
Pulmonary Eosinophilia Following Lung Transplantation for Sarcoidosis in Two Patients*

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Pulmonary eosinophilia is an uncommon problem in lung transplant recipients. We report the unique occurrence of two cases of pulmonary eosinophilia in pulmonary allografts for sarcoidosis. Both patients rapidly acquired bronchiolitis obliterans syndrome (BOS) after resolution of pulmonary eosinophilia. It is known that peripheral eosinophilia is a marker for pulmonary allograft rejection, but its potential in the pathogenesis of BOS is unclear.

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Key words: eosinophilic pneumonia; lung transplantation; sarcoidosis

Abbreviations: BOS = bronchiolitis obliterans syndrome; OB = obliterative bronchiolitis

Pulmonary eosinophilia is an uncommon problem in lung transplant recipients, perhaps because of the use of long-term steroids and other immunosuppressive agents. It is known that peripheral eosinophilia is a marker for pulmonary allograft rejection, but its potential in the pathogenesis of bronchiolitis obliterans syndrome (BOS) is unclear.1 In nontransplanted patients, pulmonary eosinophilia is a rare but clinically important pulmonary disease with diverse presentations including Loeffler syndrome, acute eosinophilic pneumonia, bronchopulmonary aspergillosis, and hypereosinophilic syndrome.2

Despite the variability in clinical presentations, histopathologic changes in the lung are alike regardless of the cause of pulmonary eosinophilia.3 The disease is largely the product of infiltration of lung parenchyma with eosinophils, and to a lesser degree, lymphocytes, neutrophils, and plasma cells.3 Giant cells and “Charcot Leyden” (eosinophilic) granules may be seen. The inflammation leads to variable alveolar wall damage, fibrous exudate, and reactive hyperplasia of type II pneumocytes.2

In pulmonary transplant recipients, peripheral eosinophilia can be a marker for episodes of acute rejection; however, the role of the eosinophil in the pathogenesis of cellular rejection is unclear.1 Data regarding the long-term outcome and complications for lung transplantation for sarcoidosis are limited. We report the unique occurrence of two cases of pulmonary eosinophilic infiltrates in the pulmonary allografts following transplantation for sarcoidosis. In both cases, the pulmonary eosinophilia was followed by the development of BOS.

CASE REPORTS

Case 1

A 51-year-old African-American woman presented with a 1-week history of increased dyspnea on exertion 27 months after single left lung transplantation for advanced fibrocystic sarcoidosis. The dyspnea progressed to marked shortness of breath at rest 2 days prior to hospital admission. She denied fever, chills, night sweats, cough, hemoptysis, or chest pain.

Her posttransplant course was complicated by the development of a native lung aspergillosis requiring right-upper lobectomy at 33 weeks posttransplant. Persistence of aspergillosis growth in BAL fluid necessitated long-term oral itraconazole treatment at a dose of 200 mg bid. Surveillance bronchoscopies had revealed two episodes of A1B0 rejection that were untreated as well as one episode of A2B0 rejection, treated with an augmented oral prednisone dose. Bronchoscopy 2 months prior to presentation revealed no aspergillosis or rejection. Her medications included tacrolimus (3 mg bid), prednisone (5 mg qd), azathioprine (50 mg qd, dose limited by low WBC count), acyclovir, omeprazole, conjugated estrogen, metoprolol, trimethoprim/sulfamethoxazole, magnesium oxide, iron sulfate, calcium, and vitamin D.

Physical examination was remarkable for labored respirations with a rate of 22 breaths/min and inspiratory crackles at the left lung base. The heart was regular with an S4 gallop and a grade 2/5 systolic murmur at the right lower sternal border. She was afebrile, and the remainder of the physical examination was normal.

Laboratory studies revealed an elevated leukocyte count of 13,100/μL with 655 eosinophils. Spirometry demonstrated a decrease in FEV1 from 1.09 to 0.93 L (32.6% predicted) and a decrease in FVC from 1.88 to 1.74 L (49.2% predicted), as compared with 4 weeks prior. Peak posttransplant values had been as high as 2.31 L for FVC and 1.60 L for FEV1. A chest radiograph revealed patchy interstitial and alveolar opacifications throughout the left lung with bronchiectasis of the right middle lung and volume loss. Chest CT scan showed patchy ground-glass opacifications throughout the left lung as well as emphysematous changes and fibrosis of the native right lung (Fig 1).

To further assess the abnormal findings of the allograft, the patient underwent bronchoscopy with transbronchial biopsies. All culture and stain results for infectious organisms from BAL and biopsies including bacterial, fungal, mycobacterial, and viral,
were negative. Biopsy specimens revealed eosinophilic infiltrates with intracellular, interstitial eosinophilic granules throughout the lung parenchyma consistent with acute eosinophilic lung disease without evidence of acute cellular rejection (Fig 2).

She was treated with 40 mg/d of prednisone, tapered to the baseline dose over 6 weeks. Trimethoprim/sulfamethoxazole and pravastatin were discontinued, as these were thought to be the most likely agents associated with an allergic reaction. Atovaquone was initiated 1 week later for *Pneumocystis carinii* pneumonia prophylaxis. Repeat bronchoscopy 2 weeks later demonstrated minimal (grade A1) cellular rejection with complete resolution of the eosinophilia, but a follow-up CT scan continued to show patchy ground-glass opacifications in the left lung. Radiographic resolution of the infiltrates did not occur for several months after treatment. Over the ensuing 4 weeks, she acquired progressive loss of lung function consistent with stage 1-a BOS, as repeat bronchoscopy showed no signs of eosinophilic disease, acute cellular rejection, or infection as a cause for the loss in pulmonary function.

**Case 2**

A 54-year-old African-American woman presented 9 months after double-lung transplantation for sarcoidosis with a 2-week history of increased dyspnea on exertion, fatigue, and cough productive of scant mucoid sputum. She also reported mild retrosternal ache and a 3-lb weight loss over 1 week. Fever, chills, night sweats, and hemoptysis were absent.

Her posttransplant course was complicated by thromboembolism to the right kidney and spleen for which she received anticoagulation. Four months prior to this presentation, she was treated for community-acquired pneumonia. Bronchoscopy 2 months prior to her current presentation showed bronchiolitis obliterans organizing pneumonia treated with an increased cyclosporine dose (from 150 to 175 mg bid). Repeat bronchoscopy 1 month later showed persistent bronchiolitis obliterans organizing pneumonia and noncaseating granulomas consistent with recurrent sarcoidosis. She was treated with methylprednisolone, 500 mg IV for 3 days, followed by daily oral prednisone (60 mg), which was tapered to the current dose of 40 mg over 4 weeks. All surveillance bronchoscopy results were negative for acute rejection.

Her medications included cyclosporine, 200 mg in the morning and 225 mg in the evening; prednisone, 1 mg/kg/d; azathioprine, 50 mg/d, dose limited by leukopenia; acyclovir; metoprolol; trimethoprim/sulfamethoxazole; omeprazole; warfarin; calcium; vitamin D; albuterol; ipratropium bromide; clotrimazole; and metaclopramide.

Physical examination showed normal vital signs without fever. Pulse oximetry was 95% on 2 L/min of nasal cannula oxygen. The lung examination showed right apical and bibasilar cackles. The remainder of the examination was unremarkable. The leukocyte count was low, at 2,560/µL with 384 eosinophils. Compared with 2 weeks prior, spirometry demonstrated a fall in FEV₁ from 1.61 to 1.38 L (59.6% predicted) and FVC from 1.78 to 1.61 L (62.1%). Peak posttransplant FVC and FEV₁ values were 2.13 L and 1.79 L, respectively. A chest radiograph showed subtle increased bibasilar lung markings with mediastinal adenopathy.

CT of the thorax showed alveolar opacification in the right upper lobe and mediastinal adenopathy (Fig 3). Transbronchial biopsies revealed diffuse eosinophilic infiltration with aggregates of eosinophils and a large number of degranulated extracellular eosinophilic granules (Fig 4).
The patient was continued on prednisone, 1 mg/kg/d, while trimethoprim/sulfamethoxazole was withdrawn. *P carinii* pneumonia prophylaxis was maintained with atovaquone. Follow-up bronchoscopy 1 month later demonstrated noncaseating granulomas without evidence of eosinophilia. Over the next 4 months, performance on pulmonary function testing deteriorated, consistent with the diagnosis of stage 1-b BOS.

**DISCUSSION**

These two patients both acquired pulmonary eosinophilia in the setting of lung transplantation for sarcoidosis, despite a background of aggressive immunosuppression with cyclosporine, prednisone, and azathioprine. In addition, both patients subsequently acquired BOS. It is of interest that these two patients both underwent transplantation for sarcoidosis, and that these are the only two cases of eosinophilic pneumonia observed in > 150 adult lung transplant recipients followed up at our center.

In comparison to case 2, case 1 exhibited a more pronounced exudative component with numerous intra-alveolar eosinophils. Degranulated granules were admixed with extravascular fibrin. Case 2 had a predominantly interstitial involvement with sparing of alveolar spaces.

Eosinophilia in the transplant patient has been described, although the occurrence of pure eosinophilic infiltrates without associated cellular rejection is extremely rare. Biopsy specimens in our patients revealed eosinophilic infiltrates as well as extravasations of extracellular eosinophilic granules. These are consistent findings in eosinophilic diseases of the lung (R. Tuder, MD; unpublished observation; December 2001). These observations may be associated with rejection, infection, or drug reaction. Although in these two patients the eosinophilic infiltrates resolved with steroids and withdrawal of medications, the combination of lung transplantation and the clinical setting of sarcoidosis make these cases unique in the sense that these conditions have not previously been linked to the development of eosinophilic lung disease.

Both patients acquired rapidly progressive BOS after resolution of eosinophilia. These cases supplant several questions: Was the pulmonary eosinophilia causal for BOS? Is it a marker for subsequent obliterative bronchiolitis (OB)? Is it simply coincidence? Does sarcoidosis predispose patients to eosinophilic disease? Is the eosinophilia a marker of rejection?

Eosinophilic infiltrates were recently seen in a pediatric allograft at our institution in a lung transplant recipient with cystic fibrosis. The eosinophilic infiltrates resolved with oral steroid treatment; nevertheless, the patient acquired acute rejection 4 weeks later. This case raised the concern whether eosinophils were...
related to the allograft rejection. It is known that eosinophilia is a marker for rejection in liver, kidney, and heart transplants. Graft eosinophilia is known to be a sensitive and specific marker of liver rejection. An association between graft eosinophilia as well as peripheral eosinophilia and kidney rejection has been observed. Blood eosinophilia is a marker of cardiac rejection, and the level of eosinophilia correlates with the severity of rejection.

In 1992, Yousem reported nine patients with tissue eosinophilia on lung allograft biopsy. Five of these cases were associated with acute rejection, and the other four were associated with infection. Each of the cases associated with rejection resolved with steroids, but one patient later acquired OB. Two of the cases associated with infection, Aspergillus and coxsackie A2 virus, resolved with treatment of the infection; two patients died of their infections.

Bewig et al. reported a series of four patients who presented with recurrent eosinophilic alveolitis on BAL. Only one patient underwent a concomitant transbronchial biopsy, and it revealed acute rejection. Each patient responded to treatment with steroids.

Several cases of sarcoidosis and pulmonary eosinophilia or chronic eosinophilic pneumonia occurring concomitantly have been described but not in the posttransplant period. A review of 140 patients with sarcoidosis found 14% had peripheral blood eosinophilia (absolute eosinophil count > 350/µL); however, the authors did not find an increase in parenchymal lung eosinophilia. Both of our patients had peripheral blood eosinophilia and pulmonary eosinophilia. Whether this was due to sarcoidosis, medications, graft rejection, or another etiology is unclear. Although there was no associated rejection on biopsy, perhaps the eosinophilic infiltrates foreshadow a decline in allograft function in patients with sarcoidosis.

In conclusion, we report two cases of acute eosinophilic pneumonia in lung transplant recipients for sarcoidosis. Although the significance of eosinophilic pneumonia is unclear, it is concerning that both patients went on to acquire BOS within a relatively short time period. Eosinophils are known to release inflammatory mediators such as eosinophil chemotactic factor, interleukin 5, and leukotriene B4. Further studies may identify a role for these in the predisposition to OB. A higher suspicion for pulmonary eosinophilia in transplanted patients with sarcoidosis is warranted. Perhaps early and aggressive treatment when pulmonary eosinophilia is diagnosed would prevent the development of OB.

REFERENCES

Sleep-Disordered Breathing Associated With Long-term Opioid Therapy*

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Three patients are described who illustrate distinctive patterns of sleep-disordered breathing that we have observed in patients who are receiving long-term, sustained-release opioid medications. Polysomnography shows respiratory disturbances occur predominantly during non-rapid eye movement (NREM) sleep and are characterized by ataxic breathing, central apneas, sustained hypoxemia, and unusually prolonged obstructive “hypopneas” secondary to delayed arousal responses. In contrast to what is usually observed in subjects with obstructive sleep apnea (OSA), oxygen desaturation is more severe and respiratory disturbances are longer during NREM sleep compared to rapid eye movement sleep. Further studies are needed regarding the effects of opioids on respiration during sleep as well as the importance of interaction with other medications and associated risk factors for OSA.

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Key words: ataxic breathing; Biot respiration; opioids; sleep apnea

Abbreviations: BMI = body mass index; CPAP = continuous positive airway pressure; NREM = non-rapid eye movement; OSA = obstructive sleep apnea; REM = rapid eye movement; Sao2 = arterial oxygen saturation