Mycobacterial Infections in Lung Transplant Recipients*

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Background: Immunosuppression and chronic lung disease are known risk factors for mycobacterial infection and might be expected to develop with an increased frequency in lung transplant recipients. We therefore sought to document the incidence and type of mycobacterial infections in a large lung transplant program.

Methods: A retrospective review of 219 transplant procedures (60 single lung transplants and 159 double lung transplants) in 210 patients was conducted. All patients had scheduled surveillance bronchoscopies at 3, 6, 9, 12, 18, and 24 months, and yearly thereafter. BAL samples were processed routinely for mycobacterium.

Results: Eight patients (3.8%) had evidence of infection (5 men, 3 women; age range, 26 to 63 years). The reasons for transplant were obstructive lung disease (six), cystic fibrosis (one), and pulmonary fibrosis (one). Five recipients had infection in their native lungs; two of five cultured mycobacterium from BAL following transplantation. At least four of five patients had nontuberculous mycobacterium (one showed acid fast bacilli and granuloma on a biopsy specimen that was not sent for culture). None of the five developed disease (mean follow-up = 22 months; range, 3 to 30 months). The organisms were Mycobacterium avium complex (three), Mycobacterium xenopi (one), and unidentified (one). Of the three remaining patients who developed infection after transplantation, one grew Mycobacterium chelonae and the others grew Mycobacterium tuberculosis (both received double lung transplants and had no evidence of mycobacterium in their native lungs). The only definite symptomatic disease occurred in the patients with M tuberculosis, one of whom had evidence of dissemination. The patients with M tuberculosis responded to standard treatment. There have been no deaths due to mycobacterium.

Conclusion: Mycobacterial disease rarely occurs following lung transplantation. Cultures for mycobacterium in surveillance BALs in the absence of symptoms are likely unnecessary.

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Abbreviation: MAC = Mycobacterium avium complex

Mycobacterial infection occurs with an increased frequency in patients with chronic lung disease compared with a normal healthy population.1–3 Infection with atypical mycobacterium in chronic lung disorders may result in disease but may also exist as a clinically silent colonizer. Hence, the presence of organisms in the abnormal environment of lung disease does not necessary require treatment. Medical treatment for tuberculosis and atypical mycobacterium should not be considered lightly, as many of the medications have relevant adverse effects. Guidelines outlining indications for treatment of tuberculosis and atypical mycobacterium are readily available.4,5

Another risk factor for mycobacterial disease is immunosuppression.6 Mycobacterial disease has been documented in the setting of organ transplantation.7 The combination of chronic lung disease and immunosuppression, as occurs in lung transplantation, might reasonably be expected to be associated with disease from mycobacterium. However, the frequency and outcome from mycobacterium in lung transplant recipients are unclear. We therefore sought to examine our experience in over 200 lung transplant recipients in order to document the incidence, type, and outcome of mycobacterial-positive cultures in lung transplant recipients.

Materials and Methods

Study Design

A retrospective review of medical records was conducted for all lung transplant recipients who had transplants between Novem-
ber 1983 and February 1996. Subjects who had positive cultures for mycobacterium or staining positive for acid-fast bacilli were included. The following information was recorded: isolation and identification of organism before and after transplantation, clinical manifestations of disease following transplantation, treatment prescribed, response to treatment, and outcomes following identification of organism.

**Surveillance Protocol**

Sputum samples were requested as part of the pretransplant evaluation. Washings from the donor lung at the time of transplantation were sent for microbiology. Following transplantation, scheduled flexible fiberoptic bronchoscopies were conducted at 2 and 6 weeks, 3, 6, 9, 12, 18, and 24 months, and yearly thereafter. BAL was obtained from the middle lobe of the right transplanted lung and the lingula of the left transplanted lung. All samples were stained for acid-fast bacilli. Cultures were prepared for bacteria, fungi, viruses, and mycobacterium. BAL was also sent for cytopathologic study. Transbronchial biopsy specimens were taken from two lobes (three to five samples from each lobe) during surveillance bronchoscopies following transplantation.

Chest radiographs were obtained weekly for approximately 8 to 12 weeks and then monthly for the first year following transplantation. Laboratory-based spirometry was obtained monthly. Home electronic spirometry was performed daily.

**Unscheduled Bronchoscopies**

Bronchoscopy with BAL and transbronchial biopsies was also performed when clinically indicated (i.e., respiratory symptoms, decline in FEV₁, or radiographic infiltrates). The procedure, including laboratory evaluation of samples, was similar to what was ordered for surveillance bronchoscopies. However, when present, samples were obtained from the location of new radiographic abnormalities.

**Immunosuppression Protocol**

Recipients received methylprednisolone, 500 mg IV, intraoperatively and were started on a regimen of cyclosporine, azathioprine, and prednisone immediately postoperatively. Whole blood trough levels of cyclosporine were maintained between 250 and 350 ng/mL over the initial 3 months and gradually reduced to between 150 and 250 ng/mL after approximately 1 year. Azathioprine was prescribed at approximately 1 mg/kg/d but was reduced if liver enzyme abnormalities or leukopenia occurred. Prednisone was initially given at approximately 0.5 mg/kg/d and reduced gradually until 1 year when the dose was 15 mg every other day. Episodes of acute rejection were treated with methylprednisolone, 1 g IV daily for 3 days, followed by a regimen of prednisone tapering to baseline.

**Infection Prophylaxis**

Since 1991, cytomegalovirus prophylaxis has been administered if either the donor or the recipient were positive for cytomegalovirus antibodies. Hyperimmune globulin and ganciclovir have been administered. Ganciclovir was prescribed at 5 mg/kg twice daily for 2 weeks followed by 5 mg/kg once every Monday, Wednesday, and Friday for a further 10 weeks. Trimethoprim-sulfamethoxazole was administered once every Monday, Wednesday, and Friday. Initial treatment with antibacterial medications was adjusted according to donor cultures.

**Results**

**Patient Population**

The records of 210 recipients (210 first transplants and 9 retransplant procedures) were reviewed. There were 159 double lung transplants and 60 single lung transplants. There were eight patients with evidence of mycobacterial infection (3.8%), all of whom received a double lung transplant. Of the eight patients, five were men and three were women. The age range was between 26 and 63 years. The reasons for transplantation were obstructive lung disease (six), cystic fibrosis (one), and pulmonary fibrosis (one).

**Isolation of the Organism**

In all but one case, mycobacterium was localized to the lungs. Five recipients had infection in their native lungs, two of which cultured mycobacterium from BAL after transplantation. At least four of the five patients had nontuberculous mycobacterium (one patient showed acid-fast bacilli and granuloma on a biopsy specimen that was not sent for culture). The organisms isolated from the explanted native lung were *Mycobacterium avium* complex (MAC) (three) and *Mycobacterium xenopi* (one).

Three patients had mycobacterium isolated only following transplantation. One patient had *Mycobacterium chelonae* repeatedly isolated from BAL. The second patient had *Mycobacterium tuberculosis* isolated from pleural fluid and BAL. The third patient had tuberculosis cultured from a biopsy specimen of a cutaneous nodule.

**Imaging**

The radiologic abnormalities on the chest radiograph are noted in Table 1. There were no radiologic abnormalities, aside from those related to the transplant procedure in the patient who developed *M. chelonae*. This patient had cystic fibrosis pretransplant. The other patients with no radiologic abnormalities compatible with mycobacterial disease were as follows: (1) a 58-year-old woman who received a double lung transplant for α₁-antitrypsin deficiency; (2) a man with a double lung transplant for α₁-antitrypsin deficiency who had systemic and cutaneous signs. MAC had been isolated repeatedly >2 years pretransplant in the native lungs. The person with tuberculosis and radiologic findings had small ill-defined patchy densities in the right upper lobe and right lower lobe along with a left pleural effusion.
Symptoms

The patient with *M chelonae* had persistent cough with yellow sputum. One of the patients with MAC had a nonproductive cough. The only patients with symptoms that one could attribute to an active infection with any degree of confidence were the two with tuberculosis. One patient had fever, cough, sputum, and dyspnea. The other patient had fever, myalgias, and multiple erythematous cutaneous nodules.

Treatment

All but one patient received treatment with antimicrobial agents (Table 1). Treatment was administered for variable periods of time and with differing combinations. Tuberculosis was treated with isoniazid and rifampin for 1 year. Pyrazinamide was given in the initial 2 months for one patient. Symptoms and signs (clinical and radiologic) improved in patients with tuberculosis. Immunosuppression protocols remained unchanged after the diagnosis. There have been no deaths due to mycobacterium in the Toronto Lung Transplant program.

Discussion

Mycobacterial infections have been reported in patients with organ transplants, chronic lung disease, and in patients with AIDS. Immunosuppression increases the risk for mycobacterial infection.\(^1\)\(^-\)\(^3\)\(^,\)\(^6\)\(^-\)\(^7\) We have reported our experience with mycobacterium in 219 transplant procedures. In our series, mycobacterium has been documented in only 3.8% of cases. Two of the patients in our series had indolent disease without extrathoracic signs or symptoms and responded well to treatment. No changes in immunosuppression were required.

Pulmonary tuberculosis has been infrequently documented following lung transplantation. Schulman and colleagues\(^8\) documented a 5-year experience with 94 lung and heart/lung transplant recipients. The incidence of infection with tuberculosis was 2%. All infections occurred within the first 3 months after bilateral lung transplantation. There was evidence implicating donor-to-recipient transmission in all cases. Of note, the radiographic appearance of tuberculosis in all cases was relatively minor. As well, full clinical and radiographic recovery occurred with standard antituberculous therapy. Other descriptions of pulmonary tuberculosis in lung transplant recipients have associated the diagnosis with augmentation of systemic steroids.\(^9\)\(^-\)\(^12\) From the few other reports, there appears to be a variety of radiographic patterns that may occur. Schulman et al\(^8\) noted narrowing of the middle lobe bronchus, a focal cluster of nodules in the left upper lobe, and small bilateral pleural effusions. Carlsen and Bergin\(^10\) described multiple bilateral small nodules and a unilateral effusion. Miller noted bilateral upper and lower lobe cavitary lesions.\(^12\) Dromer et al\(^11\) described consolidation with perihilar lymphadenopathy. Ridgeway et al\(^13\) reported two cases of tuberculosis occurring in recipients of single lung transplants who shared a common donor.
opped radiographic opacities, while the others had tuberculosis isolated from bronchoscopy without evidence of radiographic abnormalities.

There have been a total of eight previously reported cases of mycobacterium and only two case reports of atypical mycobacterium causing disease in lung transplant recipients.14,15 A case of *M chelonae* was documented by transbronchial biopsy specimen and positive cultures in a young patient who developed bronchiolitis obliterans approximately 18 months following heart/lung transplantation for primary pulmonary hypertension.14 Unfortunately, eradication of the organism in this case was not successful. Given the relatively late acquisition of the organism, it is likely that *M chelonae* was not transmitted from the donor. Baldi et al15 reported the case of a 56-year-old man undergoing bilateral lung transplantation for idiopathic pulmonary fibrosis. Purulent secretions from the wound approximately 1 month following transplantation grew *Mycobacterium fortuitum*. Antimicrobial therapy was effective in eliminating the infection.

To our knowledge, there are no data to support an approach to mycobacterial infections in lung transplant candidates that differ from that of a patient who is not a transplant candidate. Tuberculosis should be treated according to the usual standard of care. Colonization of the airways by atypical mycobacterium in the absence of disease (*ie*, otherwise unexplained symptoms and/or progressive radiographic abnormalities consistent with atypical mycobacterium) is not an indication for treatment with antinocytobacterial medications prior to transplantation. The role of therapy in simple colonization of the airways after transplantation is unknown.

Mycobacterial infections have also been documented in other solid organ transplant recipients. Hall et al16 noted a low incidence of 0.8% in renal transplant recipients, the majority of whom had their conditions diagnosed within the first year following transplantation. Of the mycobacterial cultures, 40% were atypical organisms. While the incidence of tuberculosis has been low in several series, reports of death have varied; death occurred in three of seven infected renal transplant recipients in one report, two of five infected liver transplant recipients in another, and zero of four infected liver transplant recipients in a third report.17–19 Atypical mycobacterial infection appears to be quite rare in nonlung transplants. One atypical case from 22 total cases of mycobacterial infection was documented by the series of Hall and colleagues.20 A case series of four atypical mycobacterial infections was documented in various organ systems by Patel and colleagues21 in 1994.

Acquisition of atypical mycobacterium and tuberculosis can occur through transmission from the donor, presence of the organism within the native lung, and through acquisition posttransplant. It is likely that the patients who had the same mycobacterium detected pretransplant and postransplant were colonized with mycobacteria in the upper airways above the anastomosis. There appears to be no pattern of acquisition that would suggest a high risk of serious morbidity. Potential risk factors for morbidity likely relate to the degree of immune suppression and concomitant lung pathologic condition (*ie*, bronchiolitis obliterans, remaining native lung). Nevertheless, our data indicate that mycobacterial infections are not a frequent complication after lung transplantation. Mortality and significant morbidity were not associated with transplantation infections. As mycobacterial disease rarely occurs following transplantation, cultures for mycobacterium in surveillance BAL in the absence of symptoms are likely unnecessary.

**References**