# Pulmonary pleomorphic carcinoma associated with cystic airspace and recurrent spontaneous pneumothorax: A case report

QIANGSHENG LI[1], JING ZHANG[1], YOUJIE GONG[2], XUDONG WAN[1], SONG ZHANG[1], ZHONGWANG LI[1] and JUN LIU[1]

[1]Department of Cardiothoracic Surgery, Bengbu Third People's Hospital Affiliated to Bengbu Medical University, Bengbu, Anhui 233000, P.R. China; [2]Department of Pathology, Bengbu Third People's Hospital Affiliated to Bengbu Medical University, Bengbu, Anhui 233000, P.R. China

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**Abstract.** Pulmonary pleomorphic carcinoma (PPC), classified as the predominant subtype of pulmonary sarcomatoid carcinoma under the current World Health Organization (WHO) criteria, accounts for 0.1-0.4% of all non-small cell lung carcinoma cases and typically manifests radiologically as solid masses with peripheral infiltration. In the present report, a novel clinicopathological manifestation of PPC presenting as a primary solitary cystic airspace with recurrent spontaneous pneumothorax (SP), challenging conventional diagnostic paradigms, is described. A 66-year-old man with recurrent SP was initially misdiagnosed with pulmonary bullae based on the peripheral cystic airspaces observed on computed tomography. Persistent air leakage prompted video-assisted thoracoscopic wedge resection, which revealed biphasic histology: Malignant spindle cell proliferations (vimentin-positive) mixed with conventional adenocarcinoma components (transcription termination factor 1-positive/napsin A-positive), consistent with the WHO 2021 diagnostic criteria for PPC. The patient reached sustained remission without adjuvant therapy, and disease-free survival was maintained for 29 months. The present case highlights three critical implications: First, primary cystic airspaces represent a rare but clinically significant radiological phenotype of PPC that mimic benign bullous lesions, particularly when obscured by pneumothorax; second, recurrent SP may serve as the initial manifestation of occult pulmonary malignancy, necessitating rigorous evaluation of cystic lung lesions; third, early surgical intervention offers dual diagnostic and therapeutic value, even in patients with compromised pulmonary function. These findings expand the recognized spectrum of the imaging heterogeneity of PPC and underscore the need for heightened clinical suspicion of cystic lung cancer in high-risk populations.

*Correspondence to:* Dr Jun Liu, Department of Cardiothoracic Surgery, Bengbu Third People's Hospital Affiliated to Bengbu Medical University, 38 Shengli Middle Road, Bengbu, Anhui 233000, P.R. China
E-mail: ahbbsylj2008@sina.com

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## Introduction

Pulmonary pleomorphic carcinoma (PPC) is a rare aggressive subtype of non-small cell lung cancer (NSCLC), accounting for 0.1-0.4% of cases (1,2). Histologically, PPC exhibits biphasic malignant components (such as spindle/giant cells and conventional carcinoma), and is classified by the 2021 World Health Organization criteria as a sarcomatoid carcinoma requiring ≥10% spindle or giant cell morphology (3). A large-scale study utilizing the Surveillance, Epidemiology and End Results database revealed that PPC predominantly affects Caucasian populations (80%), with a median age of 66 years at diagnosis and a male predominance (male-to-female ratio, 1.38:1) (4). PPC exhibits a significantly poorer prognosis compared with other NSCLC subtypes, and optimal therapeutic strategies remain undefined. For early stage disease, surgical resection is the preferred treatment and is critical for preventing recurrence and metastasis. Marked by aggressive behavior, invasiveness and heterogeneity, PPC is associated with a poor prognosis, with a median overall survival time of 9 months and a 5-year survival rate of only 23% (5). These findings underscore the need to explore systemic therapeutic approaches for PPC. Radiologically, PPC typically presents as peripheral solid masses, although cystic manifestations occur in exceptionally rare cases (6). Notably, only three cases of PPC-associated cystic lesions have been reported in the English literature (as of 2024) (7-9). Although spontaneous pneumothorax (SP) is a rare complication of lung malignancies (10), primary cystic PPC with recurrent SP has not yet been documented.

The present report details a histopathologically confirmed case of PPC manifesting as cystic airspaces and recurrent SP, challenging conventional diagnostic paradigms. The findings emphasize the potential of PPC to mimic benign cystic lesions and highlight the necessity of considering malignancy in patients with cystic lung disease and recurrent SP.

## Case report

A 66-year-old man (height, 166 cm; weight, 57 kg) with a 40 pack-year smoking history presented with a SP in May 2022 (Fig. 1A). Initial computed tomography (CT) results revealed bullous emphysema, prompting a left-sided closed-tube thoracostomy. Despite initial resolution, the patient experienced a recurrent pneumothorax within 2 weeks, prompting further evaluation. High-resolution CT identified a solitary cystic lesion in the left lower lobe with the following malignant features: Uneven wall thickening (maximum 5.6 mm), irregular nodular contours and heterogeneous internal septations (Fig. 1B). Concurrently, serum tumor markers were significantly elevated as follows: Carcinoembryonic antigen (CEA; 4.32 ng/ml; normal range, 0-3.4 ng/ml), carbohydrate antigen 125 (CA125; 148.90 U/ml; normal range, 0-35 U/ml) and neuron-specific enolase (NSE; 34.66 ng/ml; normal range, 0-16.3 ng/ml). Pulmonary function tests revealed mixed ventilatory dysfunction [forced expiratory volume in 1 sec (FEV1) 1.01 liters (predicted normal, 2.73 liters; 37.1% predicted; calculated postoperative FEV1, 29.3%)], corroborated by a shuttle walk test (SWT) demonstrating limited functional capacity (320 meters). Video-assisted thoracoscopic surgery (VATS) revealed a ruptured subpleural cyst, which led to a wedge resection (Fig. 1C).

Histopathological examination of the wedge resection confirmed the diagnosis of PPC with biphasic differentiation, characterized by a predominant malignant spindle cell component (80%) coexisting with conventional adenocarcinoma (20%), as demonstrated by representative histological sections (Fig. 2A and B). Immunohistochemical analysis (Data S1) revealed diffuse vimentin expression within the sarcomatoid spindle cell regions (Fig. 2C), while focal cytokeratin immunoreactivity indicated residual epithelial differentiation (Fig. 2D). The adenocarcinoma component was validated through concurrent nuclear transcription termination factor 1 (TTF-1) positivity (Fig. 2E) and cytoplasmic Napsin A co-expression (Fig. 2F). Proliferative metrics revealed aggressive biological behavior, with a Ki-67 labeling index of 70% (Fig. 2G) and EGFR upregulation detected in 90% of tumor cells, suggesting aberrant activation of oncogenic signaling pathways.

Molecular analysis revealed no actionable driver mutations in EGFR, anaplastic lymphoma kinase (ALK), ROS1, KRAS, MET, BRAF, ERBB2 or RET, and no expression of programmed death-ligand 1 (PD-L1) (combined positive score=0) (Fig. 2H and I). In accordance with the preferences of the patient, adjuvant therapy was not administered. Surveillance consisted of semi-annual head and chest CT scans combined with quarterly serum tumor marker monitoring. Notably, clinical and imaging follow-up at 29 months demonstrated sustained disease control, with no evidence of locoregional recurrence or distant metastasis. Specifically, follow-up chest CT at 29 months post-operation demonstrated the absence of locoregional recurrence and pulmonary metastases (Fig. 1D).

Comprehensive immunohistochemical protocols detailing tissue processing parameters, antibody validation data, and quality control measures are documented in Data S1.

## Discussion

PPC is the most prevalent subtype of pulmonary sarcomatoid carcinoma (PSC) and comprises both epithelial carcinoma and sarcomatous components (11). The epithelial component includes traditional NSCLC features, including squamous cell carcinoma and adenocarcinoma, while the sarcomatous component (making up at least 10% of the tumor tissue) consists of spindle cells or giant cells. Tumorigenesis and malignant progression in cancer are synergistically driven by genetic alterations and epigenetic dysregulation (12). PSC poses therapeutic challenges due to its notable genetic heterogeneity and intricate epigenetic landscape (3). Surgery is considered the optimal treatment for resectable PSC (13), and due to the low sensitivity of PSC to radiotherapy and chemotherapy, achieving negative surgical margins is crucial for extending survival time in these patients, irrespective of the tissue subtype (4,14). Adjuvant chemotherapy is recommended for patients with surgically resected stage II and III PSC (15). Traditional molecular targets such as ALK and EGFR are infrequently observed in PSC and only a small subset of patients are eligible for targeted therapy (16). Additionally, despite high levels of PD-L1 expression in PSC, the response rates to programmed cell death protein 1/PD-L1 inhibitors are only modest (40-55%) (17).

Cystic lung cancer is radiologically characterized by thick-walled cystic airspaces with irregular walls and mural nodules, which are predominantly observed in adenocarcinoma subtypes (18). Thin-walled solitary cysts in early stage lesions are frequently misdiagnosed as bullae or benign cysts (19). Notably, SP as an initial presentation of lung cancer remains exceedingly rare. Yu *et al* (20) previously reported a recurrent pneumothorax case where CT revealed a bullae-mimicking cystic lesion in the right middle lobe that was later confirmed as invasive adenocarcinoma. While PPC typically presents as solid masses on CT, to the best of our knowledge, the present study reports the first documented case of PPC manifesting as a primary solitary cystic airspace with recurrent SP, highlighting its imaging heterogeneity.

A review of the literature reveals limited reports on purely cystic PPC. Iwamura *et al* (9) described a solitary subpleural cyst exhibiting mural nodule enlargement over 5 years, diagnosed as pT2aN0M0 PPC post-resection. The patient was not administered adjuvant therapy and no recurrence was noted within 2 years. By contrast, Yang *et al* (8) documented a left lower lobe cystic lesion progressing to a 7-cm solid mass over 3 years, staged as pT4N1M0 postoperatively, suggesting a potential continuum from cystic to solid PPC. Although the present case similarly featured a subpleural cystic lesion with eventual pleural rupture, its biphasic histology (adenocarcinoma + spindle cell carcinoma) aligns with prior reports, confirming the cystic radiophenotypes across PPC subtypes.

It is of particular clinical note that the cases reported by Iwamura *et al* (9) and Yang *et al* (8), and the present case, collectively suggest that PPC may initially manifest as isolated cysts, evolving into nodular or solid lesions over time. This implies that cystic morphology might represent an uncommon early stage feature of PPC. Mechanistically, cyst formation may involve check-valve-mediated air entrapment (21), a pathophysiological process shared with cystic adenocarcinoma,

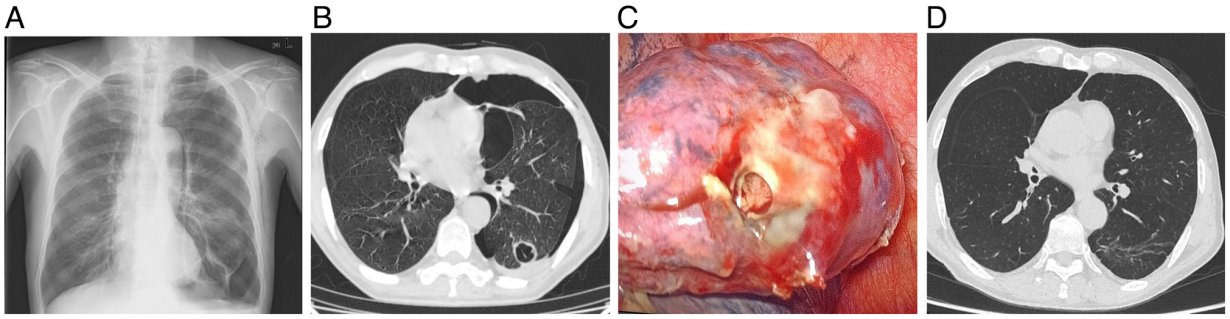


Figure 1. Imaging findings of the patient. (A) Chest radiograph on hospital day 1 demonstrating left-sided pneumothorax with pleural adhesions during the second recurrence. (B) Chest CT on hospital day 2 revealing a cystic lesion in the left lower lobe, exhibiting malignant features: Uneven wall thickening (maximum 5.6 mm), irregular margins and internal septations. (C) Intraoperative image on hospital day 7 (surgery day) showing the ruptured 0.5-cm cystic lesion with 100 ml of clear yellowish effusion. (D) Follow-up CT at postoperative month 29 confirming the absence of local recurrence or pulmonary metastases. CT, computed tomography.

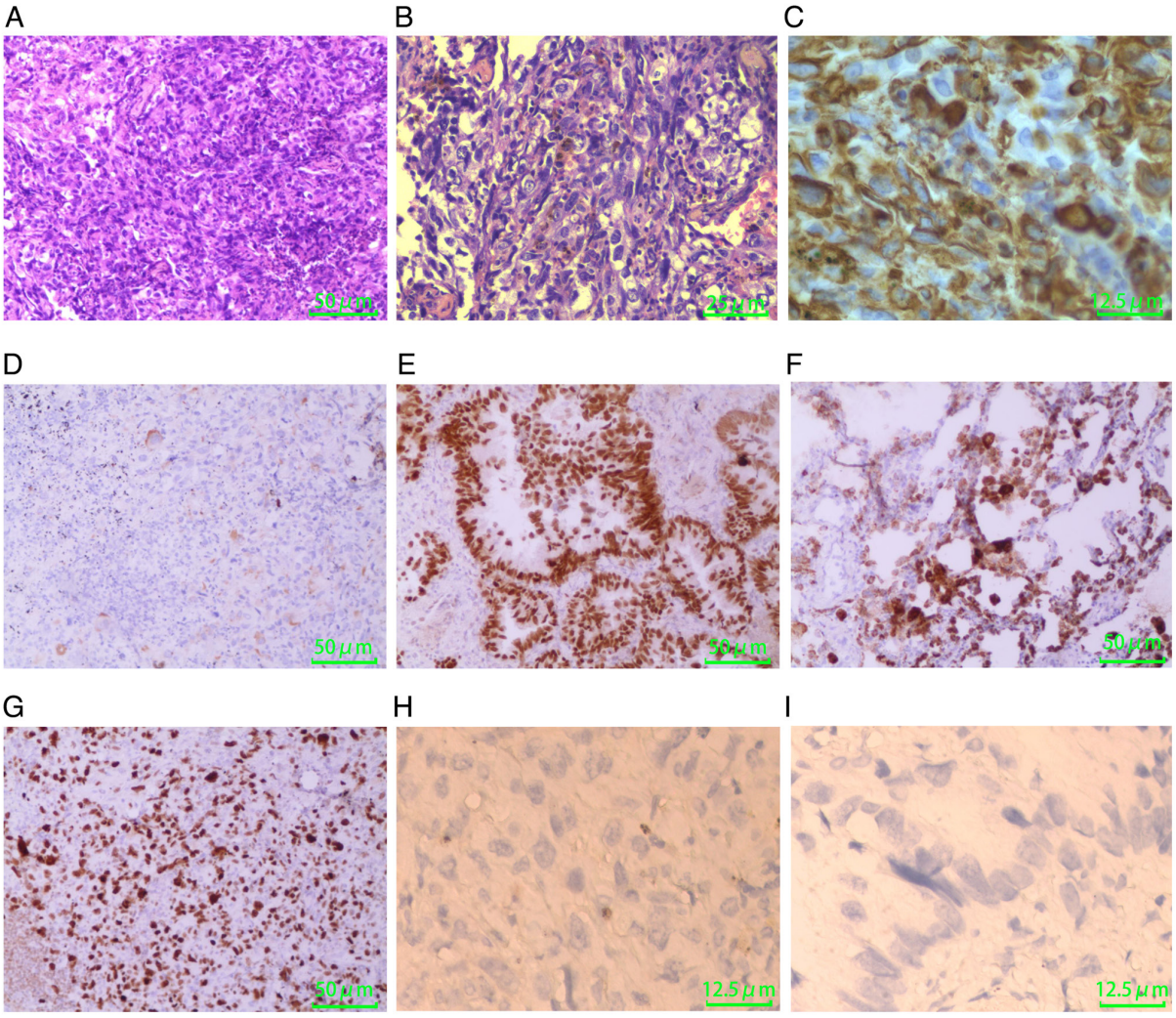


Figure 2. Histopathological and immunohistochemical features of PPC. (A) H&E staining (x100 magnification) demonstrating biphasic differentiation: PSC components with adjacent adenocarcinoma. (B) High-power H&E (x200 magnification) image highlighting spindle-shaped malignant cells in the PSC region. (C) Diffuse vimentin expression confirming the mesenchymal origin of spindle cells (x400 magnification). (D) Focal cytokeratin immunoreactivity in the PSC region (x100 magnification). (E) Focal nuclear thyroid transcription factor-1 positivity in the adenocarcinoma component (x100 magnification). (F) Cytoplasmic napsin A positivity in the adenocarcinoma component (x100 magnification). (G) Ki-67 proliferative index of 70% (x100 magnification). (H) Malignant spindle cell region: No PD-L1 expression (x400 magnification). (I) Adenocarcinoma area: No PD-L1 expression (x400 magnification). PSC, pulmonary sarcomatoid carcinoma; H&E, hematoxylin and eosin; PD-L1, programmed death-ligand 1.

necessitating an expanded classification of cystic lung cancer to include PPC. However, Yamakawa *et al* (7) documented a PPC case exhibiting triphasic histology (giant cells, spindle cells and focal adenocarcinoma) that progressed paradoxically.

Initially manifesting as a solid mass, the mass subsequently developed bilateral multifocal cystic metastases with recurrent pneumothorax, defying conventional growth patterns. These findings underscore two critical insights: i) High histological heterogeneity is associated with aggressive behavior and metastatic potential; and ii) metastatic PPC may exhibit multicystic cavities with pneumothorax, necessitating differentiation from primary cystic lesions through molecular profiling. Collectively, these observations delineate the spectrum of the cystic manifestations of PPC, of which clinical implications and biological underpinnings warrant further large-scale investigations.

The present case involved dual challenges in both diagnostic differentiation and surgical decision-making. The initial task required distinguishing cystic lung cancer from benign mimics such as bullae, cysts and tuberculous cavities, while the second task centered on optimizing surgical safety given the severe pulmonary impairment. In the present study, a 66-year-old male patient with a 40 pack-year smoking history exhibited CT features of malignancy in the left lower lobe of the lungs: A cystic lesion exhibiting uneven wall thickening (maximum 5.6 mm) with irregular contours and heterogeneous septations, consistent with high-risk radiological markers. This suspicion of malignancy was further supported by elevated CEA, CA125 and NSE serum levels (22). Progressive pneumothorax and evidence of malignancy from the imaging prompted a multidisciplinary consensus for VATS. Preoperative pulmonary function testing revealed mixed ventilatory dysfunction (predicted FEV1 of 37.1%), with a calculated postoperative FEV1 of 29.3%, which is below the 30% safety threshold established by European Respiratory Society/European Society of Thoracic Surgeons and ACCP guidelines (23,24). A 320-meter SWT further confirmed elevated perioperative risk (25), ultimately necessitating a lung-sparing wedge resection. The intraoperative findings of visceral pleural penetration with effusion suggested potential intrathoracic dissemination, justifying the limited resection strategy. This approach exemplifies precision risk-benefit analysis in patients with a marginal pulmonary reserve.

The present case underscores the diagnostic complexity of PPC. While intraoperative frozen sections confirmed malignancy, a definitive diagnosis required extensive sampling and immunohistochemical profiling of TTF-1, napsin A, cytokeratin and vimentin, reflecting the intrinsic histological heterogeneity of PPC. Despite pathological confirmation of pleural invasion (pT2a) and occult metastasis risk, the patient declined adjuvant chemotherapy, opting instead for personalized surveillance per the Chinese NSCLC postoperative follow-up consensus (26). Although subclinical metastatic risk persists, the 29-month recurrence-free survival of the patient may be attributed to early R0 resection. Certain critical reflections have emerged: First, the absence of contrast-enhanced CT may have limited the evaluation of the mural enhancement patterns; second, intraoperative cyst rupture despite saline lavage raised concerns regarding pleural seeding, compounded by the absence of cytological analysis of the effusion for staging completeness; and third, recurrent pneumothorax served as an intervention catalyst, aligning with the findings of Iwamura *et al* (9), where early surgical intervention in stage IB PPC improved the outcome. Collectively, the present case redefines the clinical trajectory of PPC, emphasizing that cystic manifestations may represent an underrecognized early phenotype requiring heightened vigilance in high-risk populations.

In conclusion, cystic airspaces represent a rare radiological phenotype of PPC, frequently misdiagnosed as pulmonary bullae. Early resection remains the cornerstone therapy of this disease. Recurrent SP may indicate occult malignancy, necessitating histopathological evaluation of any cystic lesions. These findings redefine the imaging spectrum of PPC and mandate clinical vigilance for cystic lung cancer, particularly in the context of pneumothorax.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

QL designed the study, collected the clinical data for the case and compiled the first draft. JZ and XW performed diagnostic evaluations through interpretation of imaging studies and histopathological correlation, and acquired clinical data. YG conducted histopathological analysis and immunohistochemical evaluation of the surgical specimen. SZ and ZL were responsible for preoperative patient management, participated in intraoperative surgical decision-making, supervised data collection for perioperative variables, and critically evaluated the manuscript's clinical relevance. JL designed and performed the surgical intervention, and critically revised the manuscript for intellectual content. QL and JZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The clinical study in which the patient participated was approved by the Ethics Committee of Bengbu Third People's Hospital Affiliated to Bengbu Medical University (Bengbu, China; approval no. 2024k12).

**Patient consent for publication**

Written informed consent was obtained from the patient for the publication of clinical details and images.

**Competing interests**

The authors declare that they have no competing interests.

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