

A Metastatic Pulmonary Sarcomatoid Carcinoma Patient Harboring *KIF5B-RET* Fusion Responds to First-Line Pralsetinib Treatment: A Case Report

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Abstract: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC), accounting for about 1% of cases. These tumors are characterized by their high malignancy and frequent resistance to chemotherapy, resulting in a worse prognosis compared to other NSCLC subtypes. Currently, there is no established therapeutic strategy for PSC. Recent advancements in targeted therapies have led to the development of ret proto-oncogene (RET) inhibitors, such as selpercatinib and pralsetinib, which have been approved for the treatment of *RET* fusion-positive NSCLC patients. Despite their effectiveness in *RET* fusion-positive NSCLC is observed, the efficacy of these inhibitors in PSC remains unclear. In this context, we present a case of metastatic PSC harboring de novo *KIF5B-RET* fusion. The patient responded to first-line trametinib treatment. These findings suggest that RET inhibitors could be a potential treatment option for metastatic PSC patients with *RET* fusion-positive tumors.

Keywords: pulmonary sarcomatoid carcinoma, *RET*, pralsetinib, efficacy

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare form of non-small cell lung cancer (NSCLC) with high aggressiveness and poor differentiation, accounting for approximately 1% of NSCLC cases.¹ Radical surgery is the standard treatment for early-stage PSC, while patients often experience rapid recurrence after surgical resection. Additionally, traditional palliative chemotherapy has shown limited efficacy in advanced or metastatic PSC.² Studies have indicated that PSC patients have a poor prognosis, with a median overall survival (OS) of 7–12 months and 5-year OS rates of 19.5–25.1%.^{1,3}

Recent research by Schrock et al has shed light on potential treatment options for PSC. These findings suggest that PSC frequently exhibits either targetable alterations or a high tumor mutational burden, opening up possibilities for targeted therapy or immunotherapy.^{4,5} Alterations in Ret proto-oncogene (*RET*), such as *RET* amplification and fusion, are relatively uncommon in PSC.^{4,5} *RET* amplification is observed in only 0.8% of cases,⁴ while *RET* fusion occurs in 0–6.3% of PSC patients.^{4,6}

Currently, two RET inhibitors selpercatinib and pralsetinib have been approved for the treatment of metastatic *RET* fusion-positive NSCLC.^{7,8} However, their efficacy in *RET* fusion-positive PSC patients has not been extensively studied. In this report, we present the case of a stage IV PSC patient with the canonical *KIF5B-RET* (K15:R12) rearrangement, who exhibited tumor response to first-line treatment with pralsetinib.

Case Presentation

A 67-year-old never-smoker woman with Parkinson's disease lasting for over 10 years presented with chest pain and cough for more than half a month in June 2021. The patient's treatment history is summarized in Figure 1A. She

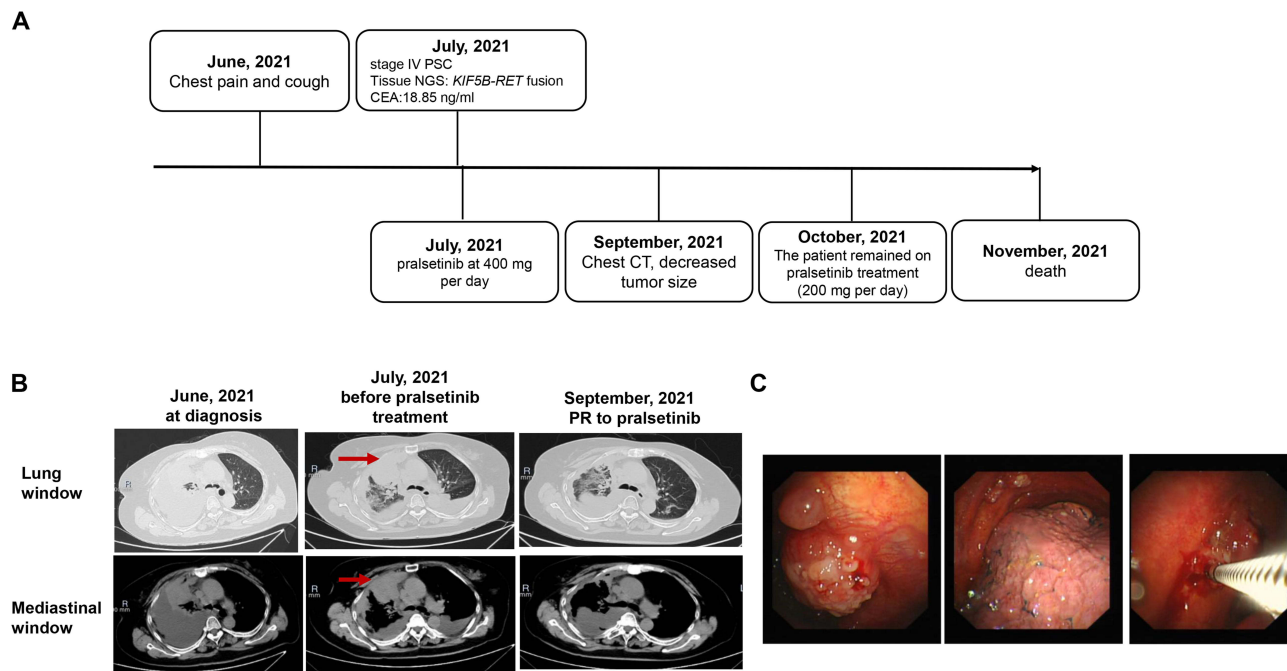


Figure 1 Summary of disease course, therapies, and molecular findings. **(A)** The entire treatment course; **(B)** Chest CT scans of the primary PSC at treatment milestones; red arrows indicate nodular thickening of the pleura. **(C)** Pleuroscopy revealed multiple neoplasms in the right parietal pleura, visceral pleura, and phrenic pleura. **Abbreviations:** CT, computed tomography; NGS, next-generation sequencing; PR, partial response; PSC, pulmonary sarcomatoid carcinoma.

had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3. Chest computed tomography (CT) scans revealed the presence of a mass in the right upper lobe, nodular thickening of the right pleura, and massive accumulation of pleural fluid on the right side (Figure 1B). The tumor marker carcinoembryonic antigen (CEA, normal range: 0–5 ng/mL) was measured at 18.85 ng/mL. The biopsy sample taken from the right supraclavicular lymph node indicated the presence of an N3 tumor. Subsequently, a pleuroscopy was performed, which revealed multiple nodules measuring 1.0–1.2 cm in diameter on the right parietal pleura, visceral pleura, and phrenic pleura (Figure 1C). Further examination of the biopsy sample taken from the right parietal pleura using hematoxylin-eosin (HE) examination and immunohistochemistry (IHC) staining with vimentin (+), Ki-67 (+, 90%), CAM5.2 (small part+), CK7 (small part+), and TTF1 (+), confirmed the presence of PSC (Figure 2). IHC staining on the tumor tissue sample also revealed a high expression of programmed cell death ligand-1 (tumor proportion score: 80%, clone number for PD-L1 antibody: 22C3). To further analyze the sample, next-generation sequencing (NGS) was conducted using the Nextseq500 platform (Illumina, Inc., San Diego, CA, USA) with paired-end reads and an average sequencing depth of 2165×. The NGS analysis employed a panel consisting of 68 cancer related-genes (LungCore™, Burning Rock Biotech, Guangzhou, China, Table S1). The results of NGS revealed a canonical *RET* rearrangement known as *KIF5B-RET* (K15:R12) (Figure 3), with an allele frequency of 23.9%. Based on these findings, the patient was diagnosed with stage IV (T4N3M1a) PSC that was positive for *KIF5B-RET* fusion in July 2021 (Figure 1B). The patient was subsequently prescribed first-line treatment with pralsetinib at a daily dose of 400 mg. After undergoing treatment for 2 months, a reduction in the size of the tumor in the right lung was observed in chest CT scans (Figure 1B). According to the RECIST criteria v1.1, the treatment response was evaluated as a partial response (Figure 1B). In October 2021, the dosage of pralsetinib was reduced to 200 mg per day due to the occurrence of treatment-related adverse events, including grade I diarrhea and grade II low albumin (less than 30g/L, normal range: 40–50g/L). The reduction in the oral pralsetinib dosage effectively relieved the low albumin level, which were classified as grade 1. Comparing the chest CT scans from September 2021, the patient's tumor remained stable in October 2021. However, in November 2021, during a follow-up call with the patient, their family informed us that the patient had passed away at another hospital in the presence of heart failure.

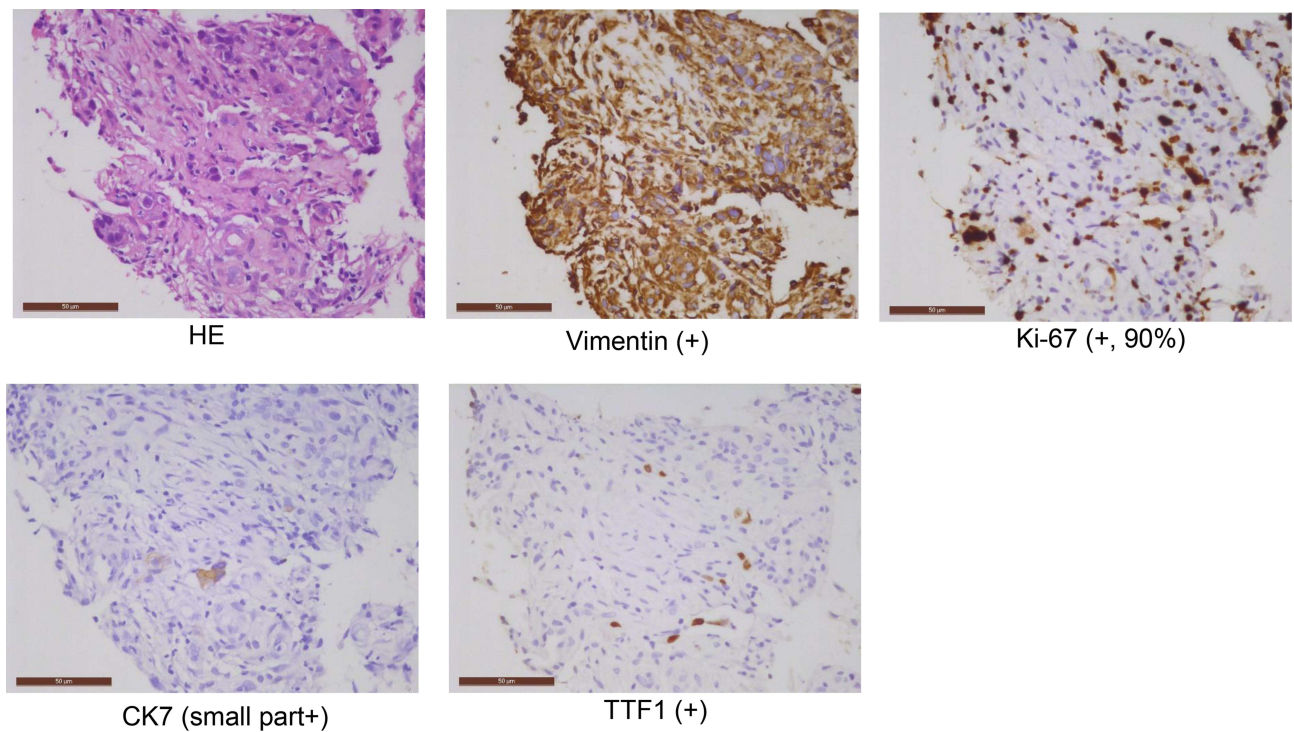


Figure 2 Hematoxylin-eosin (HE) and immunohistochemistry staining on the biopsy sample of the right parietal pleura. The rulers in Figure 2 indicate 50 µm.

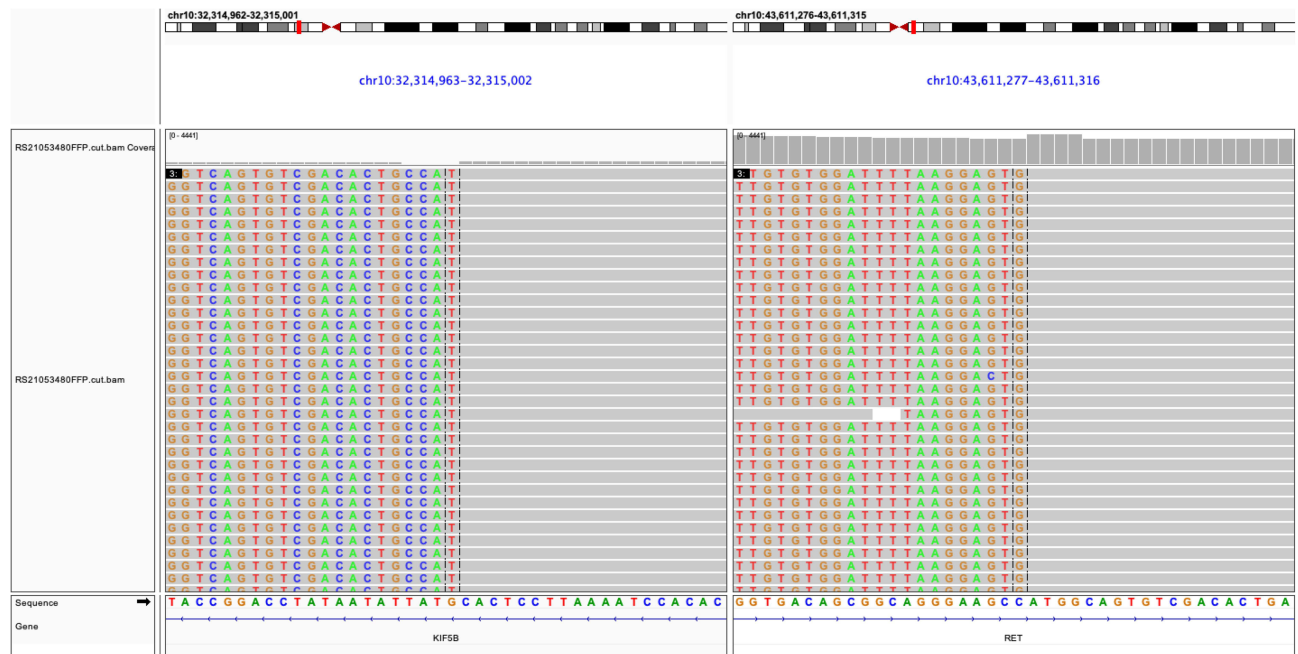


Figure 3 The integrative genomics viewer (IGV) screenshots revealed the harboring of *KIF5B-RET* fusion.

Discussion

RET encodes for a transmembrane receptor tyrosine kinase (RTK) that plays a crucial role in cell signaling. In normal conditions, *RET* is activated by binding to specific ligands, leading to the activation of downstream signaling pathways involved in cell growth, differentiation, and survival. However, in certain cases, the *RET* gene can undergo

rearrangement, resulting in abnormal activation of the receptor. These rearrangements typically involve the fusion of the 3' fragment of the *RET*, which encodes the intracellular tyrosine kinase domain, with the 5' fragment of other genes. This can occur through chromosomal inversion or translocation events.^{9,10} Aberrant activation of *RET* due to these rearrangements has been implicated in the development and progression of various solid tumors. The most extensively studied tumors associated with *RET* fusion are papillary thyroid cancer (PTC) and NSCLC. *RET* fusions have been found in 2.5–73% of sporadic PTC and 1–3% of NSCLC patients.¹⁰ *RET* fusion has also been documented to be a rare event in other solid tumors, including colorectal cancer, breast cancer, and salivary gland cancer, accounting for less than 1% of cases of each of these cancer types.^{9,11,12} To our knowledge, *RET* fusion is rare in PSC.^{5,13} Thus, the efficacies of *RET* inhibitors have not been well established in *RET*-rearranged PSC patients.

In this study, the PSC patient harbored *KIF5B-RET* fusion, which is one of the reported *RET* fusions in NSCLC. To date, more than ten *RET* fusions have been reported in NSCLC, including canonical *RET* fusions like *KIF5B-RET* and *CCDC6-RET*, as well as uncommon *RET* fusions like *NCOA4-RET*, *TRIM33-RET*, *ZNF477P-RET*, have been identified in NSCLC.¹⁴ To our knowledge, *KIF5B-RET* fusion and *TUBD1-RET* fusion have been documented in PSC.⁵

Recently, two *RET* inhibitors selpercatinib and pralsetinib, have been approved by the Food and Drug Administration (FDA) for the treatment of metastatic *RET* fusion-positive NSCLC based on promising results from ARROW (NCT03037385) and LIBRETTO-001 (NCT03157128) clinical trials.^{7,8} Given that PSC is a form of NSCLC, the patient was treated with pralsetinib. Despite the patient having a poor ECOG PS of 3, she still showed tumor response to first-line pralsetinib. This finding is supported by a published report showing a partial response to pralsetinib in an advanced PSC patient with *KIF5B-RET* fusion and poor performance,¹³ as well as the SIREN study demonstrating the efficacy of the *RET*-TKI inhibitor selpercatinib in *RET*-rearranged NSCLC patients including those with ECOG PS ≥ 2 .¹⁵ Although *RET* fusion-positive PSC patients are rare, further evaluation of the efficacy and safety of pralsetinib in *RET* fusion-positive PSC patients is warranted.

In this study, it was reported that the patient died in the presence of heart failure at another hospital. However, upon reviewing the patient's medical records from our hospital and considering the lack of medical records from the hospital where the patient died, it cannot be concluded that the patient died from heart failure. Additionally, the presence of heart failure as a side effect in clinical trials was not reported.^{8,16–18} Therefore, whether heart failure is a pralsetinib-related adverse event should be explored in further studies.

There are some limitations associated with the present work. Firstly, the study only involved one patient, and more evidence from clinical trials is necessary to evaluate the efficacy and safety of pralsetinib in *RET* fusion-positive PSC patients. Secondly, further in vitro and in vivo studies are needed to investigate whether *KIF5B-RET* is an oncogenic driver in PSC.

Our work provides clinical evidence that *RET* fusion-positive PSC patients respond to pralsetinib. This case also highlights the need for further research and clinical trials to evaluate the efficacy of *RET* inhibitors in the treatment of PSC. Identifying effective therapeutic strategies for this rare and aggressive form of lung cancer is crucial in improving patient outcomes and prognosis.

Ethics Statement

The study was reviewed and approved by the Ethic Committee of the Shanghai Changhai Hospital. The patient provided written informed consent to participate in this study.

Consent to Publish

Consent has been obtained from the patient for the publication of the case.

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Disclosure

The authors report no conflicts of interest in this work.

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