Bronchocentric Mycosis Occurring in Transplant Recipients*


Although a variety of long-term, probably immunologically induced pulmonary changes have been described in recipients of both combined heart-lung and bone marrow transplantation, pulmonary infections continue to remain causes of significant morbidity and mortality as well. Herein we describe three patients (two heart-lung and one bone marrow transplant recipient) who had bronchocentric granulomatous mycosis, a tissue manifestation of fungal infection not previously described in the setting of a transplant host.

A variety of long-term pulmonary changes have been described in recipients of organ transplantation. In recipients of heart-lung transplants, these include obliterative bronchiolitis, pleural fibrosis, bronchial mucous impaction, bronchiectasis, and vascular intimal hyperplasia.1,2 The late pulmonary complications in recipients of bone marrow transplants have included lymphoid interstitial pneumonitis,3 lymphomatoid granulomatosis,4 restrictive pulmonary disease,5 and obliterative bronchiolitis.6 The most serious and progressive complication in both groups has been obliterative bronchiolitis, which has occurred in approximately half of the long-term survivors of heart-lung transplants5,6 and in between 10 and 15 percent of recipients of bone marrow transplants;7 however, as the pool of organ recipients slowly expands, it is becoming apparent that these patients are also susceptible to other disease processes in the lungs (aside from the usual pneumonias)—some as de novo diseases, some possibly as recurrence of the primary disease, and some as a direct immunologic consequence of transplantation, eg, chronic graft-vs-host disease. Herein we report the findings in two heart-lung transplant recipients and one bone marrow transplant recipient who developed bronchocentric mycosis, a previously undescribed tissue manifestation of fungal infection in immunosuppressed patients.

CASE REPORTS

CASE 1

This 38-year-old man underwent combined heart-lung transplantation at Stanford University Hospital in June 1983 for primary pulmonary hypertension. His clinical course was remarkably uncomplicated for nearly four years, with no episodes of cardiac or pulmonary rejection, airflow limitation, or pneumonia. He was fully rehabilitated and receiving cyclosporine A and prednisone. Forty-seven months after transplantation, the patient developed a non-productive cough and minimal exertional dyspnea. An exhaustive evaluation led to a diagnosis of bronchiolitis obliterans. Various trials of augmented immunosuppression failed to ameliorate the clinical symptoms, and the patient eventually became dyspneic at rest. Because of this, the decision was made to pursue retransplantation. In preparation for this, his immunosuppression was tapered to decrease the likelihood of infection, and 52 months after the initial transplant, repeat heart-lung transplantation was performed. The pathology of the explanted lung is discussed subsequently. The patient's postoperative course was complicated by a Pseudomonas pneumonia and candidal pleuritis. Two weeks after surgery, bronchoalveolar lavage revealed Aspergillus fungal elements, and transbronchial biopsy showed cytomegalovirus. The patient's course was also complicated by oliguric acute renal failure, and on the 37th postoperative day while receiving hemodialysis, he had an acute intracerebral hemorrhage of unclear etiology. The patient never regained consciousness and died on the following day; an autopsy revealed disseminated angioinvasive (including cerebral) aspergillosis.

CASE 2

This 41-year-old man had undergone combined heart-lung transplantation at Columbia-Presbyterian Medical Center seven months...
previously for complex congenital heart disease and Eisenmenger's syndrome. His initial postoperative course was relatively unremarkable, and his exercise tolerance greatly increased. His maintenance immunosuppressive regimen consisted of cyclosporine A, prednisone, and azathioprine.

On the day of admission, the patient noted the onset of dyspnea and fever. Physical examination revealed a temperature of 39.0°C (102°F) and inspiratory rales in both pulmonary bases. The chest x-ray film revealed patchy densities in both pulmonary fields, especially in the left upper pulmonary zone. Fiberoptic bronchoscopic examination revealed copious mucopurulent secretions in all lower lobar bronchial orifices. The bronchoalveolar lavage fluid contained branched septated fungal hyphae characteristic of Aspergillus, which was subsequently cultured as well. The peripheral eosinophil count was normal. The patient was treated with daily infusions of amphotericin without improvement.

One week later, right thoracotomy was performed. At this time the right lung was firm but not grossly consolidated. Biopsies were obtained from all three lobes and showed the features described subsequently. After thoracotomy, the patient's respiratory status deteriorated further, and despite treatment with amphotericin and high doses of steroids (due to the bronchocentric granulomatosis-like nature of the pathology), he eventually died eight months after transplantation. At autopsy the lungs showed invasive aspergillosis.

CASE 3

This 30-year-old man had developed Philadelphia chromosome-positive chronic granulocytic leukemia 40 months previously. He was treated with hydroxyurea until 16 months prior to admission when he became progressively anemic and thrombocytopenic. He was referred to the Mayo Clinic, and after bone marrow and chromosome studies indicated accelerating disease, he underwent allogeneic bone marrow transplantation from his HLA-identical sister. The period after transplantation was characterized by a severe atrial catheter tunnel infection and the development of graft-vs-host disease which required treatment with high doses of steroids and cyclosporine A.

During the ensuing months, the patient's immunosuppression was gradually tapered, but he had a flare of cutaneous and hepatic graft-vs-host disease requiring resumption of cyclosporine A and high-dose therapy with steroids. His course was further complicated by herpes simplex infection of the perineal area and severe hyperglycemia requiring insulin therapy.

During a routine examination 12 months after transplantation, the patient was noted to have sinus congestion and drainage. A chest x-ray film showed large bilateral cannonball pulmonary nodules, and open lung biopsy was performed, which showed mucormycosis (discussed subsequently). The patient was treated with intravenous amphotericin, and his chest x-ray film has shown marked resolution of the nodules after seven months of follow-up.

Pathology

The primary pulmonary pathologic finding in all three surgical specimens was similar and consisted of a chronic granulomatous reaction centered on the airways (Fig 1). Particularly in case 1, the bronchiolar walls were partially destroyed and their identity confirmed by elastic tissue stains. There was granuloma formation with prominent palisading histiocytes surrounding central necrotic zones (Fig 2). Giant cells were rare in case 1 and abundant in case 3. Other inflammatory cells present were lymphocytes, neutrophils, plasma cells, and scattered eosinophils; however, features of eosinophilic pneumonia were not present in the surrounding parenchyma. Branching fungal hyphae consistent with Aspergillus organisms were identified in the necrotic zones of cases 1 and 2 and zygomycosis (mucormycosis) in case 3. There was no evidence of tissue invasion by fungus in any of the surgical specimens.

In addition to the fungus-related inflammation, the larger bronchi

in cases 1 and 3 were dilated and contained inspissated secretions admixed with cellular debris. A panlobar obliterative bronchiolitis independent of the fungus was also present in case 1. Changes of either acute pulmonary rejection with perivascular infiltrates or graft-vs-host disease were absent.

**DISCUSSION**

Pathologic findings in the airways, specifically bronchiolitis obliterans, have come to the foreground in combined heart-lung transplantation as being the most significant determinant of long-term survival.9 Now thought to be related to the process of pulmonary rejection,11 such findings have been a major factor in the death of approximately 75 percent of the long-term survivors4 and have been the stimulus for retransplantation in others (including the present case 1).

**Figure 1.** Bronchocentric mycosis (case 1). There is central necrosis surrounded by zone of palisading histiocytes. Residual elastica is identifiable at periphery of airway (arrows), confirming bronchocentric nature of process. Silver stain showed presence of fungal organisms within areas of necrosis, as in case 2 (elastic von Gieson, original magnification × 200).

**Figure 2.** Bronchocentric mycosis with giant cells (case 2) (hematoxylin-eosin, original magnification × 160). Inset; fungal organisms consistent with degenerating Aspergillus organisms within bronchirole (Grocott's methenamine silver, original magnification × 500).
Obliterative bronchiolitis is an inflammatory process of the small airways which results in variable degrees of intraluminal fibrosis and, therefore, clinical obstruction. Additionally, the large airways develop bronchiectasis and changes of chronic bronchitis associated with mucous stasis and impaction. Long-term pulmonary changes have also been a cause of significant morbidity and mortality in recipients of bone marrow transplants. The most common late complication in this group is interstitial pneumonitis; however,obliterative bronchiolitis has also been described in up to 13 percent of the patients, possibly as a manifestation of chronic graft-vs-host disease.

In both populations of patients, pulmonary infections are significant problems immediately following the grafting procedure and remain so over the long-term. The three cases described illustrate an unusual tissue manifestation of a fungal infection which has not been previously described in the setting of the transplant host and which is histologically similar to bronchocentric granulomatosis. Although most of the sections in these cases had fungi present in the center of the granulomatosus inflammation, several of the airways merely had the pattern of bronchocentric granulomatosis without identifiable organisms.

First described in 1973, bronchocentric granulomatosis is characterized by the presence of destructive granulomatous inflammation centered on conducting airways, with or without an associated incidental vasculitis. In a large series of cases reported by Katzenstein et al, approximately 50 percent of the cases had a history of asthma, and in a high percentage of these cases (90 percent), fungal hyphae were identified in the airways. As such, Katzenstein argued that these cases fell into the clinicopathologic spectrum of allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, and mucoid impaction of bronchi. In asthmatic subjects, bronchocentric granulomatosis was thought to arise as an immune reaction to fungi colonizing inspissated mucus and secretions, and the organisms were usually sparse and difficult to identify; however, the etiology in nonasthmatic subjects has not been elucidated.

Pathologic features identical to those seen in our cases have also been described by Myers and Katzenstein in four nonimmunosuppressed patients associated with both fungi (Histoplasmosis and blastomycosis) and acid-fast bacilli. These patients were nonasthmatic and otherwise healthy. These authors point out that bronchocentric granulomas are relatively common in infections due to acid-fast bacilli (27 percent) and have been identified in 8 percent of infections due to Histoplasma. In the transplant host, it is possible that a combination of factors are involved in the pathogenesis of this bronchocentric mycosis that mimics bronchocentric granulomatosis.

Bronchiectasis and mucous impaction were present in case 1; and histologically, in case 3, inspissated secretions were identified in several large airways. Although these changes may have been secondary to the fungal infection, given the fact that such changes have been described in other recipients of heart-lung transplants and bone marrow transplants, it may be that the initiating event in our patients was fungal colonization of previously abnormal airways, a conclusion we favor. Then, given an immunosuppressed, rather than an immunocompetent, host, the end result (in two of our cases) was tissue invasion and grave consequences. Our third patient continues to do well seven months following his diagnosis.

The histologic findings in the surgical material from these cases differ from the pulmonary manifestation of fungal infections usually observed in the immunocompromised host. Characteristically, such fungi cause a suppurative pneumonia with or without angioinvasion and its resultant hemorrhage and necrosis. It is also dissimilar from the reported cases of pulmonary lymphomatoid granulomatosis occurring in patients with renal transplants. Aside from the presence of fungi, the lesions in our cases were not angiocentric and, more importantly, lacked an atypical lymphoid infiltrate.

Myers and Katzenstein caution that a diagnosis of bronchocentric granulomatosis be made in a nonasthmatic patient only as a diagnosis of exclusion and that treatment with steroids be undertaken only as the last resort. We would reiterate these views based on our experience with these three transplant patients. When such a reaction is identified in an immunosuppressed patient and an organism is not immediately apparent, a diligent search for one should be undertaken.

ACKNOWLEDGMENTS: We thank Drs. Alan Glanville, Charles Lombard, and Louis Lendtendre for their contributions to the care of these patients. Dr. Thomas V. Colby for his helpful critical comments, Mr. Phil Verzola for his photographic expertise, and Ms. Michelle Turner for her secretarial assistance.

REFERENCES
4 Hammer S, Mennemeyer B. Lymphomatomoid granulomatosis in a renal transplant recipient. Hum Pathol 1976; 7:111-16
Plan to Attend
55th Annual Scientific Assembly —
XVI World Congress on Diseases of the Chest

BOSTON 1989
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Boston • October 30-November 3, 1989