Aspergillus Osteomyelitis after Heart-Lung Transplantation

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Aspergillus osteomyelitis is a severe complication of invasive aspergillosis. Fewer than 15 cases have been observed after solid organ transplantation. We describe a case of Aspergillus osteomyelitis of the ilium after heart-lung transplantation with favorable outcome after medical treatment. J Heart Lung Transplant 1997;16:436-8.

fungi of the species Aspergillus are ubiquitous in nature and occasionally cause human disease. These infections, most commonly seen in immunocompromised hosts, usually involve the lungs, but they may disseminate. Bone and joint infections caused by Aspergillus are infrequent, and fewer than 15 cases have been observed after solid organ transplantation, whereas invasive pulmonary aspergillosis occurs in 6% to 16% of patients after heart or lung transplantation. We present a case of Aspergillus osteomyelitis of the ilium after heart-lung transplantation.

CASE REPORT

A 36-year-old woman, with a history of pubic osteosynthesis in 1989 for postparturient inflammation, underwent heart and lung transplantation because of primary pulmonary hypertension in May 1992. Two graft rejections occurred in the postoperative course — the last one in September 1993 — treated by OKT3 and corticosteroid infusions. Routinely performed mycologic examinations of bronchial secretions twice showed a single Aspergillus fumigatus colony, and no specific treatment was initiated. She was admitted in December 1993 for fever, pelvic pain, and multiple subcutaneous nodules mainly disseminated on the forearms, the thighs, and the back. Laboratory tests were notable for leukocytosis (white blood cell count: 10,400/mm³, with 90% polymorphonuclear leukocytes (PMN), erythrocyte sedimentation rate (ESR): 148 mm/hr, creatine phosphate: 71 mg/L). The x-ray film of the pelvis was normal. Bone scan and nuclear magnetic resonance imaging showed osteomyelitis of the right acetabulum and adjacent ilium (Figures 1 and 2). The cultures of a nodule obtained by punch biopsy and of bone obtained by trocar biopsy yielded Aspergillus fumigatus. Histologic examinations confirmed osteomyelitis with presence of fungal hyphae. No other organs were involved on cerebral, chest, and sinus computed tomographic scans. Mycologic examinations of bronchial secretions did not yield a pathogen. The serology by three different tests (passive hemagglutination, immunodiffusion, immunoelectrophoresis) was negative. After a 45-day course of amphotericin B (total dose: 2.2 gm) and a 20-day course of 5-flucytosine (total dose: 100 gm), followed by an 8-month course of itraconazole (400 mg/day), the subcutaneous nodules had completely disappeared and there was no osseous pain (magnetic resonance imaging and bone scan were not performed). The patient was considered in remission, although ESR was persistently increased and the dosage of itraconazole was decreased to half. Three months later, she returned with a right hip infectious arthritis. The x-ray film was normal. The ultrasonography confirmed the presence of a joint effusion. The mycologic analysis of the articular fluid obtained by puncture confirmed the Aspergillus fumigatus infection. The dosage of itraconazole was increased to 800 mg/day, allowing the sterilization of the joint, confirmed by a new puncture with aspiration. Five months later, the x-ray film
showed a condensation of the ilium and a narrowing of the superolateral hip joint space.

**DISCUSSION**

Osteomyelitis is a rare complication of *Aspergillus* infection, affecting principally immunocompromised hosts: acquired immunosuppression (steroid therapy, immunosuppressive drugs, leukopenia, cancers) or inborn immunosuppression (chronic granulomatous disease). Otherwise, it has been reported after surgical manipulation (prosthetic devices, diskectomy) or penetrating injuries. In our patient the role of pubic osteosynthesis in the development of ilium osteomyelitis was unclear. It may have been related to an infection induced at the time of the surgery 4 years previously and subsequently triggered by the immunosuppression. A possible explanation for this assumption would be the absence of pulmonary aspergillosis. The underlying physiopathologic mechanism could be hematogenous spread with subsequent development of aspergillosis on a loci of minor resistance (acetabulum and ileal abnormalities, as well as pubic symphysis abnormalities). According to a review by Tack et al. fungal osteomyelitis represents a severe event in immunosuppressed patients. Nine of ten immunosuppressed patients died, whereas no deaths were reported in the nine immunocompetent patients.

The clinical presentation varies according to the age of the patient. In children, the vertebrae and ribs are the most common sites of *Aspergillus* osteomyelitis, resulting from contiguous spread from an adjacent pulmonary infection. In adults, the infection usually spreads hematogenously; this entails a disseminated *Aspergillus* infection. Lumbar involvement is the most common site (about two thirds of cases). The vertebral involvement can be destructive, with subsequent development of epidural abscess and spinal cord compression. The clinical and radiologic features are not distinctive because they reflect destruction of bone as in any other infectious process. The ESR and leukocytosis are not helpful for diagnosis. Other rare locations have been reported: tibia, ribs, wrist, sternum, pelvis, knee, humerus, and carpus.

The predominant infecting species in *Aspergillus* osteomyelitis is *Aspergillus fumigatus* (80% to 90% of cases), which is the most commonly isolated species found in all sites of infection. Less commonly, *A. flavus, A. flavipes, A. niger, A. nidulans,* and *A. terreus* have been isolated. As serologic tests and examinations of bronchial secretions may be negative, bone biopsy must be performed to obtain bacterial and/or histologic diagnosis.

Because of the rarity of these infections, optimal chemotherapy has not been defined. Amphotericin B given in doses of 0.5 to 1 mg/kg/day for 6 to 12 weeks should be considered standard therapy. Liposomal amphotericin B, less toxic than amphotericin
B. is an alternative drug, but too few patients with osteomyelitis have been treated with liposomal amphotericin B for a full appraisal of the potential of this agent. In addition to amphotericin B, many patients have also received 5-flucytosine (150 mg/kg/day), which has, in vitro, a synergistic or additive effect and a better penetration in bone than amphotericin B. Itraconazole, a newer azole derivative, may provide an effective treatment alternative (200 to 400 mg/day) in invasive aspergillosis. It has been used with success, alone or in combination with surgical therapy, in recent cases of Aspergillus diskitis, with recovery achieved after 4 to 6 months of treatment. The determination of itraconazole serum concentrations may be important in predicting outcome because failures were associated with low serum drug levels. The oral availability of this drug and the uncommon side effects represent major advantages for long-term therapy in patients with severe fungal infections.

The optimal duration of antifungal therapy still remains uncertain; it depends on the diffusion of fungal lesions, the degree of immunodeficiency, and the drugs used. In the literature, treatment has been given from 4 months to 3 years in vertebral osteomyelitis, with the shortest times observed since the introduction of itraconazole. The place of elective surgical treatment in vertebral osteomyelitis (debridement of necrotic bone) must be reassessed except in case of neurologic symptoms because new data from the literature has shown favorable outcomes with the use of medical treatment alone. In peripheral osteomyelitis combined medical-surgical therapy of Aspergillus bone and joint infections is indicated, especially if bone sequestrum is present. In conclusion, Aspergillus osteomyelitis is a rare, severe complication of invasive aspergillosis, strongly associated with defects in host defenses, particularly after solid organ transplantation. The diagnosis is obtained by mycologic or histologic examinations of bone specimen. The prognosis has been improved by the use of itraconazole, which allows long outpatient treatment, with less toxicity.

REFERENCES