

A Lung Transplant in a Woman With Bronchiolitis Obliterans Following an Allogenic Bone Marrow Transplant

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Graft-versus-host disease is a major complication for bone marrow transplant recipients and is often a cause of late mortality. It can affect any tissue, and involvement of the lungs—target organs of particular importance—can lead to chronic respiratory failure due to bronchiolitis obliterans.

We report the case of a lung transplant in a woman who developed bronchiolitis obliterans after receiving a marrow transplant to treat bone marrow aplasia. Three years later, clinical course was satisfactory, with full functional recovery.

Key words: Bone marrow aplasia. Bone marrow transplantation. Bronchiolitis obliterans. Lung transplant.

Trasplante pulmonar por bronquiolitis obliterante tras trasplante alogénico de médula ósea

La enfermedad del injerto contra el huésped es una complicación importante de los pacientes sometidos a trasplante de médula ósea, en quienes es causa de una elevada mortalidad tardía. Puede afectar a cualquier tejido y, cuando afecta a los pulmones, que son órganos diana de particular relevancia, acarrea insuficiencia respiratoria crónica secundaria al desarrollo de bronquiolitis obliterante.

Presentamos el caso de una paciente con trasplante pulmonar por bronquiolitis obliterante tras haber recibido un trasplante de médula ósea por aplasia medular. La evolución tras el trasplante pulmonar, a los 3 años de seguimiento, es favorable, con recuperación clínica y funcional completa.

Palabras clave: Aplasia medular. Trasplante de médula ósea. Bronquiolitis obliterante. Trasplante pulmonar.

Introduction

Allogenic bone marrow transplantation (ABMT) is an established treatment with good curative potential for several blood diseases.¹ Chronic graft-versus-host disease (GVHD) is a major complication of this procedure and is the main cause of late mortality after ABMT. The signs and symptoms of GVHD are similar to those of autoimmune diseases that affect various organs such as the kidney, liver, mouth, eyes, gastrointestinal tract, lungs, and soft tissues. Bronchiolitis obliterans is a particularly serious complication occurring in 10% to 15% of patients with extensive GVHD^{2,3} and is often refractory to treatment. If a patient does not respond to conventional immunosuppressive treatment after 3 to 6 months, the prognosis is poor.

We report the case of a patient with refractory bronchiolitis obliterans following an ABMT. The patient subsequently developed a terminal lung disease, for which she was successfully treated by lung transplantation.

Case Description

When the lung transplant patient we describe was an 8-year-old girl with severe aplastic anemia, she received an ABMT from her major histocompatibility complex-matched brother. Intravenous cyclophosphamide was administered as a conditioning regimen. The first week after the transplant she received intravenous methotrexate as prophylaxis for GVHD.

The immediate period after the ABMT was uneventful. On day 58 after that procedure, moderate skin and liver manifestations began to develop. Biopsy of the skin lesions confirmed GVHD, which was treated with high doses of prednisone. This dosage was later reduced to 1 mg/kg/d; then, as the patient's condition had become chronic, cyclophosphamide and azathioprine were added to the regimen, administered every other day.

One hundred twenty days after ABMT the girl developed progressive dyspnea, along with cough, purulent expectoration, and diffuse wheezing. Despite intense bronchodilator and corticosteroid treatment, her condition rapidly progressed to severe respiratory obstruction and hypoxemic respiratory failure. The chest x-ray showed lung overinflation and an evident interstitial pattern with signet ring signs indicative of diffuse bronchiectasis, which a high-resolution computed tomography (HRCT) chest scan confirmed (Figure 1). Bronchiolitis obliterans was diagnosed through fiberoptic bronchoscopy and transbronchial biopsy.

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Manuscript received April 28, 2005. Accepted for publication May 24, 2005.



Figure 1. High-resolution computed tomography scans of the chest before the lung transplant. The scan reveals bilateral saccular bronchiectases predominantly in the center. Distal to these are areas of hypoventilation and bronchial wall enlargement.

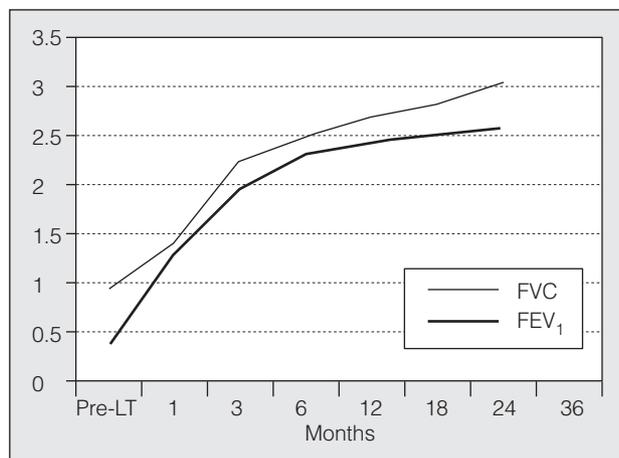


Figure 2. Course of lung functional recovery after the lung transplant. LT indicates lung transplant; FVC, forced vital capacity; FEV₁, forced expiratory volume in first second.

The patient's condition remained unchanged with few spirometric modifications for 17 years, during which she experienced multiple respiratory infections due to gram-negative microorganisms, essentially *Escherichia coli*. In the last year the patient required continuous oxygen therapy and liquid oxygen in order to walk.

She was then admitted to our hospital for lung transplant evaluation. The clinical assessment showed the patient's functional status was class III (New York Heart Association scale) with dyspnea on minimal exertion. On physical examination, Cushing-like signs, an increase of dorsal kyphosis, and clubbing in the hands were noted. Lung sounds revealed generalized decrease in vesicular murmur with diffuse crackles in both lung fields.

We discussed our recommendation for lung transplantation with the patient. She was then admitted for final evaluation

according to our unit's protocol.⁴ Assessment showed her kidney, liver, heart, and hematopoietic functions were normal, and screening for panel reactive antibodies was negative.

Spirometry revealed a forced vital capacity of 920 mL (27%), forced expiratory volume in first second of 380 mL (13%), total lung capacity of 6410 cm³ (156%), and residual volume of 5610 mL (489%). Blood gas analysis at rest showed a PaO₂ of 56 mm Hg and PaCO₂ of 48 mm Hg.

The patient was accepted as a lung transplant candidate, and after 3 months on the waiting list, she underwent bilateral sequential lung transplantation of grafts from a cadaver donor with matching blood type.

Surgery as well as recovery was uneventful. She was discharged 21 days after the intervention with no episodes of rejection or infection.

Since the lung transplant the patient has been receiving an oral antirejection immunosuppressive regimen with corticosteroids at minimum doses and mycophenolate mofetil and cyclosporin adjusted according to trough levels. Periodic outpatient revisions have found her asymptomatic, and 3 years after the transplantation she leads an active normal life with no evidence of rejection or signs of bronchiolitis obliterans. The HRCT scan of the chest at 36 months revealed normal lung parenchyma and airways. Functional recovery has been progressive since the first months after the lung transplant (Figure 2).

Discussion

Bronchiolitis obliterans following ABMT occurs between 10% and 15% of patients with GVHD. The cause of this disease remains unclear.^{2,3} Related factors include older age, viral infections, autoimmunity, total body radiation, a history of acute GVHD (1 to 2 months after ABMT), stem cell rather than bone marrow transplants, and a history of interstitial pneumonia.³

Bronchiolitis obliterans generally manifests in the first year after the ABMT, as it did in our patient. The most common symptom reported is unexplained recurrent and persistent cough. Diagnosis is established through lung function tests that demonstrate irreversible airway obstruction. Initially, chest x-rays are normal. An HRCT scan of the chest may show bronchial dilatation, a ground-glass pattern, and evidence of air trapping during expiration.¹

Management of such patients includes immunosuppressive therapy such as corticosteroids, cyclosporin, azathioprine, or mycophenolate mofetil, as well as bronchodilators, antibiotics, and immunoglobulins. If the patient does not respond after 6 months of treatment, the prognosis worsens. Despite immunosuppressive treatment, most series report a mortality rate greater than 50% during this period.⁵

Reports of sporadic cases or small case series of lung transplants to treat bronchiolitis obliterans after ABMT have appeared.⁶⁻¹⁰ Calhoun et al⁷ reported a case of a 25-year-old woman with acute lymphoblastic leukemia and restrictive lung disease treated successfully with a single-lung transplant; at 9 months of follow-up she remained asymptomatic and unrestricted in her daily activities. Gascoigne and Corries⁶ reported a similar

case in which the patient died 9 months later. In a case reported by Svendsen et al⁸ a patient received a living related lobar lung transplant as a treatment for bronchiolitis obliterans occurring after an ABMT for marrow aplasia; the patient was alive at 14 months. Rabitsch et al⁹ reported the case of a man with ABMT for chronic myeloid leukemia. He developed GVHD, for which he received a double-lung transplant 18 months after the ABMT; 23 months later he remained alive with no signs of respiratory failure. Heath et al¹⁰ reported 4 cases of chronic, irreversible lung disease between 1 and 3 years after an ABMT during childhood; one of these cases was a 6-year-old girl with marrow aplasia, similar to the case we report. In all 4 cases a significant improvement in the clinical picture was observed, and lung function became normal within 1 year.

Although in theory, a patient who had undergone ABMT might be at higher risk of acute or chronic rejection after lung transplantation because of the amount of immunocompetent leukocytes present in the donor lung, our patient experienced no episodes of acute rejection and has remained free of bronchiolitis obliterans. This observation is interesting, and duration and the amount of immunosuppressive therapy before the lung transplant therefore warrants particular attention. As mentioned above, our patient received diverse immunosuppressant drugs (methotrexate, prednisone, cyclophosphamide, and azathioprine) during the time between the bone marrow transplant and the lung transplant. The GVHD and immunosuppression could have impaired her alloreactivity, thus facilitating a better adaptation to the graft. Two of 3 reported cases^{7,8} also received immunosuppressants over long periods of time before lung transplantation with no clinical evidence of later rejection. Previous studies show that immunosuppression in the transplant recipient may lead to a low response to alloantigens. Such a state is conducive to better survival of the graft.¹¹

Another important aspect to consider is the reason for the ABMT. Among the diverse series reported we have only found 2 cases^{8,10} in which the patients underwent ABMT because of marrow aplasia, then

developed GVHD, and subsequently received lung transplants. Malignant blood disease was the reason for ABMT in the remaining cases.

It has been 21 years since our patient's bone marrow transplant and 36 months since the lung transplant, and she currently maintains complete hematologic remission and normal lung function. In our opinion, lung transplantation is an option for certain patients who develop terminal lung disease after ABMT, in whom the lung is the main target organ of GVHD, and who do not respond to conservative treatment.

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