Long term survival despite early loss of graft function after single lung transplantation for pulmonary fibrosis.

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Abstract:

We report a case of a patient who received a single left lung transplantation for idiopathic pulmonary fibrosis. The effect of the graft on the pulmonary improvement was only temporary, as the patient developed obliterative bronchiolitis (OB) resulting in complete destruction of the graft. The patient, however, is still alive 6 years after OB was diagnosed, apparently as a consequence of improvement of the native lung by triple immunosuppressive medicine.

This case is of interest for several reasons; first it shows that pulmonary fibrosis may respond to intensive immunosuppressive therapy, secondly it demonstrates that ventilation scintigraphy is useful in addition to pulmonary function tests in estimating the actual function of the graft after single lung transplantation, and thirdly it appears that the gradation of bronchiolitis obliterans syndrome after single lung transplantation may overestimate the true function of the transplant.
Chapter 6

Introduction:

Lung transplantation has become an accepted treatment option for end stage pulmonary diseases\(^1\). Worldwide, approximately 11000 single and bilateral lung transplantations have been performed (ISHLT, 17\(^{th}\) annual report\(^2\)). Unfortunately, chronic transplant dysfunction has emerged as the major impediment to long-term survival\(^3\) \(^4\) \(^5\). In affected patients, medical therapy results at best in stabilization of lung function, but has been largely ineffective to completely restore lung function\(^3\). Because of this lack of effective therapy, early treatment to try to stabilize lung function is therefore of major importance. The following case demonstrates long term survival after single lung transplantation for interstitial lung disease despite loss of graft function due to obliterative bronchiolitis (OB).

Case report:

In November 1987, a 37-year-old man was hospitalized because of progressive dyspnea, fatigue and a rapidly decreasing exercise capacity since two months. He had never smoked and his family history was negative for pulmonary diseases. He had kept a healthy parrot for the last 6 years. On examination the patient was out of breath after undressing. Auscultation of the lungs revealed end-inspiratory crackles. Autoimmune laboratory tests were negative for antineutrophil cytoplasmic antibodies, anti-double-stranded DNA, antibodies to extractable nuclear antigens, and no serum precipitines against birds could be demonstrated. The chest X-ray revealed a diffuse reticulonodular pattern (figure 1A). Pulmonary function tests showed a total lung capacity of 5.2 L (or 73% of predicted), a forced expiratory volume in one second (FEV\(_1\)) of 2.12 l/s (or 50% of predicted) and a diffusion capacity of 1.07 mmol/min/kPa/l (or 60% of predicted). A histologic diagnosis of usual interstitial pneumonia (UIP) was obtained after performing an open lung biopsy. High-dose oral and inhaled steroid treatment was started, to which later cyclophosphamide was added. Because of further clinical deterioration with a progressive decline in lung function (figure 2) cyclophosphamide was replaced by cyclosporine. He was listed for lung transplantation, and a single left lung transplantation was performed in November 1990. Histology of the explanted lung showed obvious signs of fibrosis and interstitial inflammation, confirming the diagnosis obtained by open lung biopsy.

The post-operative course was uncomplicated. Standard triple immunosuppression consisted of cyclosporine which was administered to reach whole blood trough levels of 400 µg/l directly after transplantation tapered in 3 weeks to 150 µg/l (measured by high pressure liquid chromatography), azathioprine 1-3 mg/kg and prednisolone 15mg daily, after induction therapy with Rabbit anti-T-lymphocyte Globulin (rATG) (National Institute of Public health and Hygiene (RIVM), Bilthoven, The Netherlands). He was treated three times for acute rejection with methylprednisolone 1000 mg intravenously for 3 days. Serology for cytomegalovirus of both donor and acceptor were negative. On chest X-rays the fibrotic changes in the native lung seemed to diminish 12 months after transplantation during triple immunosuppressive medication (figure 1B). From September 1992 on, a progressive decline in the ventilation on scintigraphy of the graft was observed. Until May 1993, the FEV\(_1\) improved. In December 1993, transbronchial biopsies revealed the histologic diagnosis of obliterative bronchiolitis. Analogous to the ISHLT-criteria, our patient developed BOS grade 1 and grade 2 at respectively 42 and 55 months after transplantation. A recent chest X-ray, more than 8 years after transplantation, showed a complete obliterated left lung (figure 1C). Moreover, the ventilation percentage and perfusion percentage of the graft were both <5%. Due to the improved function of the native lung, this patient will probably never reach BOS.
grade 3. Therefore, an indexed FEV\textsubscript{1} (FEV\textsubscript{1c}) was calculated by multiplying the FEV\textsubscript{1} with the percentage of ventilation of the graft, performed both in the same period of time (figure 3\textsuperscript{6}). This has been previously done in predicting postoperative lung function after lung resections\textsuperscript{7}. With the FEV\textsubscript{1c}, our patient developed BOS grade 1, 2 and 3 respectively 9, 15, and 21 months after transplantation.

Figure 1A: Chest X-ray, one year before transplantation. Visible is the reticulonodular pattern.
Figure 1B: Chest X-ray, one year after transplantation. Decrease of the reticulonodular pattern of the native lung.
Figure 1C: A recent chest X-ray, eight years after transplantation. Nearly complete obliteration of the graft and improvement of the native lung.
Figure 2: Timecourse of the FEV$_1$, the TLC and medical treatment before lung transplantation.

Figure 3: The timecourse of the FEV$_1$, the corrected FEV$_1$ of the native lung and the corrected FEV$_1$ of the transplanted lung.
Discussion:

Idiopathic pulmonary fibrosis (IPF) is a parenchymal lung disease of unknown etiology. The time course of this disease is variable with a median survival between 4 to 5 years after diagnosis. Traditional treatment consists of corticosteroids. In case of worsening of the patient’s condition adjustment of other immunosuppressive medication is recommended like cyclophosphamide, cyclosporine and azathioprine to control the inflammatory and immune cell response.

In our patient, it appeared that the UIP responded well to the combination of cyclosporine, azathioprine and prednisolone, possibly due to the more intensive maintenance immunosuppression during a longer period of time in comparison with the situation before LgTX. An improvement of pulmonary fibrosis with triple immunosuppression following LgTX is mentioned in only two other case reports, one with an initial histologic diagnosis of desquamative interstitial pneumonitis and one with UIP. These cases and our report together suggest that interstitial lung diseases may respond to more aggressive immunosuppressive treatment. Alternatively, a potential role of rATG (induction) may seem less likely, in view of the slow improvement of the native lung in time, but cannot be ruled out. Literature data on a beneficial role for ATG with respect to UIP, however, are lacking.

Abnormalities in ventilation scintigraphy and occurrence of BOS are earlier described by Halverson et al. Frequent pulmonary function tests and ventilation scintigraphy after transplantation were helpful in determining the time course of improvement of the native lung and occurrence of BOS. The TLco/Va, a marker for the diffusion capacity in which the transfer factor for carbon monoxide is corrected for the alveolar volume, continued to improve from 1.07 mmol/min/kPa/l (6 months after LgTX) until 1.69 mmol/min/kPa/l (7 years after LgTX). Shortly after transplantation, the scintigraphic percentage of ventilation of the graft was 50%. After one year, however, the ventilation percentage of the graft started to decline compared to that of the native lung, pointing at either an improvement of the native lung or a deterioration of the graft.

The FEV\textsubscript{1} started to decline nearly 2 1/2 years post-transplantation. After single lung transplantation, measurements of the pulmonary function can unpredictably be influenced by the function of the native lung. This results in an overestimation of the actual function of the graft. In this case, a diagnosis of BOS with the FEV\textsubscript{1}c was made over 33 months earlier comparing with BOS grade 1 analogous to the ISHLT-criteria. It shows that these criteria may not reflect the graft function in single lung transplant recipients.

Early detection of BOS is mandatory, as augmentation of immunosuppression or a switch in immunosuppressive medication, may slow down the progression of the decline in pulmonary function.

Our patient survived, despite loss of graft function, due to improvement of function of the native lung. His exercise capacity and quality of life are well preserved. He is kept on triple immunosuppressive therapy, although side effects of chronic cyclosporine therapy, most notably a decline in renal function, are manifest. We feel that this patient is fortunate not to have received a double lung transplant, because at the moment no medical therapy is available for end-stage BOS. We conclude that, attention should be given to protocols of triple immunosuppression for treatment of UIP.
Chapter 6

References: