



# Thirteen-Year Survival in a Patient With Diffuse Bilateral Lepidic-Predominant Adenocarcinoma: A Case Report of Lung Transplantation and Local Salvage

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## Case

A 33-year-old man with no history of smoking or unusual exposures presented with worsening cough unresponsive to several rounds of antibiotics. His chest computed tomography (CT) revealed widespread centrilobular nodules in all pulmonary lobes with a confluence of nodules in the right middle and right lower lobes, causing atelectasis (Fig. 1). Bronchoscopic biopsy performed in February 2006 revealed a well-differentiated adenocarcinoma of the lung with a lepidic growth pattern. Fluorodeoxyglucose F 18 (FDG)-positron emission tomography-CT revealed no nodal or extrapulmonary metastases. After progressing through three lines of systemic therapy, he underwent bilateral lung transplant in March of 2007 with lung from a 19-year-old donor. The explanted lungs exhibited diffuse consolidation throughout all lobes with high-grade adenocarcinoma with lepidic spread, but no definite stromal invasion. The carcinoma was negative by fluorescence in situ hybridization for *MET* amplification or *ALK* rearrangement, and negative by SNaPshot<sup>1</sup> (Thermo Fisher Scientific, Waltham, Massachusetts) for mutations in *APC*, *AKT1*, *BRAF*, *CTNNB1*, *EGFR*, *FLT3*, *JAK2*, *KIT*, *KRAS*, *MEK1*, *NOTCH1*, *NRAS*, *PIK3CA*, *PTEN*, or *TP53*.

At 17 months after transplant, he developed a small right lower lobe lung nodule (Fig. 2), for which he underwent a wedge resection in March 2009; pathology confirmed this to be adenocarcinoma with a focal bronchioloalveolar pattern, reflecting recipient origin. Genetic analysis of the wedge resection specimen was notable for an L1575Q mutation in exon 26 of *NOTCH1*.

At 42 months after transplant, he was noted to have nodular growth in the right upper lobe (Fig. 3), which was then treated with microwave ablation in November 2011.

The patient's forced expiratory volume in 1 second (FEV1) did not decrease compared with his posttransplant baseline despite these local salvage procedures (2.51 liters in July 2007, 2.50 liters in March 2014). However, despite maintenance with a standard triple immunosuppressive therapy regimen of tacrolimus, mycophenolate, and prednisone, he suffered an acute rejection episode in 2014, which caused a drop in his FEV1 to 1.77 liters. Azithromycin was added to his immunosuppressive regimen, but he continued to exhibit a gradual decline of FEV1.

At 120 months after transplant, he developed a new right middle lobe nodule. The initial biopsy was

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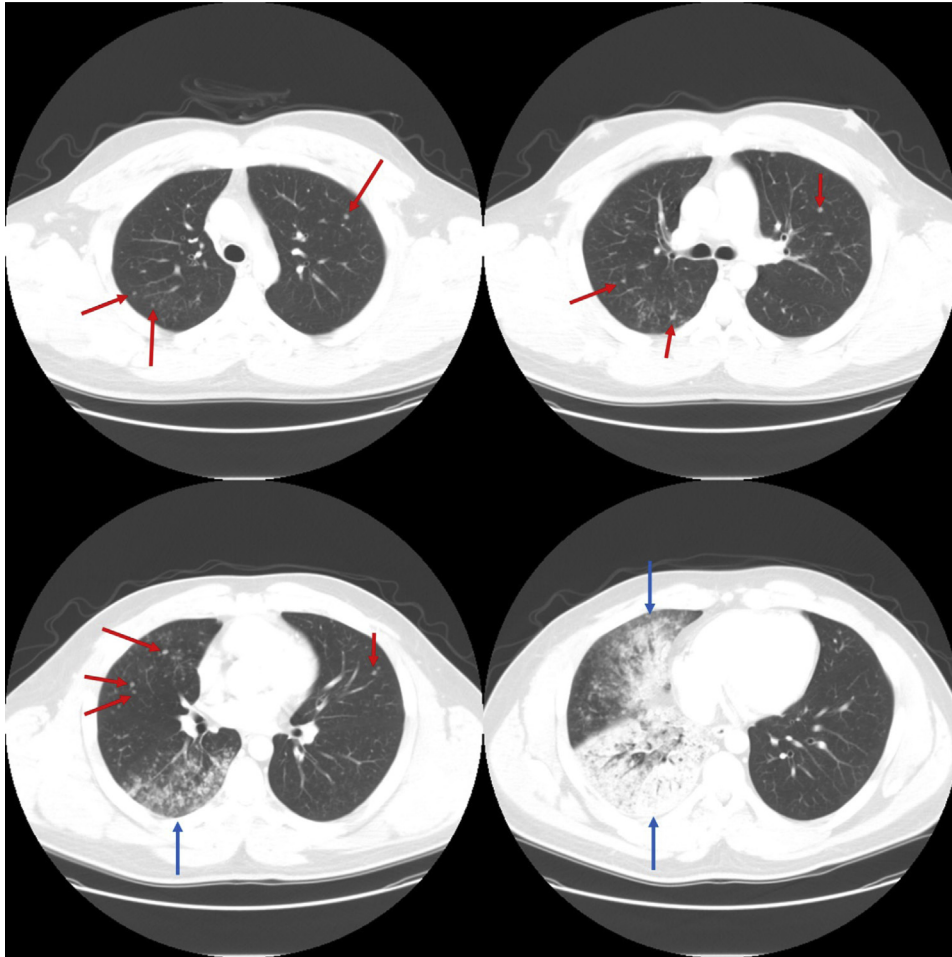
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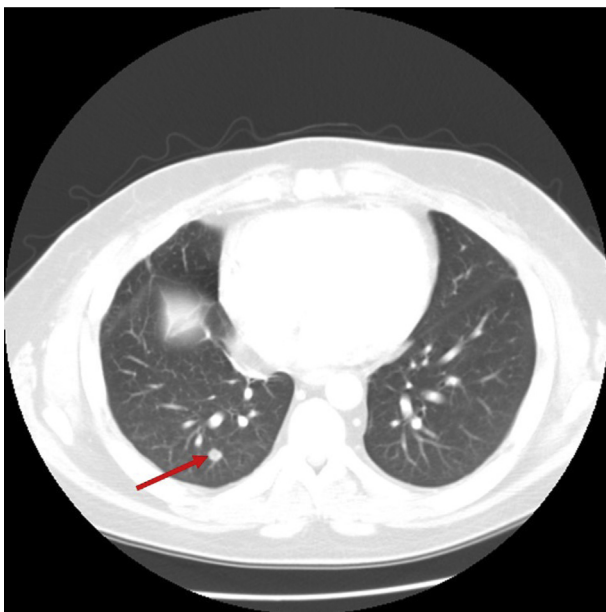
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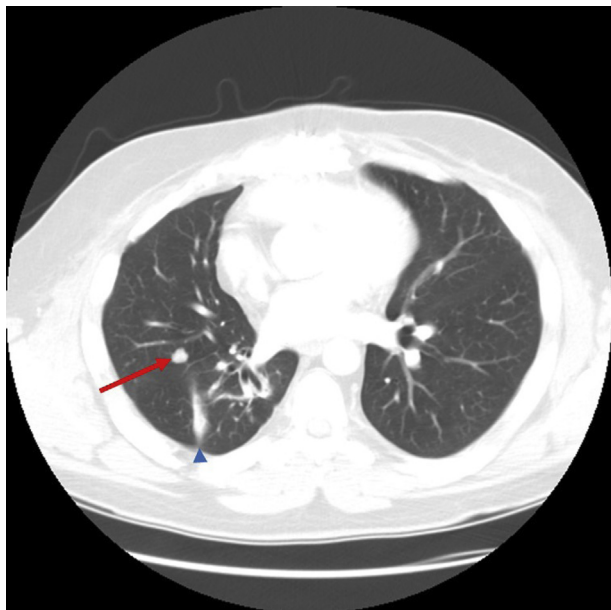
**Figure 1.** Initial diagnostic chest CT in January 2006 revealing widespread centrilobular nodules in all pulmonary lobes (red arrows). There is a confluence of these nodules in the right middle and lower lobes, in which there is associated atelectasis and volume loss (blue arrows). CT, computed tomography.



**Figure 2.** First recurrence 17 months after transplant (red arrow).

nondiagnostic, but after further radiographic progression, a repeat biopsy was done confirming recurrent adenocarcinoma. The restaging FDG-positron emission tomography-CT at 139 months after transplant unfortunately revealed four FDG-avid nodules in his bilateral lungs (Fig. 4), the largest of which was the biopsy-proven 3.5 cm right middle lobe recurrence. Although his lesions were limited and no lesion exhibited encroachment of the bronchi or bronchioles, he had poor lung function (FEV1: 0.70 liters and forced vital capacity: 1.80 liters) owing to chronic lung allograft dysfunction.

The patient's poor renal function (attributed to long-term tacrolimus toxicity versus suboptimally controlled hypertension and steroid-induced diabetes), limited chemotherapeutic options, and his history of previous lung transplantation prevented immunotherapy. Despite treatment with photopheresis, his lung function continued to decline. He transitioned to hospice care and expired 13 years after his initial diagnosis.



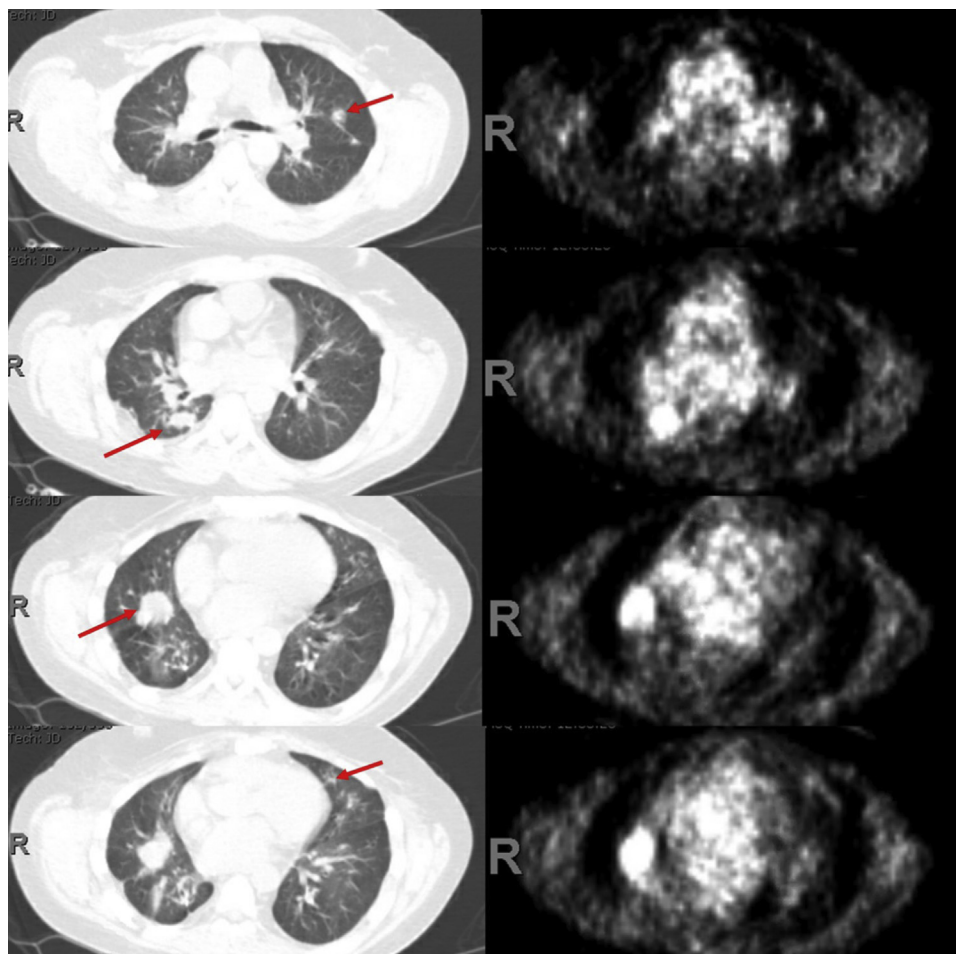
**Figure 3.** Second recurrence 42 months after transplant (red arrow) with an adjacent scar from the wedge resection of a previous recurrence (blue arrowhead).

## Discussion

Lepidic-predominant adenocarcinoma with diffuse bilateral presentation has a poor prognosis, with a median survival of 4.3 months.<sup>2</sup> Pulmonary transplantation is a controversial treatment owing to high rates of recurrence within the donor's lungs.<sup>3,4</sup> However, recurrence often occurs in a delayed fashion with slow-growing<sup>3</sup> nodules, which are often discrete, and, therefore, potentially amenable to local salvage.<sup>4,5</sup> Thus, it may be possible to treat with local salvaging and close surveillance to minimize the clinical impact of recurrences.

Here, we report a patient who developed sequential recurrences at 17 months, 42 months, and 120 months after transplant. The indolent course of the patient's recurrences and the use of close radiographic surveillance allowed early detection and salvage of his first two recurrences. Although the patient ultimately developed a multifocal disease, his death was caused by chronic lung allograft dysfunction rather than disease progression.

The clinical impact of the patient's development of an exon 26 *NOTCH1* mutation at the 17-month mark



**Figure 4.** Multifocal third recurrence 139 months after transplant. R, right.

is unclear. The patient had an L1575Q mutation specifically, which would be expected to up-regulate ligand-independent NOTCH1 signaling.<sup>6-8</sup> Clinically, a meta-analysis of NOTCH expression in NSCLC found that increased expression of *NOTCH1*, NOTCH ligand *DLL4*, and target gene *HES1* were significant predictors of worsened overall survival.<sup>9</sup> In the light of these data, it is possible that the *NOTCH1* L1575Q mutation may have played a role in shaping the course of his disease.

The patient's survival to 12 years after transplant and 13 years after the initial diagnosis, despite his multiple sequential recurrences, is in stark contrast to the lethal natural history of the lung-limited, lepidic-predominant adenocarcinoma,<sup>1</sup> far exceeding the typical long-term survival in patients who received lung transplantation for this type of cancer<sup>4,10</sup> or for any indication.<sup>11</sup> This case supports the notion that concern for a high rate of recurrence after lung transplantation should be weighed against the ability to sequentially salvage recurrences with close radiographic surveillance.

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