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Case report

# Immunosuppression and lung cancer of donor origin after bilateral lung transplantation

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ABSTRACT

Analysis of databases from transplant recipients revealed a 3–5 fold higher risk to develop *de novo* malignancies under continued immunosuppression. The underlying mechanisms are poorly understood. Here we describe a patient who received a bilateral lung transplantation for end-stage 'Usual Interstitial Pneumonia' (UIP) resulting in idiopathic lung fibrosis. The recipient presented with a non-small cell lung carcinoma (NSCLC) in the donor lung 7 months later. Molecular and immunological typing of the tumor revealed a cancer of donor origin with a prominent intratumoral immune cell infiltrate without detectable effector function. This is a unique case of *de novo* outgrowth of a NSCLC of donor origin under continued immunosuppression, supporting the concept of tumor immunosurveillance *in vivo*.


## 1. Introduction

Advances in transplantation medicine have resulted in improved overall survival of organ transplant recipients. With longer survival, chronic complications, including the development of secondary malignancies, are more likely to occur. Analysis of databases from transplant recipients showed that the risk to develop *de novo* malignancies is 3–5 fold higher in organ transplant recipients under continued immunosuppression [1–3]. Over the past 20 years, non-small cell lung carcinoma (NSCLC) development has been described in the setting of single lung transplantation. The carcinoma was found in the recipient's native lung [4]. After bilateral lung transplantation, there is one report of *de novo* NSCLC of recipient's origin [6]. A case of donor acquired small cell lung carcinoma (SCLC) has been described in the setting of bilateral lung transplantation [5].

Here we describe a patient, who received a bilateral lung transplant as treatment for end-stage 'Usual Interstitial Pneumonia' (UIP) resulting in 'Idiopathic Lung Fibrosis'. The recipient developed a non-small cell lung carcinoma in the donor lung 7 months later. Molecular and immunological typing of the tumor revealed a cancer of donor origin with a prominent intratumoral immune cell infiltrate deficient of any detectable effector function.

## 2. Materials and methods

### 2.1. Laboratory parameters

Retrospective analysis of hospital electronic laboratory records was performed. Hematological, biochemical and coagulation samples were obtained.

### 2.2. Molecular typing

An representative paraffin block containing tumor tissue was selected for analysis after reviewing the hematoxilin-eosin (HE) stained slides. The tumor content of the slides was evaluated by an experienced pathologist. Punch extracted tissue was then used for DNA extraction using Qiagen QIAamp DNA Mini Kit. DNA yield and purity was determined by standard methods and stored at 4 °C

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until amplification by SSP. Tissue-typing by SSP was done using the GenoVision Kit according to the manufacturer's instructions. The amplified products were visualized on 2% agarose gel in 0.5 × TBE buffer.

### 2.3. Immunohistochemistry

Three μm thick sections of formalin-fixed, paraffin-embedded tissues were mounted on glass slides, deparaffinized, rehydrated and stained with hematoxylin-eosin using standard histological techniques. For immunohistochemical staining, the Ventana Benchmark automated staining system (Ventana Medical Systems, Tucson, AZ) and Ventana reagents were used. After deparaffinization in xylene, slides were rehydrated in decreasing concentrations of ethanol. Endogenous peroxidase was blocked using the Ventana endogenous peroxidase blocking kit after a rinse with distilled water. For antigen retrieval, slides were heated with cell conditioning solution (CC1, Ventana) according to the manufacturer's instructions. Primary antibodies against CD4 (clone 1F6, dilution: 1:30, Novocastra, Newcastle Upon Tyne, UK), CD8 (clone C8/114B, dilution: 1:100, DAKO), perforin (clone 5B10, dilution: 1:20, Novocastra Laboratories LTD), granzyme (clone Gr B-7, dilution: 1:25, DAKO), FoxP3 (code ab10563, dilution: 1:400, Abcam) and MHC-I (β2-microglobulin) (clone 2I, dilution: 1:1000, RDI Research Diagnostic Inc.) were applied adjusted to the Ventana Benchmark system after performing titrations. iVIEW-DAB was used as chromogen. For each section, sixteen high power fields ($16 \times 100\ \mu m^2$) were identified randomly. The amount of stained cells in the sixteen fields was averaged. Areas of normal lung, scar tissue, necrosis and clusters of anthracotic pigment were excluded from the analysis.

## 3. Results

### 3.1. Patient's history

A 61 year-old Caucasian woman with end-stage UIP underwent bilateral, sequential lung transplantation through bilateral anterio-lateral thoracotomy in September 2008. The patient had a 20 pack-year history of smoking, suspended twenty years earlier, a history of tuberculosis lymphadenitis at the age of 26, treated by 6 months of tuberculostatic drugs and an early stage cervical cancer at the age of 41, cured by surgery. The donor lung was obtained from a 60 year-old Caucasian woman, a non-smoker, who was healthy except for type II diabetes mellitus. The arterial $pO_2$ prior to explantation of the donor lung was on 100% oxygen up to 400 mmHg and preoperative imaging showed no abnormalities.

The recipient's clinical course after transplantation was without any complications. She was extubated one day after surgery and was transferred from the ICU to the regular ward on the second day after transplantation. She had a low-risk status with regard to CMV, EBV and Toxoplasma, as determined by standard procedures. Immunosuppression was started with cyclosporine, mycophenolat and steroids and she was discharged from the hospital 4 weeks after transplantation. Surveillance bronchoscopy before discharge showed unremarkable anastomoses and mild signs of acute rejection (ISHLT-classification A1, B0 [7]). There was no evidence of pathologic microorganisms in the bronchoalveolar lavage fluid.

Surveillance bronchoscopy, transbronchial biopsy and lung function tests were carried out once per month for about 6 months and revealed unremarkable results. Signs of rejection (ISHLT A0, B0) had resolved, and no dysplasia or malignancy was seen, except for a generalised epithelial metaplasia and mild inflammatory reaction.

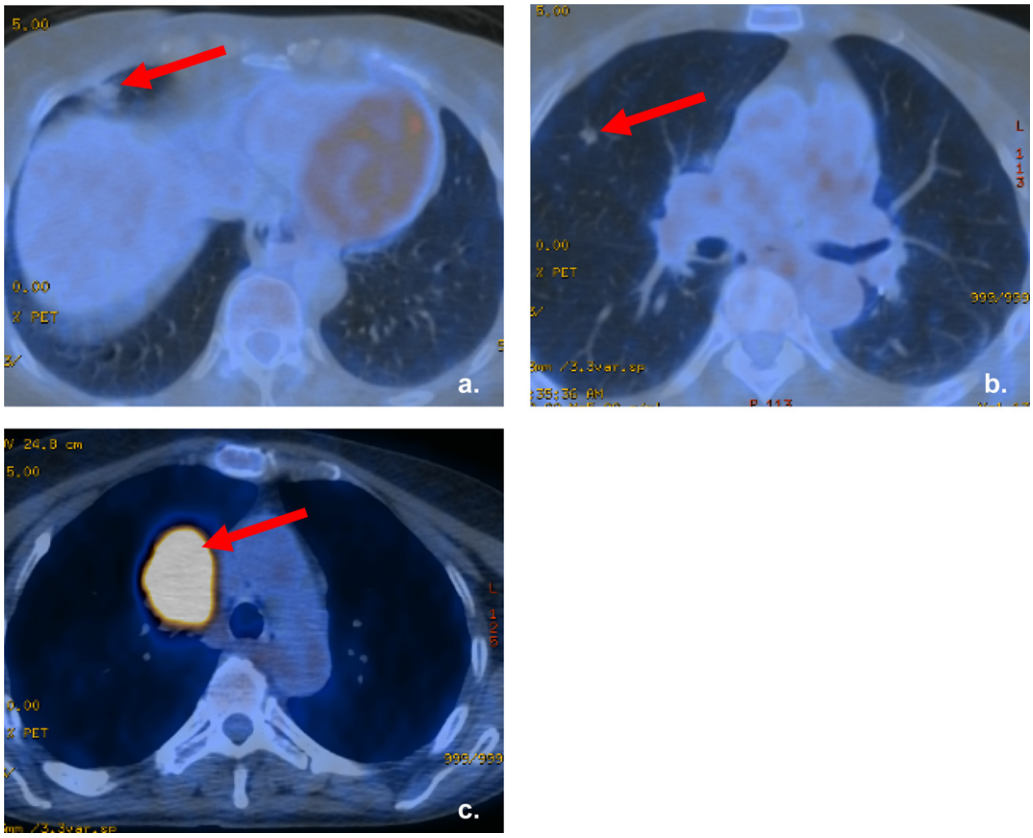


**Fig. 1.** PET-CT. Seven months after bilateral lung transplantation a PET-CT analysis was performed. (a,b) Two intrapulmonary nodules in the middle lobe (red arrows). (c) The large right-sided paracarinar lymph node with high FDG accumulation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)