Recurrence of intravenous talc granulomatosis following single lung transplantation

Richard C Cook MD, Guy Fradet MD, John C English MD, John Soos PhD, Nestor L Müller MD, Thomas P Connolly MD, Robert D Levy MD FCCP

University of British Columbia Lung Transplant Program, Department of Pathology, Department of Psychology and Department of Radiology, Vancouver Hospital and Health Sciences Centre, Vancouver, British Columbia

Advanced pulmonary disease is an unusual consequence of the intravenous injection of oral medications, usually developing over a period of several years. A number of patients with this condition have undergone lung transplantation for respiratory failure. However, a history of drug abuse is often considered to be a contraindication to transplantation in the context of limited donor resources. A patient with pulmonary talc granulomatosis secondary to intravenous methylphenidate injection who underwent successful lung transplantation and subsequently presented with recurrence of the underlying disease in the transplanted lung 18 months after transplantation is reported.

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Intravenous injection of oral medications is an unusual cause of progressive pulmonary dysfunction (1). A 48-year-old woman with a remote history of intravenous methylphenidate (Ritalin, Novartis) abuse underwent single lung transplantation for advanced respiratory failure. Eighteen months after transplantation, she was evaluated for a new onset of cough and breathlessness. Transbronchial biopsies demonstrated numerous talc granulomas in the transplanted lung.

Recurrence of the primary lung disease following lung transplantation is uncommon (2) and has not previously been reported in patients who have received transplants for respi-
Figure 1) a Low power photomicrograph of the patient’s explanted lung demonstrating numerous discrete interstitial nodules. Although the intervening alveolar walls are of relatively normal thickness, there is diffuse loss of parenchyma in a pattern of panacinar emphysema. Movat pentachrome, original magnification 25x. b Higher magnification of a. The nodules are multinucleated histiocytic granulomas directed against foreign material in the form of birefringent plate-like crystals consistent with talc (large arrow). Note that the granulomas are mostly extravascular (small arrows denote small pulmonary artery). Movat pentachrome, original magnification 100x, polarized illumination

CASE PRESENTATION

A 48-year-old woman was referred to the University of British Columbia Lung Transplant Program with respiratory failure in July 1995. She had a 40-pack-year history of smoking and a 20-year history of intravenous drug abuse beginning in her 20s, with five to six years of heroin addiction. She was enrolled in a methadone detoxification program in the late 1970s but soon thereafter became addicted to intravenous methylenidate (Ritalin). Between 1980 and 1988, she injected three to four tablets of methylphenidate at least five months after transplantation.

Beginning in 1983, the patient noted progressive dyspnea. In 1988, she had an episode of respiratory failure related to septic pulmonary emboli and required intubation. At that time, she stopped smoking and all intravenous drug use. Despite this, her pulmonary function status worsened to the point where she became oxygen-dependent. Computed tomography (CT) scan of the chest demonstrated severe panacinar emphysema in the native left lung (Figure 2). The appearance of the transplanted right lung was unchanged from the stable post-transplantation appearance. She was started on azithromycin and oral prednisone (1 mg/kg/day orally) after consultation with her transplant respiratory.

The patient was seen in the lung transplant clinic three days later, by which time her symptoms had improved. Pulmonary function studies demonstrated FEV$_1$ 1.43 L (51% predicted), similar to stable post-transplantation baseline values. A high resolution CT scan of the chest demonstrated severe panacinar emphysema in the native left lung (Figure 2). The appearance of the transplanted right lung was unremarkable and was unchanged from that seen on the CT scan that was performed one month post-transplantation.

The patient underwent fibre optic bronchoscopy, at which time bronchoalveolar lavage and transbronchial biopsy specimens were obtained from the transplanted right lung. Cultures were negative for bacterial, viral and fungal infection. Transbronchial biopsies revealed minimal acute rejection (International Society for Heart and Lung Transplantation grade A1). The specimens also revealed numerous small birefringent particles lying within the alveolar capillary lu-
mens or attended by a poorly formed (early) histiocytic response, much different in size from those in the explanted lung (Figure 3). Subsequently, the patient admitted to recurrent intravenous drug abuse.

**DISCUSSION**

Only four diseases—sarcoidosis, lymphangioleiomyomatosis, giant cell interstitial pneumonitis and diffuse panbronchiolitis—have been reported to recur in the lung allograft (2). This is the first report of recurrence of talc granulomatosis due to relapse of drug abuse. The finding of talc granulomas in this patient’s transplanted lung was unexpected, with none of the previous transbronchial biopsies showing talc granulomas. The patient presented with documented lung pathology after a relatively small exposure to the intravenous talc compared with that of previously reported cases of talc granulomatosis in nontransplant patients.

Pulmonary disease has been well described in individuals who have chronically engaged in the intravenous injection of drugs intended for oral use (1). The pills are crushed, mixed in water, heated and subsequently drawn into a syringe to be injected intravenously. Many drugs have been abused in this fashion, including amphetamines (1), methylphenidate hydrochloride (1) and a variety of narcotic preparations, especially methadone hydrochloride (3). These oral medications are bound to an insoluble filler (eg, talc in methylphenidate), which is important both as a binding agent as well as to prevent the tablet from sticking to the manufacturing equipment (1).

When injected intravenously, talc particles become lodged in pulmonary (and systemic) arterioles and capillaries, resulting in thrombosis, vascular and perivascular fibrosis, and chronic inflammation (1). Eventually the particles migrate to the pulmonary interstitium where they provoke a foreign body giant cell reaction. These lesions have been reported to result in pulmonary hypertension (4) and interstitial pulmonary fibrosis (1). They can also be associated, as in our patient, with physiological changes characteristic of emphysema, including chronic airflow limitation, gas trapping and hyperinflation, and decreased diffusing capacity (3).

The patient’s clinical signs, symptoms and spirometry improved rapidly with azithromycin and corticosteroids within several days, with FEV₁ returning to the stable posttransplantation baseline level within several days. This raises the possibility that unidentified infection may have been the cause of the deterioration. Alternatively, the augmented steroids may have served a role in reducing bronchial hyperresponsiveness related to an acute inflammatory response from the granulomatous process. This is supported by the presence of wheezing at the time of presentation as well as reversible airflow limitation on spirometry.

Although this patient’s high resolution CT of the transplanted lung was unremarkable, the usual findings with talc granulomatosis consist of ground-glass opacities or fine nodularity throughout the lungs (5). The nodules measure 1 mm or less in diameter. In patients with more advanced disease, the nodules coalesce into larger nodules and eventually produce a pattern of conglomerate masses in the upper lobes with compensatory overinflation of the lower lobes, a pattern that is similar to that of progressive massive fibrosis in silicosis (5). In patients with intravenous methylphenidate abuse, a relatively common finding on high resolution CT is the presence of bilateral, primarily panacinar emphysema (6).

The transbronchial biopsies demonstrated the most significant abnormality. The short time between transplantation and biopsy demonstration of the lesions (18 months) suggests that extensive and diffuse involvement can occur with a relatively limited exposure to intravenous talc. The disposi-
tion of fine talc particles within the alveolar capillaries in the absence of a significant host granulomatous response suggests that the implantation was relatively recent, because granulomas tend to appear more in the interstitium with greater drug exposure (7). This may be the explanation for the lack of permanent change in pulmonary function, as well as the absence of significant abnormalities in the transplant lung on the high resolution CT scan. Alternatively, the patient’s immunosuppressive regimen may have retarded the typical foreign body response. It will be of interest to follow subsequent lung biopsies in this patient to document the progression of the granulomatous response to residual talc.

This case emphasizes the importance of careful pretransplantation assessment of psychosocial factors in the selection of appropriate candidates for transplantation. Ongoing substance abuse is generally considered a psychosocial contraindication to transplantation (8). Many centres, including our own, require a six-month abstinence as a minimum condition for attaining transplant candidacy status. However, recent work questions the predictive utility of this approach. For example, Gerhardt et al (9) found no correspondence between the duration of pretransplantation abstinence and subsequent recidivism in their sample of patients with alcoholic cirrhosis being referred for liver transplantation. This patient’s evolution reinforces the often cited observation that substance abuse is a chronic, remitting condition (10). After a remarkable seven-year abstinence, amidst a re-emergence of psychosocial stressors, she regressed to self-destructive attempts at coping with recurrent intravenous drug use. Clearly, every case has to be considered on its own merits. However a history of substance abuse, even in the remote past, should raise substantial concerns as to the likelihood of a long term successful transplantation, especially when considering the prevailing limited donor supply.

REFERENCES