

Peer Review File

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Reviewer A

In their manuscript, the authors describe the case of a male COPD patient who underwent single lung transplantation (Tx) on the right side. In the Tx lung, a pulmonary nodule of the right lower lobe had developed following Tx, which had increased in size after further three and eight months. Lobectomy was performed and patient was still in need of ventilatory support.

The authors report on a classical case we observe in great numbers during the follow up of lung Tx patients. In general, the report appears very short and is lacking of essential descriptive and explanatory information that can make this case with its images a teachable moment for colleagues in the field.

The following points need to be addressed, discussed and/or added:

Comment 1: Please state why computed tomography (CT) was performed one year after lung transplantation! If you have a cancer surveillance protocol for lung transplant patients, please describe it!

Reply 1: Thank you very much for your comments.

For the first year following lung transplantation, patients at our center are scheduled for chest CT scans every three months. Pulmonary nodules were identified in this patient during a routine follow-up chest CT scan one-year post-surgery.

Changes in the text: The patient undergoes a chest CT scan every three months after surgery, and a chest CT scan one year later revealed a small solid nodule with a diameter of ~0.5 cm in the posterior basal segment of the right lower lung (Panel A, blue arrow).

Comment 2: 2. On what basis did you decide on the follow up CT interval: why three and then eight months? Maybe a time line would help visualize better the events of the case!

Reply 2: Thank you very much for your comments. Please accept my apologies for the miscommunication. It's not Eight months later, but about 8 months (To be precise, it's 7.5 months) after the discovery of pulmonary nodules. We recommend patients to have a chest CT scan every three months. However, due to personal reasons, the patient waited 4.5 months and then underwent a chest CT scan, revealing a pulmonary nodule about 2.5cm in diameter.

Changes in the text: After four and a half months the chest CT showed an enlarged pulmonary nodule ~2.5 cm in diameter with shallow lobulation, short hair spurs on the edge and the presence of pleural traction, suggesting peripheral lung cancer.

Comment 3: Is clinical information of the lung donor available: smoking/occupational history, other malignant disease that could have increased the risk of developing lung cancer?

Reply 3: Thank you very much for your comments. He has been a smoker for over 30 years, consuming approximately one pack of cigarettes daily. However, the donor of the transplanted lung had no history of smoking or malignant tumors.

Changes in the text: He has been a smoker for over 30 years, consuming approximately one pack of cigarettes daily. However, the donor of the transplanted lung had no history of smoking or malignant tumors.

Comment 4: Molecular imaging from positron emission tomography (PET), including the maximum intensity projections image, would help show that the nodule was the only lesion found. Were hilar or mediastinal lymphadenopathy present?

Reply 4 : Thank you very much for your comments. Preoperative PET/CT: No hypermetabolic lymph nodes were detected in either the hilar or mediastinal regions of both lungs. The nodule in the lower right lung exhibited hypermetabolism, with an SUV value of 7.2.

Changes in the text: Whole-body PETCT imaging revealed hypermetabolism in the right lower lung nodule, with no hypermetabolic lymph nodes in the bilateral hilar or mediastinal regions, and no metastatic tumors throughout the body.

Comment 5: Did the preoperative bronchoscopy show any suspicious bronchial mucosa?

Reply 5: Thank you very much for your suggestions. Yes, the bronchoscopy showed no abnormal mucosa.

Changes in the text: Tracheoscopy examination identified no abnormal mucosa.

Comment 6: Please give full information on the clinical and pathological cancer stage including TNM with its version!

Reply 6: Thank you very much for your suggestions. Preoperative PET/CT showed no lymph node or distant metastasis; Postoperative pathology also suggests that the tumor has no pleura or lymph node metastasis. Both clinical and pathological staging are T1N0M0, stage IA, 8 edition.

Changes in the text: Whole-body PETCT imaging revealed hypermetabolism in the right lower lung nodule, with no hypermetabolic lymph nodes in the bilateral hilar or

mediastinal regions, and no metastatic tumors throughout the body. The pathology results confirmed a diagnosis of squamous cell carcinoma, with the pathological staging being T1N0M0, stage IA.

Comment 7: Did you find any molecular alterations?

Reply 7: Thank you very much for your comments. Owing to the patient's pathology being squamous cell carcinoma, genetic testing was not performed.

Changes in the text:

Comment 8: Please be more specific on the surgical procedure: "radical surgery for right lower lung cancer..." does not relate to any pulmonary structure, e.g. better "lower lobectomy on the right side".

Reply 8: Thank you very much for your suggestions.

Changes in the text: The patient underwent right lower lobectomy and lymph node dissection of the hilum and mediastinum.

Comment 9: What was the immunosuppression regimen before lung cancer diagnosis, how did you manage perioperative immunosuppression and do you consider a change in this regimen due to cancer diagnosis.

Reply 9: Thank you very much for your suggestions. The immunosuppressive regimen prior to the cancer diagnosis comprised oral prednisone acetate 15mg daily and mycophenolate mofetil tablets 0.18g every 12 hours. Tacrolimus was maintained at a concentration of about 10ng/mL. To reduce the risk of infection and promote healing during the perioperative period, we reduced the dosage of immunosuppressive drugs. Specifically, we discontinued mycophenolate mofetil, adjusted the target concentration of tacrolimus to approximately 8ng/ml, and maintained the 15mg daily dose of prednisone acetate.

Changes in the text: For most solid organ transplant recipients who develop new cancer post-transplantation, research recommends reducing immunosuppressive therapy^[1,2] instead of continuing with standard immunosuppressive therapy. During the perioperative period, the patient discontinued mycophenolate mofetil, lowered the target concentration of tacrolimus to approximately 8ng/mL, and maintained a dosage of 15mg prednisone acetate.

Comment 10: How have the perioperative pulmonary function tests developed. Please give more information on how fit patient was before lung cancer surgery! Please describe more specific what "assisted ventilation" entails: i.e., invasive ventilation via tracheostoma, or non-invasive ventilation via mask, what oxygen flow or oxygen fraction is still needed. Is rehabilitation planned?

Reply 10: Thank you very much for your suggestions. The patient underwent preoperative lung function examination: DLCOcor was 63% of the predicted value; FEV1 was 1.89L, accounting for 61% of the predicted value. Pulmonary ventilation-perfusion scanning indicated that the right lower lung perfusion accounted for 37% of the total, while ventilation accounted for 42%.

Three days after surgery, the patient was admitted to the ICU for dyspnea and underwent invasive ventilation via endotracheal intubation. The settings were PRVC mode, oxygen concentration at 65%, tidal volume of 430ml, PEEP at 5cm H₂O, and a rate of 22 breaths per minute. The rehabilitation plan is to control lung infections, provide ventilator support, and regularly assess the recurrence and metastasis of lung cancer.

Changes in the text: Preoperative lung function examination showed diffusing capacity of the lung for carbon monoxide was 63% of the predicted value; FEV1 was 1.89L, accounting for 61% of the predicted value. Pulmonary ventilation-perfusion scanning indicated that the right lower lung perfusion accounted for 37% of the total, while ventilation accounted for 42%. Three days after surgery, the patient was admitted to the ICU for dyspnea and underwent invasive ventilation via endotracheal intubation.

Comment 11: The authors proposed that the patient "plans to undergo bilateral lung transplantation surgery". Please discuss the criteria for lung Tx following cancer diagnosis: e.g., cancer-free interval five years after diagnosis etc.

Reply 11: Thank you very much for your comments.

The stringent criteria for lung transplantation following a cancer diagnosis aim to ensure patients' long-term survival and quality of life post-surgery. Based on international expert consensus, patients should be cancer-free for at least 3-5 years prior to lung transplantation to minimize postoperative cancer recurrence and enhance the success rate of the procedure^[3]. Prior to considering lung transplantation, imaging (such as CT and PET scans) and pathological tests must confirm the absence of cancer recurrence. A thorough evaluation of the patient's overall health is conducted, including cardiopulmonary, renal, and hepatic functions. Patients must possess adequate physical stamina and organ functionality to endure the transplant surgery and postoperative recovery. Therefore, we apologize for our team's oversight. A more comprehensive assessment is essential to determine whether a patient is eligible for a double-lung transplant post-surgery, particularly in assessing infection management, overall health status, and regular monitoring for lung cancer recurrence and metastasis. The patient's preoperative lung function was compromised, with a disproportionately high ventilation perfusion in the right lower lobe. Following right lower lobectomy, the pulmonary ventilation may fall short of the patient's requirements. Consequently, bilateral lung transplantation is another viable option worth considering.

Changes in the text: Based on international expert consensus, patients should be cancer-free for at least 3-5 years prior to lung transplantation to minimize postoperative cancer recurrence and enhance the success rate of the procedure^[3]. However, for patients with early lung cancer, particularly those ineligible for conventional surgical removal due to pulmonary limitations or multifocal tumors, lung transplantation may be a viable option^[2]. The patient's preoperative lung function was compromised, with a disproportionately high ventilation perfusion in the right lower lobe. Following right lower lobectomy, the pulmonary ventilation may fall short of the patient's requirements. Consequently, bilateral lung transplantation is another viable option worth considering.

Comment 12: Did the cancer stage required an adjuvant therapy? Please discuss and refer to point 6!

Reply 12: The patient's postoperative pathological staging is T1N0M0, stage Ia, thus eliminating the need for postoperative adjuvant therapy.

Changes in the text:

Comment 13: How do you plan follow up imaging in terms of restaging.

Reply 13: Chest CT scans are typically conducted every 3 months^[2], and if deemed necessary, PET/CT scans are performed to evaluate metabolic activity and identify distant metastases.

Changes in the text:

Comment: In conclusion, based on my comments, this manuscript requires a major revision.

From my experience we do see new nodules in lung Tx patients very often. Considering the article type "Images in Clinical Medicine", the authors should more focus on the graphical presentation and what made their case so special. PET imaging and showing a time lime could help.

In addition, a full description of pulmonary and oncological status as well as a comprehensive discussion on further management of lung Tx and lung cancer is essential, in my eyes! Lung Tx must be seen very critical in lung cancer patients, even though curatively treated!

Reply: Thank you very much for your comments. Based on your suggestions, we have made revisions to the entire text, including a timeline chart, a comprehensive description of lung and tumor conditions, a discussion on immunosuppressive drugs during the perioperative period of lung transplant for lung cancer, and a discussion on lung transplantation after lung cancer.

Changes in the text: Figure 1. A. One year after lung transplantation, a chest computed tomography scan revealed a small solid nodule with a diameter of ~0.5 cm in the

posterior basal segment of the right lower lung. (blue arrow); B. Three months later, the pulmonary nodule increased to a diameter of 1 cm after 3 months. (blue arrow); C. Four and a half months later, chest computed tomography showed an enlarged pulmonary nodule ~2.5 cm in diameter with shallow lobulation, short hair spurs on the edge and the presence of pleural traction. (blue arrow)

Patients with chronic obstructive pulmonary disease (COPD) secondary to smoking face a significantly elevated risk of lung cancer following lung transplantation, particularly single-lung transplantation, with lung cancer rarely originating from the donor lung^[4]. A case series study encompassing 520 lung transplant cases from a single center over 17 years revealed that 12 patients developed lung cancer, with only one instance being in the donor lung^[5]. For most solid organ transplant recipients who develop new cancer post-transplantation, research recommends reducing immunosuppressive therapy^[1, 2] instead of continuing with standard immunosuppressive therapy. During the perioperative period, the patient discontinued mycophenolate mofetil, lowered the target concentration of tacrolimus to approximately 8ng/mL, and maintained a dosage of 15mg prednisone acetate. Based on international expert consensus, patients should be cancer-free for at least 3-5 years prior to lung transplantation to minimize postoperative cancer recurrence and enhance the success rate of the procedure^[3]. However, for patients with early lung cancer, particularly those ineligible for conventional surgical removal due to pulmonary limitations or multifocal tumors, lung transplantation may be a viable option^[2]. The patient's preoperative lung function was compromised, with a disproportionately high ventilation perfusion in the right lower lobe. Following right lower lobectomy, the pulmonary ventilation may fall short of the patient's requirements. Consequently, bilateral lung transplantation is another viable option worth considering.

Reviewer B

Comment: The risk of cancer in transplant patients is known, particularly the risk of lung cancer in former smokers after solid organ transplantation. The diagnosis of adenocarcinoma is more frequent, but the development of squamous cell carcinoma is known in this population. Imaging did not provide any original nor additional information. This clinical case provides nothing new in this field of expertise.

Reply: Thank you very much for your comments. Based on reviewer's suggestions, we have made revisions to the entire text, including a timeline chart, a comprehensive description of lung and tumor conditions, a discussion on immunosuppressive drugs during the perioperative period of lung transplant for lung cancer, and a discussion on

lung transplantation after lung cancer. I hope the newly added information and discussions can bring new things to this professional field.

Changes in the text: See the overall manuscript.