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Case Report
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Lung Cancer Lymphatic Drainage and Bilateral Lung Transplantation

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Abstract

A 25-year-old female patient with cystic fibrosis underwent bilateral lung transplantation. A solitary lung nodule was discovered in the left upper lobe two years following transplantation. After thorough work-up and a biopsy proving the nodule to be an adenocarcinoma, a left upper lobectomy including complete mediastinal lymphadenectomy was performed. The analysis demonstrated adenocarcinoma with hilar and mediastinal metastatic lymph nodes, confirming that the lymphatic vessels draining the transplanted lungs restored their continuity to the mediastinum. However, the immunological response to the lymphatic system of donors is poorly understood and the genetics of cancers occurring in such lungs deserve further study.

Keywords: Lung transplantation; Donor derived cancer; NSCLC; Lymph nodes

Introduction

Unlike normal lungs, there is little data on the anatomy and physiology of Lymph Nodes (LN) and Lymphatic Vessels (LV) that drain the transplanted lungs (LTx). The edema observed immediately after LTx ("primary graft failure"), is mainly the consequence of LVs interruption [1]. The regeneration of LVs might play a role in the rejection induction, local immune response and occurrence of obliterative bronchiolitis [1]. Lung Cancer (LC) is a disease that can now be encountered in recipients of a graft lung: we observed a NSCLC that occurred after a bilateral LTx and whose pathological examination recalled a more banal role of the LV regenerated after their interruption.

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Case Report/Description

A 25-year-old woman with cystic fibrosis diagnosed at birth, suffered from history of chronic methicillin-resistant Staphylococcus aureus and Pseudomonas related colonization. She presented several episodes of allergic bronchopulmonary aspergillosis and a progressive chronic respiratory failure that finally evolved towards severe hypoxemia with acute respiratory distress syndrome. Despite continuous non invasive ventilation and antibiotic therapy, no improvement was observed: the partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2) was 65 mmHg and 80 mmHg, respectively, with a pH of 7, 28. She was treated by veno-venous Extracorporeal Membrane Oxygenation (ECMO) as a bridge to lung transplantation and inscribed on the high-emergency national waiting list.

Three days after the inscription, in June 2014, she underwent bilateral LTx. The donor was a 48-year-old man, with smoking history (28PA) and discrete diffuse pulmonary emphysema. The PaO2/FiO2 ratio (oxygen fraction of inspired air) was correct (517 with 100% FiO2). Postoperative course was marked by hemodynamic instability requiring ECMO support for five days. Immunosuppressive treatment was conventional with Prednisone, Tacrolimus and Mycophenolatemofetil. The patient was discharged 31 days after surgery.

Eighteen months after LTx, a pulmonary embolism was diagnosed. The chest CT revealed a solitary pulmonary nodule in the left upper lobe measuring 12mm, with 18F-FDG uptake SUV (standardized uptake value) max of 6.5. There were two suspect peribronchial LNs, one near the lower lobe bronchus – behind the left main bronchus (SUVmax of 5.4), and the other one, on the bifurcation of upper and lower lobe bronchi (SUV max of 5.2). The cerebral magnetic resonance imaging was normal, and the bronchial fibroscopy was not contributive. Lung scintigraphy showed a left lung perfusion of 42%. Spirometry was subnormal with forced expiratory volume in one second of 71% and vital capacity of 93% of predicted values. The CT-guided biopsy revealed

an adenocarcinoma. After multidisciplinary discussion, surgery was decided. Intra-operative examination revealed a para-aortic LN (mediastinal LN station 6) besides the clinically identified LNs (station 11 and 10). An isolated 5 mm posterior parietal pleural lesion was also discovered and completely resected. A left upper lobectomy with complete mediastinal lymphadenectomy was performed. The postoperative course was uneventful.

Pathologic analysis confirmed a poorly differentiated invasive adenocarcinoma measuring 20mm with lymphovascular involvement. All resected LNs were tumoral. The cross section of the left upper bronchus presented some lymphatic emboli. Pathology classification was pT1N2M1a, the visceral pleura was not involved, and the parietal pleural nodule was metastatic. Cytogenetic analysis of the tumor confirmed that the cancer originated from the donor cells. A k-Ras mutation was also discovered. Because of massive lymphovascular involvement, the multidisciplinary team decided a platinum-based chemotherapy associated with Paclitaxel and Bevacizumab. The Tacrolimus treatment was reduced and the MycophenolateMofetil was stopped. Paclitaxel treatment was stopped for peripheral neuropathy. The patient developed multiple hepatic and bone metastasis and died 8 months after surgery.

Comment

The incidence of cancers in 1000 person-years after LTx is 19.8 and LC is the one with the highest incidence (5.94%), followed by posttransplant lymphoproliferative disorder (5.72%) and colorectal cancer (1.38%) [2]. LC may be observed on the explanted lung [3]. More frequently, it is observed on the native lung after single LTx. Dickson and colleagues [4] observed that 6.9% of the single LTx recipients developed primary NSCLC as compared with 0% of the bilateral LTx recipients after a mean of 52 months: it is worth stressing that the NSCLC were present in the native lung of patients with smoking history. Grewal and colleagues [3] reported similar results. However, they also observed one LC originating in the allograft and potentially donor related [3]. LC in the donor lung is not frequent. In a series of 13 patients who developed LC, 9 occurred in the native lung in 92 single LTx and 4 were donor related, all after bilateral LTx (n = 224) [5]. The incidence of post LTx NSCLC will probably increase in the future. The limited number of available donor compared to the increase of patients on the waiting list leads to liberalization of donor criteria with older patients, tobacco history and chest radiograph with abnormality as was the case in our observation. In addition, it was a highly urgent lung transplant: the condition of our patient was extremely serious and her life dramatically endangered which urged to accept a donor of an advanced age with tobacco history and lung emphysema.

During the donor lung transplantation the LVs are overlooked and their anastomosis not performed. It has been demonstrated in dogs that lung lymphatic drainage is re-established 7-28 days after auto LTx and becomes relatively sufficient shortly thereafter [6]. Although such study does not exist in man, it is logical to postulate that LVs are similarly regenerating. However, the immunological response to transplanted donor LNs and LVs is poorly known and remains a topic of research [1]. Similarly, the genetics and immunogenicity of NSCLC from such lungs may be those of the recipient or donor, as many questions as future studies may elucidate further. Whatever it may be, the NSCLC generally occurs due to risks factors inherent to the donor of the lung, mainly the tobacco smoking habits. The presence of the k-ras mutation supports this theory. In fact, NSCLC is not induced by posttransplantation immunosuppressive drug therapy, and in the same way, NSCLC postoperative course was demonstrated to be independent from a continuation of this treatment [7]. In 2006, Sleeman JP [8] reminded that there was an active relationship between the tumor and the lymphatic system. To form LN metastasis, the tumor is able to produce some growth factors (VEGF-C, VEGF-D) that lead to activation of some receptors as VEGFR-3. In our observation, the pulmonary LNs involved originate from the donor and the mediastinal LNs are from the recipient. The relationship between the tumor and the lymphatic system does not seem to have been altered.

To our knowledge, this is the first case report describing a metastatic NSCLC to mediastinal LN that comes from a donor lung and demonstrates the recovery of lymph drainage after LTx. Such an observation raises the problem of the immunological response to the transplanted lymphatic system and the genetics of cancer in the lung of the donor.

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