Aspergillus Pancarditis following Bone Marrow Transplantation for Chronic Myelogenous Leukemia

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A 34-year-old man with chronic myelogenous leukemia developed hemoptysis, pain in the left side of the chest, and a systolic heart murmur eight weeks following an allogeneic bone marrow transplant. His clinical status deteriorated, and he died ten weeks after transplantation. Autopsy revealed unsuspected disseminated aspergillosis, including the unusual finding of Aspergillus pancarditis and pericarditis. Cardiac aspergillosis is a uniformly lethal disease in immunocompromised persons and must be aggressively diagnosed following early symptoms.

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Cardiac aspergillosis is associated with a grim prognosis. 1-3 Aspergillus has a propensity for invasion and thrombosis of the coronary arterial branches, often resulting in extensive myonecrosis. 1-3 Cultures of blood are usually sterile, causing delays in diagnosis, and the organism responds poorly to medical management. 4-6 Involvement of all three layers of the heart by Aspergillus is rare, and only several cases of pancarditis have been reported. 3

This report describes a patient having massive Aspergillus pancarditis and pericarditis associated with disseminated fungemia following a bone marrow transplant for chronic myelogenous leukemia. To our knowledge, this is the first reported occurrence of Aspergillus pancarditis following bone marrow transplantation.

CASE REPORT

A 34-year-old man was admitted to the hospital for an allogeneic bone marrow transplant. He had been diagnosed as having chronic myelogenous leukemia two years previously, and treatment with multiple agents had failed to gain remission. At the time of admission, the peripheral white blood cell count was 15,000/cu mm, with 64 percent neutrophils, 8 percent band forms, 3 percent metamyelocytes, 2 percent myelocytes, 6 percent lymphocytes, 7 percent monocytes and 10 percent basophils. Bone marrow biopsy showed 90 percent cellularity and was consistent with chronic myelogenous leukemia. Following pre-transplant treatment with cyclophosphamide (Cytoxan) and busulfan, the patient received 1,500 ml of bone marrow from his HLA-compatible brother. The patient developed graft-vs-host disease, which worsened over the subsequent weeks despite administration of high-dose therapy with methylprednisolone sodium succinate (Solu-Medrol). Eight weeks after the transplant, the patient developed hemoptysis, but an ECG and chest roentgenogram were normal. Two weeks later, he developed lethargy and dull left-sided pain in the chest. Following episodes of apnea and obtundation, the patient was intubated. A grade 1/6 systolic murmur was noted at this time, and an ECG showed sinus tachycardia. Chest roentgenograms revealed bilateral pulmonary infiltrates which increased in severity. A bronchoscopic biopsy was performed, which showed reactive cells, and culture grew Pseudomonas aeruginosa. Although fungal cultures were sterile, empiric therapy with amphotericin B was begun. The patient became hypotensive, developed ventricular fibrillation, and died ten weeks after transplantation.

PATHOLOGIC FINDINGS

At autopsy, disseminated aspergillosis was present, involving the lungs, brain, kidneys, liver, small intestine, liver, urinary bladder, spleen, and diaphragm. Postmortem cultures from multiple organs were positive for A fumigatus.

Gross examination of the heart revealed biventricular dilatation, elevated green epicardial and pericardial plaques, a mottled tan-green myocardium, and numerous vegetations present on the endocardium, papillary muscles, and chordae tendineae (Fig 1).

Microscopic examination revealed extensive patchy myocardial fungal abscesses associated with extensive mycotic thrombosis of small coronary blood vessels. Occasional mycotic thrombosis of large coronary arteries was present (Fig 2). Aspergillus vegetations were present on the endocardial surfaces of all four chambers of the heart, consisting of septate hyphae radiating from subendocardial microabscesses. Similarly, epicardial mycotic plaques originated from subepicardial abscesses. No vegetations were present on the cardiac valvular leaflets.

DISCUSSION

Although the role of bone marrow transplantation in the management of leukemia is well established, infectious complications continue to be a major source of morbidity in these patients. It has become evident that post-transplant infections occur in three phases, each characterized by susceptibility to different organisms. 7 It is during the first phase, occurring immediately following transplantation and lasting approximately one month, that susceptibility to bacterial, fungal, and herpes simplex infections is most pronounced. Aspergillosis may occur during this period following inhalation of airborne spores or, less frequently, disseminating from a preexisting upper respiratory focus

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such as sinusitis. Following the development of pulmonary infection, systemic disease can occur by hematogenous spread, most frequently involving the central nervous system, followed by infection of the heart, kidneys, gastrointestinal tract, liver, and spleen. However, extrapulmonary symptoms are unusual, except from lesions of the central nervous system, and disseminated aspergillosis is usually only diagnosed at autopsy.

The reported frequency of cardiac aspergillosis varies, occurring in 22 percent of patients having disseminated aspergillosis and constituting 7 percent of all cases of Aspergillus infection from the National Institutes of Health, in 10 percent of the patients with cancer who have aspergillosis seen at the Memorial Sloan-Kettering Cancer Center, and in 7 percent of the patients with aspergillosis who have acute leukemia seen at the University of California San Francisco Medical Center. There is scant information on the prevalence of aspergillosis in recipients of bone marrow transplants.

Cardiac involvement by Aspergillus is one of the most serious complications of disseminated aspergillosis. Electrocardiographic changes are often nonspecific, and pericardial friction rubs can be masked by severe coexisting pulmonary disease. A review of 37 cases of myocardial aspergillosis revealed that in only six were electrocardiographic changes consistent with ischemia or infarction present. It is difficult to determine the extent to which cardiac aspergillosis contributes to the death of patients having disseminated infection; however, review of the literature failed to reveal survival of patients having either isolated Aspergillus myocarditis or cardiac aspergillosis accompanied by disseminated disease. The only reported medical cures of cardiac aspergillosis occur in those leukemic patients having Aspergillus infection of prosthetic cardiac valves.

The typical histologic findings of cardiac aspergillosis are formation of myocardial abscesses, either focal or diffuse, isolated or in combination with endocardial, epicardial, or pericardial involvement. The predilection of Aspergillus for blood vessel invasion results in characteristic mycotic thrombosis, in which fungal hyphae may be seen within the lumen and invading blood vessel walls. In some cases the infection may extend from the myocardium into the endocardium, where it results in a mural endocarditis which typically affects the left side of the heart. Isolated pericardial abscess or valvular endocarditis is uncommon.

Involvement of all three layers of the heart by Aspergillus, as was present in our patient, is rare. Previous cases of Aspergillus pancarditis have occurred in patients with gram-negative sepsis and leukemia and following abdominal surgery. Pancarditis is believed to develop by progression of fungal myocarditis to involve the endocardium and pericardium and can demonstrate two histologic patterns. One is a continuous pattern of transmural erosion through adjacent areas of endocardium, myocardium, and pericardium, associated with extensive tissue necrosis. The second pattern consists of a diffuse embolic pancarditis in which small, widespread nodular vegetations are present on the pericardial and endocardial surfaces, in continuity with myocardial abscesses. The present case probably represents this latter pathogenesis, as the Aspergillus did not appear to spread contiguousy through the heart. The distribution of the lesions appeared to follow the pattern of the coronary arteries, suggesting embolic dissemination. These emboli probably originated in the lung, which showed severe aspergillosis with pronounced involvement of the pulmonary vessels.

This report documents a case of Aspergillus pancarditis, an unusual manifestation of cardiac aspergillosis. The severe involvement of all three layers of the heart, which remained undiagnosed until autopsy, emphasizes the lethal potential of cardiac aspergillosis in recipients of bone marrow transplants, as well as other immunocompromised patients.

REFERENCES