Metachronous Pulmonary Neoplasms in Lung Transplantation—When They Arise in the Donor Lung: A Case Report

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ABSTRACT

Lung cancer (LC) is uncommon among lung transplant recipients, being most often described in the native lung of single-lung transplant recipients. Its appearance in the transplanted lung is a very uncommon phenomenon, in which donor and recipient factors appear to be involved. We present a case of 2 distinct metachronous lung neoplasms diagnosed in the transplanted lung of a non-smoker patient with progressive massive silicosis (PMS), who underwent left unipulmonary transplantation at 39 years. The donor was a smoker and thoracic computed tomography (CT) performed before the organ collection showed no abnormalities. Thirty months after transplantation, a new node with significant avidity in positron emission tomography (PET)-CT was diagnosed in the upper left lobe (ULL). The Thoracic Surgery team chose to proceed directly to surgery with atypical resection of the nodule. Anatomopathologic study revealed an epidermoid carcinoma (pT1aNx). Multidisciplinary group decided clinical surveillance; however, 2 years later, the appearance of 2 new nodules in the ULL (PET-CT positive) was observed. It was again decided to proceed to the surgery with a second atypical resection. The anatomopathologic study of one nodule revealed pulmonary adenocarcinoma (pT1aNx), and the other was compatible with epidermoid carcinoma (pT1aNx). One month later, the patient was hospitalized with a pulmonary abscess and posteriorly developed a probable acute allograft rejection, eventually dying at the age of 44, 51 months after transplantation. This case raises relevant questions regarding the donor selection criteria and the approach to LC diagnosed in the post-transplantation period.

LUNG cancer is an uncommon but increasingly recognized complication in lung transplant recipients. The global survival improvement, the increased number of transplants in patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, and the liberalization of donor selection criteria seem to contribute to the increase of cancer diagnoses in this population. Although lung cancer is more frequently found in the native lung of unitransplanted patients, it is also seen in transplanted lungs, raising additional questions about the exact role of immunosuppression, receptor, and donor factors in oncogenesis.

We present what we believe to be the first case of 2 histologically distinct metachronous neoplasms in the donor lung of an unitransplanted non-smoker patient. A literature review of lung cancer cases in transplanted lungs is also performed.

CLINICAL CASE

A Portuguese 43-year-old man was diagnosed in 2007 with silicosis with progressive massive fibrosis. He worked for 24 years in the drilling of wells with sand jets. There was no smoking history. The disease progressively evolved with chronic respiratory failure requiring oxygen therapy. Functionally, there was a moderately severe restrictive syndrome (forced vital capacity: 3300 mL [59%]) with a moderate defect in lung diffusing capacity for carbon monoxide (20.2 mL/min/mm Hg [52%]). He was referred to lung

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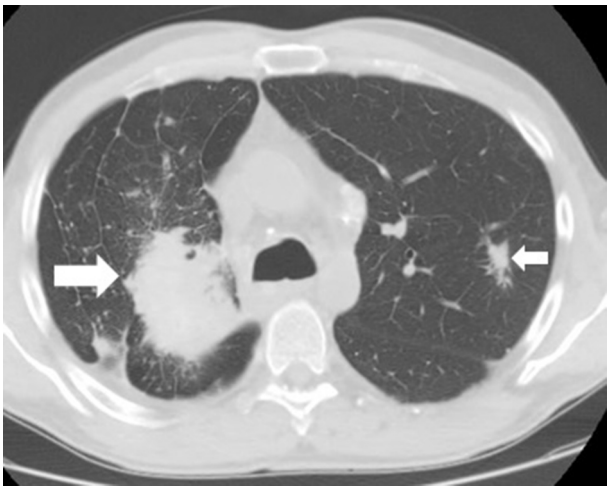

Fig 1. Thoracic CT (parenchymal window): spiculate pulmonary nodule in the left upper lobe with 1 cm maximum diameter (small arrow) and pulmonary mass in the right upper lobe corresponding to a previously known silicotic lesion (large arrow).

transplantation in Coruña center (Complexo Hospitalar A Coruña, Spain) and submitted to a left unipulmonary transplantation in March 2011. His donor was a smoker and had a normal thoracic computed tomography (CT) before the transplantation. There were no complications in perioperative period. An immunosuppression scheme including tacrolimus, mycophenolate mofetil, and prednisolone was initiated. The patient maintained clinical surveillance with functional autonomy. In September 2013, 30 months after transplantation, thoracic CT revealed a spiculate pulmonary nodule of 1 cm in left upper lobe (LUL) (Fig 1). Hilar and mediastinal ganglia presented similar characteristics when compared to previous images. In positron emission tomography-computed tomography (PET-CT) there was an abnormal fluorodeoxyglucose avidity in the newly described lesion (maximum standardized uptake value: 4.4), but also in right bronchohilar and bilateral mediastinal ganglia, as well as in a perihilar right mass corresponding to a previously known silicotic lesion. Cardiothoracic surgery decided to proceed to surgery. The patient underwent left video-assisted thoracoscopic surgery with atypical resection in the LUL (after extemporaneous exam confirming malignancy) and excision of a periaortic ganglion. The anatomopathologic study revealed an epidermoid carcinoma (pT1a). There was no invasion of visceral pleura, and surgical margins were negative. There was no evidence of malignancy in the removed ganglia. In a multidisciplinary group, a conservative approach with clinical and imagologic surveillance was decided. The patient maintained clinical stability and autonomy for daily activities.

Two years later, routine thoracic CT revealed 2 new nodules of 1 and 1.1 cm in the LUL (Fig 2). In PET-CT, there was significant avidity for both lesions with no other new findings comparing the previous exam. It was again decided to proceed to a second atypical resection with nodule excision by video-assisted thoracoscopic surgery. Postoperative recovery was uneventful and the patient was again discharged. Anatomopathologic examination of surgical specimen revealed a pulmonary adenocarcinoma (pT1aNxR0) in one nodule and an epidermoid carcinoma (pT1aNxR0) in the other nodule, both lesions with no signs of invasion of visceral pleura. Mycophenolate mofetil was replaced by everolimus considering the antiproliferative properties of the latter and the patient maintained surveillance.

A month after surgery he was admitted in our institution with a pulmonary abscess in left lower lobe. Large-spectrum antibiotic treatment was initiated with clinical and radiologic response.

One month after discharge, he was again admitted with hemoptysis and type 1 respiratory failure. Thoracic CT presented a ground glass infiltrate with thickening of interlobular septa in the left lower lobe. After a careful exclusion of infectious causes, an acute allograft rejection was suspected and the patient was transferred to Coruña hospital.

Considering the diagnosis of lung cancer of unknown stage and the possibility of metastization of the tumor diagnosed in 2013, it was decided in multidisciplinary group that the patient was not a candidate to a pulmonary

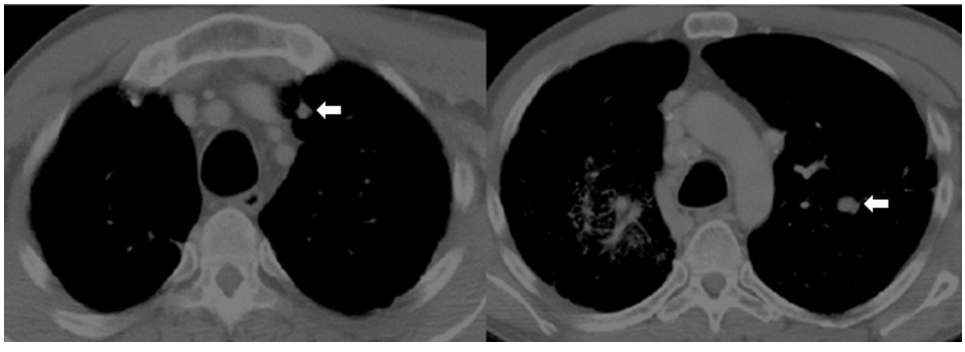

Fig 2. Thoracic CT (mediastinal window): 2 new pulmonary nodules (small arrows) in the left upper lobe with maximum diameters of 1 cm (right) and 1.1 cm (left).

retransplant. Despite the treatment with systemic corticosteroid pulses, there was a progressive deterioration of respiratory failure, and palliative care was prioritized. The patient was transferred to our institution, initially requiring continuous non-invasive ventilation. High flow oxygen therapy was initiated and continued in a palliative care unit with a significant comfort gain for the patient. Death occurred in April 2015, 51 months after lung transplantation, at 44 years of age.

DISCUSSION

Lung transplantation is a life-saving treatment for end-stage lung disease [1]. Malignant disease is a prominent complication in this setting, with non-melanocytic skin cancer and post-transplant lymphoproliferative disease constituting the most frequent post-transplant neoplasms [2]. In the last decade, lung cancer has been identified as an increasingly frequent condition after lung transplantation [3].

Pérez-Callejo recently reported a lung cancer incidence of 3.63% in a sample of 633 lung transplantations performed in his institution for 23 years (1994–2016) [4]. In the retrospective 10-year analysis performed by Belli et al, primary lung cancer after lung transplantation was identified in 13 of 335 cases (3.88%). Six tumors were diagnosed in the explanted lung, 6 in the native lung, and 1 in the donor lung. One-year survival in patients with cancer was 42.8%, while global survival for all lung transplantations was 85.7%. The only case of lung cancer of donor origin was diagnosed 1170 days after transplantation and referred to a 15-pack-year (PY) smoker donor. In this case, radiofrequency ablation was performed (stage IA) and the patient was alive at 11.2 months of follow-up [5].

The main reasons pointed to for the increased incidence of lung cancer in lung transplant recipients are the longer survival of lung recipients due to the improvement of the current treatments and care, the increasing proportion of patients receiving transplants for chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, and the liberalization of strict ideal donor selection criteria [6,7].

Lung cancer in lung transplant is more frequently found in the recipient's lung after unilateral transplantation (with an estimated incidence of 9%) [1,2], then in explanted lung (0.8%–2.0%) [8,9], and less often in donor lung (less than 1%) [1,2].

Due to the effectiveness of screening strategies for donor candidates, the incidence of lung cancer in the transplanted lung remains a rare event. The first case was reported in 2001 with a 25-year-old patient with cystic fibrosis with minimal smoker habits who developed metastatic small cell carcinoma 13 months after bilateral transplantation from a 50-year-old 10-PY patient. The patient started palliative chemotherapy with carboplatin and etoposide with no adverse reactions but eventually died a month later. Interestingly, molecular genetic analysis was performed confirming that the tumor was of donor origin [10].

Currently, there are some publications reporting lung cancer cases in transplanted lungs [7,10–21].

To our knowledge to date, this is the first case reporting 2 histologically distinct primary lung neoplasms in a transplanted lung. In this case, we believe that 3 main susceptibility factors should be pointed: the recipient heavy and prolonged exposure to silica, the immunosuppressor treatment, and the donor's smoking habits. Unilateral transplantation is also associated to an increased risk of lung cancer when comparing to bilateral transplantation, even after adjustment for native disease, age, and smoking history [22], which is attributed to a potential synergistic interaction between the recipient risk factors and the long-term immunosuppression effects. The carcinogenic potential of immunosuppressors seems to be related with a direct pharmacologic effect and with an indirect mechanism of breaking of immunologic antitumoral surveillance. Calcineurin inhibitors have recognized carcinogenic effects, mainly related to the inhibition of DNA repair mechanisms. Among this group, cyclosporine exhibits a higher risk of malignancy comparing to tacrolimus. Among purine synthesis inhibitors, azathioprine is associated with mutagenic proprieties, but mycophenolate mofetil seems to have no carcinogenic effect. In fact, its antiangiogenic proprieties and its interaction with adhesion molecules can have a potential role in lung transplantation setting. Mammalian target of rapamycin inhibitors exert antitumoral effects for several pathways, namely inhibiting vascular endothelial growth factor, signal transducer and activator of transcription 3, and protein kinase B pathway, being also suggested in observational studies as cancer modifier agents [23]. The switch for everolimus in our patient, after the knowledge of new tumors, was in line with that evidence.

Another reflection should be made about donor susceptibility factors. Unfortunately we could not access additional information about the donor (age, sex, quantification of smoking habits, and other expositional factors). In what concerns donor smoking habits, we know that in recent decades extended criteria for lung donors (including donors with smoking habits of more than 20 PYs) have been used cautiously to try to overcome the scarcity of organs. Although there is evidence reporting similar early outcomes for extended criteria comparing conventionally selected lung donors [6,24], middle- and long-term outcomes, as associated complications like lung cancer, are poorly known. In a single-center retrospective analysis from Shigemura et al, 532 lung transplant recipients were divided in subgroups according to their donor's age (<20 and ≥ 20 years) and smoking habits (nonsmokers, <20, 20–40, and >40 PYs). Surprisingly, in multivariate analysis, younger ages of donors were a risk factor for 5-year mortality in the non-smoking donor group. In the smoking donor group, heavy smoking (>40 PYs) was associated with severe primary graft dysfunction and higher short- and long-term mortality ($P < .05$) [25]. Nevertheless, current standards still contemplate the use of smoking donors, since the probability of survival is

higher in these patients compared to non-transplanted patients on the waiting list [26].

One year after atypical resection for epidermoid carcinoma, our patient presented with 2 new ipsilateral nodules in CT. The epidermoid carcinoma could represent a recurrence of the first neoplasm diagnosed in 2013 (and incompletely staged at that time). In both situations it was decided not to pursue with invasive ganglionic staging with endobronchial ultrasound-guided transbronchial needle aspiration or mediastinoscopy and to proceed directly to surgery. In fact, after the appearance of the 2 new nodules in 2015, lung biopsy of the lesions could have been performed and radiotherapy or chemotherapy could have been considered according to tumor staging.

Experience from chemo and radiotherapy for lung cancer in lung transplant recipients comes from small series reports. In advanced stages, prognosis seems to be significantly worse in transplanted comparing with non-transplanted patients [4,20]. Treatment-related toxicities seem to be remarkable in the first group. Du et al retrospectively revised a series of 847 lung transplant recipients.

From the 17 lung cancer cases (2%), 10 had chemotherapy (mainly platin-based duplets), and 30% of them developed grade 5 sepsis during treatment. Median survival after the initiation of chemotherapy was 7.5 months [20]. In Pérez-Callejo's series, the majority of deaths in patients with lung cancer were related to the primary tumor. The median time from lung cancer diagnosis to death was 10.6 months [4].

After genetic analysis, some of the lung cancers diagnosed in transplanted lungs are found to be of recipient origin. Chimerism is a key concept in this phenomena. It is known that from the first month after the transplantation, recipient macrophages and lymphocytes can be found in lung graft. In this case, considering the appearance of 2 histologically distinct neoplasms, it would have been useful to proceed to genetic analysis (fluorescence in situ hybridization, genotyping, or HLA phenotyping) [27].

Unfortunately, we could not access additional information about the donor (such as age, past medical history, quantification of smoking habits, and chronic medication). Despite this limitation, we believe that this rare and challenging case is of particular interest, allowing us to reflect on several aspects concerning the approach of neoplastic pathology in lung transplant recipients.

Given the inherent complexity and the still limited experience in lung cancer management in this population, their follow-up should be carried out by a multidisciplinary team.

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