Isolated Pulmonary Aspergillar Infection in Cardiac Transplant Recipients: Case Report and Review

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Aspergillar infections occur in 2%-28% of patients with solid organ transplants [1-5]. For those with CNS or disseminated disease, outcome has been fatal except in a few isolated cases [1-8]. The prognosis is better for cardiac and renal transplant recipients who have isolated pulmonary infection; in such cases, survival rates range from 28% to 82% [1, 2, 9, 10]. The optimal treatment and duration of therapy is not clear. The case of a cardiac transplant recipient with invasive pulmonary aspergillosis who had persistent disease despite therapy with >3 g of amphotericin B is presented.

A 58-year-old male underwent cardiac transplantation at the Department of Veteran’s Affairs Hospital, Salt Lake City, on 3 August 1990 for end-stage ischemic cardiomyopathy. His postoperative course was complicated by grade III rejection on 30 August 1990, for which he was treated with plasmapheresis and iv Solu-Medrol (Upjohn, Kalamazoo, MI), methotrexate, and Orthoclone OKT3 (Ortho Pharmaceutical, Raritan, NJ). On 14 September, cardiac biopsy showed improvement to grade II rejection. That evening he was febrile (temperatures to 101°F). He had a leukocyte count of 5.5 X 10^9/L, with 3% bands and 97% neutrophils; normal liver chemistries; and a creatinine concentration of 1.1 mg/dL. Oxygen saturation while he breathed room air was 95%. Therapy with vancomycin and gentamicin was begun empirically. The next morning (15 September), a chest radiograph revealed 4+ polymorphonuclear leukocytes but no organisms. Erythromycin was added to the treatment regimen. On 20 September, the lavage specimen yielded 1-2 cfu of Aspergillus fumigatus. A computed tomography-guided needle aspiration specimen of the lesion in the right lower lobe was grossly purulent. Gram staining revealed 4+ polymorphonuclear leukocytes but no organisms.

On 22 September the cultured aspirate yielded A. fumigatus. Administration of antibiotics was discontinued, and he started to receive 100 mg of amphotericin B daily (1 mg/kg). Use of cytoxan (Meud Johnson, Evansville, IN) was discontinued. His steroid dose was tapered. On 26 September a cardiac biopsy showed improvement to grade II rejection, but his chest radiograph showed that the right-lower-lobe infiltrate had increased in size (to 7 X 7 cm) and that an additional lesion (1½ X 1 cm) had formed in the left lower lobe. On 28 September therapy with the experimental immunosuppressant RS61443 (Syntex Laboratories, Palo Alto, CA), a lymphocyte and monocyte inhibitor, was begun. After he had received 2½ weeks of therapy with amphotericin B, his chest radiograph showed improvement.

He was discharged on 14 November and was receiving the following drugs: prednisone (15 mg daily), cyclosporine, azacyclovir, RS61443, trimethoprim-sulfamethoxazole, and amoxicillin. He received amphotericin B (100 mg iv weekly) for 5 weeks.

He was readmitted on 23 December because of catheter sepsis due to Pseudomonas aeruginosa. Use of amphotericin B was discontinued secondary to an increased creatinine concentration of 4.3 mg/dL (total dose received, 3,287 mg). Since the pulmonary lesion had decreased in size to a 3 X 2-cm right-lower-lobe nodule, wedge resection was performed on 22 January 1991. Pathology revealed a large necrotizing fungal abscess (figure 1). On 26 January the patient became hypotensive, with grade IV rejection. Despite treatment with plasmapheresis and antilymphocyte globulin, he died on 30 January 1991. At autopsy, death was felt to be secondary to rejection of the transplant. There was no evidence of persistent aspergillar infection.

Aspergillus is a frequent cause of infection in immunocompromised hosts, including solid organ transplant recipients [1-3]. Predisposing factors to aspergillar infection include immunosuppression, organ rejection, and concurrent infections, all of which were evidenced in our patient.
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Most reported cardiac and renal transplant recipients with CNS infections or diffuse pulmonary disease do not survive [1, 2, 6, 7]. However, isolated pulmonary disease, as that in our patient, is associated with a higher treatment success rate than are disseminated or CNS infections. Weiland et al. [1] described 25 renal transplant recipients infected with Aspergillus, 16 of whom received therapy with amphotericin B. Seventeen of these patients died; however, 8 of 11 patients with primary cavitary pulmonary disease survived, and 5 of the 8 retained viable grafts [1]. Likewise, among 5 of 18 cardiac transplant recipients at Stanford University (Stanford, CA), 2 patients with isolated pulmonary disease who were treated medically survived during long-term therapy [2].

The optimal therapy for aspergillic infection is not well defined. Amphotericin B remains the mainstay of therapy. However, treatment with other antifungal agents such as itraconazole and liposomal amphotericin B is under investigation [11-13]. Twenty-one patients with aspergillic infections were treated with itraconazole by Denning et al. [13]. Twelve of 15 evaluable patients responded well, but therapy failed for the two renal transplant recipients [13].

The optimal dosages for antifungal therapy are also not clear. Lower doses have been used with better success in transplant recipients than in neutropenic patients. In a review of 34 renal or cardiac transplant recipients with pulmonary aspergillosis, 10 of 26 successfully treated patients received <30 mg of amphotericin B each day. A higher percentage of those for whom therapy failed, however, received lower doses [10]. Our patient initially received amphotericin B at high daily dosages. Despite immunosuppression, improvement of his infection continued as the dosage was reduced to a weekly maintenance regimen. Burton et al. [9] reduced the use of amphotericin B to weekly maintenance dosages for two renal transplant recipients with pulmonary aspergillosis when clinical and radiographic improvement were seen after 6 weeks of daily therapy. The weekly therapy produced effective fungistatic levels and controlled the aspergillosis in both patients despite their immunosuppression [9]. Lower doses of amphotericin B are of particular importance to transplant recipients who are already receiving nephrotoxic agents such as cyclosporine.

Recommendations regarding the total dose of amphotericin B range from 1.5 to 4 g, depending upon the individual patient, radiographic evidence of resolution of lesions, and bone marrow recovery [10]. The rate of relapse of fungal pneumonia in patients with hematologic malignancies during neutropenia is high (75%) even after large doses of amphotericin B have been given [14]. It is not clear what length of therapy is necessary to treat transplant recipients with aspergillic infection who are receiving continual immunosuppressive therapy. With some solid organ transplant recipients, as with renal recipients, it is possible to reduce the immunosuppression, a reduction which would likely enhance the success rate [1, 8]. A reduction of immunosuppression in cardiac transplant patients, however, can be life-threatening, as evidenced in our patient.

Although our patient received >3 g of amphotericin B, hyphae were still seen in his lesion at surgery, suggesting the occurrence of suppression but not eradication. Surgical excision of an isolated lesion is a therapeutic option that may be curative. Shamberger et al. [15] performed surgical resection in four children with acute myelocytic leukemia and localized pulmonary fungal infections, two of which were secondary to aspergillic infection. All were cured except one patient who died 2 weeks postsurgery with a fungal brain abscess, a circumstance suggesting there may have been dissemination of infection before surgery [15]. In the review of Weiland et al., all three patients treated with excisional surgery and short courses of amphotericin B responded to therapy [1]. In our patient, there was no evidence of disseminated disease at autopsy, and earlier surgery may have diminished the need for continued therapy with amphotericin B.

In summary, isolated pulmonary disease due to Aspergillus may be less aggressive in solid organ transplant recipients than in other immunocompromised patients. Our patient had persistent but controlled disease despite long-term, high-dose amphotericin B therapy. In spite of immunosuppressive therapy, his lesion continued to decrease in size with a weekly maintenance regimen of amphotericin B after daily high-dose therapy brought about clinical and radiographic improvement. Despite administration of a large total dose of amphotericin, hyphae were present in the lesion removed at surgery, a fact suggesting that suppression occurred but not eradication. If a pulmonary lesion is too large to be resected, amphotericin B could be given until the lesion decreases in size. Although excisional surgery reportedly has been per-
formed in only a small number of patients, it may be curative in patients such as ours and is worthy of consideration.

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References