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Case Report

# A 49-Year-Old Woman with a Well-Circumscribed PET Avid Lesion after Lung Transplantation: Thinking Outside the Box

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**Received:** November 18, 2017; **Published:** December 18, 2017

## Abstract

Lung transplantation is increasingly being utilized as therapy for patients with end stage lung diseases. Incidence of lung cancer after lung transplantation is rare (1 - 4%), but is associated with high mortality and morbidity. Lung transplant recipients have one of the highest standardized risk of developing lung cancers among all solid organ transplants. Origin of such cancers can be localized to one of the following: incidental cancer on lung explant, donor derived malignancy, lung cancer in the native lung of single lung transplant recipients and new lung cancers developing after lung transplant without prior association. Clinical and radiographic presentations can be atypical in these immunosuppressed patients and hence a high index of suspicion is required. We present an interesting case of a 49-year old non-smoker woman who presented with fever, weakness, myalgia and a well circumscribed left lower lobe lung mass one year after bilateral lung transplantation. The diagnosis was made while she was being treated for Aspergillus tracheobronchitis. CT revealed a 25 x 19 mm left lower lobe lung base nodule and transthoracic CT guided biopsy revealed poorly differentiated squamous cell carcinoma. Staging PET scan confirmed a stage IA tumor for which she underwent lobectomy with systematic lymph node sampling. Her immunosuppression has been lowered to target lower troughs while she undergoes close clinical surveillance.

***Keywords:*** *PET; Lung Transplantation; Lung Cancer*

## Introduction

Lung transplantation has become the treatment of choice for patients with end stage lung diseases like chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), idiopathic pulmonary hypertension (PAH) and few other rare conditions [1]. The recent post-lung allocation score (LAS) era has seen an increasing number of lung transplant recipients [1], shorter waitlist times [1], increased recipient age at transplant [1] and a rising number of lung transplant recipients for idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases [1]. With increasing number of potential lung transplant recipients on the waitlist, older donors [1,2] are increasingly being considered for transplant. Donors with a heavy smoking history but without emphysema on imaging constitute a upto 13% of bilateral lung transplants [3]. Lung cancer after lung transplantation occurs in between 1 - 4% of lung transplant recipients [4,5]. Although relatively rare, primary lung cancer has the highest standardized incidence rates after lung transplantation compared to other solid organ transplants [6]. Lung nodules and mass lesions are relatively common after lung transplantation with the

etiology being infection on most instances [7]. Hence a high index of suspicion is required in diagnosing lung cancer in lung transplant recipients due to the high associated mortality and morbidity [4].

## Case Report

A 49-year old non-smoker Indian woman underwent bilateral sequential lung transplantation for end-stage fibrotic lung disease suspected from chronic hypersensitivity pneumonitis. Her donor was a 49-year woman with a 16 pack-year smoking history. Both donor and recipient were positive for cytomegalovirus (CMV) and Epstein barr virus (EBV) serology. Induction immunotherapy consisted of rituximab, intravenous immunoglobulin and methylprednisolone. Maintenance immunosuppression included mycophenolate mofetil, tacrolimus, and prednisone. Post-transplant anti-microbial prophylaxis included trimethoprim-sulfamethoxazole, valganciclovir, and itraconazole. Pathological analysis of her lung explant and the excised lymph nodes showed end stage fibrotic interstitial lung disease without any evidence of malignancy. Her post-transplant course was fairly unremarkable except for weak donor specific antibodies to HLA class I and class II antigens for which her dose of mycophenolate was increased to 750 mg twice daily.

On her annual surveillance bronchoscopy, a big endobronchial mucus plug was aspirated from the left lower lobe with pathology showing a collection of fungal hyphae and spore-like structures and culture positive for *Aspergillus fumigatus*. Her corresponding chest x-ray showed a 15 X 10 mm lung nodule. Two weeks after her annual bronchoscopy, she presented to the hospital ED with symptoms of subjective fever, weakness, and myalgia. Physical examination was unremarkable. Laboratory data was significant for hyponatremia of 127 mmol/L and hypomagnesemia of 1.5 mg/dl (Normal 1.6 - 2.6 mg/dl). Her CMV and EBV titers were normal. A computerized tomogram (CT) of the chest showed an interval increase of left lower lobe (LLL) nodule to 25 X 19 mm (Figure 1) from its previous size of 15 X 10 mm. The nodule was solid, well circumscribed and without any evidence of satellite nodules or a halo sign. She had already been on treatment for pulmonary aspergillosis with isavuconazonium sulfate. Empiric antibiotics were initiated on admission with meropenem, levofloxacin, and vancomycin pending blood cultures and were de-escalated with negative cultures.

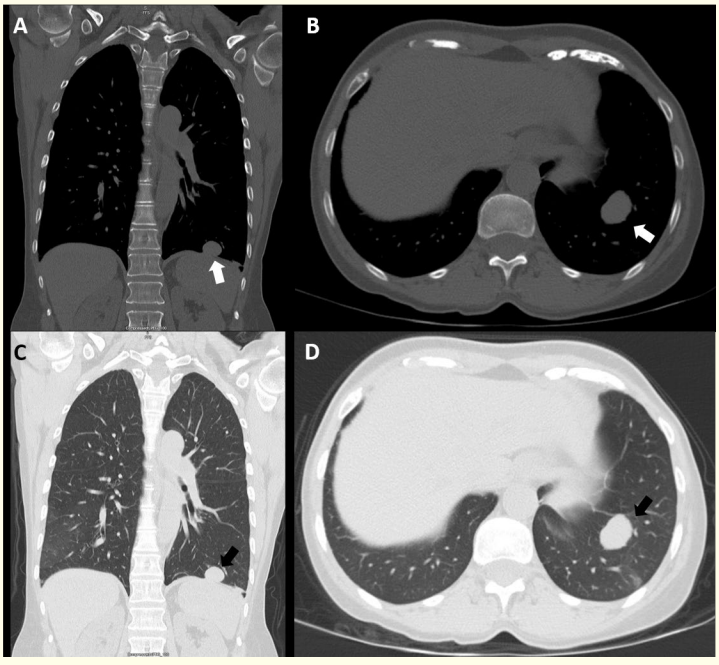


***Figure 1:*** *Computerized tomogram (CT) of the Chest in mediastinal (A and B) and lung windows (C and D). There is a well circumscribed solid mass in the left lower lobe (white and black arrows) closely abutting the diaphragm without any evidence of mediastinal adenopathy.*

The rapid increase in the size of the LLL was concerning – post-transplant lymphoproliferative disorder (PTLD) was the leading differential diagnosis. The rounded margins along with her history of being a non-smoker made primary lung cancer unlikely and similarly, the lack of satellite nodules or halo sign made infection less likely. CT guided core needle biopsy of the LLL nodule revealed poorly differentiated squamous cell carcinoma, which stained positive for CK5/6 and p63 but negative for TTF-1; all consistent with the squamous cell etiology (Figure 2). Clinical staging with a positron emission tomography (PET) scan showed an FDG avid left lower lobe lung mass (SUV = 6.1) without any evidence of nodal or distant metastasis (Figure 3). Her lung function post-transplant was excellent at FEV1 of 1.86 L (70 % predicted) and FVC of 2.45 L (74 % predicted). Given her clinical stage IA SCC and excellent lung allograft function, she underwent posterolateral thoracotomy, left lower lobectomy with lymph node sampling. The final pathology revealed a T1bN0 (AJCC stage IA) moderately differentiated pulmonary squamous cell carcinoma. Her lung explant was re-reviewed and absence of malignancy was re-affirmed. Her only risk factor for developing SCC after lung transplant was the 16 pack year smoking history in her donor.

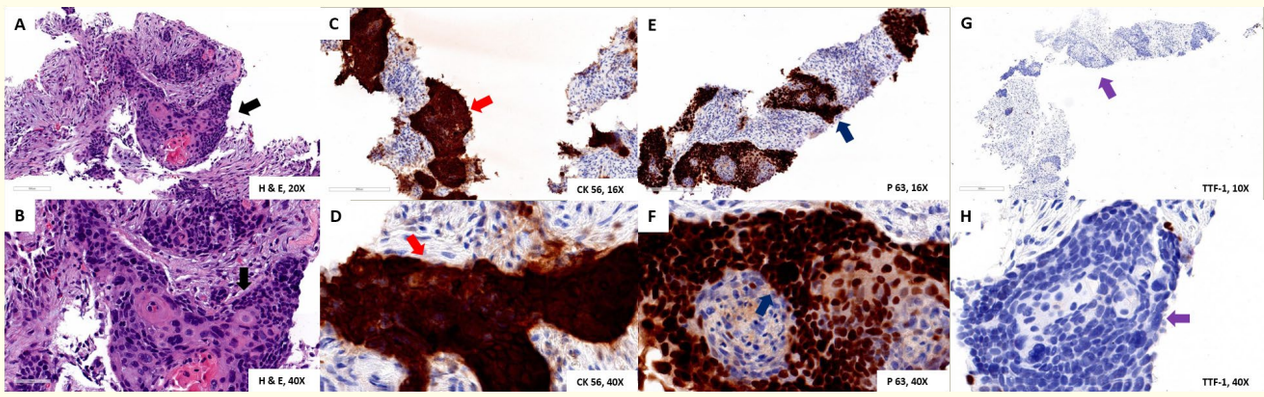


***Figure 2:*** *Figures A (20X magnification) and B (40X magnification) respectively show a poorly differentiated non-small cell carcinoma with clusters and sheets of neoplastic cells with irregular nuclear contours and eosinophilic cytoplasm (black arrow). There is evidence of keratinization with intercellular bridges. Figures C (16X magnification) and D (40X magnification) show the tumor cells reacting positively to immunostain CK 56 (red arrow) while the background bronchial cells do not. Figures E (16X magnification) and F (40X magnification) show the tumor cells reacting positively to immunostain P 63 (blue arrow). Figures G (10X magnification) and H (40X magnification) show no reactivity to TTF-1 immunostain in the tumor cells (purple arrow). This histologic pattern with the immunostain positivity for CK 56, P 63 with negative TTF-1 staining support the diagnosis of poorly differentiated squamous cell carcinoma.*

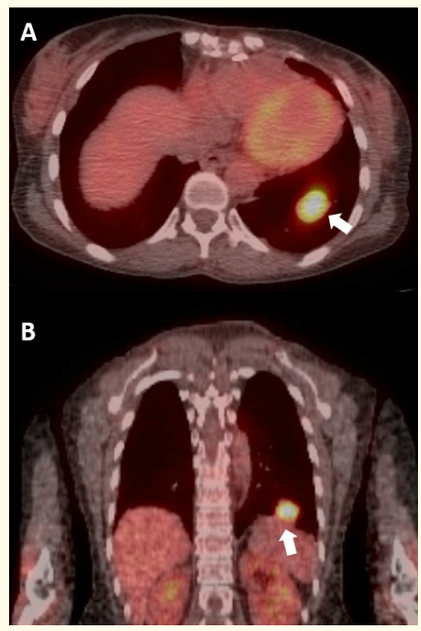


***Figure 3:*** *PET CT showing the FDG avid left lower lobe lung mass (SUV = 6.1) (white arrow) in horizontal (A) and vertical (B) cuts without any evidence to suggest metastatic disease.*

## Discussion

Lung transplantation is being increasingly used in patients with end stage lung diseases. The major pulmonary diagnoses for lung transplantation include chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), and pulmonary hypertension (PAH). With implementation of the LAS system to prioritize lung allocation in the United States, the number and proportion of IPF patients undergoing lung transplantation has increased. Malignancies have become an important cause of death after the first post-transplant year, after graft failure and infection [8]. Although non-melanoma skin cancer and non-Hodgkin's lymphomas remain the most common forms of neoplasia seen in this patient population [6], solid organ tumors like cancers of the head and neck, post-transplant lymphoproliferative disorders and lung are also seen [9]. Patients undergoing lung transplantation have a higher risk for developing lung cancer [6]. IPF confers an independent risk for lung cancer due to shared molecular pathways [10].

Lung cancer in lung transplant recipients can have one of the following etiopathogenesis: incidental findings in explanted lungs, arising from a pre-existing focus in the donor lung after lung transplantation, arising in the native lung after a single lung transplant, and primary bronchogenic cancer in the transplanted lung. Recipients of single lung transplants and those with a smoking history > 60 pack-years are at the highest risk of developing lung cancer after transplantation. In addition, donors frequently have history of smoking, which may increase the odds of lung cancer development after lung transplantation. Post-transplant immunosuppression like calcineurin inhibitors (tacrolimus or cyclosporine), anti-metabolite drugs (mycophenolate mofetil or azathioprine) and prednisone also increase the risk of developing malignancy after transplantation, as these drugs reduce the body's natural anti-tumor responses.

As seen in our case, most cases of lung cancer in the transplanted lung present as an incidental solitary lung nodule visualized on imaging obtained for another indication [4]. Common differential diagnoses for solitary lung nodules in transplant patients include infections like *Aspergillus* or *Mucor*, atypical mycobacteria, bacterial abscess, and PTLD. Primary lung cancer is a relatively rare differential, and may present as a well-circumscribed solid or sub-solid nodule with smooth borders at initial presentation. Radiographic patterns of a malignant nodule, like spiculated appearance or scalloped border maybe absent, as demonstrated in the present case. Interval growth on serial CT scans maybe the only suspicious finding but the doubling time can be short enough to mimic an infectious etiology. The prognosis of lung cancer in the setting of immunosuppression in lung transplant population remains poor, especially in late stages not amenable to surgical cure. A high index of suspicion supported by appropriate tissue sampling is critical.

## Conclusion

Diagnostic work up of lung nodules in lung transplant recipients both in the lung allograft and the native lung (of single lung transplant recipients) requires careful follow up. The significant immunosuppression after lung transplant can potentiate aggressive growth of malignant neoplasms. While primary lung cancer in the lung allograft in the absence of tumor in explanted lung is rare, it still needs to be kept on the differential diagnosis as it significantly affects the outcomes in lung transplant recipients.

## Conflict of Interest Statement

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

## Bibliography

1. M Valapour., *et al*. "OPTN/SRTR 2015 Annual Data Report: Lung". *American Journal of Transplant* 17.1 (2017): 357-424.

2. GJ Bittle., *et al*. "The use of lung donors older than 55 years: a review of the United Network of Organ Sharing database". *The Journal of Heart and Lung Transplantation* 32.8 (2013): 760-768.

3. S Taghavi., *et al*. "Double-lung transplantation can be safely performed using donors with heavy smoking history". *Annals of Thoracic Surgery* 95.6 (2013): 1912-1917.

4. J Yserbyt., *et al*. "Bronchial carcinoma after lung transplantation: a single-center experience". *The Journal of Heart and Lung Transplantation* 31.6 (2012): 585-590.

5. EV Belli., *et al*. "Lung cancer following lung transplant: single institution 10 year experience". *Lung Cancer* 81.3 (2013): 451-454.

6. D Collett., *et al*. "Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit". *American Journal of Transplantation* 10.8 (2010): 1889-1896.

7. LL Schulman., *et al*. "Pulmonary nodules and masses after lung and heart-lung transplantation". *Journal of Thoracic Imaging* 15.3 (2000): 173-179.

8. RD Yusen., *et al*. "The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation". *The Journal of Heart and Lung Transplantation* 33.10 (2014): 1009-1024.

9. S Roithmaier., *et al*. "Incidence of malignancies in heart and/or lung transplant recipients: a single-institution experience". *The Journal of Heart and Lung Transplantation* 26.8 (2007): 845-849.

10. CE Daniels and JR Jett. "Does interstitial lung disease predispose to lung cancer?" *Current Opinion in Pulmonary Medicine* 11.5 (2005): 431-437.

**Volume 6 Issue 1 December 2017**