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CASE REPORT

High Efficacy of Chemoimmunotherapy in Advanced ALK-Rearranged Lung Squamous Cell Carcinoma: A Case Report

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Abstract: Anaplastic lymphoma kinase (ALK) rearrangement represents a rare molecular subtype of lung squamous cell carcinoma (LSCC). Although ALK tyrosine kinase inhibitors (TKIs) are established as first-line therapy for advanced ALK-rearranged non-small cell lung cancer (NSCLC), their efficacy in LSCC appears inferior to that in adenocarcinoma. Furthermore, the clinical benefit of chemoimmunotherapy in this rare population remains poorly defined. Here, we report a case of ALK-rearranged LSCC exhibiting primary resistance to ALK-TKI therapy but achieving a remarkable and durable response to combined chemotherapy and immunotherapy, leading to long-term disease control. This case highlights the potential therapeutic benefit of chemoimmunotherapy in ALK-rearranged lung squamous cell carcinoma and suggests that it may represent a viable priority option worthy of exploration in advanced settings.

Keywords: anaplastic lymphoma kinase, ALK, lung squamous cell carcinoma, chemoimmunotherapy

Introduction

Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) are the current standard of care for patients with advanced ALK-positive NSCLC. Potent next-generation ALK inhibitors such as alectinib and lorlatinib have shown significant efficacy and durable responses in lung adenocarcinoma, based on multiple pivotal Phase III trials.[1,2] However, evidence regarding their effectiveness in lung squamous cell carcinoma (LSCC) is limited, as most clinical trials have excluded patients with squamous histology. Nonetheless, isolated case reports have documented radiographic responses to crizotinib and alectinib in ALK-rearranged LSCC.[3,4]

Despite these observations, resistance to ALK-TKIs develops rapidly in a subset of LSCC patients, and the subsequent therapeutic options remain unclear. While immunotherapy has demonstrated limited efficacy in unselected ALK-positive adenocarcinoma cohorts, particularly in PD-L1–negative tumors,[5] its role in ALK-rearranged LSCC is scarcely documented. We present a rare case of ALK-rearranged LSCC exhibiting primary resistance to alectinib but achieving a durable and deep response to platinum-based chemoimmunotherapy.

Case Report

A 70-year-old male with a 40-year smoking history presented with cough, mild hemoptysis, and exertional dyspnea. Chest computed tomography (CT) revealed a right upper lobe consolidation with mediastinal lymphadenopathy (Figure 1A). Per RECIST v1.1 criteria, the right upper lobe consolidation was identified as the target lesion, with a baseline longest diameter of 59 mm. Follow-up CT on July 7, 2022, revealed progressive disease (Figure 1B), with the

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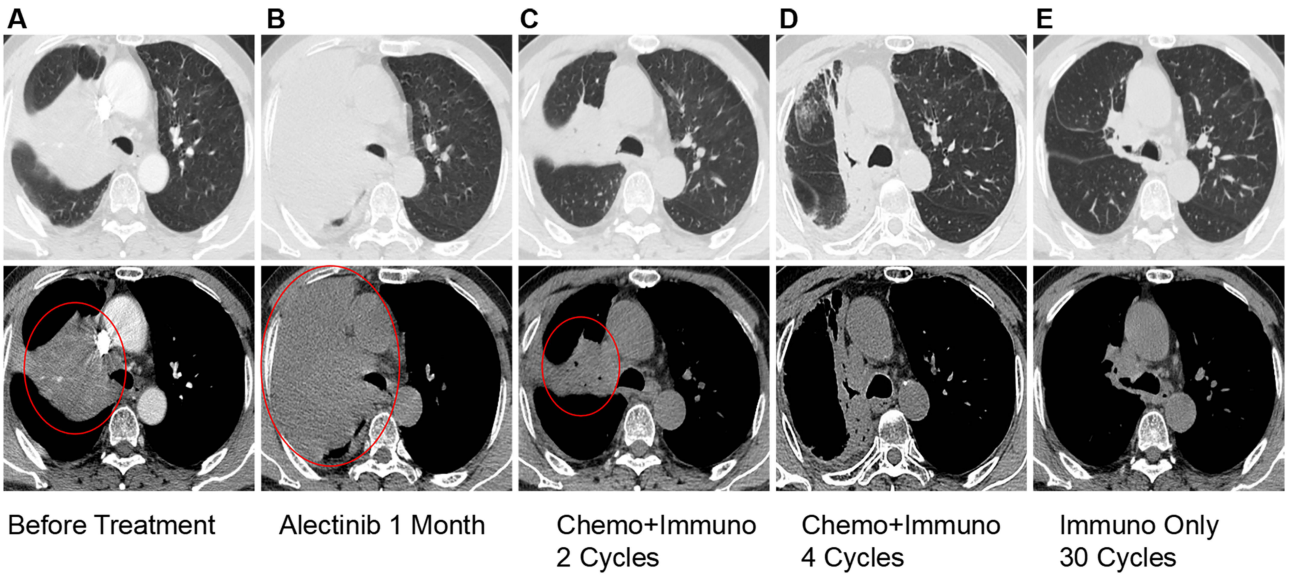

Figure 1 Computed tomography (CT) scans for the case. The chest CT showed changes in the primary lung carcinoma (indicated by red circles in **A**–**C**): (**A**) at baseline, (**B**) after one month with alectinib treatment, (**C**) after two cycles of chemoimmunotherapy, (**D**) after four cycles of chemoimmunotherapy, and (**E**) after thirty cycles of immunotherapy.

target lesion increasing to 128.5 mm (117.8% increase from baseline). After two cycles of subsequent chemoimmunotherapy, restaging CT showed a partial response (PR) (Figure 1C), with the lesion decreasing to 34.9 mm, representing a 72.9% reduction from the pre-chemoimmunotherapy baseline (128.5 mm) and consistent with partial response criteria (≥30% decrease). Two additional cycles maintained the response (Figure 1D). A follow-up chest CT in March 2025 showed persistent remission after pembrolizumab monotherapy (Figure 1E).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of the right hilar mass demonstrated squamous cell carcinoma (Figure 2A). Immunohistochemistry (IHC) was positive for p40 and negative for TTF-1

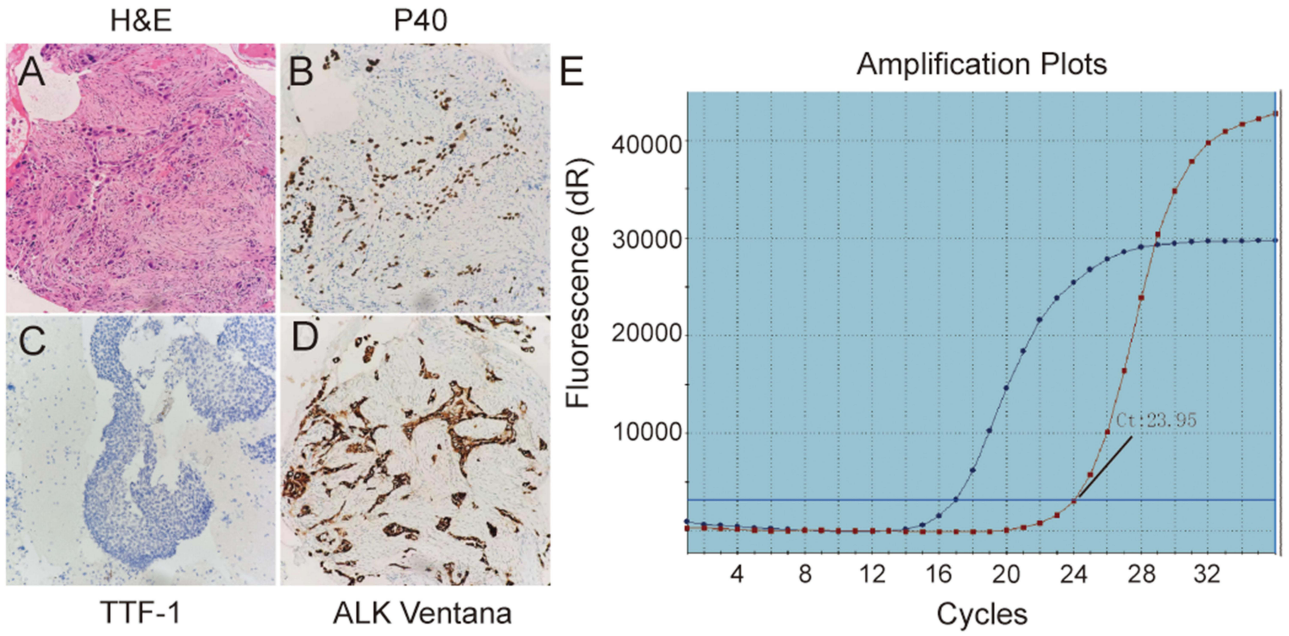

Figure 2 Lung squamous-cell carcinoma case entirely identified by histopathological examination with HE (**A**), positive P40 expression (**B**) and negative TTF-1 expression (**C**). Moderate focal expression of ALK protein by Ventana D5F3 ALK immunohistochemistry (IHC) (**D**). Magnification in all cases was 200×. ALK fusion gene presence using the ARMS-PCR technique (**E**).

Abbreviations: HE, hematoxylin and eosin; ALK, anaplastic lymphoma kinase; ARMS-PCR, amplification refractory mutation system- polymerase chain reaction.

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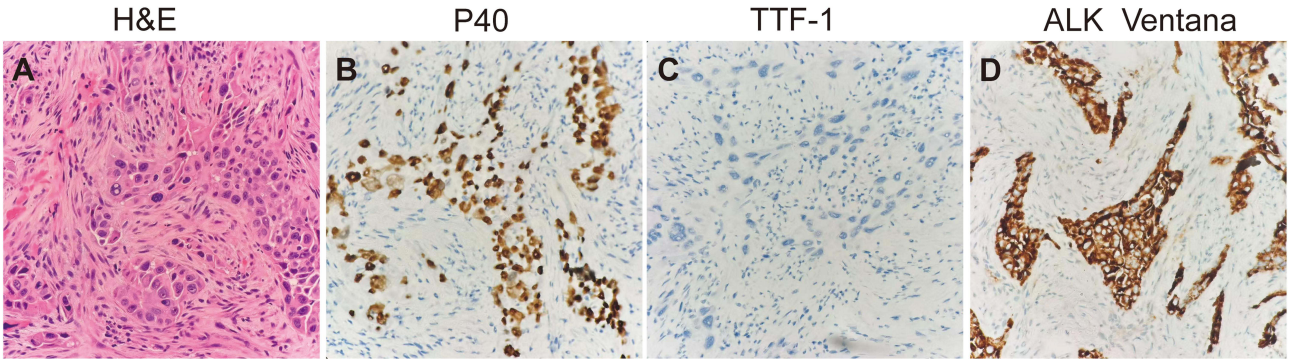

Figure 3 Lung squamous-cell carcinoma case entirely identified by histopathological examination with HE (**A**), positive P40 expression (**B**) and negative TTF-1 expression (**C**). Moderate focal expression of ALK protein by Ventana D5F3 ALK immunohistochemistry (IHC) (**D**). Magnification in all cases was 400×.

(Figure 2B and C). ALK protein overexpression was detected using the Ventana D5F3 assay (Figure 2D), and EML4–ALK fusion was confirmed by real-time PCR (Figure 2E). We performed a re-biopsy of the right lung lesion, and the pathological findings remained consistent with squamous cell carcinoma, which continued to show positive ALK immunohistochemistry (IHC), as demonstrated in Figure 3.

PD-L1 expression, assessed using the 22C3 pharmDx assay, was <1%. Positron emission tomography–computed tomography (PET-CT) identified right upper lobe intrapulmonary nodules, mediastinal and supraclavicular lymphadenopathy, and osteolytic metastases at L3–L4, consistent with stage IVB LSCC (cT2aN3M1c). The patient initiated first-line alectinib (600 mg twice daily) on June 10, 2022. PD-L1 expression on re-biopsy, assessed using the 22C3 pharmDx assay, was still negative. The treatment was subsequently switched to chemoimmunotherapy with nab-paclitaxel (400 mg), carboplatin (AUC 5), and pembrolizumab (200 mg) every 3 weeks, beginning July 12, 2022. Treatment-related adverse events during chemoimmunotherapy included Grade 2 myelosuppression and Grade 1 nausea and fatigue, which were managed with supportive care and resolved without treatment interruption or dose reduction. Thereafter, pembrolizumab maintenance therapy (200 mg every 3 weeks) was continued for 30 cycles, maintaining disease stability for over 30 months.

Discussion

For advanced LSCC without actionable driver mutations, chemoimmunotherapy represents the standard first-line approach, as demonstrated by landmark trials such as KEYNOTE-407 and RATIONALE-307, which showed survival benefits irrespective of PD-L1 status.[6,7] "In patients with metastatic squamous NSCLC, the addition of pembrolizumab to platinum-based chemotherapy demonstrated significant survival benefit independent of PD-L1 expression status. In the Phase 3 KEYNOTE-407 trial, pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel achieved a median overall survival of 15.9 months versus 11.3 months with chemotherapy alone (hazard ratio for death, 0.64; 95% CI, 0.49–0.85; P<0.001), with consistent benefit observed across all PD-L1 subgroups, including those with PD-L1 tumor proportion score <1% (1-year survival rate 64.2% vs. 43.3%; hazard ratio, 0.61; 95% CI, 0.38–0.98)." However, ALK-rearranged LSCC is a rare molecular subset, and its optimal management remains undefined. While ALK-TKIs are highly effective in adenocarcinoma, their efficacy in squamous histology appears inconsistent, with some cases showing primary resistance.[3,4,8]

Our patient exemplifies this clinical challenge: despite confirmed EML4–ALK fusion and ALK protein expression, he experienced rapid disease progression on first-line alectinib. Notably, PD-L1 expression was <1%, and re-biopsy confirmed persistent ALK-positive squamous histology without phenotypic shift. Switching to platinum-based chemoimmunotherapy (nab-paclitaxel/carboplatin/pembrolizumab) induced a rapid partial response, which was maintained for over 20 months on pembrolizumab monotherapy. This suggests that chemoimmunotherapy can be a highly effective salvage strategy in ALK-rearranged LSCC, even in PD-L1–negative and TKI-resistant settings. "Despite PD-L1 negativity, the patient's robust response to chemoimmunotherapy suggests alternative immune-activating features in the tumor microenvironment. Multi-omics analyses[9] have demonstrated that lung squamous cell carcinoma harbors a high proportion of TMB-high tumors

(28.1%), and smoking exposure significantly correlates with increased TMB in lung cancer. Notably, TMB-high tumors exhibit enhanced immunostimulatory signatures (higher $CD8^+$ T cell infiltration and immunostimulatory/immunoinhibitory ratios) independent of PD-L1 status, which may underlie the clinical benefit observed in this case." Different EML4-ALK fusion variants (such as V1/E13;A20 and V3/E6;A20) can significantly affect TKI sensitivity and downstream signaling intensity. Diaz-Jimenez et al[10] demonstrated using autochthonous lung cancer models that the V3 variant, which lacks the HELP domain of EML4, exhibits profound intrinsic resistance to lorlatinib, whereas the V1 variant remains highly sensitive. Furthermore, PTEN inactivation in V3-driven tumors exacerbates this resistance, suggesting that structural differences in fusion partners mediate drug resistance through activation of bypass pathways such as PI3K-AKT. Although this study was limited to adenocarcinoma models, the variant-specific efficacy mechanisms identified suggest that molecular subtyping of ALK-positive LSCC (eg., long versus short variants) may hold similar predictive value and warrants future clinical investigation.

In ALK-positive lung adenocarcinoma, immunotherapy monotherapy has shown limited efficacy after TKI failure,[11] particularly in PD-L1–negative tumors. The efficacy of combining ICI with multi-targeted tyrosine kinase inhibitors (Multi-TKI) is significantly lower in patients with ALK-positive non-small cell lung cancer (NSCLC) receiving second- or later-line therapy, yielding a median progression-free survival (mPFS) of only 3.17 months.[12] However, retrospective data suggest that immunotherapy-based combinations may benefit some patients with ALK-TKI resistance, especially those with PD-L1 positivity.[5] Our case extends these observations to squamous histology and underscores that PD-L1 negativity does not preclude a profound response to chemoimmunotherapy. The clinical heterogeneity of ALK-rearranged LSCC—possibly influenced by smoking history, specific fusion variants, or coexisting genomic alterations—may explain divergent responses to TKIs and immunotherapy.[8] The absence of immune-related adverse events in our patient further highlights the feasibility of this approach.

Our report has several limitations. First, detailed molecular profiling—such as ALK fusion variant typing and assessment of coexisting mutations—was not performed, which could have provided insights into the mechanisms of TKI resistance and immunotherapy sensitivity. Second, as a single case, our findings require validation in larger cohorts.

Conclusion

This case demonstrates that in patients with ALK-rearranged LSCC, platinum-based chemoimmunotherapy can induce a deep and durable clinical response even in the setting of PD-L1-negative expression and primary resistance to ALK-TKIs, providing a crucial strategy for achieving long-term disease control. This finding challenges the current clinical paradigm that predominantly relies on single-driver-gene-targeted therapy and underscores the necessity of comprehensive therapeutic evaluation for specific molecular subtypes of squamous cell carcinoma. From a clinical practice persp12ective, our study suggests that chemoimmunotherapy represents an effective and feasible salvage option after failure of first-line TKI therapy. Given the heterogeneity of this population, future diagnostic and therapeutic approaches should integrate more comprehensive molecular profiling—such as ALK fusion variant subtyping, tumor mutational burden, and immune microenvironment features—to accurately identify potential beneficiaries. To advance the field, prospective multicenter studies are warranted to clarify the real-world efficacy and safety of chemoimmunotherapy in this rare cohort, to explore predictive biomarkers (eg., specific fusion subtypes, immune-cell infiltration patterns, or coexisting genomic alterations), and to evaluate its potential as a first-line treatment option for highly selected patients. Only through systematic clinical and translational research can the overall management of such patients be optimized and their long-term prognosis improved.

Ethics and Consent Statements

Ethical approval was not required for the study involving human samples in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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Disclosure

Yongliang Niu, Bowen Ding, and Jingfeng Shi are co-first authors for this study. The authors report no conflicts of interest in this work.

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