Lung Cancer: Targets and Therapy

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CASE REPORT

Pulmonary Spindle Cell Carcinoma Mimicking Granulomatous Inflammation: A Rare Case Report and Brief Review of the Literature

Qian Liu[1,*], Jun Zhang[2,*], Mingqin Wei[1], Xue Zhou[3], Hao Sun[4], Youhong Dong[1], Dongdong Zhang[1]

[1]Department of Oncology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000, People's Republic of China; [2]Department of Neurology, Xiangyang No.1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000, People's Republic of China; [3]Department of Pathology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000, People's Republic of China; [4]Department of Oncology, Baokang County People's Hospital, Xiangyang, 441000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Youhong Dong, Dongdong Zhang, Department of Oncology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, Jiefang Road No. 15, Xiangyang, Hubei, 441000, People's Republic of China, Tel +8615072278600, Email dongyouhong2005@163.com; zhangdongdong@whu.edu.cn

Background: Pulmonary spindle cell carcinoma (PSCC), a highly malignant tumor, often exhibits cell pleomorphism, a histopathological characteristic. Owing to its extremely low incidence, atypical imaging and clinical presentations, and insufficient awareness among clinicians, PSCC is often misdiagnosed, which results in delays in treatment. Herein, we reported a rare case of PSCC that was initially misdiagnosed as granulomatous inflammation.

Case Presentation: A 66-year-old male visited a local hospital with symptoms such as cough and hemoptysis. A computed tomography (CT) scan of the chest revealed a mass in his right lung, and no mediastinal lymphadenopathy was observed. Bronchoscopy showed no major abnormalities, and the results of fine needle aspiration biopsy showed granulomatous inflammation. Even though the patient received anti-infection treatment, his symptoms did not improve markedly. After two months, a follow-up CT scan of the lung showed a noticeably enlarged mass accompanied by multiple instances of mediastinal lymphadenopathy in the upper lobe of the right lung. Consequently, he underwent a second CT-guided lung biopsy at our hospital. The pathology report indicated PSCC. Due to financial constraints, genetic testing was not performed. Given his poor overall physical condition, the patient was unable to undergo systemic chemotherapy and instead received palliative radiotherapy. The prescribed radiotherapy dose for the right upper lobe lung cancer and multiple metastatic lymph nodes was 60 Gy, administered in 30 fractions. Unfortunately, he failed to adhere to scheduled follow-ups and succumbed to the disease 6 months later, as confirmed during a telephone follow-up.

Conclusion: PSCC is a rare but highly malignant lung cancer. Multiple pathological biopsies are necessary to accurately and promptly diagnose the disease, which is crucial for early treatment intervention as well as improving patient prognosis.

Keywords: pulmonary spindle cell carcinoma, granulomatous inflammation, radiotherapy, multiple pathological biopsies

Introduction

Pulmonary sarcomatoid carcinoma (PSC), a rare and aggressive subtype of non-small cell lung cancer (NSCLC), is characterized by the presence of sarcomatoid and carcinomatous elements. Pulmonary spindle cell carcinoma (PSCC) is a rare and special histological subtype of PSC, which accounts for 28.7% of total PSC cases and 0.1%–0.4% of all lung cancer cases.[1] Owing to the rarity of PSCC, its distinctive clinical and pathological features as well as treatment strategies and overall survival rates associated with it, have been scarcely studied. Due to the aggressive nature of PSCC, the disease is often in its advanced stage at the time of diagnosis as well as renders it resistant to traditional chemotherapy regimens used for other NSCLC types. Even when diagnosed at an early stage, PSCC exhibits suboptimal prognostic outcomes.[2]

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The clinical presentations and radiological features of PSCC do not markedly differ from those of other lung cancers, its pathological diagnosis is crucial for its definitive diagnosis. Morphological and immunohistochemical examinations are crucial for the accurate diagnosis of PSCC.[3] However, not all patients can undergo surgery, and tissues obtained from lung biopsies are often limited, sometimes resulting in difficulties in diagnosis. Additionally, PSCC can be manifested by various morphological and histological characteristics that are easily misdiagnosed. Herein, we present a rare case of PSCC initially misdiagnosed as granulomatosis. The present patient exhibited rapid disease progression after 2 months, and the final diagnosis was confirmed after the second biopsy. Additionally, we provide a comprehensive review of PSCC diagnosis and management.

Case Presentation

A 66-year-old male, with an extended history of smoking (30 packs/year) and a medical history of chronic obstructive pulmonary disease (COPD), visited a local hospital for symptoms such as cough, blood in sputum, chest tightness, and bilateral chest pain. A computed tomography (CT) scan of the chest showed a circular, low-density shadow of 1.5×1.0 cm without discernible borders in the upper lobe of the right lung (Figure 1A and B). A CT-guided biopsy of the upper right lung tubercle was performed to clarify the nature of the tumor, and the pathology report indicated granulomatous inflammation (Figure 1C). Subsequently, he underwent bronchoscopy; however, the tumor was not definitively diagnosed. The patient received anti-infection symptomatic supportive therapy, which relieved his symptoms such as cough and blood in sputum. However, the patient's cough symptoms did not show considerable improvement. Additionally, the chest CT scan showed a significantly increased lesion in the upper right lung and a mediastinal lesion after following him up for 2 months. Subsequently, the patient visited our hospital for further evaluation. The lung CT scan revealed right upper lobe lung cancer with multiple metastatic lymph node enlargements in the left supraclavicular area, bilateral axillae, and mediastinum. Superior vena cava and pulmonary artery invasion was noted in addition to a tumor thrombus in the superior vena cava, which narrowed the vessel. Moderate bilateral pleural and pericardial effusion was observed, with the possibility of pericardial metastasis (Figure 2A and B).

We performed another CT-guided percutaneous biopsy of the right lung mass and mediastinal mass. The pathological examination of the biopsies from the right upper lung and mediastinum indicated a malignant spindle cell tumor, with a tendency towards primary lung origin (Figure 2C–H). The histopathological features were as follows: Hematoxylin and eosin staining showed that the tumor cells were entirely composed of spindle cells in diffuse or storiform patterns (Figure 2C). Typical features of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma were not observed. The immunohistochemical analysis revealed negative staining for P40 (Figure 2D), whereas it revealed positive staining for SMA, Cam5.2, and CK7 (lesion area) (Figure 2E–G). Ki67 indicated a high tumor proliferation index (about 60%+) (Figure 2H). The final diagnosis was PSCC with a tumor stage of cT2N3M1 (stage IV). The patient did not undergo genetic testing due to financial constraints. Considering the patient's poor physical condition and intolerance to chemotherapy, radiation therapy was recommended after thorough communication with him. The prescribed dose for the right upper lobe lung cancer and multiple metastatic lymph nodes was 60 Gy in 30 fractions. Detailed delineation of

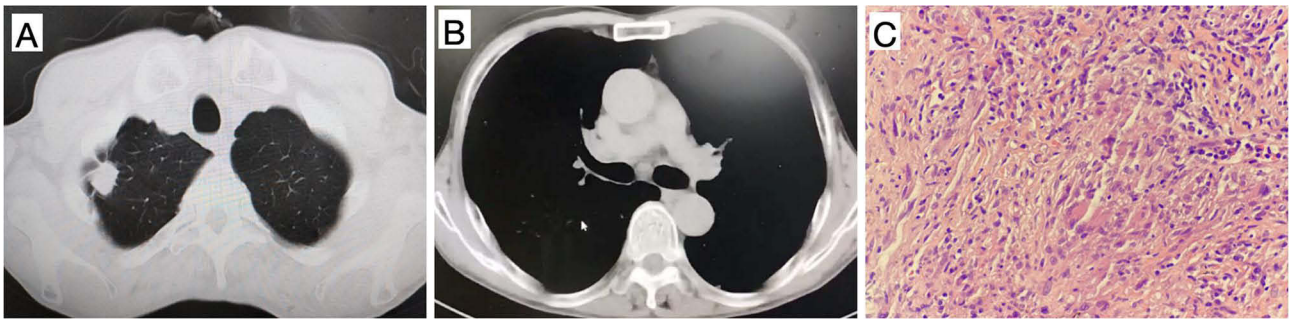

Figure 1 The initial imaging and pathological examinations of the patient. (**A** and **B**): CT indicates a mass in the upper lobe of the right lung (**A**), and no evident lymphadenopathy can be seen in the mediastinal window (**B** and **C**) HE demonstrates that the lung tissue exhibits interstitial fibrosis and scattered infiltration of lymphocytes and plasma cells, with some epithelioid cells visible, indicative of granulomatous inflammation at 100× magnification.

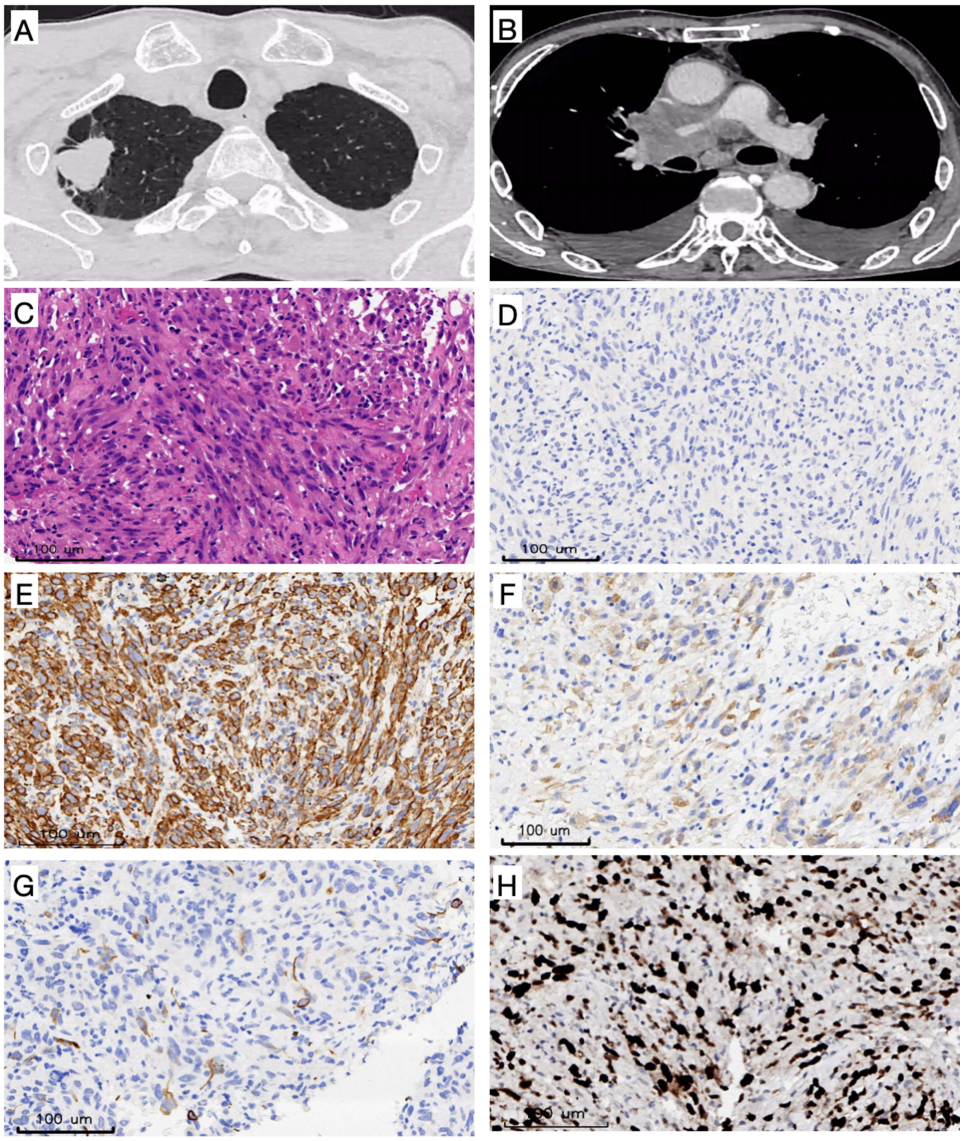

Figure 2 The second CT imaging examinations and pathological findings of the tumor mass in the right lung lobe. (**A** and **B**) CT indicates that the mass in the right lung has enlarged compared to that before (**A**), along with an enlargement of multiple mediastinal lymph nodes (**B** and **C**): The HE staining indicates that the tumor is predominantly composed of spindle cells. (**D**–**H**): Immunohistochemistry shows that the tumor cells are negative for expression of P40 (**D**) and positive for expression of SMA (**E**), Cam5.2 (**F**), CK7 (**G**), and Ki-67 (**H**) at the magnification of ×200.

the target area is presented in Figure 3A–D. The patient did not return to the hospital for a scheduled follow-up after successfully completing radiotherapy. During a telephone follow-up 6 months post-radiotherapy, the patient reported disease progression. The diagnosis and treatment flow chart is shown in Figure 3E.

Discussion

Lung cancer is one of the malignant tumors with high incidence and mortality rates worldwide. PSC is a rare pathological lung cancer. According to the 2015 World Health Organization histological classification of lung tumors, PSC can be divided into PSCC, pleomorphic carcinoma (PC), giant cell carcinoma, carcinosarcoma, and pulmonary blastoma.[4] PSCC incidence accounts for 0.17%–0.40% of all lung malignancies, occurring more frequently in males with smoking habits, with a male-to-female sex ratio of 4:1–5:1. Additionally, it occurs in patients whose age ranges from 50–80 years.[5] Most of the patients diagnosed were already advanced, with 42.4% having stage IV at diagnosis.[6] Herein, we outline the case of a patient who was ultimately diagnosed with PSCC after two histological examinations.

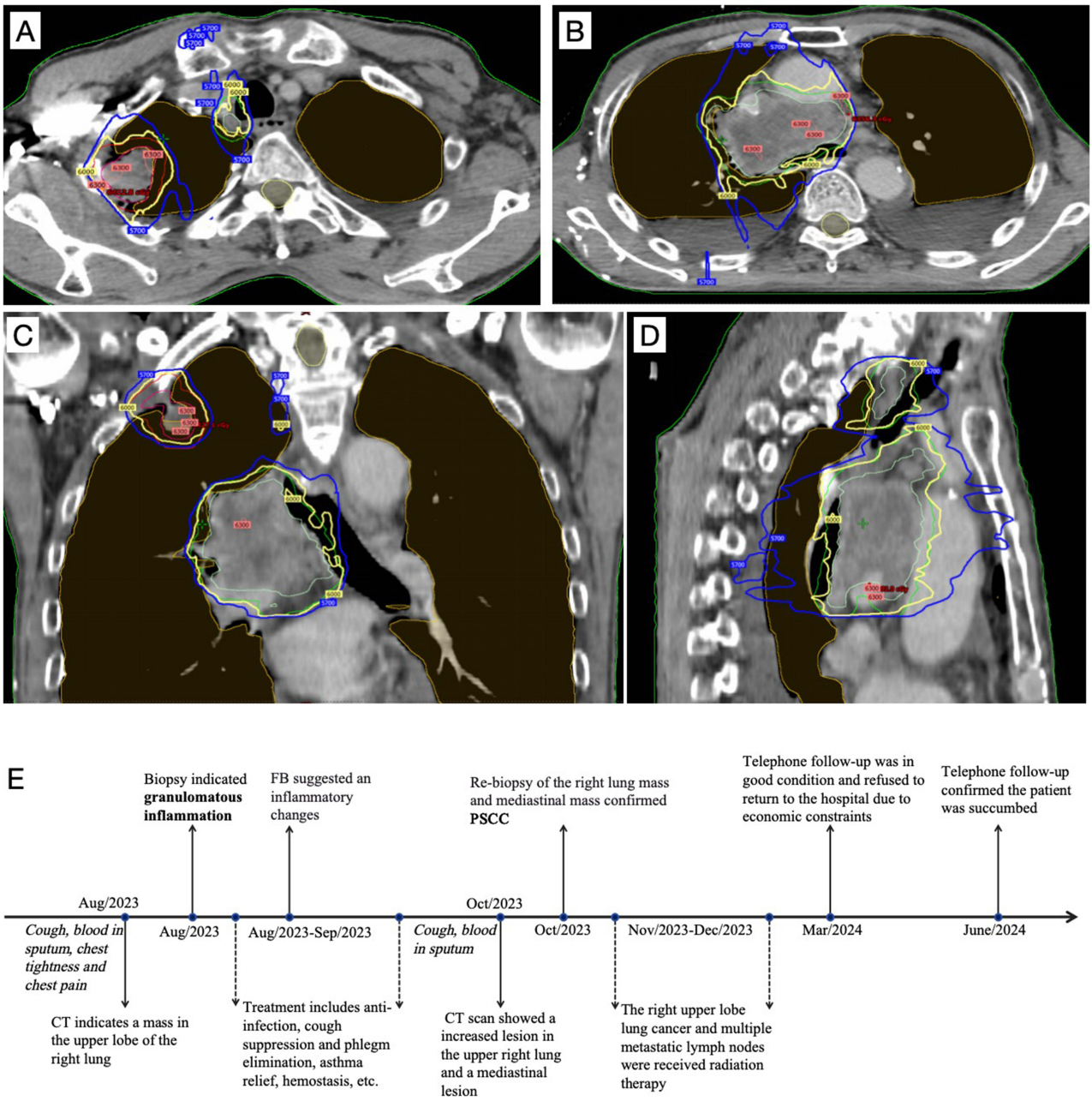

Figure 3 The radiation therapy plan and the diagnosis and treatment flow chart. (**A**–**D**): Radiation treatment plan for VMAT (volumetric modulated arc radiotherapy) targeting the right upper lobe tumor and multiple metastatic lymph nodes with a total dose of 60 Gy in 30 fractions. (**A** and **B**): Axial mediastinal window; (**C**) Coronal lung window; (**D**) Sagittal lung window. Color areas are the radiation isodose curves, yellow represents 60 Gy, red 63 Gy, and blue 57 Gy. (**E**). The diagnosis and treatment flow chart.

The clinical and radiological manifestations of PSCC are not specific; consequently, the rate of its misdiagnosis is high. The clinical symptoms of patients with PSCC are closely associated with the growth and location of the tumor, with the main symptoms being cough, expectoration, hemoptysis, chest pain, and dyspnea. These symptoms are not specific to PSCC and are associated with the location of the tumor. Central PSCC can cause cough and hemoptysis with the tumor growing into the lumen, which may be accompanied by dyspnea when the tumor leads to bronchial stenosis. Peripheral PSCC is often asymptomatic in the early stages, and imaging results typically indicate a large-volume tumor, predominantly located in the periphery, often in the upper lung lobe, with clear boundaries and visible spiculations.[7] Chest pain occurs when tumor cells or inflammatory obstructions spread to the pleura or chest wall. A few patients may experience fever probably because of tumor tissue necrosis or obstructive pneumonia.[8] Ouziane et al documented that imaging

characteristics of PSC predominantly appear in the upper lobe of the lung, presenting with distinct borders and large tumor sizes, often exceeding 5 cm in diameter and reaching up to 18 cm. These tumors frequently infiltrate the chest wall and mediastinum, which is consistent with our reported case.[9] If imaging patterns indicative of malignancy are observed without confirmed pathology, it is prudent to promptly reassess the imaging. Additionally, performing a timely endobronchial ultrasound (EBUS) examination or a secondary biopsy can greatly reduce the likelihood of misdiagnosis and diagnostic oversights.

PSCC can be definitively diagnosed based on pathological examinations.[10] Advances in immunohistochemistry, ultrastructure, and molecular biology research have led to the notion that PSCC originates from primitive epithelial stem cells. Epithelial–mesenchymal transition leads to cancer cells losing typical epithelial characteristics and acquiring interlobular characteristics.[11] The transformation of the PSCC tumor from epithelial-cell morphology to spindle-cell morphology is correlated to a shift from cytokeratin expression to vimentin expression. The morphology of these spindle cells does not show the typical characteristics of epithelial-derived tumors but resembles those of sarcoma. However, the tumor cells express mesenchymal immunomarkers; thus, the disease must be differentiated from true sarcoma. Additionally, it should be differentiated from other conditions such as pulmonary infarction. Rossi et al[12] reported four cases of infarct-like spindle cell carcinoma of the lung. Histologically, these lesions comprised nodules with large ischemic necrotic areas, which could be easily confused with pulmonary infarction. The failure of initial biopsies in the present case has likely been stemming from the challenging nature of PSCC pathological diagnosis. When encountering similar cases in future clinical practice, it is recommended to consider multi-site biopsies to improve diagnostic yield. Additionally, consulting with a pathologist is crucial to further refine diagnostic accuracy.

No standard surgical procedures, chemotherapy regimens, and radiation therapy regimes exist for PSCC. A retrospective study revealed remarkable correlations between N stage, M stage, and surgery with survival outcomes in PSCC, suggesting that early diagnosis and treatment play vital roles in extending patient survival.[13] The majority of literature pertaining to PSCC are case reports. In the present study, we comprehensively reviewed recent case reports and analyzed their clinical profiles and treatment outcomes (Table 1). Radiotherapy is pivotal for treating patients with lung cancer.[14] A case of a stage IIA PSCC with COPD with a performance status (PS) of 2 has been reported in which the patient achieved good local control after receiving stereotactic body radiation therapy (SBRT) for lesions present in the right upper lobe.[15] For patients with a poor PS score who cannot undergo surgery or receive systemic therapy, radiotherapy is a crucial option for controlling tumor growth. The present patient with a PS score of 3 was intolerant to chemotherapy; therefore, palliative radiotherapy was recommended to effectively control the tumor. Further, combinations of carboplatin with albumin-bound paclitaxel, pemetrexed, or traditional Chinese medicine have exhibited efficacy in prolonging patient survival in PSCC.[16,17] Nevertheless, comprehensively evaluating the efficacy of each treatment regimen is impossible because of the limited number of cases. Further studies with larger sample sizes are warranted to validate the present findings.

Several recent studies have focused on targeted therapy and immunotherapy. Weissferdt et al[18] performed immunohistochemical tests on 86 patients with PSCC and PC and revealed that 42% of the lesions could be reclassified as poorly differentiated adenocarcinomas, thereby suggesting that if some patients with PSCC contain genetic mutations, they may be sensitive to targeted therapy. However, patients with PSCC complicated with an EGFR mutation did not respond well to treatment with gefitinib, which indicated that PSCC development may not solely or predominantly depend on the EGFR signaling pathway and that other pathways may primarily trigger its pathogenesis.[19] Further, a patient with PSCC and ALK rearrangement exhibited rapid disease progression within two months of treatment with alectinib, an ALK inhibitor. When switched to lorlatinib, the treatment failed to control tumor growth, which suggested that patients with PSCC complicated with ALK rearrangement may respond poorly to ALK inhibitors.[20] Thus, the approach of applying targeted therapy to manage PSCC is challenging.

Dominant signaling pathways associated with PSCC should be further investigated in order to advance the development of therapeutic strategies against PSCC.[21–23] Due to a more comprehensive understanding of the mechanisms that facilitate tumor evasion, several studies have shown that programmed cell death-ligand 1 (PD-L1) is highly expressed in PSCC tissues.[24] Tsurumi et al initially described a PSCC case treated successfully with pembrolizumab, where elevated PD-L1 levels were detected in the patient's lung tissue biopsy. Remarkably, the tumor volume significantly reduced after

Table 1 Review of the Literature on PSCC

References	Age/Sex	Symptoms	Primary Disease	Imaging	PD-L1/Genetic Results	Stage	Treatment	OS
Awobajo MD[15]	69Y/female	Chronic cough, shortness of breath and decreased, appetite.	Chronic obstructive pulmonary disease (COPD)	The right upper lobe nodule to 2.4×1.8cm	PD-L1 TPS 90%	IIA stage	SBRT to the right upper lobe primary tumour, First line: pembrolizumab	>6 months
Li W[16]	58Y/female	Cough, haemoptysis	None	A large mass located in right lung invading the right hilum with mediastinal lymph node enlargement	No detection	cT4N3Mx	Traditional Chinese medicine (TCM) components consisted of Ma-xing-shi-gan (MXSG) decoction.	>48 months
Tsuji T[17]	65Y/male	Progressing right hypochondrial pain	Not mentioned	74-mm irregular tumor in the right lower lobe with diaphragm invasion	No detection	cT4N1M1c IVB stage (pleura, liver, gluteal muscles)	First line: cisplatin and docetaxel Second line: carboplatin and nab-PTX Maintenance therapy: nab-PTX	>9 months
Ikushima H[19]	82Y/female	Fever and dyspnoea	None	75-mm mass surrounded by infiltrates and atelectasis in the right upper lobe	EGFR exon 19 delete	cT4N2M1c IVB stage (both adrenal glands)	First line: gefitinib	89 days
Sonehara K[20]	60Y/female	Headache and nausea	None	A mass shadow in the right lower lobe and mediastinal lymph nodes	PD-L1 TPS 85%/ ALK rearrangements	cT3N2M1c IVB stage (brain, heart, bilateral adrenal glands, and ilium)	First line: pembrolizumab Second line: alectinib Third line: lorlatinib Fourth line: Brigatinib	9 months
Tsurumi K[25]	76Y/male	Dry cough and right-sided neck pain	Type 2 diabetes, angina pectoris, atrial fibrillation, hypertension, hyperlipidemia	A mass with a thick-walled cavity in the right upper lobe of the lung	PD-L1 TPS >90%/ Gene negative	cT4N2M1c, stage IVB(right adrenal gland, and trapezius muscle)	First line: pembrolizumab	>21 weeks
Mizushina Y[26]	52Y/male	Postoperative progression	Not mentioned	Brain metastasis in the right temporal lobe	PD-L1 TPS >95%/ Gene negative	pT4aN1M0, stage III B	First line:paclitaxel, carboplatin, and bevacizumab. Second line: pembrolizumab.	28 months

9 weeks and completely resolved after 21 weeks of immunotherapy.[25] Additionally, another case study observed a significant response of PSCC to pembrolizumab.[26] While sporadic case reports have highlighted the effectiveness of PD-1 inhibitors in treating PSCC, the scarcity of this disease limits the feasibility of conducting large-scale clinical trials to verify its therapeutic efficacy.

In conclusion, we report the case of a patient with PSCC who was initially misdiagnosed as granulomatous inflammation. PSCC is a rare cancer characterized by high malignancy, poor prognosis, and non-specific clinical and imaging manifestations. Diagnosis primarily depends on pathological detection. However, the disease is prone to misdiagnosis. Clinicians should deepen their understanding of the disease, promote research on PSCC, improve treatment strategies, and improve patient prognosis.

Ethics Approval

This study was approved by the Ethics and Scientific Committee of Hubei University of Medicine with approval number 2022PR-H002. Written informed consent was obtained from the individual for the publication of any potentially identifiable images included in this article. Institutional approval was obtained from Xiangyang No.1 hospital for the publication of the case detail.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors listed above have no conflicts of interest to declare in this work.

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