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Case report

Incidental extensive adenocarcinoma in lungs explanted from a transplant recipient with an idiopathic pulmonary fibrosis flare-up: A clinical dilemma

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ABSTRACT

Patients under consideration for lung transplantation as treatment for end-stage lung diseases such as idiopathic pulmonary fibrosis (IPF) often have risk factors such as a history of smoking or concomitant emphysema, both of which can predispose the patient to lung cancer. In fact, IPF itself increases the risk of lung cancer development by 6.8% to 20%. Solid organ malignancy (non-skin) is an established contraindication for lung transplantation. We encountered a clinical dilemma in a patient who presented with an IPF flare-up and underwent urgent evaluation for lung transplantation. After transplant, the patient's explanted lungs showed extensive adenocarcinoma *in situ*, with the foci of invasion and metastatic adenocarcinoma in N1-level lymph nodes, as well as usual interstitial pneumonia. Retrospectively, we saw no evidence to suggest malignancy in addition to the IPF flare-up. Clinical diagnostic dilemmas such as this emphasize the need for new noninvasive testing that would facilitate malignancy diagnosis in patients too sick to undergo invasive tissue biopsy for diagnosis. Careful pathological examination of explanted lungs in patients with IPF is critical, as it can majorly influence immunosuppressive regimens, surveillance imaging, and overall prognosis after lung transplant.

1. Introduction

Lung transplantation has gained acceptance as a modality for management of end-stage lung diseases such as idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs), chronic obstructive pulmonary disease, cystic fibrosis, and pulmonary arterial hypertension [1]. The Lung Allocation Score (LAS), introduced in the United States in 2005, was instituted in an effort to identify patients in greater need for lung transplantation and to prioritize these patients for transplant [2]. The LAS system has decreased the average time patients spend on the waitlist pre-transplant; however, it has also resulted in sicker patients who have significantly increased supplemental oxygen needs undergoing transplant [2]. As a result, median age at the time of transplant has increased, and more patients are undergoing lung transplant for IPF and other ILDs [2].

Patients diagnosed with IPF and other ILDs frequently present in hypoxic respiratory failure with an acute disease flare-up, and most major transplant centers in the United States consider such patients for lung transplant [3]. However, imaging features associated with IPF/ILD occasionally make it difficult to differentiate between fibrotic foci and growing lung nodules. Ground-glass opacities, consolidation, or both further hinder clinicians' ability to detect underlying nodules or masses [4,5]. Patients on the transplant wait-list are often too sick to survive the recommended 2-year surveillance period for stability for indeterminate nodules, hence; clinicians often have a lower threshold to biopsy these patients. However, increased oxygen requirements and/or respiratory insufficiency often make invasive tissue diagnosis challenging due to the narrow window of transplantation and the risk of worsening respiratory failure from pneumothorax, which may make it impossible to oxygenate or ventilate patients [6].

Solid organ malignancy (non-skin) is a known contraindication to lung transplantation [7]. Several recent publications have described the incidence and management of unexpected neoplasms in explanted lungs between 0.8% and 2.2% [5,8–10]. Diagnosing an underlying malignancy is even more complicated in the setting of an IPF flare-up, given that IPF is a known risk factor for primary lung cancer, with a reported prevalence ranging from 6.8% to 20% (which is significantly higher than in the general population) [11]. We present an interesting clinical

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Abbreviations

AIS	adenocarcinoma *in situ*
CT	computed tomography
IPF	idiopathic pulmonary fibrosis
ILD	interstitial lung disease
LAS	Lung Allocation Score
MRI	magnetic resonance imaging
NSCLC	non–small cell lung cancer
PET	positron emission tomography
UIP	usual interstitial pneumonia

case in which extensive adenocarcinoma *in situ* (AIS) with foci of invasion on the explanted lungs was found in a lung transplant recipient who underwent transplant for a flare-up of IPF.

2. Case report

A 69-year-old white man diagnosed with IPF 5 years earlier was referred to our institution for consideration for lung transplant. Previous evaluation for autoimmune diseases was negative. He had a remote smoking history of 12 pack-years, and had quit smoking more than 20 years earlier. He was in robust clinical shape, with typical clinical stigmata of IPF, with a restrictive lung defect on pulmonary function tests (forced vital capacity: 39% predicted); severely reduced diffusion capacity (25% predicted); clubbed fingers; and coarse, leathery crackles. Desaturations were noted to 70% on his 6-minute walk test on 30 L of supplemental high-flow oxygen via nasal cannula. Computed tomography (CT) of the chest showed an interstitial lung process with an apical-to-basal gradient, with peripheral reticulation and honeycomb formation (Fig. 1), consistent with a usual interstitial pneumonia (UIP) pattern.

The patient's chest CT also showed a bilateral, dense consolidative process involving both lower lobes of the lungs with imaging features consistent with superimposed pneumonia on the background UIP or a UIP flare-up (Fig. 1). He was admitted to the inpatient lung transplant service for evaluation for potential lung transplant candidacy. Evaluation for concurrent pneumonia, including blood and sputum cultures, urine *Streptococcus pneumoniae* and legionella antigens, serum mycoplasma serology, and viral respiratory polymerase chain reaction from nasopharyngeal swab were negative. Empiric antibiotics, which were originally initiated due to imaging features that triggered concern for a superimposed consolidative process, were de-escalated.

The patient ultimately underwent bilateral sequential lung transplantation off cardiopulmonary bypass (cytomegalovirus: donor +, recipient+) 2 weeks after initial presentation. Induction immunosuppression was initiated, with basiliximab on days 1 and 4. Post-transplant immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone.

On day 3, the explanted lungs showed pathological evidence of UIP with subpleural fibrosis, foci of honeycomb formation, and organizing pneumonia. The lungs also showed a diffuse, non-mucinous, lepidic-predominant AIS with foci of microinvasion diffusely involving all lobes, measuring 19 cm on the right lung with negative resection margins and no evidence of tumor in resected lymph nodes (Fig. 2). The left lung showed a 13-cm non-mucinous AIS with multiple foci of invasion (largest invasive focus was 0.8 cm), with negative resection margins. Two of twelve left-sided lymph nodes removed at the time of transplant were positive for metastatic adenocarcinoma (N1 lymph nodes; largest metastatic focus was 2 mm). Although systematic staging of the mediastinum is not performed at the time of transplant, the most likely pathological stage based on available data consistent with bilateral T4 tumors (independent primaries) [12] with N1 disease on the left side was IIIA [12]. This clinical picture suggested two separate T4 lung adenocarcinomas in the background of diffuse AIS.

The patient had an uneventful post-transplant course and was discharged home on postoperative day 9. Given the risk of metastatic spread of tumor foci due to ongoing immunosuppression, mycophenolate mofetil was discontinued and the patient was maintained on tacrolimus and prednisone-based immunosuppression. Staging magnetic

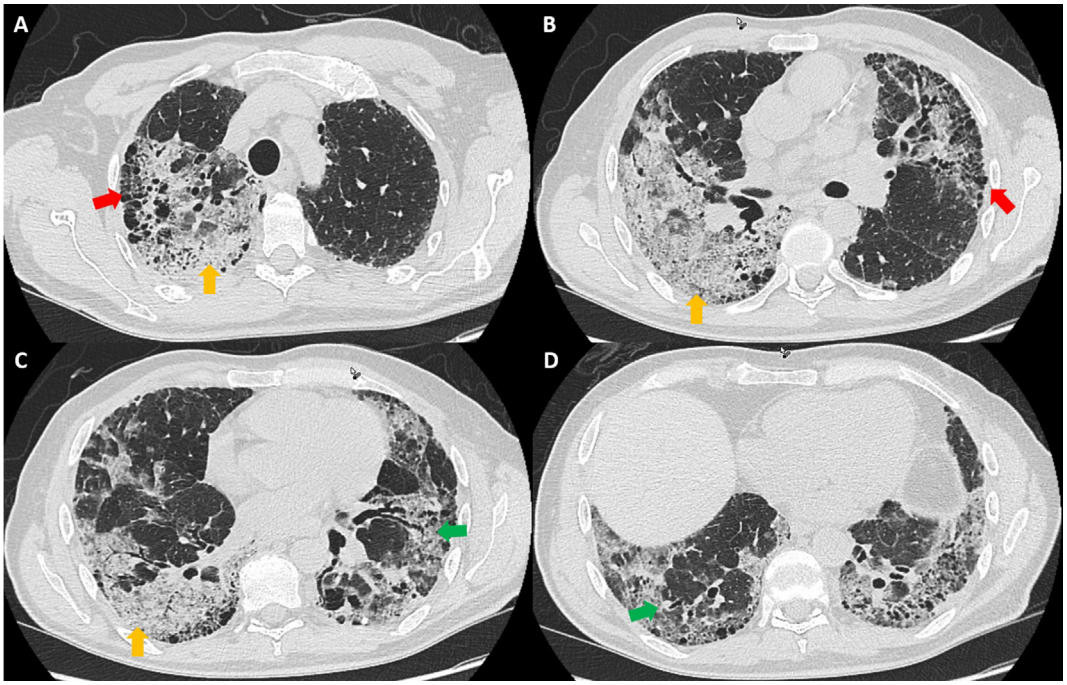

Fig. 1. Computed tomogram of the chest in lung windows shows honeycombing (red arrows), subpleural reticulation (green arrows), and extensive consolidation (yellow arrows) that pathologically demonstrated organizing pneumonia with adenocarcinoma *in situ* with invasion on explant pathology.