

Lymphangitic breast cancer in explanted lungs with interstitial lung disease: an unexpected finding

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Summary

A 60-year-old woman with end-stage fibrosing interstitial lung disease (ILD) underwent bilateral lung transplantation. Systematic histological analysis of the explanted lungs revealed extensive lymphangitic carcinomatosis and hilar lymph node metastases from a previously undiagnosed breast carcinoma. Retrospective imaging review identified a suspicious mammographic finding that had not been further investigated. The patient was later diagnosed with metastatic breast cancer and passed away at 12 months post-transplant. This case emphasizes the challenging diagnosis of neoplasia in end-stage lung disease. The incidence of malignancies in explanted lungs is approximately 1.65%, with metastatic cases being extremely rare.

This report underscores the importance of thorough histopathological evaluation of explant lungs, advocating for standardized examination protocols to improve the accuracy and depth of pathological diagnosis.

Keywords: lung transplantation, explant lung pathology, interstitial lung disease, lymphangitic metastasis, sampling protocols

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Dear Editor-in-Chief,

Thorough macroscopic and microscopic evaluation of explanted lungs remains a key task in pathology, yet no standardized protocol has been universally adopted, and each center typically relies on internal procedures. We report a rare case of a patient undergoing bilateral lung transplantation for end-stage interstitial lung disease (ILD), in whom extended sampling of hilar lymph nodes and lung parenchyma unexpectedly revealed diffuse bilateral metastases from a clinically undiagnosed breast carcinoma.

The patient, a 60-year-old woman with end-stage fibrosing unclassifiable ILD, first presented in 2018 with chronic cough and dyspnoea, initially treated with steroids and cyclosporine without benefit. Progressive fibrotic changes with bilateral bronchiectasis, honeycombing, and reduced respiratory volumes on high-resolution computed tomography, led to the nintedanib (antifibrotic therapy) administration from 2022 onward. Despite the treatment, worsening of respiratory function (oxygen therapy at 3 L/min at rest; 6 L/min during exertion) qualified her for bilateral lung transplantation in 2023 in our center. Post-operative recovery was uneventful: monitoring trans-bronchial biopsy revealed no signs of acute rejection but only mild signs of ischemia-reperfusion injury. She was discharged on the thirtieth post-operative day in good

clinical condition with immunosuppressive therapy (steroids, mycophenolate mofetil and tacrolimus). A careful histopathological examination of the explanted lungs showed epithelial malignant cells infiltration of hilar lymph nodes and lymphangitic spread to both lungs parenchyma, along thickened septa. Immunohistochemistry suggested a breast origin. During multidisciplinary discussion, a thorough review of the records revealed a suspicious breast lesion on the latest mammogram that had been flagged but never investigated by the patient. Post-discharge, a new mammography with biopsy confirmed breast malignancy. Oncologists prescribed hormone therapy and immunosuppression was shifted to everolimus (low dosage). The patient died 12 months later from pluri-metastatic (bones and peritoneum) breast cancer.

Freshly explanted lungs were processed according to our center's protocol: fixation via airways perfusion in 10% phosphate-buffered formalin, followed by sections with at least 3 samples of each lobe, including hilar structures, vascular and bronchial margins and lymph nodes for both lungs. Macroscopic and gross examination of lungs were unremarkable (Fig. 1). Histological examination demonstrated bilateral extensive architectural fibrotic remodelling, associated with moderate-to-severe polymorphic inflammation (occasionally forming nodular aggregates both in interstitial septa and peribronchial tract) and marked fibrosis with rare fibroblastic foci and honeycombing. The microscopic examination of the right hilar lymph nodes revealed dilated subcortical spaces containing isolated cells and small aggregates of atypical cells. Immunohistochemistry demonstrated: CK AE1-AE3 [+], Calretinin [-], GATA-3 [+], ER [+], PR [+], and HER2 [2+] (Fig. 1). Subsequent re-examination of lung parenchyma revealed multiple foci of inconspicuous medium-to-large-sized cells in peribronchiolar and perivascular areas and following the septa, in a lymphangitic fashion. The final diagnosis was bilateral lymphangitic breast cancer and lymph node metastasis in unclassified fibrosing ILD. Unexpected lung malignancies in explanted lungs are uncommon but well documented. Most series report an incidence between 0.7 and 2.9% of explanted lungs, predominantly primary lung carcinomas¹⁻⁵. Metastatic tumors represent only a small subset of incidental findings (well below 0.5% of explants in the largest cohorts)^{2,5-7}. In the experience of our center, the rate of unexpected pulmonary neoplasia in transplanted lungs is slightly higher (2%; unpublished data). Among patients with fibrosing interstitial lung disease, lung cancer is a recognized complication both before and after transplantation, particularly in idiopathic pulmonary fibrosis^{8,9}. To the

best of our knowledge, breast carcinoma metastases discovered at the time of lung transplantation are exceptionally rare. Strollo et al. reported a single case of ductal breast carcinoma presenting as an isolated hilar nodal deposit²; no previous report has described diffuse lymphangitic spread with bilateral lymph node and parenchymal involvement, as in our patient.

Grossing and sampling methods are inconsistently reported across the explant literature: several studies provide explicit protocols^{1,2,4,6,9}, whereas others focus on incidence/outcomes without detailing how lungs and lymph nodes were processed. Across reports, bronchial and vascular margins are routinely submitted, and hilar lymph nodes are generally sampled. However, the extent of nodal evaluation varies: some recommend targeting only the largest hilar nodes and expanding the assessment only if a parenchymal malignancy is detected⁶ while, others underline the diagnostic value of a more systematic nodal dissection—an approach that remains uncommon in routine transplant surgical practice^{3,4}.

For the parenchyma, systematic thin-sectioning is repeatedly emphasized (typically 0.5-1.0 cm slices), usually along parasagittal or coronal planes, with additional blocks from any grossly abnormal area^{2,6,9}. Some protocols explicitly stress careful airway and vascular dissection to maximize diagnostic yield^{2,9}. Strollo et al. also describe leveraging pre-transplant PET-CT scan to direct sampling of suspected nodules; nevertheless, in advanced fibrosing ILD/IPF, focal lesions can be obscured by remodelling, limiting preoperative targeting^{2,6}. Overall, margins and hilar nodes are consistent elements, but the inclusion of additional nodal stations and the extent of systematic parenchymal sampling remain variable, supporting the need for harmonized protocols to improve diagnostic accuracy and inter-institutional comparability^{4,6}.

In line with to these proposals, our center performs complete hilar lymph node dissection and obtains at least three samples per lobe (fibrosis-preserved interface, pleura–parenchyma transition and any suspicious area), in addition to margins. This approach increases workload but improves the likelihood of detecting inconspicuous neoplastic foci, particularly in severely remodeled fibrosing lungs.

Taken together, three key points emerge: (I) in fibrosing ILDs, identifying neoplasia is challenging due to marked parenchymal remodelling, further complicated by lymphangitic spread along distorted septa; (II) systematic pathological assessment, including hilar lymph nodes is essential; (III) ancillary tools such as immunohistochemistry support identification and characterization of unsuspected malignancy. The review of the literature highlighted the pressing

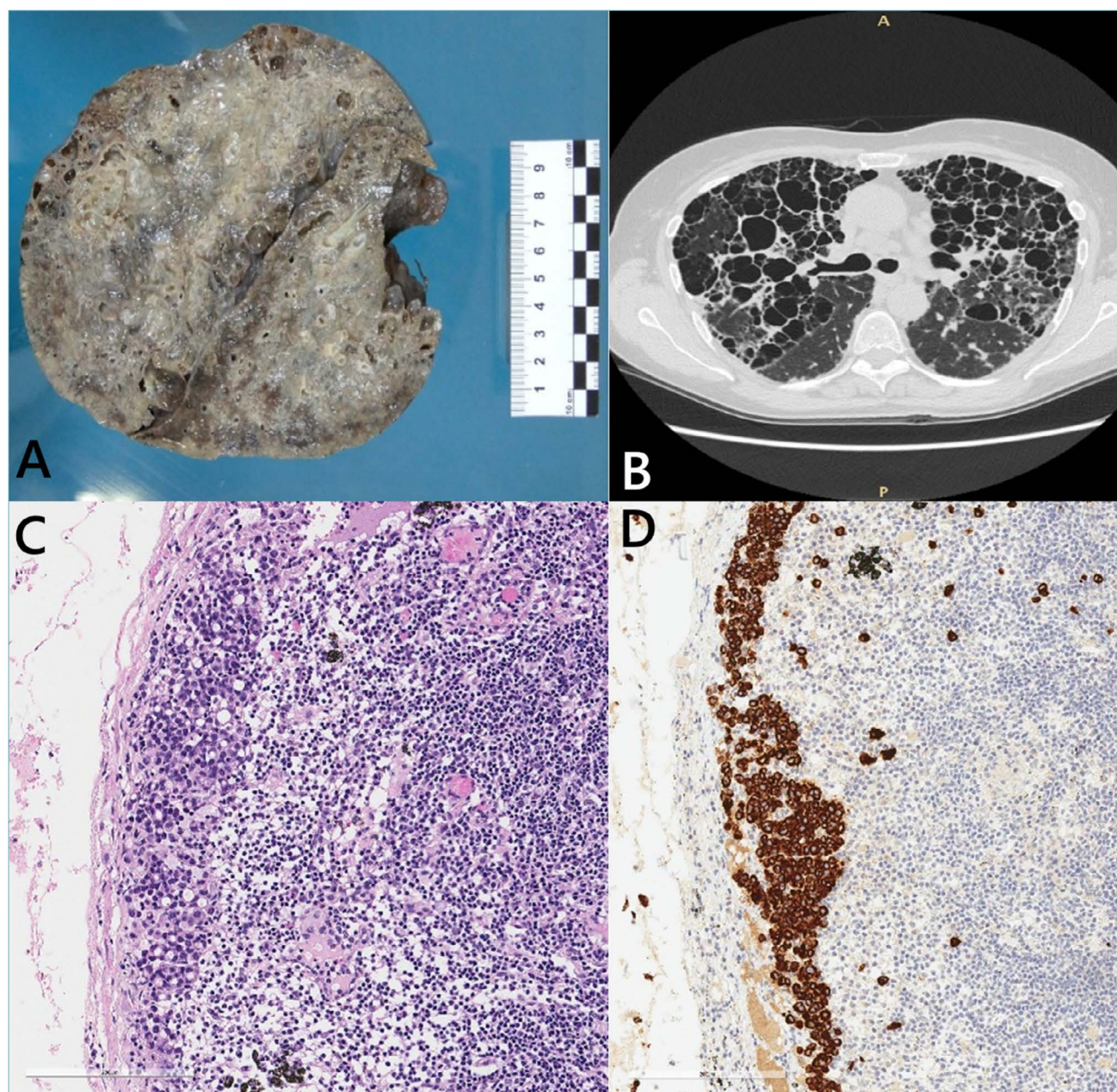


Figure 1. A) Cut surface of right lung. B) Pre-transplant chest CT scan: Both upper (not shown) and lower lobes were completely replaced by bronchiectasis and honeycombing. No signs of neoplastic lymphangitis detected. C) Hematoxylin and eosin (H&E) slide (20x magnification) showing the population of neoplastic cells in the subcortical space of the lymph node. D) Same section- immunohistochemistry for cytokeratin AE1-AE3 slide (20x magnification) showing the population of neoplastic cells in the subcortical space of the lymph node.

need to harmonize protocols in the assessment of end-stage native diseases. Standardizing explant lung evaluation will enable multicenter studies, thereby allowing a more accurate epidemiological understanding of these unexpected findings.

CONFLICT OF INTERESTS STATEMENT

The authors declare no conflicts of interest and have nothing to disclose.

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