DISCUSSION

Invasive aspergillosis is not uncommon in the various types of patients who receive immunosuppressive therapy, including heart, bone marrow, and renal transplant patients. The diagnosis of Aspergillus infection in the lung is not easy, because the pulmonary infiltration seen on chest X-ray is usually nonspecific, and frequently sputum cultures may be contaminated with Aspergillus during routine laboratory processing. There is general agreement, however, that the presence of Aspergillus species in multiple sputum cultures from the same patient is the most common reason for performing a lung biopsy. Controversy over the technique of lung biopsy continues, with biopsy during bronchoscopy, percutaneous needle aspiration, and open-lung biopsy used in various centers with different degrees of frequency. There is little question, however, that biopsy during bronchoscopy, transbronchial needle biopsy, and percutaneous needle aspiration are less useful than open-lung biopsy—often producing misleading results. The presence of Aspergillus species on a histopathologic section from a lung biopsy obtained in any manner is a significant finding and should alert the physician to the presence of pulmonary infection.

There are important factors that lead to a high rate of pulmonary infection in heart transplant patients. Our patient had been treated with high-dose steroids for graft rejection several weeks before the onset of pulmonary Aspergillus infection, and this was a major predisposing factor. The only effective agent previously known for treatment of pulmonary aspergillosis was amphotericin B. The intravenous use of high dosages has been recommended, and if a resectable lesion is identified, successful treatment may be achieved by using both amphotericin B and surgical resection. In addition, local instillation into cavities has also been done with mixed results. It is of interest that in our experience with the concomitant use of amphotericin B and cyclosporin A, we have noted early changes in renal function, which may limit the dosage and duration of amphotericin B. The recent use of an encapsulated form of amphotericin B into liposomes has been tested in animal models, and the evidence for both decreased toxicity and greater efficacy in the treatment of disseminated candida infections has been promising. In addition, it has been well documented that encapsulation of amphotericin B into the liposomes has enhanced delivery to the liver, spleen, lung, kidney, and brain. More recently, twelve patients with hematologic malignancies complicated by serious fungal infections, including Aspergillus species, received liposomal amphotericin B preparation. Although several patients with advanced infection were severely immunosuppressed and had minimal response—or failed to respond—three similar patients were in complete remission from their infection after the administration of liposomal amphotericin B. It is important to note that there were minimal or no changes in the hematologic and blood chemistry values related specifically to the use of this preparation.

There are still many unknown factors concerning liposomal amphotericin B, and the dosage necessary for effective treatment of infections is not yet well established. In the case of our patient, approximately 1 gm was effective in eradicating Aspergillus from his lung. We strongly believe that an early diagnosis based on an aggressive approach, with a biopsy, culture, and histopathologic staining of lung tissue, is extremely important and can lead to the treatment of serious infections. Although experience with liposomal amphotericin B is limited, successful treatment of a single invasive case of pulmonary aspergillosis is encouraging to us, and will lead to further evaluation of a potentially important antifungal agent.

REFERENCES


