Multidrug resistant tuberculosis following lung transplantation: treatment with pulmonary resection

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Recipients of organ transplants are at increased risk for infection owing to their immunosuppressed state and the possibility of contamination of the donor organ. We report a case of multidrug resistant tuberculosis (MDR) transmission via a donor lung. After medical treatment with four drugs had failed, the patient underwent right upper lobectomy. There were no signs of disease on follow up more than 2 years later. To our knowledge, this is the first report of MDR tuberculosis in a lung transplant recipient. The need for a non-conservative approach, including pulmonary resection, to eradicate the infection is emphasised.

A 16 year old boy was diagnosed in 1996 with primary pulmonary hypertension and was treated for 2 years with continuous intravenous prostacyclin. His condition, however, deteriorated and in 1999 he underwent heart-lung transplantation. The operative and immediate post-operative courses were uneventful. Maintenance antirejection therapy consisted of prednisone, azathioprine, and tacrolimus. The patient also received prophylaxis with itraconazole, trimethoprim-sulfamethoxazole, ganciclovir, and oral nystatin.

Purified protein derivative (PPD) of the recipient before transplantation was negative.

Two and a half months after transplantation the patient presented with fever (38.5°C) and non-productive cough, without dyspnoea or other complaints. Pulmonary function tests showed no remarkable change from his previous tests. Surveillance bronchoscopy with transbronchial biopsy performed 1 week earlier had revealed no signs of graft infection or rejection. The chest radiograph showed no infiltrate or pleural effusion. To cover suspected upper respiratory infection, the patient was started on oral amoxicillin/clavulanic acid 500 mg three times a day as an outpatient. However, the fever continued during the following week and the patient was admitted to hospital. Blood cultures were negative. Bronchoscopic examination revealed a preserved anastomosis with no dehiscence. Transbronchial biopsy samples showed no evidence of rejection or of infection with either cytomegalovirus (CMV) or Pneumocystis carinii pneumonia (PCP). Direct staining of the bronchoalveolar lavage (BAL) fluid revealed acid fast bacteria. On the same day the cultures taken from the last surveillance bronchoscopy 2 weeks previously were found to be positive for Mycobacterium tuberculosis complex. Treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide was immediately started.

The recipient had emigrated from Russia 8 years before the transplantation. He did not undergo BCG vaccination. No history of travel or contact was noted. Because of his generally good condition the patient was discharged, but he remained on direct observed therapy (DOT) with isolation for 2 weeks. During that time the fever remained high and a weight loss of 3 kg was noted. Chest radiography showed a new infiltrate in the anterior segment of the right upper lobe which proved on bronchoscopic examination to be due to an obstructing polypoid mass (fig 1). Pathological examination of biopsy samples from the mass revealed numerous acid fast bacteria with a few giant cells but without granuloma formation. No rejection was seen on transbrachial biopsy samples. Cultures for other bacteria, CMV, and fungi were negative. However, 2 weeks later the culture results showed M tuberculosis organisms which were highly resistant to isoniazid, rifampicin, streptomycin, and ethionamide; moderately resistant to pyrazinamide; borderline sensitive to capreomycin; and highly sensitive to ethambutol, clarithromycin, ciprofloxacin, and cycloserine. The empirical regimen was changed accordingly to ethambutol 800 mg daily, cycloserine 750 mg daily, ciprofloxacin 500 mg twice a day, and clarithromycin 500 mg twice a day. In the following weeks the fever did not recur and the patient began to gain weight. At this time a detailed history of the donor’s family was obtained after contact was established with his home country. His mother, with whom he had been living in close contact until his immigration to Israel, had had active tuberculosis for at least 1 year. There were no data on her treatment or her mycobacterium drug sensitivity. The donor did not receive any prophylaxis.

Two months after specific treatment the patient again presented with low grade fever and weakness, without dyspnoea or cough. A chest radiograph showed an infiltrate in the anterior segment of the right upper lobe, and bronchoscopic examination revealed a markedly enlarged endobronchial mass. Direct staining of the specimens yielded numerous acid fast bacteria. Right upper lobectomy was performed. The surgical and postoperative courses were uneventful. Amikacin and clofasemine were added to the antituberculosis regimen. At a follow up examination 18 months later the patient had normal temperature, normal pulmonary function test results, and there were no chest infiltrates on the radiograph. Bronchoscopic examination showed no endobronchial lesion and the anastomosis and right upper lobe stump were preserved. BAL fluid and biopsy specimens were negative for acid fast bacteria.

DISCUSSION

The immunosuppression required for graft survival after transplantation increases patient susceptibility to infection.1 In transplant recipients M tuberculosis infection can be acquired by transmission from the donor, a latent infection in the native lung, or the environment. It is likely that, in our patient, the infection arose from a dormant focus in the donor lung. This assumption is supported by the negative PPD of the recipient before transplantation and the donor’s history of close contact with active tuberculosis. To our
knowledge, this is the first report of multidrug resistant tuberculosis in a lung transplant recipient.

In western countries the incidence of mycobacterial infection is 0.77–3.8% in patients after lung transplantation compared with 0.1% in the general population. Most of these infections are caused by atypical mycobacteria. The lung is the most common site of *M. tuberculosis* infection in recipients of all solid organ transplants.

In transplant recipients tuberculosis should be treated according to the usual standards of care, and treatment should be administered for at least 24 months after conversion as immunosuppression remains indefinitely.

The prevention of disease transmission from donor to recipient is difficult. PPD is irrelevant in donors, and medical histories are often unavailable or incomplete at the time of harvesting. Moreover, results of tuberculosis cultures from the donor tend to arrive long after transplantation. A normal chest radiograph and absence of active pulmonary infection in the donor are prerequisites for organ donation.

Our case also highlights the role of pulmonary resection in multidrug resistant tuberculosis. Medical treatment is often disappointing and surgery is an important ancillary option.

The main indication for operation is failure of conversion of sputum smear or culture despite treatment for at least 4–6 months. Other indications are previous relapses and a high profile of drug resistance. There is only one report of pulmonary resection due to tuberculosis in a lung transplant recipient.

Our case illustrates the complexity of the management of organ transplantation. Heroic procedures such as heart-lung transplantation can cure diseases once thought incurable. At the same time, diseases once thought curable (such as tuberculosis) or almost eradicated may reappear and easily jeopardise these efforts.

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