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## CASE REPORT

# Comprehensive Diagnostic and Therapeutic Insights into a Rare Lung Carcinoma with Mixed Histology

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### ABSTRACT

***Background:*** **Mixed histology lung carcinoma comprising squamous cell carcinoma and sarcomatoid carcinoma is exceptionally rare and poses diagnostic and therapeutic challenges. Accurate diagnosis depends on a multidisciplinary laboratory approach integrating histopathology, immunohistochemistry, and imaging findings.**
***Methods:*** **We report a 78-year-old male with a mixed histology lung carcinoma. Diagnostic evaluation included enhanced chest CT, bronchoscopy-guided biopsy, and comprehensive immunohistochemical profiling.**
***Results:*** **Histopathological analysis revealed squamous differentiation admixed with spindle-cell sarcomatoid components. Immunohistochemistry demonstrated CK5/6 and p40 positivity supporting squamous origin, while vimentin positivity confirmed sarcomatoid features. PD-L1 expression was approximately 1%. Based on these laboratory findings, a final diagnosis of mixed squamous cell carcinoma and sarcomatoid carcinoma was established. The patient was treated with sintilimab followed by envafolimab, resulting in marked reduction of the left lower lobe mass and complete resolution of bronchial nodules, confirming a favorable immunotherapy response.**
***Conclusions:*** **This case highlights the critical role of an integrated laboratory diagnostic approach in identifying rare mixed-type lung carcinomas and demonstrates that immunotherapy targeting PD-L1 may offer clinical benefit even in histologically complex tumors. Coordinated diagnostic assessment is essential for guiding precise and effective treatment strategies in such uncommon pulmonary malignancies.**
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### KEYWORDS

squamous cell carcinoma, pulmonary sarcomatoid carcinoma, diagnosis, treatment, case report

### INTRODUCTION

In 2022, the GLOBOCAN 2022 database reported 2,480,301 new cases of lung cancer globally, resulting in 1,817,172 deaths, making it the leading cause of both incidence and mortality among all malignant tumors worldwide [1]. Lung cancer is categorized histologically into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC constitutes roughly 85% of lung cancer cases and encompasses adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Squamous cell carcinoma, specifically, makes up 20% - 30% of NSCLC cases. Pulmonary sarcomatoid

carcinoma (PSC), a rare subtype of NSCLC combining features of both carcinoma and sarcoma, constitutes 0.1% to 0.4% of primary lung cancers and is typically diagnosed at an advanced stage with a poor prognosis [2]. In this report, we presented a case of mixed histology lung carcinoma in a 78-year-old male, along with an updated literature review on laboratory features and management strategies for squamous cell carcinoma and sarcomatoid carcinoma of the lung, aiming to deepen clinicians' understanding of this intricate tumor type.

## CASE PRESENTATION

A 78-year-old male presented with a persistent cough and shortness of breath lasting approximately four months. He had a 40-year history of cigarette smoking, averaging 20 cigarettes per day, and had not quit. Physical examination revealed a barrel-shaped chest, symmetrical respiratory movements, diminished breath sounds bilaterally, and coarse crackles in the upper lung fields. No superficial lymphadenopathy was detected. Serum tumor marker testing showed elevated levels of neuron-specific enolase (NSE, 23.2 ng/mL) and cytokeratin 19 fragment (CYFRA21-1, 4.2 ng/mL), while squamous cell carcinoma antigen (SCC) was 2 μg/L. Enhanced chest CT revealed a soft tissue density lesion measuring approximately 17 x 24 mm in the trachea, obstructing the entrance of the left main bronchus and extending toward the carina (Figure 1A). Bronchoscopy demonstrated a cauliflower-like endobronchial mass completely occluding the left main bronchial opening. Histopathological biopsy confirmed squamous cell carcinoma, with immunohistochemical staining positive for P63 (+++), P40 (++), EMA (+), and CK (+++), and negative for vimentin and SMA-α; Ki-67 was positive in approximately 30% of tumor cells (Figure 1B).

The patient underwent endoscopic resection of the intratracheal tumor under general anesthesia, followed by intensity-modulated radiotherapy (IMRT) and eight cycles of anti-angiogenic therapy. Subsequent evaluations showed temporary remission; however, recurrence occurred within one year (Figure 1C). Repeat bronchoscopy and histopathological examination confirmed sarcomatoid carcinoma, characterized by positive staining for vimentin (+++), focal positivity for SMA-α and S-100, and negative results for P63, P40, and CK5/6; Ki-67 expression reached 60% (Figure 1D).

Further testing for driver gene mutations (EGFR, ALK, ROS1, MET, and BRAF V600E) was negative, while PD-L1 expression was observed in 1% of tumor cells. Sintilimab immunotherapy was initiated and maintained for 18 cycles, resulting in partial tumor regression (Figure 1E). However, new interstitial changes developed in the right lower lung, consistent with immune-related pneumonitis, which resolved following corticosteroid therapy (Figure 1F - G).

Subsequent imaging revealed disease progression, with new nodular densities in the left lower lobe and near the left main bronchus (Figure 1H). Envafolimab therapy was then administered for five cycles, achieving further tumor reduction (Figure 1I). The patient remains under regular follow-up and maintenance immunotherapy with envafolimab.

## DISCUSSION

Squamous cell lung cancer is a slow-growing malignancy often diagnosed in advanced stages and typically found centrally in the lungs. It commonly coexists with other cardiopulmonary conditions and rarely displays targetable genetic mutations [3]. While immunotherapy may benefit some patients, effective options are limited and ongoing research on relevant medications is exploring new avenues. Traditional platinum-based chemotherapy, though effective, is associated with significant side effects, complicating treatment. Moreover, bleeding risks further limit the use of anti-angiogenic therapies [4]. Currently, the mainstays of treatment for squamous cell lung cancer are chemotherapy and immunotherapy. Overall, its prognosis is generally poorer compared to lung adenocarcinoma.

PSC is an exceedingly rare subtype of NSCLC, comprising less than 1% of all lung cancer cases. The rarity of PSC and its histological diversity contribute to gaps in understanding its oncogenic mechanisms and optimal treatment strategies [5]. Current histopathological studies suggest that PSC originates from monoclonal primitive epithelial tissue, undergoing an epithelial-mesenchymal transition to acquire sarcomatoid characteristics [6-8]. The National Cancer Database highlights that a significant majority of PSC cases are diagnosed at advanced stages, with AJCC stages III and IV accounting for 24% and 48% of cases, respectively, demonstrating worse prognosis and accelerated disease progression compared to other NSCLC types [9]. Given its histological profile, immunohistochemical analysis plays a crucial role in diagnosis and differentiation, utilizing common epithelial cell markers such as cytokeratin (CK), cytokeratin 5/6 (CK5/6), and P40, along with mesenchymal markers primarily including vimentin and desmin [10]. In initial immunohistochemical analyses of this case, the results showed high expression levels of CK (+++), P63 (+++), P40 (++), and EMA (+), while vimentin was negative, were consistent with characteristics of squamous cell carcinoma. Following a course of treatment, subsequent immunohistochemical analysis revealed a shift: P63 and P40 were no longer detected, CK5/CK6 was negative, focal CK staining was observed, and vimentin showed strong (+++) positivity. These updated results aligned more closely with the features of sarcomatoid carcinoma. The pathological transition from squamous cell carcinoma to sarcomatoid carcinoma is rarely documented in histological reports, posing a challenge for interpretation. Initially, the pathology in this case was considered a mixed tumor comprising predominantly squamous carcinoma with a lesser compo-

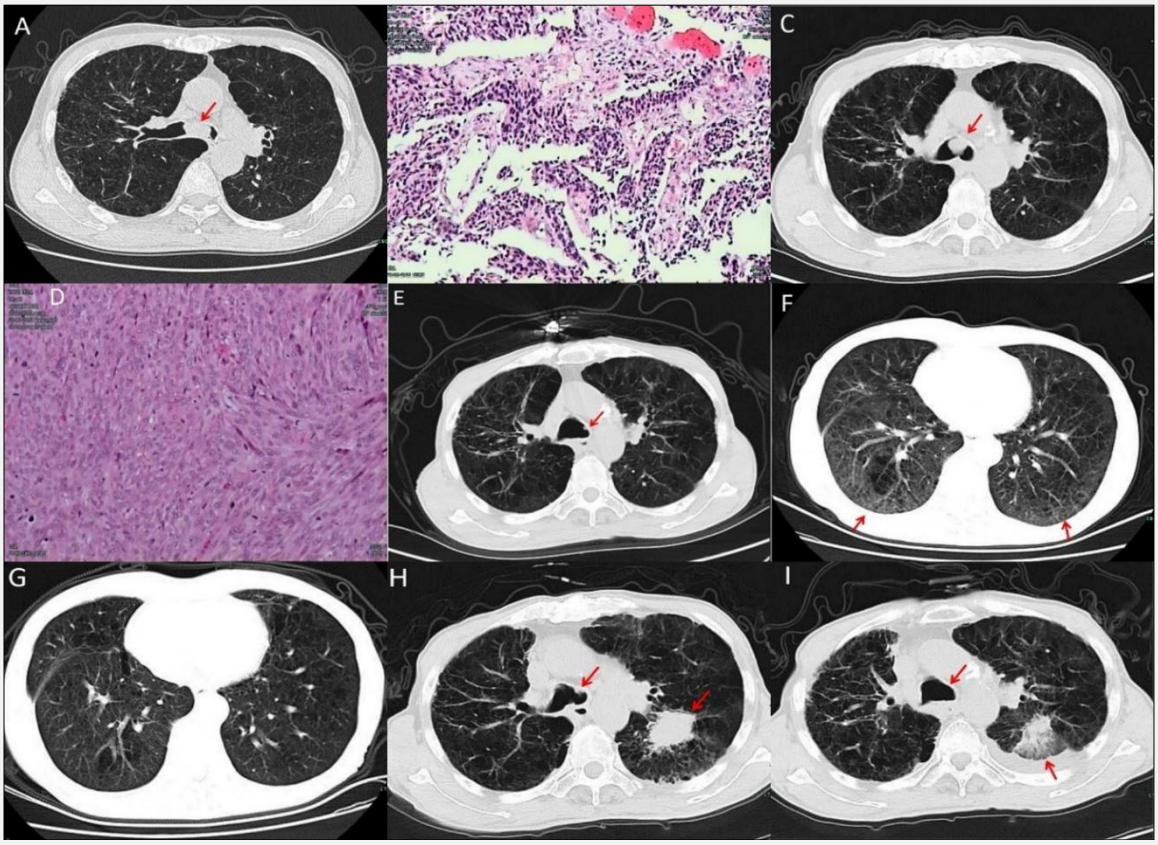


**Figure 1.**

**A: chest CT revealed a mass near the carina involving the main bronchus; B: bronchoscopic biopsy pathology confirmed squamous cell carcinoma; C: follow-up chest CT showed further enlargement of the nodules near the carina; D: bronchoscopic biopsy pathology indicates sarcomatoid carcinoma; E: follow-up chest CT showed only minimal nodules at the start of the left main bronchus after treatment with sintilimab; F: developed immune-related pneumonia following sintilimab immunotherapy; G: improved resolution of pneumonia compared to previous; H: new lesion detected in the left lower lobe; tiny nodules found at the beginning of the left main bronchus; I: reduction of the lesion in the left lower lobe and disappearance of tiny nodules at the beginning of the left main bronchus following continued treatment with envafolimab for 5 cycles.**

nent of sarcomatoid carcinoma. The early immunohistochemical profile resembled that of squamous carcinoma, but with ongoing treatment, there was a noticeable reduction in squamous carcinoma tissue, resulting in an immunohistochemical profile more characteristic of sarcomatoid carcinoma.

Similar to other NSCLCs, early-stage PSC is best managed surgically, yet recurrence rates post-surgery are high, and advanced PSC shows limited response to conventional radiotherapy and chemotherapy. Recent advances in targeted therapies and immunotherapy have revolutionized PSC treatment. Lee et al. [11] reported effective treatment of a PSC patient with a MET exon 14 deletion using crizotinib. In contrast to NSCLC, EGFR mutations are less common in PSC. Furthermore, EGFR-targeting tyrosine kinase inhibitors (TKIs) show variable efficacy in PSC patients with EGFR mutations [12], reflecting genetic differences that may contribute to targeted therapy challenges. Immunotherapy, particularly PD-1 and PD-L1 inhibitors, represents a promising frontier for PSC treatment by enhancing T-cell responses against tumors through PD-1/PD-L1 blockade [13]. Previous cases have demonstrated prolonged progression-free survival, and overall survival in PSC patients with high PD-L1 expression [14,15], making immunotherapy a viable option for these patients. In this case, the initial diagnosis was stage IIIA squamous cell carcinoma of the lung (T4N0M0) with a performance status score of 1. Due to chemotherapy resistance, treatment followed the 2019 Chinese guidelines for advanced NSCLC without driver mutations and PS scores of 0 - 1. The regimen included recombinant human en-

dostatin with gemcitabine and cisplatin for 2 - 4 cycles [2B], with potential extension based on tolerance [Class 3]. Anti-angiogenic therapy, radiotherapy, and bronchoscopic local interventions achieved a near PR response. By November 3, 2020, pathology indicated pulmonary sarcomatoid carcinoma with negative driver gene mutations. Despite low PD-L1 expression (1%), sintilimab monotherapy showed efficacy, suggesting benefits for PSC patients with low PD-L1 expression in immunotherapy. Treatment was paused due to immune-related pneumonitis, resuming later with envafolimab for another PR. The patient completed 5 cycles without immune-related adverse events and continues treatment and follow-up.

## CONCLUSION

This case underscores the importance of an integrated diagnostic approach combining histopathology, immunohistochemistry, and imaging findings in accurately identifying rare mixed-histology lung carcinomas. The coexistence of squamous cell carcinoma and sarcomatoid carcinoma highlights the morphological and immunophenotypic diversity of lung cancer. Moreover, the patient's favorable response to PD-L1–targeted immunotherapy suggests that immune checkpoint inhibitors may represent a promising therapeutic option even for uncommon, histologically complex subtypes. Early and precise pathological characterization is therefore essential to guide individualized treatment and improve clinical outcomes.

**Declaration of Generative AI in Scientific Writing:**
No generative AI tools were used for writing, editing, data analysis, or any other part of the preparation of this manuscript.

**Declaration of Interest:**
The authors declare no conflict of interest.

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