Accelerated form of interstitial pulmonary fibrosis in the native lung after single lung transplantation*

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Abstract

We report the case of a 56-year-old patient who underwent left single lung transplantation for idiopathic pulmonary fibrosis (IPF). Despite the high level of immunosuppression after the surgery, there was rapid progression to IPF in the native (right) lung as demonstrated by thoracoscopic lung biopsy. After 104 days on mechanical ventilation (MV), the patient underwent right lung transplant and was discharged from the hospital on postoperative day 26.

Keywords: Idiopathic pulmonary fibrosis; Lung transplantation; Case reports [publication type].

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic disease with progressive evolution to incapacitating respiratory failure, despite drug treatment. Other idiopathic interstitial pneumonias, such as desquamative interstitial pneumonia, acute interstitial pneumonia/diffuse alveolar damage, lymphocytic interstitial pneumonia, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, and respiratory bronchiolitis accompanied by interstitial lung disease, can present a more favorable clinical, therapeutic, and prognostic evolution than does IPF.¹ As a result, lung transplantation qualifies as one of the treatment options in IPF patients.

Lung transplantation center reports collected and published by the International Society for Heart and Lung Transplantation in 2003 cited that IPF is the second leading indication for transplantation, after pulmonary emphysema.² The criteria for indication of lung transplantation are not the same for all diseases. In patients with IPF, the criteria considered are vital capacity or total lung capacity ≤ 60% of the predicted value, diffusing capacity of the lung for carbon monoxide corrected for alveolar volume ≤ 50% of the predicted value, arterial blood gas analysis with arterial oxygen tension (PaO₂) ≤ 55 mmHg, and alveolar-arterial oxygen gradient ≥ 30 mmHg at rest.² In the clinical criteria, the progressive increase of dyspnea indicates transplantation. However, it should be accompanied by worsening of pulmonary function or exacerbation of labor capacity scores.¹,³,⁴

In clinical, tomographic and pathological terms, the case presented here demonstrates the accelerated fibrosing evolution in the native contralateral lung, characterizing a subtype of IPF, with exacerbation of the clinical profile,

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deterioration of pulmonary function, intensification of pulmonary infiltrates, and maintenance of the histological pattern of usual interstitial pneumonia (UIP).  

**Case Report**

A 56-year-old man diagnosed with IPF (using clinical, functional, tomographic and pathological criteria) five years prior, progressively evolved to dyspnea upon exertion and intense difficult-to-control cough with sparse mucoid expectoration. In the month preceding the lung transplantation, he presented hypoxemia and hypercapnia (arterial blood gas analysis with a PaO₂ of 57 mmHg and arterial carbon dioxide tension of 45 mmHg at rest on room air at sea level), diffusing capacity of the lung for carbon monoxide at 29% of the predicted value, forced vital capacity of 40.8% (1.41 L), and forced expiratory volume in one second of 52.6% (1.31 L). Pulmonary perfusion scintigraphy revealed arterial flow of 76.7% for the right lung and 23.3% for the left lung. The laboratory tests for collagen-related diseases and the epidemiological investigation of known interstitial diseases were negative. During the five years of outpatient monitoring, the patient had been treated with corticosteroids (prednisone, 0.25 to 1 mg/kg/day), immunosuppressive agents (azathioprine or cyclophosphamide, 0.5 to 2 mg/kg/day), and an antifibrotic/immunomodulatory agent (interferon-γ1b) for four months. The transplantation was unilateral at left, corresponding to the minimal arterial perfusion and the greater intensity of the interstitial involvement according to the high-resolution computed tomography (HRCT) scan. Immediately after surgery, the patient evolved to thoracic instability due to the fracture of three ribs as a result of the osteopenic rib traction during the closure of the incision. He also presented ischemia of severe pulmonary reperfusion (arterial blood gas analysis with a PaO₂/fraction of inspired oxygen ratio = 124). The patient was tracheostomized and remained on invasive mechanic ventilation (MV) for ten days, progressively recovering from hypoxemia. The immunosuppressive regimen began with 5 mg/kg of cyclosporine (12/12 h), 0.5 mg/kg/day of prednisone, and 2 mg/kg/day of azathioprine. In addition, anti-basiliximab interleukin-2 antibody was administered on postoperative days 1 and 4. Anti-methylprednisolone antibody (1 g) was also administered postoperatively. The patient was discharged from the intensive care unit to the semi-intensive care unit. However, on the eighth day in the semi-intensive care unit, he presented exacerbation of dyspnea, accompanied by the return of the dry cough and progressive crackling rales throughout the right hemithorax, and was therefore re-admitted to the intensive care unit. The patient was again submitted to an HRCT scan. In addition, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was performed, together with transbronchial biopsy of the left lower lobe and the right upper lobe. All cultures tested negative, the BAL fluid presented a neutrophilic pattern, without eosinophils or hemosiderin-laden macrophages, and the histopathological analysis was inconclusive. A pulmonary arteriogram was performed, followed by thoracoscopic lung biopsy in three different regions of the right upper lobe to ensure that the disease was representative (Figures 1 and 2). The pulmonary arteriogram did not demonstrate thromboembolic disease. The biopsy culture was negative for bacteria, fungi, and mycobacteria. Herpes simplex virus and cytomegalovirus tests were also negative. Direct immunofluorescence for *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*, as well as for antigenuria for *L. pneumophila* serotype 1, were negative. The histological study of the biopsy of the...
three right lung areas showed an exclusive pattern of UIP, similar to the left native lung (Figure 3). Pulse therapy with 1 g of methylprednisolone was performed for three consecutive days. The patient remained on invasive MV, then evolved to sepsis caused by infection with *Klebsiella pneumophila* and *Pseudomonas aeruginosa*. On day 141 of the hospital stay, after the patient had been on invasive MV and using noradrenaline (0.2 µg/kg/day) for 109 days, transplant of the right native lung was carried out – bilateral sequential transplantation with more than a month interval – regardless of the relative contraindications: high dose of corticosteroid (>20 mg/day), MV, and sepsis treatment. On day 31 after the second transplantation, the patient was discharged from the hospital, without the need for oxygen supplementation. Two years later, he was still in follow-up treatment with a new immunosuppressive regimen: sirolimus (2.5 mg/day), azathioprine (50 mg/day), and prednisone (5 mg/day).

**Discussion**

In the 1960s, studies on idiopathic interstitial lung diseases were conducted using lung biopsy material, and various histological patterns for idiopathic interstitial pneumonias were established. Currently, it is known that the histological pattern can be similar in several diseases. For example, the UIP pattern is seen in IPF, collagen-related diseases, and asbestosis. Therefore, it is necessary to evaluate HRCT findings, pulmonary function, clinical status, and therapeutic response in conjunction in order to establish an accurate diagnosis. The patient presented an UIP pattern in the lung biopsy performed five years prior to the transplantations.

The acute interstitial pneumonia/diffuse alveolar damage syndrome, or Hammam-Rich disease, presents rapid clinical progression (weeks), areas of diffuse ground-glass attenuation on the HRCT scan, and indistinguishable histological pattern of acute respiratory distress syndrome. In this case, the hyaline membrane that characterizes the acute respiratory distress syndrome and the diffuse alveolar damage was not identified in the material studied.

Nosocomial pneumonia (bacterial, viral, protozoan or fungal), acute eosinophilic pneumonia, cryptogenic organizing pneumonia, and pulmonary thromboembolism were investigated using the gold standard methods (biopsy for the parenchymatous infectious and infiltrating processes and arterio-
The radiological imaging demonstrated condensation in the middle, upper, and lower right lobes, and the established diagnosis was IPF exacerbation in the native lung, mainly characterized by the UIP histological aspect (nonuniform and multifocal infiltrate, with inflammatory and fibrous thickening of the alveolar interstitium, pulmonary cysts, peribronchial fibrosis, alveolar hyperplasia, and absence of hyaline membranes), and the absence of microbial increase in lung tissues and cardiovascular decompensation. It is known that, in IPF, the lung becomes progressively collapsed, which can simulate images of pulmonary condensation. The accelerated variant of IPF has recently been described and should have its diagnosis characterized by ruling out other causes of exacerbation. The literature mentions, in unilateral lung transplantation, chronic progression of IPF in the native lung. However, there have been no reports of acute progression. This is the first case described in the national literature as IPF in its accelerated phase.

Acknowledgement

The authors would like to thank Dr. Roberto José de Lima and Dr. Margareth Pretti Dalcolmo, as well as the entire postoperative ICU team of the Barra D’Or Hospital.

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