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Efficacy of Neoadjuvant Therapy for ROS1-Positive Locally-Advanced Lung Adenocarcinoma: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 49-year-old
Final Diagnosis: Adenocarcinoma of lung
Symptoms: Coughing
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual clinical course

Background: ROS1 fusion-positive locally-advanced lung adenocarcinoma is a rare malignant tumor with no clear neoadjuvant therapy guidelines and a poor prognosis. This report describes a 49-year-old man with a ROS1 fusion-positive locally-advanced lung adenocarcinoma with a pathological complete response (pCR) to the tyrosine kinase inhibitor crizotinib combined with chemotherapy.

Case Report: A 49-year-old Chinese man visited the hospital with a cough and phlegm that began over 20 days ago. Computed tomography (CT) revealed a 4.5-cm diameter mass in the lower lobe of the left lung with enlarged lymph nodes fused together in the left hilum, staging stage IIIA (cT2bN2aM0). Given the pathological diagnosis of adenocarcinoma of lung from the transbronchial lung biopsy (TBLB), the patient subsequently underwent chemotherapy with the lobaplatin and paclitaxel regimen. Subsequently, genetic tests using fluorescence quantitative polymerase chain reaction (PCR) assay for biopsy pathology showed ROS1 fusion-positivity. Based on this, after completing 1 cycle of chemotherapy, the patient continued with daily oral treatment with 500 mg of crizotinib. A follow-up CT after 30 days of crizotinib therapy showed the tumor had vanished. Radical surgery confirmed pCR, and the patient continues crizotinib maintenance therapy with no signs of recurrence on subsequent chest CTs.

Conclusions: This case serves to underscore the excellent efficacy of neoadjuvant therapy in a patient with ROS1 fusion-positive locally-advanced lung adenocarcinoma. Neoadjuvant lobaplatin/paclitaxel combined with crizotinib can be considered for such patients, but attention should be paid to the difficulty of surgery, timing selection, and formulation of management guidelines.

Keywords: Lung Neoplasms • Neoadjuvant Therapy • Pathological Conditions, Anatomical • ROS1 protein, human

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Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality rates worldwide. At the time of diagnosis, 43.3% of lung cancer patients in China have already reached the locally-advanced stage (stage III) [1]. For these patients, particularly those with stage N2, the prognosis following surgical intervention alone is poor [2]. Hence, the 5-year survival rate for lung cancer in China is only 19.7% [3], contrasted with 23% in the United States [4]. Consequently, enhancing the treatment outcomes for patients diagnosed with stage III lung cancer is pivotal to elevating these survival rates. At present, the results of the EMERGING CTONG 1103, CheckMate-159, LCMC3, NADIM, and NADIM II studies indicate that multiple regimens, including chemotherapy, targeted therapy, and immunotherapy, are potential neoadjuvant treatment options for patients with locally-advanced non-small cell lung cancer (NSCLC) [5-9].

The goal of such programs is to perform surgery in low-risk conditions to completely remove the lesion and improve the surgical success rate to achieve better treatment results [10,11]. Regarding the protocol for neoadjuvant therapy, there are no specific guidelines. Typically, it encompasses 3 cycles of chemotherapy [12]. In contrast, the duration of targeted therapy varies significantly, ranging from 3 to 17 weeks [5,13-17].

We report the case of a 49-year-old Chinese man diagnosed with ROS1 fusion-positive lung adenocarcinoma, achieving successful pCR after a single cycle of neoadjuvant chemotherapy and 30 days of targeted therapy. The primary objective of this report is to highlight the potential excellent efficacy of neoadjuvant therapy based on chemotherapy combined with targeted agents for ROS1 fusion-positive locally-advanced lung adenocarcinoma.

Case Report

A 49-year-old Chinese man, with a 20-year smoking history of 40 cigarettes per day, a 25-year drinking history of 60 g per day, and a 2-year subtotal gastrectomy history of gastric malignancy presented with coughing and sputum for 20 days on 1 May 2023. Based on the history of gastric malignancy, he underwent a yearly CT screening of the lungs.

The chest CT scan performed on the patient on May 25, 2022 revealed 2 small nodules in the left lower-lobe dorsal segment. The larger nodule was thin-walled cavitary type, measuring 0.8×0.7×0.7 cm, and the smaller one was a solid nodule measuring 0.5×0.4×0.4 cm (see **Figure 1**). By May 1, 2023, a chest CT scan showed a mass measuring 3.5×3.1×4.5 cm at the left hilum, accompanied by obstructive pneumonia and mediastinal lymphadenopathy. The patient subsequently chose to be hospitalized for further examination. Tumor markers were CYFRA21-1 6.260 ng/ml and SCCA 3.49 ng/ml. Bronchoscopy revealed a narrowed bronchial lumen in the dorsal segment of the left lower lobe with congestion and edema of the mucosa. The pathology obtained with bronchoscopy were considered for lung adenocarcinoma (**Figure 2**). Following a comprehensive assessment with cranial MRI, abdominal ultrasound (including examinations of the liver, bile, pancreas, kidney, adrenal gland), and emission computed tomography (ECT), no lymph node enlargement or metastasis was detected.

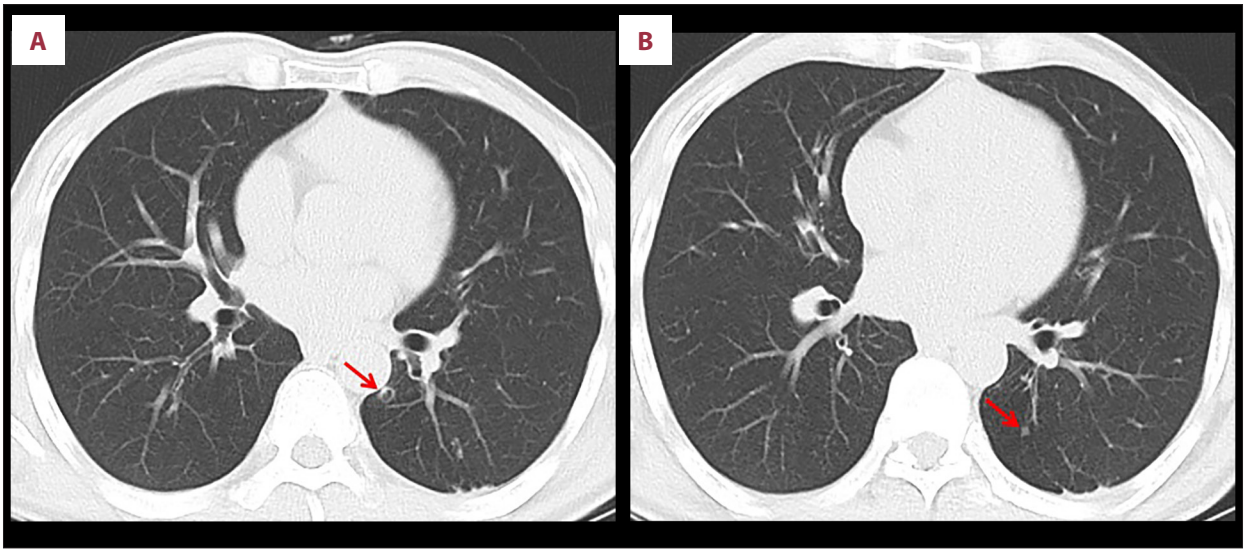

Figure 1. 2022.05.25 chest computed tomography (CT) images. (**A**) As indicated by the red arrow, the larger one was a thin-walled vacuole measuring 0.8×0.7×0.7 cm. (**B**) As indicated by the red arrow, the smaller one was a solid nodule measuring 0.5×0.4×0.4 cm.

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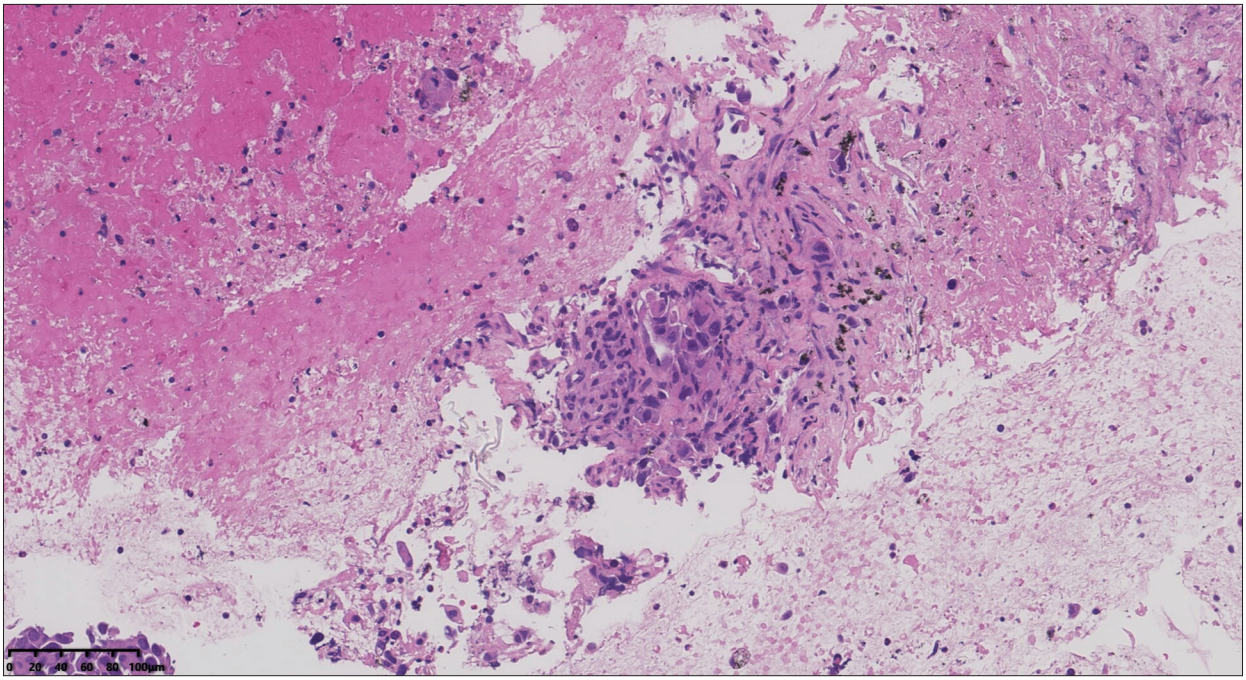

Figure 2. Bronchoscopic pathological section. A small number of heterologous cell nests were found in the specimen, which combined with immunohistochemical tendency of adenocarcinoma (hematoxylin and eosin staining, ×400). Immunohistochemical results: TTF-1 (+), P40 (-), NapsinA (some weak +), CK5/6 (a small amount of +).

Consequently, a positron emission tomography-computed tomography (PET-CT) scan was deemed unnecessary. After detailed clinical evaluation and pathological examination, it was diagnosed as stage IIIA (cT2bN2aM0) adenocarcinoma of the left lower lobe of the lung.

Due to locally-advanced lung cancer, he received neoadjuvant treatment. Since paclitaxel does not require pre-administration of oral folic acid, unlike pemetrexed, he received a chemotherapy regimen of lobaplatin 50 mg + paclitaxel 400 mg. At the same time, the amplification refractory mutation system (ARMS) fluorescence quantitative PCR results of the tumor tissue showed a fusion-positive ROS1 fusion gene. Therefore, after receiving 1 cycle of lobaplatin and paclitaxel chemotherapy, he began daily oral treatment with 500 mg of crizotinib targeted therapy. The course of treatment was smooth and there were no adverse reactions associated with chemotherapy or targeted therapy. Given the patient's strong desire for surgical treatment, a follow-up chest CT scan was performed after 30 days of oral administration of crizotinib. A chest CT scan on June 8, 2023 revealed complete disappearance of the tumor in the lower lobe of the left lung, leaving behind a small thin-walled cystic cavity, and there was significant reduction in size observed in left hilar and mediastinum lymph nodes compared to their previous state (**Figures 3, 4**).

According to the evaluation results, left lower lobectomy and hilar mediastinal lymph node dissection were performed. During surgery, fibrous tissue filling the hilar tissue space caused by the complete disappearance of the tumor made the surgical procedure challenging. The gross specimen of the surgery exhibited no apparent tumor tissue, while pathological examination confirmed complete remission without detectable residual cancer cells. Neoplastic lesions were not found in hilar mediastinal lymph nodes (**Figure 5**). Surgery-related rib fractures resulting from thoracoscopic conversion to thoracotomy due to the presence of severe hilar fibrosis caused the patient to develop severe chest pain in the short term after surgery, which was significantly relieved 2 weeks later. To date, the patient has been orally treated with crizotinib for 10 months and has followed the standardized follow-up procedures, with no tumor recurrence detected so far.

Discussion

The ROS1 gene is a tyrosine kinase receptor, whose fusions or translocations are associated with the occurrence of several malignancies, including lung cancer, gastric cancer, pancreatic cancer, and liver cancer. As the second solid tumor found to harbor ROS1 rearrangement, NSCLC has a frequency of ROS1 fusion gene mutations of 1-2% [18]. ROS1 status is usually established by fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS), and the most common ROS1 fusion partner gene is CD74-ROS1 [18-20]. Although the fluorescence

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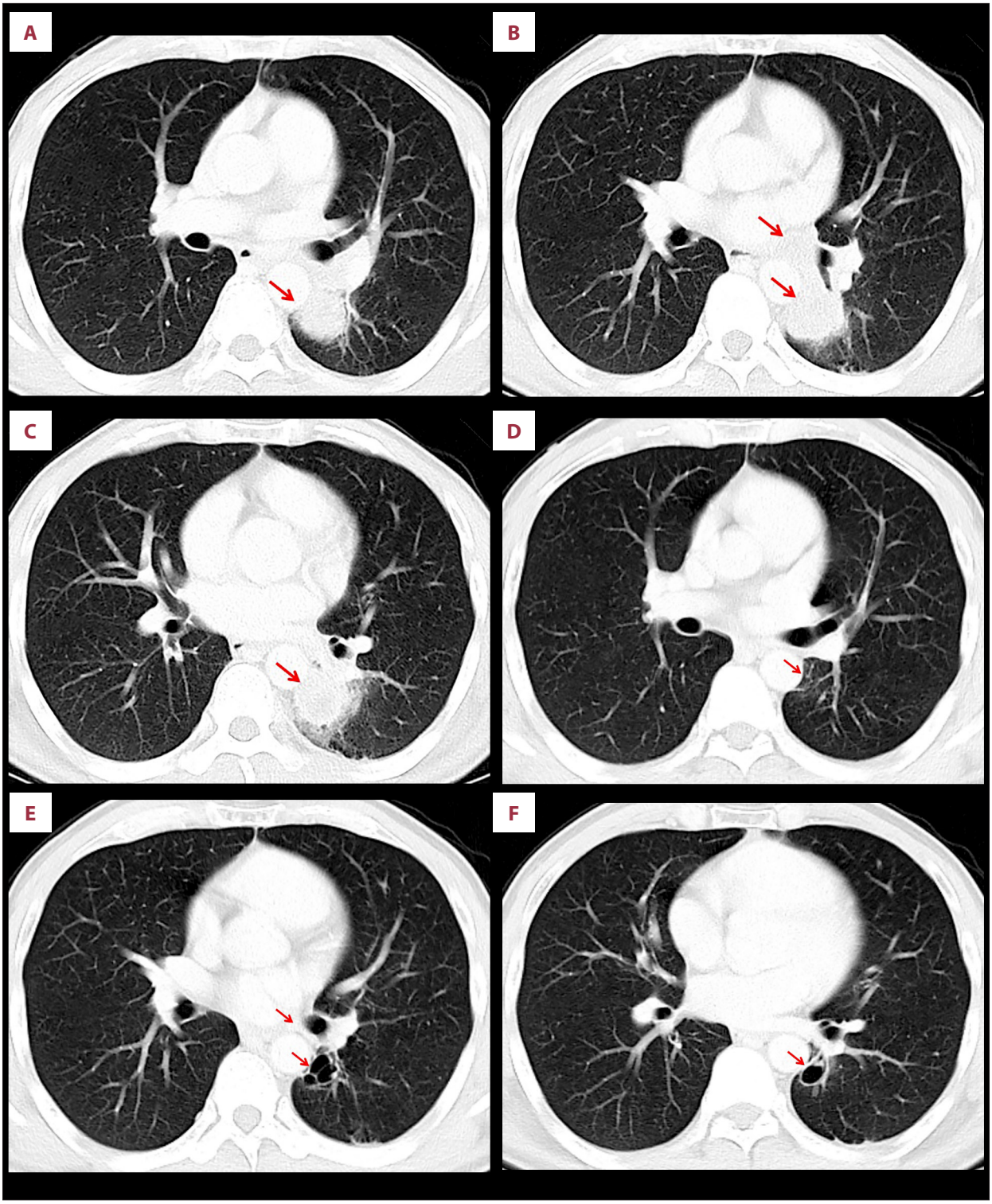

Figure 3. CT images of lung cancer before and after neoadjuvant therapy. (**A-C**) The CT examination on 2023.05.01 showed a mass (red arrow) in the dorsal segment of the lower lobe of the left lung, involving the bronchus and trunk of the lower lobe of the left lung. (**D-F**) CT showed that after completing 1 cycle of neoadjuvant chemotherapy and targeted therapy on June 08, 2023.06.08, the tumor completely disappeared and formed cysts (red arrow) and hilar lymph nodes.

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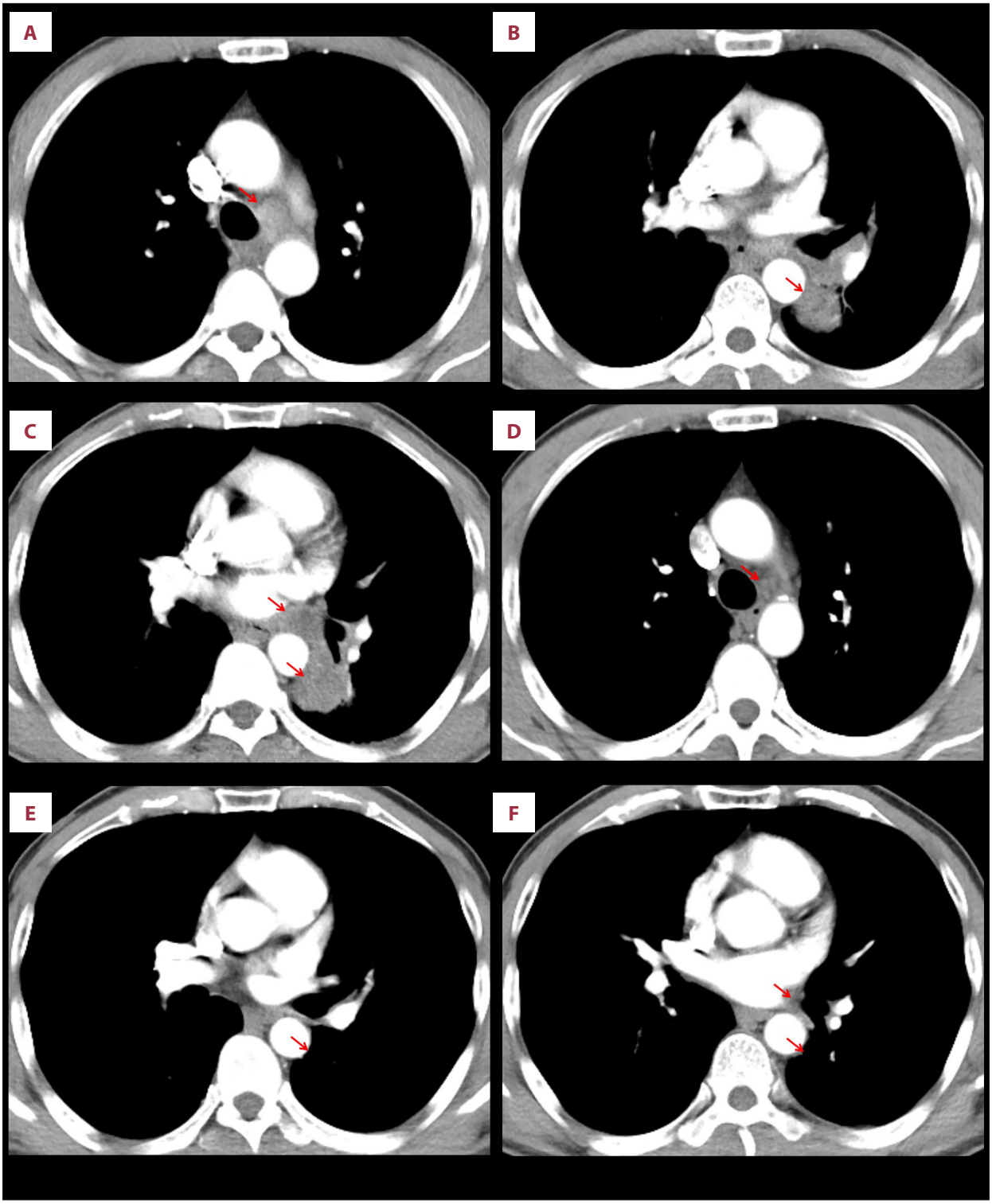

Figure 4. (**A-F**) CT images of lymph nodes before and after neoadjuvant therapy. Enhanced chest CT mediastinal window showing lymph node changes at different levels (red arrow).

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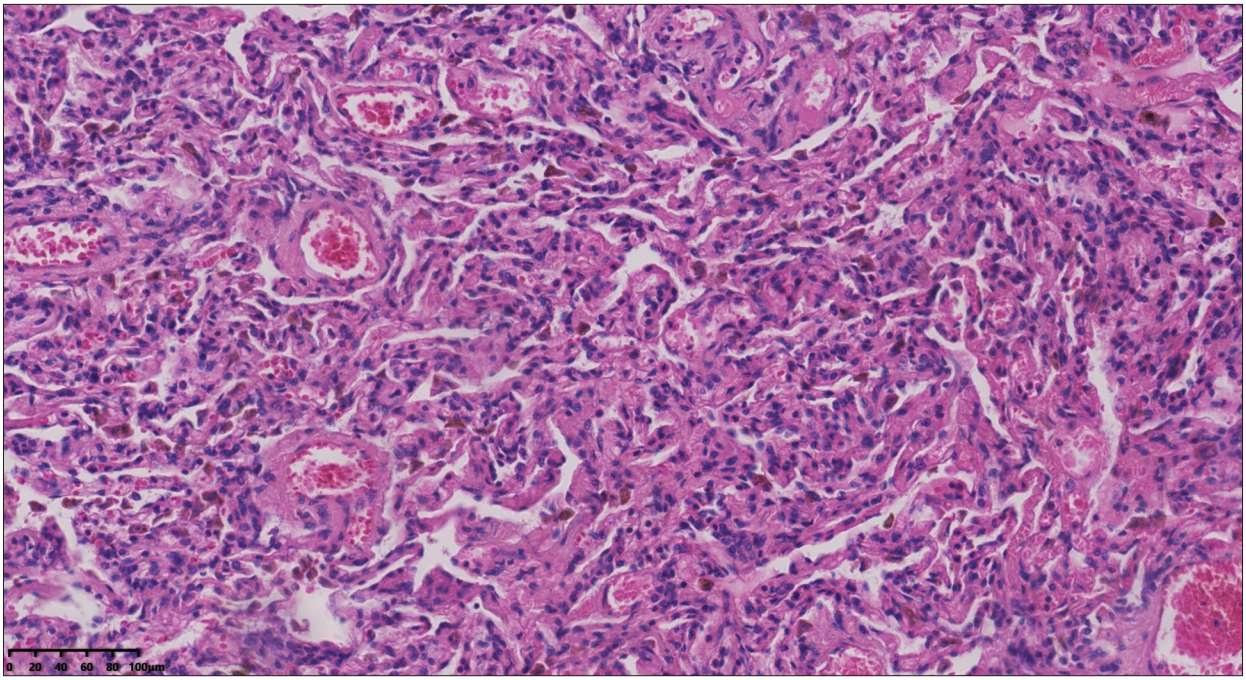

Figure 5. Pathological section of lung cancer after neoadjuvant therapy. The microscopic photograph indicates chronic inflammation, increased fibrous tissue, lymphocyte aggregation, and necrosis, along with the presence of foam cells and hemosiderin deposition. However, no cancer cells are observed, which is consistent with changes following neoadjuvant therapy. (Hematoxylin and eosin staining, ×100).

quantitative PCR detection method we used is faster, it does not provide detailed information on the fusion gene of ROS1, which limited further exploration. If possible, we recommend using NGS or FISH detection, although it has a longer detection cycle. These methods, however, can precisely identify both known and unknown gene fusions.

Initially developed as a mesenchymal-to-epithelial transition factor (MET) inhibitor, crizotinib is currently used to treat NSCLC with advanced anaplastic lymphoma kinase (ALK) gene rearrangements and ROS1 fusion genes. In a trial cohort of 50 patients with ROS1-rearranged NSCLCs, the objective response rate (ORR) to crizotinib was 72%, the disease control rate (DCR) was 90%, and the median progression-free survival (PFS) was 19.2 months [21]. Crizotinib was approved to treat patients with advanced NSCLC with ROS1 gene fusion in 2016, and has been used as first-line treatment in this group of patients since then [22].

The structural basis for ALK tyrosine kinase inhibitors (TKIs) activity against ROS1 may come from the high homology of ROS1 and ALK in the kinase domain and adenosine triphosphate (ATP) binding sites. TKI resistance is the main reason for the emergence of tumor progression in almost all targeted therapies. Mutations located within the kinase domain of ROS1 have been observed in approximately 50-60% of tumors that develop resistance to crizotinib. G2032R is the first and most common solvent-frontier crizotinib resistance mechanism reported in patients with ROS1-rearrangement lung adenocarcinoma, similar to ALKG1202R [20,23].

Neoadjuvant therapy, including chemotherapy, targeted therapy, and immunotherapy, aims to reduce tumor burden before surgery to improve the surgery success rate. This approach helps to determine tumor sensitivity, optimize subsequent treatment plans, enhance efficacy and tolerance, and reduce adverse effects. Studies have shown that neoadjuvant targeted therapy is better tolerated than chemotherapy, has a higher response rate, and fewer severe complications [5]. Patients with epithelial growth factor receptor (EGFR)-positive NSCLC treated with EGFR-TKI have shown good clinical outcomes. More clinical data is needed to support neoadjuvant targeted therapy for ALK and ROS1 fusion-positive NSCLC. Studies [24] have shown that crizotinib neoadjuvant therapy alone for 10 months is beneficial for surgical resection of locally-advanced NSCLC patients, but the procedure can also be complicated by problems such as chest adhesion and fibrosis around the tumor tissue. In addition, the 10-month duration of the course is excessively prolonged, making it unsuitable for implementation as a neoadjuvant therapy cycle. By contrast, our case exhibited a pathological complete response to the combined treatment of chemotherapy and crizotinib within a 1-month treatment cycle. This underscores the potential for combination therapy to outperform single-drug therapy in certain scenarios. In our

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case, after undergoing a brief course of chemotherapy in conjunction with targeted therapy, the tumor underwent notable shrinkage, and no substantial adverse reactions emerged. This outcome paved the way for a successful and subsequent radical surgical intervention. Future research should delve deeper into the mechanisms of screening to accurately identify patients who have heightened sensitivity to combination therapy. Additionally, there is a need to refine combination therapy protocols to maximize the achievement of pCR and concurrently mitigate treatment-related adverse effects.

Tumor doubling time is one of the risk factors affecting tumor prognosis. For lung cancer, the doubling time was reported to be 533 days for adenocarcinoma, 129 days for squamous cell carcinoma, and 97 days for small cell lung cancer [25]. Two suspicious microscopic nodules were found on CT images taken 1 year ago, one vacuolar nodule with a diameter of 0.8×0.7×0.7 cm and the other solid nodule with a diameter of 0.5×0.4×0.4 cm. They grew to 3.5×3.1×4.5cm in 341 days. Based on the modified Schwartz formula, the doubling times of the 2 suspected nodules were 49 days and 37 days, respectively. The doubling time of these 2 nodules to develop into masses is even shorter than that of small cell lung cancer, indicating that tumor cell proliferation is abnormally active. Due to the extremely limited number of lung biopsy specimens used in the diagnosis of adenocarcinoma of lung, the possibility of small cell lung cancer (SCLC) cannot be completely ruled out. Although there is currently no research on the mechanism of transformation of ROS1 fusion-positive adenocarcinoma of lung into SCLC, some scholars [26] have proposed 3 explanations for the transformation of adenocarcinoma into small cell carcinoma after EGFR-TKI resistance: (1) The patient's tumor had SCLC components before treatment; (2) SCLC is derived from adenocarcinoma transdifferentiation after TKI treatment; and (3) SCLC may be a new tumor that develops after TKI treatment. Given the extremely high response rate to chemotherapy + targeted therapy in this case and the presence of 2 suspected nodules, the first mechanism seems to be the most plausible explanation for our case. For ROS1 fusion-positive locally-advanced adenocarcinoma of lung with rapid growth, the strategy of neoadjuvant chemotherapy combined with targeted therapy can achieve significant therapeutic effects, thereby increasing the feasibility of surgical resection.

Although temporary postoperative pain occurred, there was an opportunity to remove the tumor completely with neoadjuvant therapy, achieving a potentially longer survival compared to conservative therapy. However, neoadjuvant therapy also has potential disadvantages. If the preoperative therapy is ineffective, progression of the disease will lead to complete loss of the opportunity for surgical treatment, can increase the complexity of the operation, and can lead to more serious postoperative complications. In our patient, we observed severe hilar desmoplasia, possibly related to tumor regression after neoadjuvant therapy [27]. Determining the time at which the operation is least affected by the hyperplasia of hilar fibrous tissue caused by tumor regression is a problem worthy of attention.

Some studies have indicated that pCR following neoadjuvant chemotherapy is a favorable prognostic factor in IB-II stage NSCLC patients [28]. Although neoadjuvant therapy followed by surgical intervention has been shown to improve resection rates and prognosis in NSCLC patients [29], there is limited evidence regarding whether surgery provides additional benefits to those achieving pCR through neoadjuvant therapy alone. Hence, it remains worthwhile to explore whether lung cancer patients achieving pCR through neoadjuvant therapy can potentially avoid surgical interventions. In the treatment of breast cancer, clinical studies of surgical exemptions in cases of complete pathological response after neoadjuvant therapy have shown promising results [30,31]. However, accurately assessing pCR remains a formidable challenge. Currently, imaging technology falls short in providing precise determination of lymph node metastasis [32]. Patient-exempt surgery for complete pathological response after neoadjuvant therapy is a potential area of research that requires highly sensitive pathological assessment and imaging follow-up, as well as more clinical study.

Conclusions

We report a ROS1 fusion-positive patient with locally-advanced adenocarcinoma of lung who received 1 cycle of neoadjuvant chemotherapy combined with 30 days of targeted therapy and achieved pCR. Our findings highlight the potential high sensitivity of ROS1 fusion-positive locally-advanced lung adenocarcinoma to lobaplatin/paclitaxel and crizotinib neoadjuvant therapy, and the need to pay attention to treatment formulation, surgical timing, and increased surgical difficulty, although further clinical trials are needed to confirm its safety and efficacy.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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