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A 68-Year-Old Lung Transplant Recipient With Shortness of Breath, Weight Loss, and Abnormal Chest CT



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CASE PRESENTATION: A 68-year-old man presented to our ED with shortness of breath, weakness, and a 25-lb unintentional weight loss. He had undergone bilateral lung transplantation (cytomegalovirus [CMV]: donor+, recipient+; Epstein-Barr virus: donor+, recipient+) for idiopathic pulmonary fibrosis (IPF) 18 months prior. His posttransplant course was fairly unremarkable until 1 month earlier, when he was admitted for breathlessness and weakness. CT of the chest during that admission revealed mild intralobular and interlobular septal thickening. A bronchoscopy with BAL and transbronchial biopsies did not show acute cellular rejection, but the BAL fluid was positive for coronavirus. His cortisol level was undetectable; he was diagnosed with adrenal insufficiency and fludrocortisone was initiated. He was taking prednisone, tacrolimus, and everolimus for immunosuppression and valganciclovir, itraconazole, and trimethoprim-sulfamethoxazole for antimicrobial prophylaxis. His 25-lb weight loss occurred over the span of just one month.

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Physical Examination Findings

The patient was thin and weak with mildly labored breathing, and his O₂ saturation was 96% on 3 L/min supplemental oxygen. The rest of his vital signs were normal. Breath sounds were slightly decreased at the left apex and base without adventitious sounds. No palpable lymphadenopathy was appreciated.

Diagnostic Studies

Laboratory test results, including CBC and metabolic panel, were normal. CMV and Epstein-Barr virus polymerase chain reaction testing were negative. CT of the

chest showed bilateral, small, layering pleural effusions as well as a new left-sided loculated pleural effusion with diffuse interlobular and intralobular septal thickening that were more prominent compared with prior CT imaging (Figs 1A and 1B). Also noted were new mild reticulonodular opacities. No evidence of enlarged thoracic lymphadenopathy or lung masses was observed. A left thoracentesis revealed 200 mL of pale yellow exudative fluid without evidence of lymphocytosis. Cytology of the pleural fluid did not reveal malignant cells. Because of these negative results, a video-assisted thoracoscopic surgery (VATS) lung biopsy was performed (Figs 2A-C).

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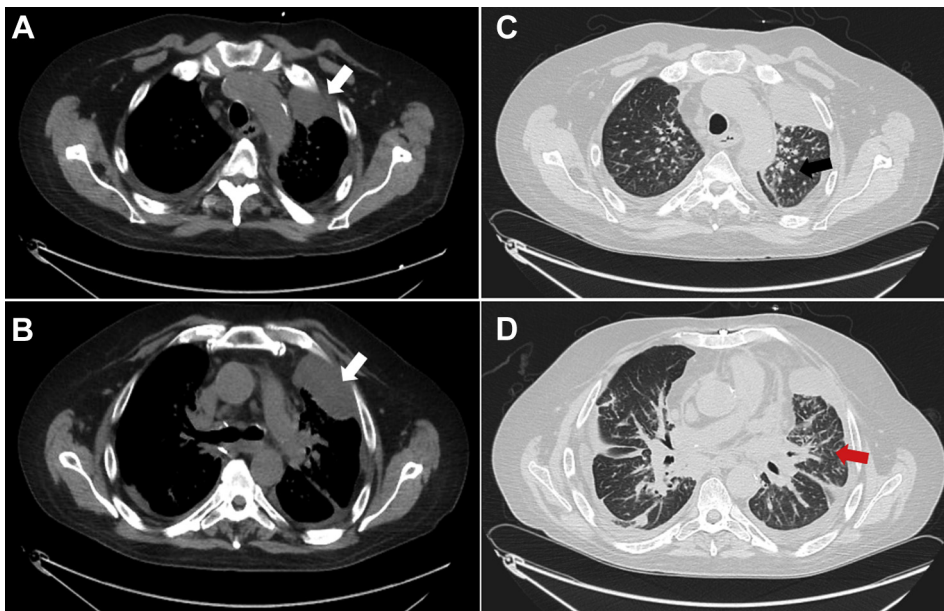


Figure 1 – CT of the chest. A, B, mediastinal window. C, D, lung window. The CT demonstrates a loculated left pleural effusion (white arrow), nodular opacities (black arrow), and prominent interlobular septal thickening (red arrow).

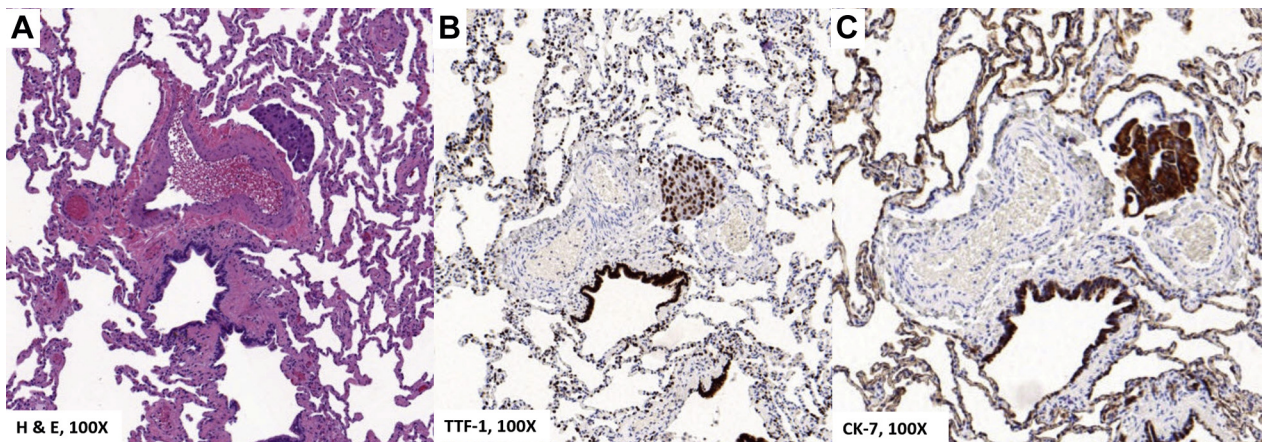


Figure 2 – A high-power view (100×) of the VATS lung biopsy. A, hematoxylin and eosin stain. B, TTF-1 stain. C, CK7 stain.

What is the diagnosis?

Diagnosis: Lymphangitic carcinomatosis from primary lung adenocarcinoma after bilateral lung transplantation

Discussion

Lung transplantation is a treatment option for patients with end-stage lung diseases such as IPF, COPD, cystic fibrosis, and pulmonary arterial hypertension. Lung cancer after lung transplantation is generally rare, with a reported incidence of 1.0% to 4.1%. Individuals who undergo lung transplantation for diseases such as COPD and IPF have a higher chance of developing primary lung malignancy because of smoking history; those with fibrotic lung diseases (eg, IPF) are also at increased risk because of the fibrotic interstitial process. 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 a history of smoking, which may increase the odds of lung cancer development after lung transplantation. Posttransplant immunosuppression that includes calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolite drugs (mycophenolate mofetil or azathioprine), and prednisone also increases the risk of developing malignancy after transplantation because these drugs reduce the body's natural antitumor responses.

Primary lung malignancy after lung transplantation generally falls into one of the following categories:

1. Cancer in the recipient's explanted lung, incidentally detected upon pathological examination of the lung.
2. Donor-derived lung cancer from a malignant focus in the donor's lungs, undetected preimplantation.
3. Lung cancer in the native lung of a single-lung transplant recipient.
4. New primary malignancy in the lung allograft after transplantation, without any prior evidence of donor or recipient malignancy.

Most lung transplant recipients who develop bronchogenic cancer have nonspecific symptoms at presentation, and they present within the first 3 years of transplant. Unless their cancer is amenable to surgical resection, their response to therapy is generally extremely poor (even when the cancer is diagnosed early). Hence, new lung nodules in the native lung in a patient who has undergone single lung transplant or in the lung allografts should be evaluated to rule out malignancy.

Lymphangitic carcinomatosis is a pulmonary tumor embolization syndrome. Foreign material, including tumor cells, can enter the venous and lymphatic systems of the lung, causing local lymphatic vessel obstruction and fluid accumulation. This in turn leads to thickening of the alveolar septae and the bronchovascular bundles, giving rise to the typical radiographic pattern of diffuse intralobular and interlobular septal thickening. The true incidence of lymphangitic carcinomatosis is unknown, but less than 1% of all solid tumors present with this pattern. Lymphangitic carcinomatosis can occur in adenocarcinomas from the breast, kidney, lung, and gastrointestinal tract (ie, liver, pancreas, and stomach). Lymphangitic carcinomatosis is an end-stage manifestation of disease that carries extremely poor prognosis.

In lung transplant recipients, the presence of interlobular and intralobular septal thickening can be seen in a variety of different clinical scenarios, including acute cellular rejection and antibody-mediated rejection, pulmonary edema, CMV pneumonitis, posttransplant lymphoproliferative disorder, malignancy (from a pulmonary or an extrapulmonary source), and, rarely, recurrence of the primary lung disease (eg, sarcoidosis). Tissue diagnosis is key because the clinical presentations associated with this radiographic feature are quite diverse. Bronchoscopy with BAL and transbronchial lung biopsies are likely the first diagnostic modalities for obtaining tissue, as many modalities for differential diagnoses (eg, acute cellular or antibody-mediated rejection, CMV pneumonitis, posttransplant lymphoproliferative disorder, recurrence of primary disease) have high diagnostic yields. Although the specific yield of transbronchial biopsies in lymphangitic carcinomatosis has been sparsely studied, its average diagnostic yield is thought to be about 60%. Positron emission tomography has demonstrated high specificity for detecting lymphangitic carcinomatosis, especially when it is not close to the primary tumor. VATS remains the procedure of choice for obtaining lung biopsies in patients who can tolerate the surgical procedure or when no other evidence points to the diagnosis.

Clinical Course

Our patient underwent a bronchoscopy with transbronchial lung biopsies and BAL 1 month before the current admission; these examinations showed no evidence of cellular rejection. The BAL fluid was positive for coronavirus, for which a prednisone burst was

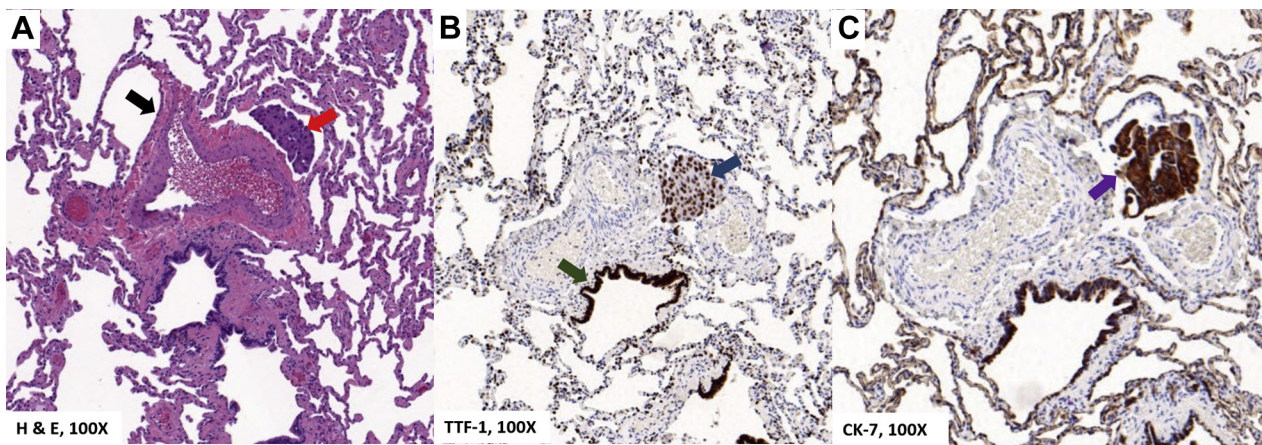


Figure 3 – A, High-power magnification of lung with a centrally located bronchus/pulmonary artery/lymphatic channel complex (black arrow). The lymphatic channel contains a cohesive cluster of large malignant cells (red arrow) demonstrating increased nuclear size, increased nuclear/cytoplasmic ratios, nuclear pleomorphism, and coarsely clumped chromatin (hematoxylin and eosin stain, 100×). B, Lymphatic involvement by adenocarcinoma TTF-1-positive brown nuclear stain (blue arrow). Epithelium of bronchiole staining nuclei darker than the nuclei of the carcinoma (green arrow) (TTF-1 immunostain, 100×). C, Lymphatic involvement by adenocarcinoma CK7-positive brown cytoplasmic stain (purple arrow; CK7 immunostain, 100×).

administered. Given the patient's dramatic weight loss and the significant worsening of interlobular and intralobular septal thickening with the new left pleural effusion, malignancy was high on the list of differential diagnoses. Cytology on thoracentesis was nondiagnostic; hence, a VATS biopsy was performed of the lower lobe of the left lung.

Pathological biopsy analysis showed cohesive clusters of malignant cells in the lymphatic circulation (Fig 3A). Upon immunohistochemical analysis, the tumor cells were found to be positive for TTF-1 (Fig 3B) and CK7 (Fig 3C), both of which are consistent with a diagnosis of pulmonary adenocarcinoma. The donor in this case was younger than 20 years of age and had no risk factors for malignancy. The recipient, however, had a 30 pack-year history of smoking. The native lung explant originally showed no evidence of cancer and was reviewed again with the same conclusion; therefore, this adenocarcinoma most likely originated in the recipient after lung transplantation. The patient and his family opted for comfort care measures once the diagnosis was made and the patient was transferred to hospice services. He died 2 days later.

Clinical Pearls

1. Lung cancer in lung transplant recipients is more likely to occur in the native lung of single-lung transplant recipients. Incidental tumors are occasionally found in the explanted lung; transmission of malignancy from the donor is exceedingly rare.
2. Primary lung malignancy in the allograft may have atypical presentations and/or typical presentations

(eg, lung masses, mediastinal adenopathy). Differential diagnoses in lung transplant recipients include a broad range of opportunistic infections, post-transplant lymphoproliferative disorder, and malignancy (from pulmonary and nonpulmonary origins). A high index of suspicion is required given the rapid progression of malignancy in these immunosuppressed patients and the associated poor clinical outcomes.

3. Lymphangitic carcinomatosis is a rare primary presentation of lung cancer and is generally seen in an advanced disease state. Diagnosis of lymphangitic carcinomatosis is challenging in lung transplant recipients, and differential diagnoses may include acute cellular rejection and antibody-mediated rejection, pulmonary edema, CMV pneumonitis, posttransplant lymphoproliferative disorder, malignancy (from a pulmonary or an extrapulmonary source) and, rarely, recurrence of the primary lung disease (eg, sarcoidosis). Tissue biopsy via bronchoscopy or thoracoscopy is often required to establish the diagnosis.

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