Recurrence of Sarcoidosis Following Bilateral Allogeneic Lung Transplantation*

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We report the first case of recurrent sarcoidosis manifested by clinical symptoms, radiographic abnormalities, and pathologic changes in a patient following sequential double allogeneic lung transplantation. A 40-year-old male patient underwent bilateral allogeneic lung transplantation for end-stage pulmonary sarcoidosis. Thirteen months posttransplantation, he developed fatigue, shortness of breath, and bilateral upper lobe pulmonary infiltrates. Transbronchial biopsy specimens revealed noncaseating granulomata. The patient’s symptoms and radiographic abnormalities resolved with an increased dose of oral prednisone.

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BLT = bilateral lung transplantation; IL-2 = interleukin 2

Allogeneic lung or heart-lung transplantation has been successfully performed for refractory cases of pulmonary sarcoidosis with respiratory failure.1-4 Since sarcoidosis is a disease characterized by an augmented immune response, with activated lymphocytes and mononuclear phagocytes at sites of disease activity,5 the potential for recurrent disease in lung allografts is plausible. Limited data are available regarding long-term survival, the incidence of allograft rejection or other complications, and the rate of recurrent granulomatous disease in the lung allografts. Recent preliminary reports suggest that noncaseating granulomata can be seen in the lung and heart allograft early after transplantation.1-3 Despite these findings, clinical symptoms and radiographic abnormalities associated with these histologic granulomatous lesions have not been reported previously (to our knowledge). We describe the first case of a patient with symptoms, radiographs, and pathologic changes indicative of recurrent sarcoidosis following bilateral allogeneic lung transplantation.

CASE REPORT

A 40-year-old nonsmoking black man was diagnosed as having sarcoidosis by scalene lymph node and transbronchial biopsy specimens 18 years prior to transplantation. He was treated intermittently throughout this time with high-dose corticosteroids for severe shortness of breath. Despite corticosteroid therapy, he developed progressive bilateral pulmonary infiltrates, severe bullous emphysematous changes, worsening pulmonary function, and hypoxemia. In December 1991, following 2 years of disabling symptoms, sequential bilateral lung transplantation (BLT) was performed. The immediate postoperative course was complicated by bilateral pulmonary infiltrates that cleared with intravenous corticosteroids and diuresis. Since the recipient was seronegative for cytomegalovirus and the donor was seropositive, cytomegalovirus prophylaxis with intravenous ganciclovir therapy was initiated beginning on postoperative day 7 and continued for 45 days. The subsequent course was uneventful, with progressive improvement in pulmonary function and exercise capacity. Oral corticosteroid therapy was tapered to 17.5 mg of prednisone per day 8 months after transplantation. Routine surveillance bronchoscopy and transbronchial biopsies performed at 4, 8, and 11 months after transplantation were negative for inflammation, rejection, infection, or granulomata.

In January 1993, 15 months after BLT, the patient complained of fatigue and shortness of breath. Chest radiographs revealed bilateral upper lobe miliary infiltrates (Fig 1). High-resolution computed tomographic scans of the lungs confirmed the predominantly upper lobe micronodular infiltration (Fig 2). Bronchoscopy with transbronchial biopsy specimens revealed noncaseating granulomatous inflammation consistent with sarcoidosis (Fig 3). All stains and cultures were negative for fungal, viral, tuberculous, and other bacterial infections. Treatment with oral corticosteroids was increased with prompt resolution of the radiographic abnormalities and symptoms. Despite this, follow-up transbronchial biopsy specimens 6 weeks after initiation of therapy revealed persistence of noncaseating granulomata. Subsequent specimens from transbronchial biopsies performed at 3, 6, and 9 months have revealed persistent noncaseating granulomas. Not withstanding these histologic abnormalities, the patient remains clinically asymptomatic with normal chest radiographs and stable pulmonary function.

FIGURE 1. Coned down view of right upper lobe from posteroanterior chest radiograph obtained 13 months following bilateral lung transplantation: fine, miliary stippling in the upper lobe is apparent.
FIGURE 2. High-resolution chest computed tomographic scan confirming bilateral upper lobe nodular infiltrates (1 to 1.5 mm in diameter) scattered throughout the lung parenchyma.

FIGURE 3. Noncaseating granuloma. Multinucleated giant cells and epithelioid histiocytes are surrounded by small numbers of lymphocytes. The granuloma was located within an alveolar wall. Special stains were negative for acid-fast bacilli and fungi (hematoxylin-eosin, original magnification ×250).

DISCUSSION

Solid organ transplantation, including liver, kidney, heart, heart-lung, and lung have been successfully performed in patients with sarcoidosis.1,2,6-11 The incidence of sarcoid granulomata developing in the solid organ allografts and long-term outcome have not been assessed. The utility of lung transplantation for sarcoidosis has not been critically assessed. Limited data are available regarding long-term survival, the incidence of allograft rejection or other complications, and the rate of recurrent granulomatous disease in the lung allografts. Data obtained from the St. Louis Transplant Registry indicates that only 17 single and 5 BLTs have been performed worldwide for sarcoidosis as of January 1, 1993 (St. Louis Transplant Registry, personal communication). Four patients have died, but none as a result of recurrent sarcoidosis. Actuarial survival at 1 year for patients with sarcoidosis following transplantation is 79 percent, which is similar to that reported for other underlying disorders for which transplantation has been performed.1 Data regarding recurrence of sarcoidosis following lung transplantation are limited. Recent preliminary reports suggest that noncaseating granulomata can be seen in the lung and heart allograft early after transplantation;1-3 however, to our knowledge, there are no reports of significant clinical symptoms or radiographic abnormalities associated with these lesions. We describe the first case of a patient with symptoms, radiographs, and pathologic changes indicative of recurrent sarcoidosis following BLT.

Recently, there have been three brief reports documenting the development of noncaseating granulomata in lung allografts early after transplantation.1-3 One recent abstract cited the development of similar granulomata on transbronchial biopsy specimens from the lung allograft in four of five patients with sarcoidosis undergoing lung transplantation.1 Scott and Higenbottam1,3 have observed sarcoid granulomata within the lung allograft following heart-lung transplantation for sarcoidosis, but provided no specific data in this regard. However, none of the patients in either report had clinical or radiographic abnormalities to suggest recurrent disease. In a recent review of lung transplantation, Stewart3 alluded to the fact that noncaseating granulomata have been noted in transbronchial lung biopsy specimens as early as 3 months following heart-lung transplantation for sarcoidosis. However, no specific data were provided and nothing was stated regarding the presence or absence of clinical signs or symptoms. We have also performed combined heart-lung transplantation in a 43-year-old woman with end-stage pulmonary sarcoidosis complicated by severe pulmonary hypertension. Noncaseating granulomata were noted in the lung allografts as early as 3 months posttransplantation, and were seen on each of 3 subsequent serial transbronchial biopsy specimens over a period of 9 months. Despite these histologic findings, she has remained clinically well, with no radiographic or physiologic evidence of disease recurrence.

Importantly, we have performed more than 200 transbronchial lung biopsies in 42 patients who have undergone single or double lung transplantation for disorders other than sarcoidosis. Foreign body granulomas were observed in only one patient who experienced repetitive aspiration due to vocal cord paralysis. Granulomas were not observed in any other lung transplant recipient. On the basis of our experience and that of others,1 histologic evidence for noncaseating granulomata appears to be common following lung transplantation for sarcoidosis. Clinical disease due to recurrent sarcoidosis appears rare, with our patient being the first well-described case. In our patient, disease recurrence responded to intensification of immunosuppressive therapy. Prednisone, azathioprine, and cyclosporine, agents used to prevent allograft rejection, may ablate the inflammatory response, which may limit or prevent clinically significant sarcoid lesions from developing.

In addition to the potential for recurrence of sarcoidosis in lung allografts, Johnson and coworkers1 noted a greater mean severity score for acute rejection during the first 3 months after transplantation compared with 44 contemporaneous, nonsarcoid transplant recipients. This

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may be extremely important since it is speculated that severe early acute rejection as well as recurrent bouts of rejection and infection may lead to a higher rate of development of irreversible bronchiolitis obliterans. The lung lesion in sarcoidosis is characterized by an intense alveolitis mediated by activated T cells and mononuclear phagocytes. Increased expression of interleukin 2 (IL-2) and IL-2 receptors have also been noted in serum and bronchoalveolar lavage fluid in patients with active sarcoidosis. In addition, augmented levels of soluble IL-2 receptors have been demonstrated in patients without sarcoidosis with lung, heart–lung, or hepatic allograft rejection. Thus, allograft rejection and evolution of sarcoid granulomas may share common immunopathogenetic mechanisms.

Limited data are available regarding the development of sarcoid granulomata in liver, heart, and kidney transplants. Casavilla et al recently described nine patients with sarcoidosis who underwent orthotopic liver transplantation; three patients died of complications, but overall patient and graft survival was similar to patients without sarcoidosis undergoing hepatic transplantation. In addition, there was no evidence of recurrent sarcoidosis in any patient over a follow-up period of 6.3 years. The authors speculated that the doses of immunosuppressive medications used to prevent organ rejection were adequate to prevent reactivation or further progression of sarcoidosis. A dearth of reports have been published regarding long-term outcome following cardiac transplantation for sarcoidosis. Valentine et al described three patients who had cardiac transplantation for myocardial sarcoidosis. One patient died of infectious complications 3.5 years post-transplantation; no granulomata were noted at necropsy. The other two patients were alive at 16 and 20 months posttransplantation without clinical evidence for recurrent disease. Recurrent granulomatous inflammatory changes associated with graft impairment occurred in one patient following renal transplantation. In three other reports of renal transplantation, there was no clinical evidence of recurrence of sarcoidosis in the transplanted kidney. However, one patient at 3 months posttransplant developed optic neuritis secondary to sarcoidosis which responded to high-dose prednisone therapy. Recurrence of disease can therefore be seen, albeit rarely. Long-term follow-up is scanty.

In summary, recurrent sarcoid-like granulomata were observed in the lung allografts in both of our patients with sarcoidosis following lung transplantation. However, only one patient had clinical symptoms and radiographic abnormalities associated with these histologic lesions. To our knowledge, our case is the first report of recurrence of clinical symptoms and radiographic changes of sarcoidosis following lung transplantation. Prompt clinical and radiographic improvement was noted following intensification of corticosteroid therapy. On the basis of our experience and that of others, we believe that lung transplantation remains the only viable life-saving option for patients with end-stage sarcoidosis. However, close clinical, radiographic, and histologic follow-up will be imperative to determine the ultimate efficacy of lung transplantation for patients with end-stage sarcoidosis.

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Endobronchial Metastasis From Giant Cell Tumor of Bone*

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A young woman presented with cough, dyspnea on exertion, and weight loss. A chest roentgenogram revealed collapse of the left lung. On doing fiberoptic bronchos-