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CASE REPORT

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A case of neoadjuvant targeted therapy with pralsetinib for locally advanced lung adenocarcinoma with RET fusion mutation

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Abstract

This case report details the successful treatment of a 68-year-old male patient with locally advanced RET-rearranged lung adenocarcinoma using neoadjuvant pralsetinib. The patient initially presented with a suspicious right upper lobe nodule, which was later diagnosed as lung adenocarcinoma following genetic testing that revealed a RET exon 12 fusion. After 2 months of neoadjuvant treatment with pralsetinib, a significant radiological response was observed, with a reduction in tumor size and metabolic activity. Subsequently, the patient underwent video-assisted thoracoscopic right upper lobectomy and mediastinal lymph node dissection. Postoperative pathological analysis revealed a major pathological response, with only 5% residual tumor cells in the primary lesion and no viable tumor cells in the lymph nodes. Postoperative pathological staging of TNM was ypT1aN0M0, stage IA1(AJCC, 8th edition). The patient recovered well after surgery, demonstrating the potential efficacy of neoadjuvant pralsetinib in locally advanced RET-rearranged lung adenocarcinoma. However, further clinical validation is required to establish the role of neoadjuvant targeted therapy and postoperative adjuvant therapy in this patient population.

Keywords RET fusion mutation, Pralsetinib, Locally advanced (stage III) non-small cell lung cancer, Neoadjuvant targeted therapy

Locally advanced non-small cell lung cancer (NSCLC) poses a considerable challenge owing to its intrinsic heterogeneity, which complicates management for clinicians [1]. Despite the integration of multidimensional treatment strategies and multidisciplinary consultations, the prognosis for these patients continues to be suboptimal [2]. Currently, two primary treatment modalities are available for patients with locally advanced disease: definitive concurrent chemoradiotherapy and surgical intervention in conjunction with chemotherapy or chemoradiotherapy [3]. Relevant randomized trials and meta-analyses have demonstrated that neoadjuvant or adjuvant chemotherapy improves survival outcomes compared to surgery alone, leading to a 6% increase in the 5-year recurrence-free survival rate for operable locally advanced NSCLC [4, 5]. Although neoadjuvant chemoradiotherapy is acknowledged as a standard clinical practice in accordance with the current National Comprehensive Cancer Network guidelines, the implementation of multimodal treatment for these patients remains inconsistent, lacking specific evidence-based protocols. The RET gene is implicated in normal embryonic development. RET fusions are infrequent, occurring in 1-2% of all patients with NSCLC [6]. Pralsetinib demonstrated a significant effect in patients

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with advanced NSCLC, with a response rate of 63% [7]. Pralsetinib received approval from the Food and Drug Administration (FDA) in 2020 for the treatment of RET fusion-positive NSCLC.

Neoadjuvant targeted therapy has been widely used in the treatment of locally advanced lung adenocarcinoma patients with EGFR-positive sensitive mutations, achieving a good radiological response rate and significantly prolonging the patients' disease-free survival [8, 9]. However, there are relatively few reports on the rare sensitive mutation of RET fusion. This article reports the recent neoadjuvant targeted therapy with pralsetinib in a case of locally advanced lung adenocarcinoma treated at Beijing Chest Hospital, Capital Medical University. To the best of our knowledge, there are few reports on the neoadjuvant treatment of RET fusion-positive lung adenocarcinoma patients with pralsetinib domestically and internationally. The treatment experience of this case may provide reference for the treatment of stage IIIA lung adenocarcinoma with RET fusion positivity.

Case data

A 68-year-old male patient was admitted to the hospital with a history of a right upper lobe lung nodule discovered 51 months ago, and a diagnosis of lung adenocarcinoma was made over a month ago. Laboratory tests indicated that the blood protein level was 100 g/L. Additionally, the patient was diagnosed with coronary heart disease and diabetes about 10 years ago. One month ago, the patient underwent an enhanced computed tomography (CT) scan, which revealed a mass with a diameter of 2.8 cm located in the right lower lung with enlarged mediastinal and hilar lymph nodes (stations 2, 4, 7, and 10). The CT findings were confirmed by 18 F-fluorodeoxyglucose (FDG) positron emission tomography (PET) as cT1N2M0, IIIA (AJCC, 8th edition). The PET revealed a hypermetabolic nodule (2.8 cm*2.0 cm) in the right upper lobe, SUVmax10.9, considering the possibility of malignancy. Multiple small nodules with partial calcification were noted in both lungs, along with multiple mediastinal and hilar lymph nodes showing increased metabolic activity, suggestive of inflammatory lymphadenopathy. The mediastinal lymph node group 7 was measured the diameter of 1.8 cm, accompanied by radiometabolic concentrations, SUVmax 8.5, and the possibility of metastasis was considered. A CT-guided lung biopsy was performed, with pathology indicating poorly differentiated adenocarcinoma. Genetic testing by PCR revealed a RET exon 12 fusion. After a multiple disciplinary team (MDT) discussion, the patient was diagnosed with a resectable stage IIIA lung adenocarcinoma. Based on RET fusion mutation results, we recommended neoadjuvant treatment followed by surgical resection. After obtaining informed consent from the patient, we prescribed pralsetinib at a dosage of 400 mg per day. After two months of treatment, a chest CT scan showed a significant reduction in tumor diameter to 1.7 cm. A PET-CT scan exhibited significantly decreased F18-FDG uptake in the tumor and mediastinal lymph node station 7. Chest CT imaging before and after neoadjuvant pralsetinib treatment was shown in Fig. 1. During the treatment of pralsetinib, some treatment-related adverse effects were observed, including throat pain and dryness and moderately increased blood pressure.

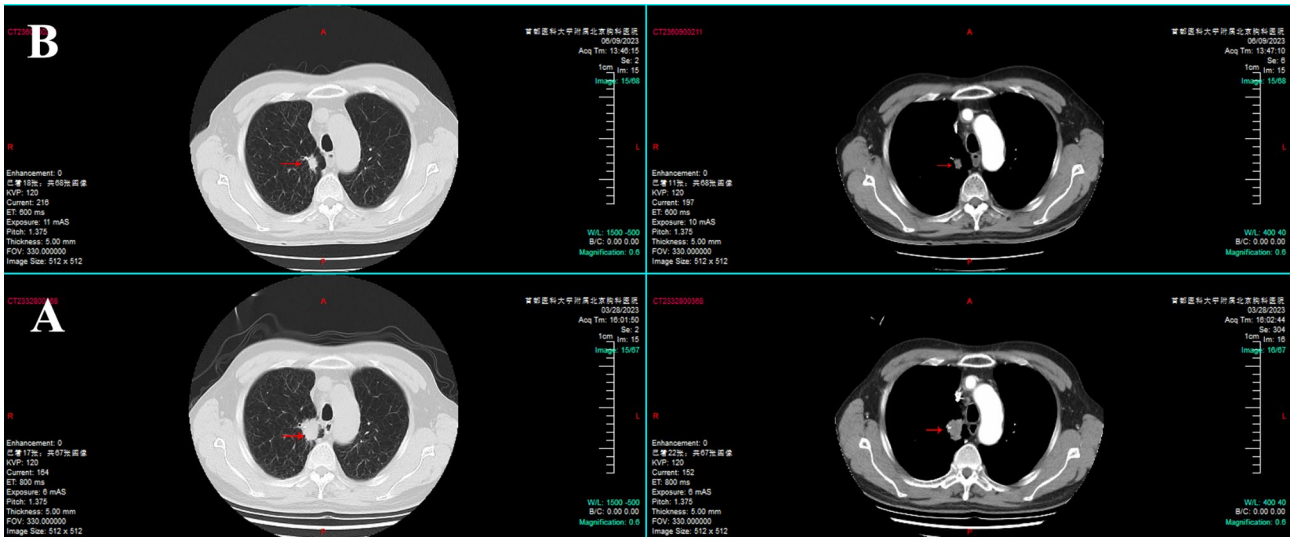

Fig. 1 Radiologic response to neoadjuvant pralsetinib. Computed tomography (CT) imaging of chest before and after neoadjuvant pralsetinib treatment is shown. (**A**) A baseline CT of the chest before pralsetinib initiation revealed a left lung mass measuring 2.8 cm (red arrow). (**B**) A follow-up CT of the chest after two months of pralsetinib showed disease regression to 1.7 cm in the same mass (red arrow). This was classified as partial response by RECIST v1.1 per investigator assessment. RECIST, Response Evaluation Criteria in Solid Tumors

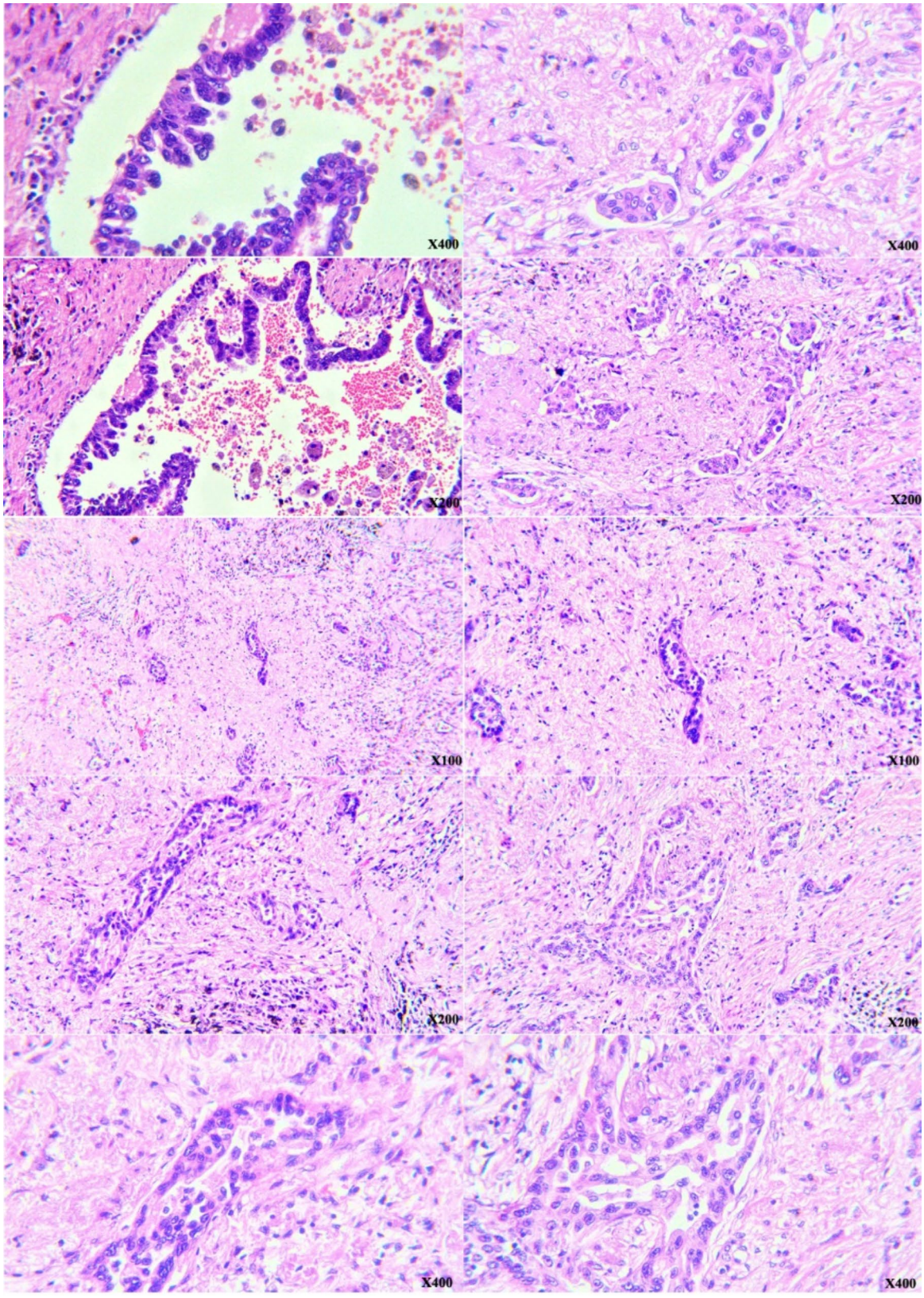

Fig. 2 Pathologic response to neoadjuvant pralsetinib. Resected tumor after 8 weeks of pralsetinib treatment with HE staining showed massive fibrous tissue proliferation, lymphocytic infiltration and a minimal vital cell count of 5% (×100, ×200, ×400). HE hematoxylin and eosin

Considering that radiologic downstaging was showed, a video-assisted thoracoscopic right upper lobectomy and mediastinal lymph nodes dissection was successfully performed three weeks after the last dose of pralsetinib. During the surgery, adhesions and fibrosis of the hilar tissue can be seen, but these do not prevent us from performing a lobectomy. No other particular abnormalities were seen intraoperatively. The patient lost 600 ml of blood and received 2 units of packed red blood cells. The chest tube was removed on the 4th postoperative day, and the patient was discharged one week after surgery.

The postoperative pathology report revealed a resected specimen of the right upper lobe measuring 11 cm *10 cm *3 cm, with a lesion measuring 1.5 cm *1.5 cm *1.0 cm. The pathological diagnosis was invasive non-mucinous adenocarcinoma, predominantly acinar type (100%), classified as moderately differentiated adenocarcinoma according to the 2021 WHO classification of lung adenocarcinoma. Chronic inflammation was observed in the remaining lung tissue, characterized by fibrous tissue proliferation and lymphocytic infiltration, consistent with post-treatment changes. Pathological evaluation of the surgical specimen post-neoadjuvant therapy revealed tumor cells occupying 5%, stroma 90%, necrosis 5%, consistent with major pathological response (MPR) as shown in Fig. 2. Vascular tumor emboli were present, with no evidence of aerogenous spread or pleural invasion. Lymph nodes (stations 2, 4, 7, 10, 11, 12, a total of 20 were removed) showed no evidence of metastasis. Immunohistochemistry results were positive for CKpan, TTF-1, Napsin-A, CD31, CD34 (vascular +), and D2-40 (lymphatic vessel +). Postoperative pathological staging (AJCC, 8th edition;) was ypT1aN0M0, stage IA. Nest generation sequencing (NGS) testing of the paraffin-embedded specimen revealed a RET fusion mutation, nucleotide mutation KIF5B-RET, mutation abundance/DNF −3.2545 in Fig. 3. Follow-up evaluations at 1, 4, and 9 months postoperatively showed no signs of tumor recurrence or metastatic changes.

Discussion

The incidence of RET gene fusion mutations in NSCLC is only 1-2% [6]. KIF5B-RET is the most common subtype of RET fusion in NSCLC, accounting for approximately 68.3% of all RET fusions [10]. Early clinical trials in RET fusion-positive NSCLC assessed multikinase inhibitors exhibiting anti-RET activity, such as cabozantinib, vandetanib, and lenvatinib. However, these agents demonstrated only modest clinical efficacy accompanied by elevated rates of treatment-related toxicity [11]. Pralsetinib is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusions and mutations, including the V804 gatekeeper mutations associated with resistance to multikinase inhibitors. It has demonstrated a high selectivity for RET compared to other tyrosine kinases [12]. In the ARROW I/II study, pralsetinib achieved an objective response rate (ORR) of 63% in NSCLC patients with RET fusion positivity, with subgroup data showing an ORR of 56% in Chinese patients who had failed platinum-based therapy, and a disease control rate (DCR) of 97% [7, 13, 14]. Pralsetinib is currently mainly used to treat locally advanced or metastatic NSCLC patients who are RET fusion-positive and have failed platinum-based chemotherapy.

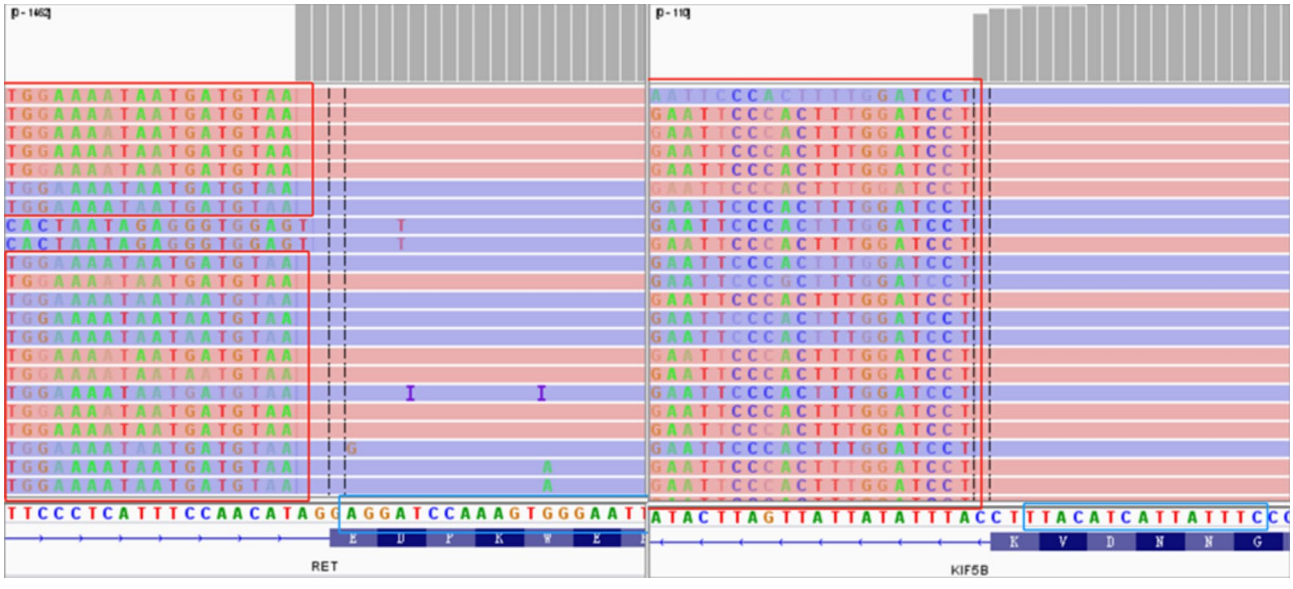

Fig. 3 Sequencing reads of RET fusion mutation were visualized with the Integrative Genomics Viewer (IGV). The exact location and read segment coverage of the RET fusion mutation in lung cancer can be clearly seen by the IGV map. The fusion site is located between the RET and KIF5B genes, and the dense read segment coverage verifies the presence of the fusion mutation

In recent years, the clinical value of neoadjuvant targeted therapy for lung adenocarcinoma patients with EGFR and ALK fusion gene mutations has been confirmed [15, 16]. However, there are few reports on neoadjuvant targeted therapy for RET fusion. Here, we report a case of a male patient diagnosed with stage IIIA lung adenocarcinoma, with genetic testing revealing a RET rearrangement mutation. After two months of neoadjuvant targeted therapy with pralsetinib, a 39.3% radiological stage reduction was achieved. Pathological results showed major pathological remission with 95% of the tumor mass consisting of fibrous tissue and necrosis followed by surgical treatment. Histopathological analysis showed only 5% residual tumor cells in the primary lesion. Lymph node dissection revealed no viable tumor cells, indicating complete clearance of metastatic disease. This case suggests that neoadjuvant targeted therapy with pralsetinib is feasible for locally advanced lung adenocarcinoma patients with RET rearrangements. Jonathan W. Goldman et al. first reported the efficacy of another RET inhibitor, selpercatinib, in neoadjuvant targeted therapy. A case of a KIF5B-RET fusion-positive NSCLC patient who received neoadjuvant treatment with selpercatinib showed complete pathological remission [17]. These study results provide new treatment options for non-small cell lung cancer patients with RET fusion.

In summary, neoadjuvant pralsetinib demonstrated efficacy in a patient with RET fusion-positive NSCLC. The neoadjuvant therapy led to notable radiologic downstaging and low-grade treatment-emergent adverse events (TEAEs), without hindering or complicating the subsequent definitive surgical intervention. The activity of preoperative pralsetinib in this prospective case provides proof of concept for the potential application of pralsetinib in early-stage RET fusion-positive NSCLC. However, this case report is limited to a single patient. The role of pralsetinib in neoadjuvant therapy for locally advanced NSCLC and postoperative adjuvant-targeted therapy remains to be determined for early-stage NSCLC. For NSCLC patients with RET rearrangements, further case accumulation and clinical trials are necessary to assess the impact of pralsetinib in both locally advanced and early-stage NSCLC.

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Author contributions
Wang Chunmao wrote the main manuscript text and Cheng Haijie, Wang zitong prepared Figs. 1-3. Yang zhi reviewed the manuscript."

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Data availability
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Declarations

Ethical approval
Not applicable.

Competing interests
The authors declare no competing interests.

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