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Neoadjuvant Lorlatinib Induces Pathological Complete Response in Advanced ALK-Positive Lung Cancer: A Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 54-year-old
Final Diagnosis: Lung adenocarcinoma
Symptoms: Cough
Clinical Procedure: —
Specialty: Oncology • Pulmonology

Objective: Unusual or unexpected effect of treatment

Background: Chemotherapy has been the conventional treatment method for advanced non-small-cell lung cancer (NSCLC). Nevertheless, the identification and comprehension of oncogenic driver alterations have paved the way for targeted therapies, significantly enhancing patient outcomes. The management of locally advanced NSCLC that is positive for ALK presents a challenge due to the lack of reported randomized controlled trials. The efficacy of neoadjuvant and adjuvant targeted therapy in this context remains uncertain.

Case Report: A 54-year-old man was diagnosed with stage IIIB (pT1N3M0) upper right lung adenocarcinoma carrying the EML4-ALK fusion gene. Clinically, the patient had multiple enlarged lymph nodes in the right hilum and mediastinum, with the largest measuring approximately 28×19 mm by CT scan and we found that the L4 lymph node was invaded by metastasis. Then, the patient received 1 cycle of chemotherapy with paclitaxel in combination with nedaplatin and subsequently received maintenance treatment involving lorlatinib. Two months later, clinical evaluations revealed progressive reduction of the lesions, especially the reduced size of the mediastinal lymph nodes. Therefore, the patient underwent thoracoscopic partial lobectomy and lymphadenectomy and achieved pathological complete response (pCR). After 3 months, a follow-up CT scan was similar to the first postoperative CT scan and no tumor was found.

Conclusions: This case demonstrates the potential advantage of lorlatinib as a neoadjuvant therapy in advanced ALK-positive NSCLC. It emphasizes the importance of identifying new therapeutic targets by next-generation sequencing (NGS) and implementing precise treatment strategies in clinical practice.

Keywords: Lorlatinib • Neoadjuvant Therapy • Adenocarcinoma of Lung

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Background

The majority of patients with stage III non-small cell lung cancer (NSCLC) are ineligible for curative surgery upon initial diagnosis. In certain cases where adjuvant chemotherapy is warranted, neoadjuvant chemotherapy can be employed as a treatment option. Nevertheless, the addition of neoadjuvant chemotherapy to surgery alone only yields a 5-6% rate of 5-year progression-free survival (PFS) [1,2]. Anaplastic lymphoma kinase (ALK) fusion gene is the second most common tumor driver gene, accounting for 3-7% of NSCLC cases [3,4]. Therefore, ALK tyrosine kinase inhibitors (TKIs) were used to create a treatment model for ALK-positive advanced NSCLC. Clinical trials, including the CROWN trial, demonstrated lorlatinib significantly improve PFS for ALK-positive NSCLC compared with crizotinib, indicating lorlatinib can eliminate rare preexisting subclones harboring ALK resistance mutations in untreated patients [5].

Here, we report the case of a patient with stage IIIb metastatic lung adenocarcinoma (pT1N3M0) with ALK alteration (EML4-ALK [E18: A20]), highlighting the potential application of lorlatinib as neoadjuvant therapy to treat NSCLC patients. Following neoadjuvant therapy, the patient underwent thoracoscopic partial lobectomy and lymphadenectomy. To date, the patient has achieved pCR.

Case Report

A 53-year-old man was admitted to hospital because of "discovered right lung nodules for 5 months in the local hospital". On March 26, 2023, contrast-enhanced computed tomography (CT) revealed a solid nodule in the right upper lobe, measuring approximately 10×9 mm, with irregular margins (showing moderate inhomogeneous enhancement) (**Figure 1A**) and an enlarged L4 lymph node was also found in the mediastinum, suggesting metastasis(**Figure 1B**). Endobronchial ultrasound-guided

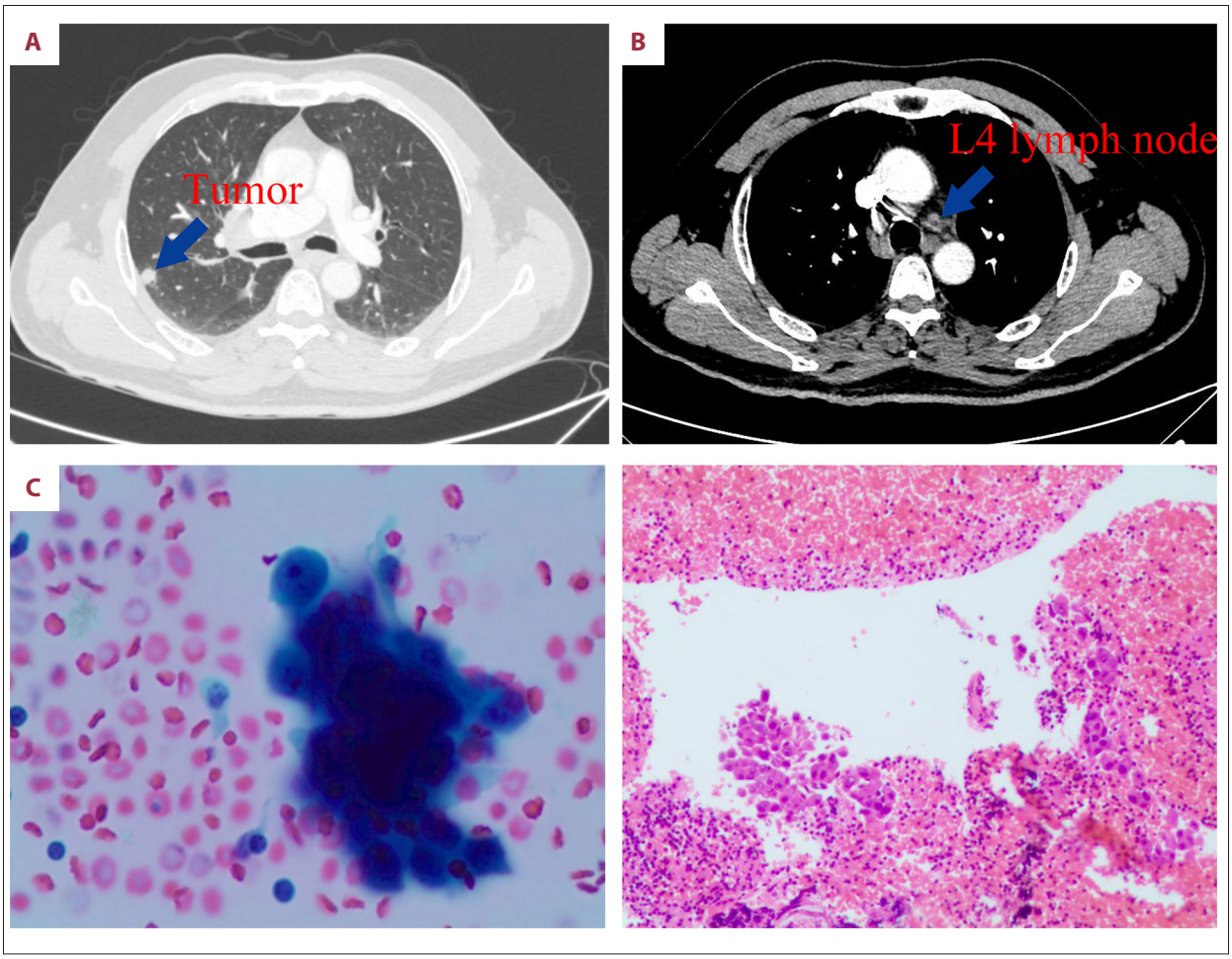

Figure 1. Examinations before treatment. (**A**) CT scan revealed a solid nodule beneath the pleura in the posterior segment of the right upper lobe with irregular margins. (**B**) CT scan shows enlarged L4 lymph node in the mediastinum. (**C**) **Left:** a few clusters of atypical cells within the blood clot tissue; **Right:** Metastatic adenocarcinoma cells were found in lymph node (4L).

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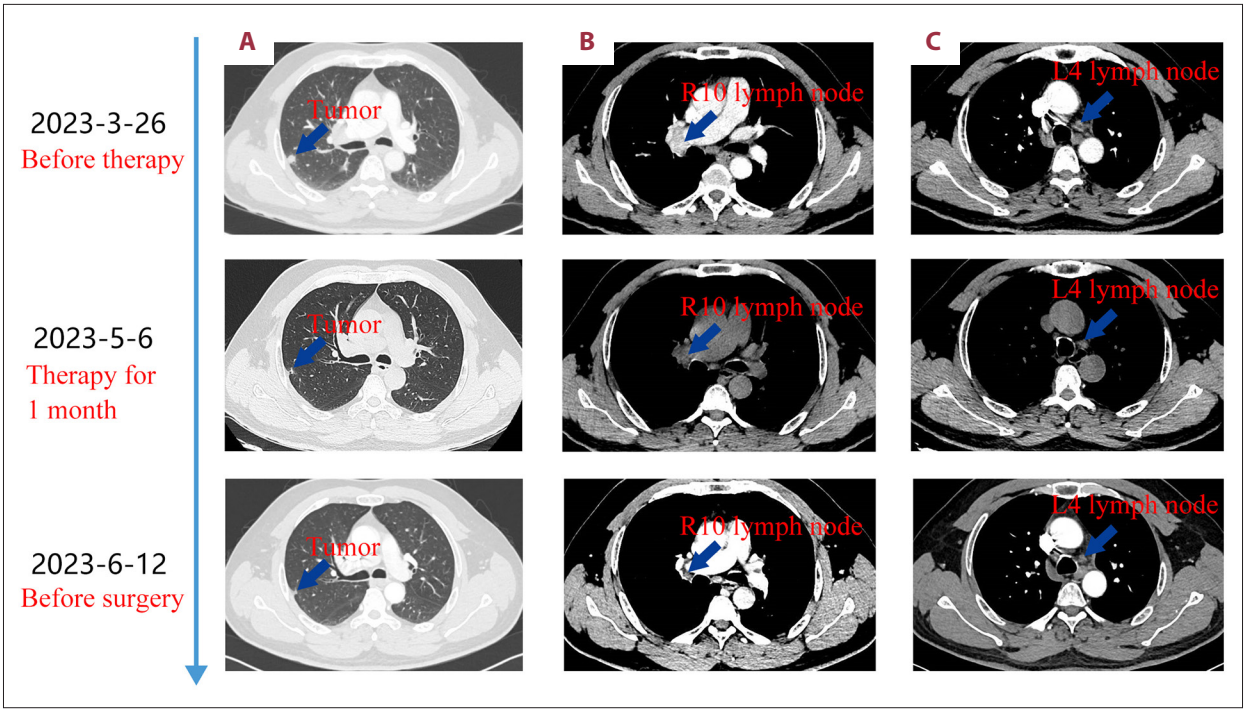

Figure 2. Timeline of CT examinations before surgery. (**A**) On the first CT before therapy, a solid nodule was found in the right upper lobe, measuring approximately 10×9 mm, with irregular margins. Enlarged R10 and L4 lymph nodes were also found in the mediastinum. (**B**) One month after neoadjuvant therapies, CT showed decreased size of the nodule beneath the pleura (from 10×9 mm to 5×4 mm) and reduced size of R10 and L4 lymph nodes. (**C**) Two months after neoadjuvant therapies but before surgery, CT showed the nodule beneath the pleura had remained the same size (5×4 mm) and the lymph node had decreased in size (from 28×18 mm to 17×16 mm).

transbronchial needle aspiration (EBUS-TBNA) revealed a few clusters of atypical cells in the L4 lymph node, suggesting metastatic poorly differentiated carcinoma with clinical stage IIIb (pT1N3M0). IHC highly expressed PD-L1 (Tumor Proportion Score approximately 70%) (**Figure 1C, 1D**). At the same time, tumor tissues were delivered to Genecast (Wuxi, China) for high-throughput gene sequencing. We found 0.57% abundance of EML4-ALK (E18: A20) gene fusion and 1.09% TP53 gene mutation (NM_000546 Exon 8 c.818G>C p.R273P), and no other mutations were detected. Therefore, on April 1, 2023, the patient received 1 cycle of chemotherapy with paclitaxel 430 mg in combination with nedaplatin 120 mg. He also received maintenance treatment lorlatinib (100 mg per day until June 8, 2023).

After the neoadjuvant chemotherapy and lorlatinib, on May 6, 2023, the nodule beneath the pleura had decreased in size from 10×9 mm to 5×4 mm, and the R10 and L4 lymph nodes also had become smaller. On June 12, 2023, the R10 lymph node was found to have a decreased in size to 17×16 mm from 28×18 mm on March 26, 2023 (**Figure 2**), suggesting the patient had responded to the neoadjuvant therapy. After consulting with specialists (a thoracic surgeon, respiratory physician, medical oncologist, radiation oncologist, pathologist, and a palliative care physician) in multiple disciplinary teams, the patient underwent right-sided thoracoscopic partial lobectomy and lymphadenectomy on June 2023. During the surgical procedure, we cleaned the ipsilateral hilum and mediastinum, proceeding with the liberation of the upper segment of the esophagus and the right main bronchus and we successfully removed the L4 lymph node.

A postoperative CT scan found inflammation reactions in the mediastinum (**Figure 3A-3C**). The specimens, including right upper lung lobe and regional lymph node (fourth group (7 specimens), seventh group (8 specimens), ninth group (1 specimen), tenth group (1 specimen), eleventh group (1 specimen), and para-tracheal lymph node (1 specimen), were submitted for pathology testing. In the right upper lung lobe, the results showed interstitial fibrous tissue proliferation accompanied by chronic inflammatory cell infiltration, hemosiderin deposition, and aggregation of tissue cells within the pulmonary alveoli. Surprisingly, no residual tumor was observed (**Figure 3D**). Considering the patient's medical history, these findings were consistent with a significant treatment response. No tumor was found in the bronchial stump, vascular stump, or staple line tissues. Examined lymph nodes in all the groups exhibited reactive hyperplasia, suggesting the patient had achieved pathological staging: ypT0N0Mx. The timeline of therapy is shown in **Figure 4**. On September 22, 2023, the patient had a

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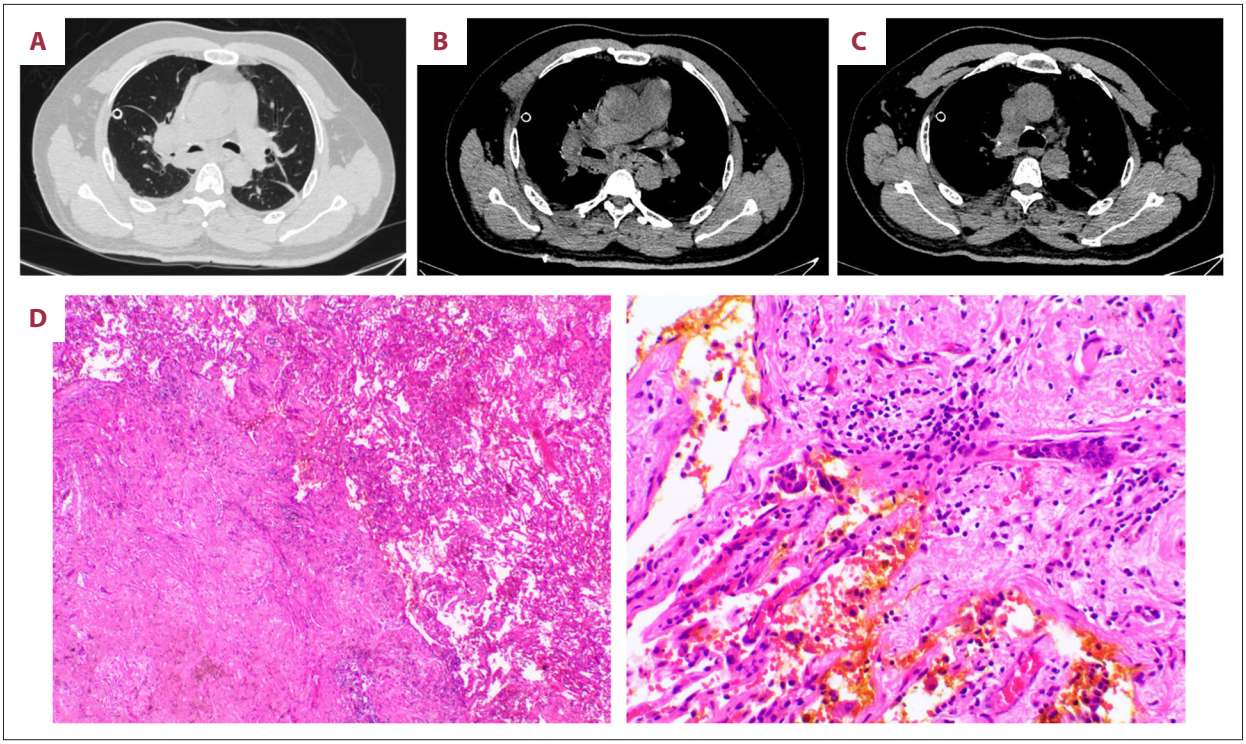

Figure 3. Evaluation after the surgery. (**A-C**) CT image of chest after surgery. (**D**) HE stain of right upper lung showed interstitial fibrous tissue proliferation accompanied by chronic inflammatory cell infiltration, hemosiderin deposition, and aggregation of tissue cells within the pulmonary alveoli. No residual tumor was observed.

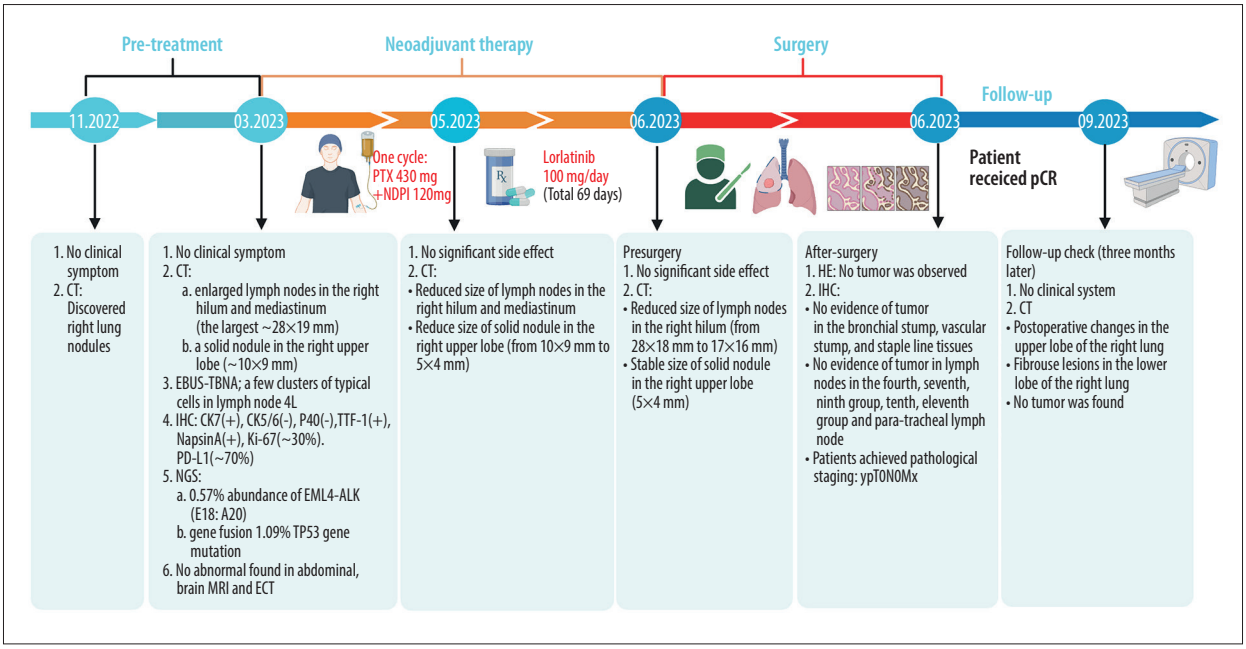

Figure 4. Schematic of timeline with therapy and disease status.

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follow-up CT scan, which showed results similar to the postoperative CT scan (June 18, 2023) showing postoperative changes in the upper lobe of the right lung and fibrous lesions in the lower lobe of the right lung. No tumor was found.

Discussion

While most studies on neoadjuvant targeted therapy focus on patients with EGFR-mutated NSCLC, there is limited evidence on using ALK TKIs in the neoadjuvant setting for resectable ALK-positive NSCLC [6]. To date, these limited cases suggest the potential value achieving either partial response or pathological complete response of neoadjuvant ALK TKI therapy, but all focused on other ALK TKIs (alectinib, ceritinib, or ciritinib) [7-9]. In addition, patients received chemotherapy at the same time at neoadjuvant settings. However, compared with other ALK+ inhibitors, lorlatinib has been structurally optimized to inhibit mutations that confer resistance, such as G1202R, as well as those with a high propensity for CNS migration [10]. To the best of our knowledge, there is currently a lack of documented cases in which patients with advanced ALK-positive lung cancer have achieved a pCR in the lung lesion following neoadjuvant chemotherapy with lorlatinib.

Earlier studies also indicated that ALK gene mutations can lead to expression of PD-L1 but can negatively affect immunotherapy [11-13] Therefore, patients with ALK mutations have been excluded from various immunotherapy studies, including KEYNOTE, Checkmate, and Impower [11-13]. Our patient with stage IIIB ALK+ NSCLC before surgery received a single 2-month cycle of chemotherapy with lorlatinib to downsize the stage of the cancer, and achieved pCR after the surgery. No significant adverse effect due to treatment was observed in our patient. In addition, we emphasize the importance of incidental findings discovered during preoperative work-up, which have immense value in the healthcare. For example, the patient's specimen was tested by high-throughput gene sequencing. These unexpected discoveries can significantly impact treatment success and patient outcomes, as well as a reduction in complications, healthcare costs, and the invasiveness of procedures [14].

Conclusions

We presented a case of metastatic ALK-positive NSCLC treated with neoadjuvant chemotherapy with lorlatinib, resulting in a complete pathological response (pCR). However, whether the benefit of neoadjuvant ALK inhibitors can be achieved in larger patient cohorts remains unclear due to the limitation of a relatively short mid-term follow-up in our study. Further investigation through large-scale clinical trials is warranted to assess the safety and efficacy of this innovative treatment approach, as well as its potential combination with other therapies.

Ethic Statement

The study was approved by the Institutional Review Board and Ethics Committee of Zhongnan Hospital of Wuhan University.

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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