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CASE REPORT

Dual EGFR L858R and KRAS G12A Mutations in Lung Adenocarcinoma: A Rare Case Report and Literature Review

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Background: KRAS mutations are typically mutually exclusive in non-small cell lung cancer (NSCLC), with the G12C mutation being the most common subtype. The coexistence of KRAS and EGFR mutations is exceedingly rare and is typically emerges as a secondary event following acquired resistance to EGFR-targeted therapies. We presented a case of a newly diagnosed NSCLC patient harboring concurrent EGFR L858R and KRAS G12A mutations.

Case Presentation: A 64-year-old male with a 30-pack-year smoking history presented with a 3-month history of progressive shortness of breath and chest tightness. Contrast-enhanced chest CT revealed a 5 cm spiculated mass in the right upper lobe, abutting the mediastinum, along with bronchial obstruction, right middle lobe atelectasis, and pleural effusion. A CT-guided transthoracic needle biopsy confirmed lung adenocarcinoma. Next-generation sequencing (NGS) identified a c.2573T>G (p.L858R) mutation in exon 21 of the EGFR gene and a c.35G>C (p.G12A) mutation in exon 2 of the KRAS gene. The patient started first-line therapy with osimertinib combined with pemetrexed/nedaplatin, resulting in a transient partial response, significant resolution of pleural effusion, and partial regression of the primary tumor. However, disease progression occurred within 6 months, marked by the appearance of a new cerebellar metastasis, confirmed by MRI. The patient continued osimertinib maintenance therapy and underwent stereotactic radiotherapy for the brain lesion. Despite initial stabilization, pulmonary progression was observed 11 months after the start of treatment. Due to declining performance status and personal preferences, the patient declined further treatment and was lost to follow-up.

Conclusion: We report a rare case of treatment-naïve lung adenocarcinoma harboring concurrent KRAS G12A and EGFR L858R mutations. The patient achieved only transient disease control following treatment with a third-generation EGFR TKI combined with chemoradiotherapy. Further research to explore optimal therapeutic strategies for such complex molecular profiles is needed.

Keywords: non-small cell lung cancer, EGFR, KRAS, concurrent mutation

Introduction

Lung cancer is one of the most prevalent malignancies worldwide, with non-small cell lung cancer (NSCLC) representing over 85% of cases.[1] Among the various subtypes of NSCLC, lung adenocarcinoma (LUAD) is the most common, comprising approximately 55–60% of all NSCLC cases. In recent years, the advent of targeted therapies, particularly those targeting specific genetic driver mutations, has revolutionized the treatment landscape for LUAD, leading to substantial improvements in clinical outcomes for patients with advanced-stage disease. These advances have surpassed the efficacy of traditional chemotherapy in many instances, particularly in tumors harboring actionable mutations such as EGFR and ALK.

EGFR and KRAS mutations are among the most extensively characterized and clinically relevant genetic alterations in NSCLC. EGFR mutations are detected in approximately 50–60% of NSCLC cases, with a higher prevalence observed in East Asian populations, where mutations in EGFR are often associated with a more favorable prognosis

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when treated with EGFR-targeted therapies. EGFR tyrosine kinase inhibitors (EGFR-TKIs) outperform chemotherapy in efficacy and safety, making them the standard first-line treatment for advanced EGFR-mutant NSCLC.[2] Despite initial success, most patients experience disease progression after treatment with first- or second-generation EGFR-TKIs. The T790M mutation is the primary resistance mechanism against first- and second-generation EGFR-TKIs.[3] The challenge of resistance led to the development of third-generation EGFR-TKIs, notably osimertinib. Recent FLAURA2 study results demonstrate that combining osimertinib with chemotherapy offers improved disease control in advanced EGFR-mutant non-small cell lung cancer compared to using osimertinib alone.[4] KRAS mutations occur in approximately 10% of NSCLC cases, with a greater frequency in smokers and often associated with a more aggressive disease course.[5] Interestingly, EGFR and KRAS mutations are typically mutually exclusive; patients harboring KRAS mutations rarely exhibit coexisting EGFR mutations. This mutual exclusivity has significant clinical implications, as it suggests distinct molecular mechanisms driving tumorigenesis in these two subsets of patients. Moreover, KRAS mutations are known to confer resistance to EGFR-TKIs, which are a cornerstone of targeted therapy for NSCLC patients with EGFR-mutant tumors. The presence of KRAS mutations in tumors that initially respond to EGFR-TKIs may lead to secondary resistance, rendering EGFR-TKI treatment ineffective and limiting the therapeutic options available for such patients. This phenomenon presents a considerable clinical challenge in the management of NSCLC, as the resistance mechanisms remain poorly understood and strategies to overcome this resistance are still under investigation.[6] Here, we report a rare case of a newly diagnosed LUAD patient with coexisting EGFR Exon 21 L858R and KRAS G12A mutations.

Case Presentation

A 64-year-old male with a 30-pack-year smoking history presented with a 3-month history of chest tightness and dyspnea. Contrast-enhanced chest CT revealed a 5.0×3.5 cm^2 mass in the anterior segment of the right upper lobe, suggesting malignancy. The mass was associated with bronchial obstruction, superior mediastinal involvement, right middle lobe atelectasis, pleural effusion, and incomplete expansion of the right lower lung (Figure 1A and B). Cranial and abdominal MRIs showed no significant neoplastic lesions (Figure 1C and D). CT-guided biopsy of the pulmonary mass confirmed adenocarcinoma (Figure 2A). Immunohistochemistry results were positive for CK7, TTF-1, NapsinA, and EGFR (Figure 2B–E). Ki-67 showed 10% proliferative activity (Figure 2F). Next-generation sequencing (NGS) identified a c.2573T>G (p.L858R) mutation in EGFR exon 21 and a c.35G>C (p.G12A) mutation in KRAS exon 2 (Figure 3).

The patient was diagnosed with stage IVa lung adenocarcinoma, classified as T2bN1M1a according to the Eighth Edition of the TNM Classification of Malignant Tumors and had an ECOG performance status of 1. Based on the FLAURA2 study findings, the patient underwent two cycles of pemetrexed-cisplatin chemotherapy in conjunction with osimertinib targeted therapy, followed by osimertinib maintenance therapy. Throughout the treatment, the patient demonstrated good tolerance and did not experience any Grade 3 or higher treatment-related adverse effects. Two months after treatment, follow-up imaging showed significant resolution of the pleural effusion and partial regression of the right upper lobe mass (Figure 4A). The patient then received definitive intensity-modulated radiotherapy (60 Gy in 30 fractions) to the primary tumor and mediastinal/hilar nodal stations (Figure 4B), along with concurrent osimertinib administration. Six months later, neuroimaging revealed a new enhancing lesion in the left cerebellar hemisphere, consistent with metastatic progression (Figure 4C). Stereotactic radiotherapy (45 Gy in 10 fractions) was administered to the solitary brain metastasis (Figure 4D), while osimertinib treatment was continued. Eleven months post-treatment, chest CT showed progression of pulmonary lesions, with increased surrounding inflammatory changes, multiple bilateral lung nodules, and right pleural metastases (Figure S1). Due to a decline in performance status and financial constraints, the patient declined further treatment and discontinued follow-up.

Discussion

The most researched targeted therapies for lung cancer are EGFR and ALK inhibitors, both showing significant clinical efficacy. Despite their efficacy, acquired resistance poses a significant challenge in treating oncogene-driven NSCLC. The resistance process is driven by various complex molecular mechanisms. While some mechanisms have been clarified, others are still not fully understood and require further investigation.[7] EGFR and KRAS represent the two most prevalent driver

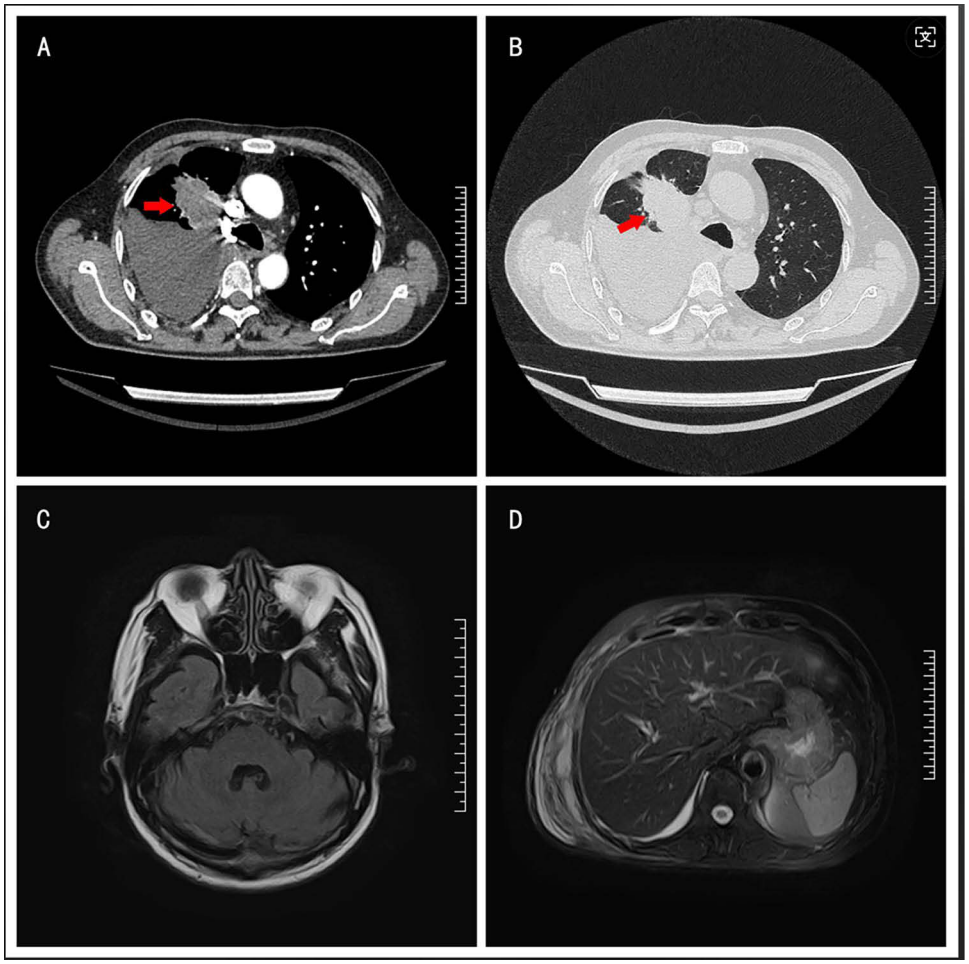

Figure 1 Initial imaging findings of the patient. (**A** and **B**) Chest CT: A well-defined, heterogeneously enhancing mass (5.0 × 3.5 cm^2) was observed in the anterior segment of the right upper lobe, abutting the mediastinum. The lesion demonstrated bronchial obstruction with secondary involvement of the superior mediastinum and adjacent right lung parenchyma. Associated findings included segmental atelectasis of the right middle lobe, moderate right pleural effusion, and partial collapse of the right lower lung. (**C** and **D**) Cranial and Abdominal MRI: No evidence of metastatic neoplastic lesions was identified in the brain or abdominal viscera. The lesions are indicated by the red arrows.

mutations in NSCLC, both operating within the EGFR signaling pathway. EGFR mutations promote tumor cell proliferation by enhancing receptor tyrosine kinase activity, whereas KRAS mutations drive constitutive downstream signaling through GTPase inactivation. Clinically, EGFR mutations are predominantly observed in non-smoking adenocarcinoma patients, with common alterations including exon 19 deletions and the L858R point mutation in exon 21, both of which exhibit favorable responses to tyrosine kinase inhibitors (TKIs).[8] In contrast, KRAS mutations are frequently associated with smoking-related NSCLC, primarily involving exon 2 (codons G12 and G13), and confer resistance to TKI therapy, correlating with poorer prognosis.[9] Historically, these mutations were considered mutually exclusive due to functional redundancy within the same signaling cascade. However, with the widespread adoption of next-generation sequencing (NGS), this rare co-mutation has been increasingly identified, garnering significant clinical and research interest.

The coexistence of EGFR and KRAS mutations suggests that dual driver signaling may exert more profound effects on tumor biology than singular mutations. KRAS-mutated NSCLC is a genetically heterogeneous subgroup, with 53.5% of cases harboring at least one additional mutation in cancer-associated pathways.[10] Common co-mutations include TP53 (39.4%) and STK11 (19.8%), while targetable mutations in EGFR and BRAF are rare, occurring in only 1.2% of cases.[10] Notably, EGFR/KRAS co-mutations are relatively prevalent in patients developing acquired resistance following TKI treatment.[11–13] In the present case, baseline NGS identified coexisting EGFR and KRAS mutations prior to treatment, likely reflecting intratumoral heterogeneity.

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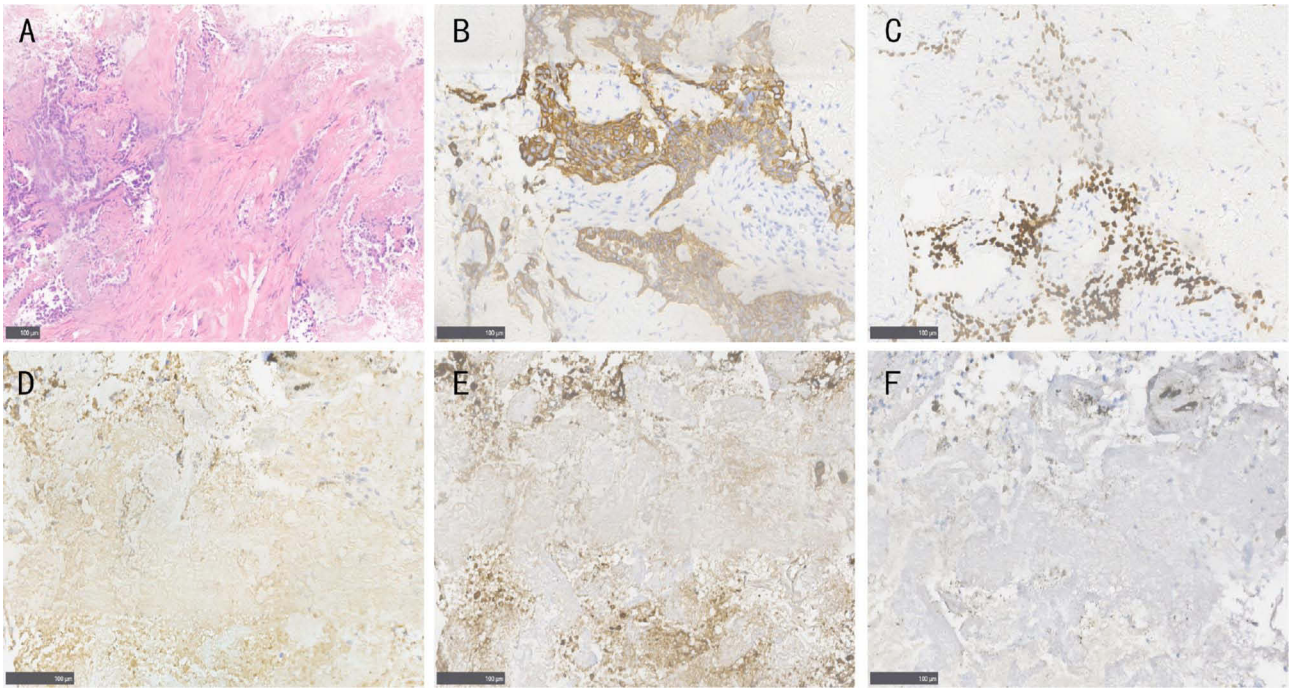

Figure 2 Pathological findings. (**A**) Hematoxylin-eosin (HE) staining shows complete disruption of native alveolar architecture, replaced by infiltrating tumor cells with nuclear enlargement and prominent eosinophilic nucleoli (×100 magnification). (**B–E**) Immunohistochemical analysis revealed the neoplastic cells were strong and diffuse positivity for CK7 (**B**), TTF-1 (**C**), NapsinA (**D**), and EGFR (**E**); Ki67 positivity was around 10% (**F**) at ×200 magnification.

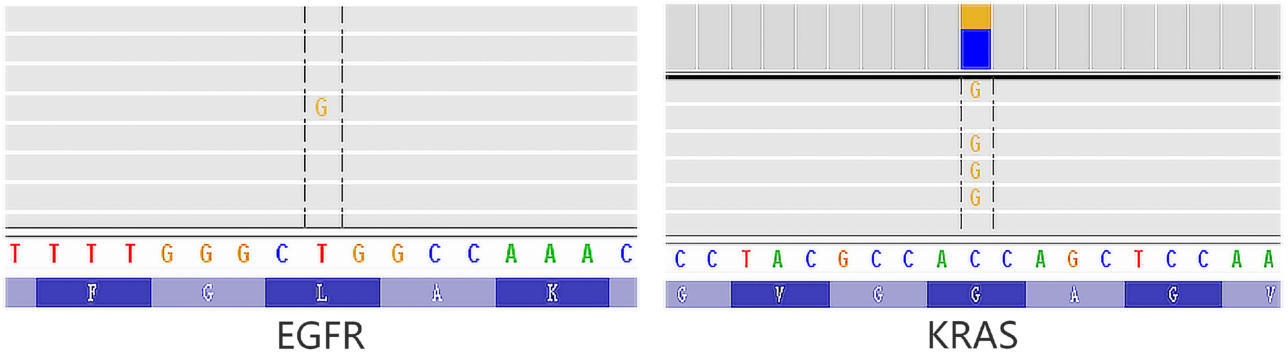

Figure 3 Genetic testing results. NGS analysis identified a c.2573T>G (p.L858R) mutation in exon 21 of the EGFR gene and a c.35G>C (p.G12A) mutation in exon 2 of the KRAS gene.

The mechanisms underlying EGFR/KRAS co-mutation-mediated resistance remain under investigation. Specific KRAS mutation subtypes and their activation domains dictate the preferential activation of distinct signaling pathways, such as the RAF-MEK-ERK axis versus the PI3K-AKT-mTOR cascade, creating a complex, multilayered synergistic network that amplifies oncogenic signaling in EGFR-mutant tumors and contributes to tumor progression and therapeutic resistance.[10,14] Current evidence suggests that KRAS mutations may attenuate EGFR-targeted therapy by competitively activating the RAF-MEK-ERK cascade, thereby serving as a bypass mechanism to drive resistance during EGFR-targeted therapy. Additionally, hyperactivated KRAS promotes apoptosis resistance and accelerates tumor cell survival and expansion.[15] The coexistence of these mutations likely creates a synergistic network that strengthens oncogenic signaling, further complicating therapeutic strategies.

Patients with concurrent EGFR and KRAS mutations present significant clinical challenges. Studies have shown that these patients exhibit significantly higher tumor mutational burden (TMB) and shorter progression-free survival (PFS) compared to those with EGFR mutations alone.[16,17] While targeted therapies for EGFR-mutant tumors have

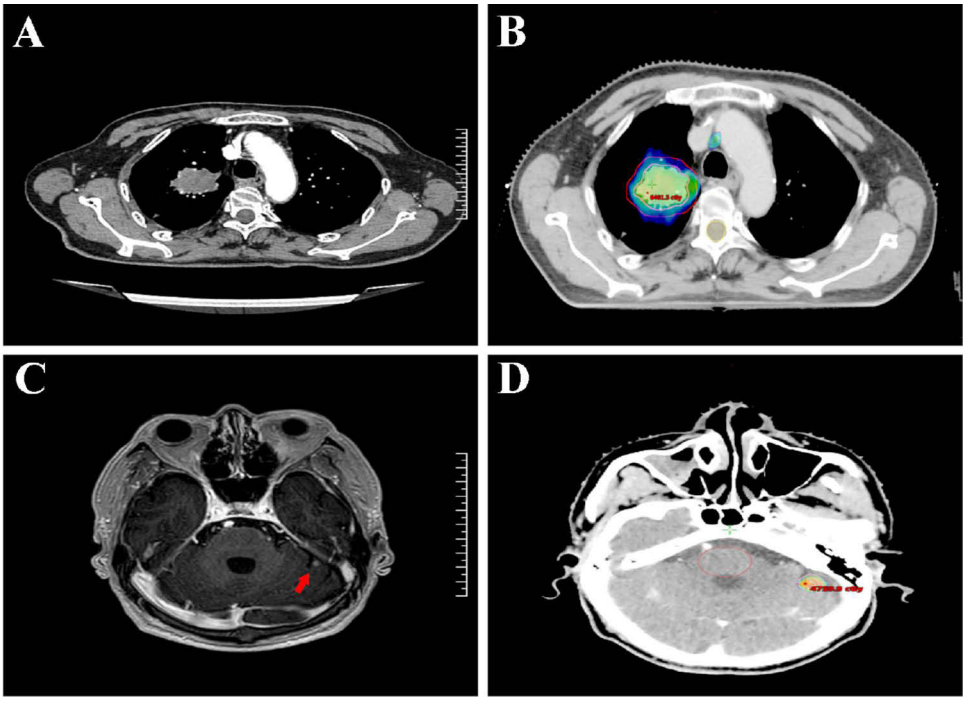

Figure 4 Imaging findings after two courses of radiotherapy. (**A**) Chest CT after two treatment cycles shows a decrease in right-sided pleural effusion volume; the mass in the right upper lobe has reduced to approximately 3.4×2.1 cm^2. (**B**) Radiotherapy targeting pulmonary carcinoma lesions and adjacent lymph nodes. (**C**) Contrast-enhanced head MRI shows nodular abnormal enhancement in the left cerebellar hemisphere. (**D**) Radiotherapy targeting cerebellar metastatic lesions. The lesion is indicated by the red arrow.

revolutionized NSCLC treatment, options for dual EGFR/KRAS-mutant tumors remain limited.[18,19] The G12C KRAS mutation, the most prevalent KRAS variant, has garnered attention for targeted therapy development;[20] however, current targeted therapies are designed to bind to the cysteine residue within the Switch-II pocket (S-IIP) of the KRAS-GDP complex specifically in KRAS G12C mutants, which are restricted to this specific mutation subtype.[21]

Although KRAS mutations impact the efficacy of EGFR TKIs, they do not appear to affect the response to chemotherapy.[22] Therefore, the National Comprehensive Cancer Network (NCCN) NSCLC guidelines recommend systemic therapy as the first-line treatment for NSCLC patients with KRAS mutations.[23] KRAS-mutant tumors are often more immunogenic, exhibiting elevated PD-L1 expression and higher TMB, both of which are predictive of better responses to immune checkpoint inhibitors (ICIs).[24,25] In patients with KRAS-mutant metastatic NSCLC, the response rate to ICI monotherapy is approximately 26%.[26,27] A retrospective study further demonstrated that immunotherapy, regardless of treatment line, yields superior outcomes compared to conventional chemotherapy in KRAS-positive patients.[28] Additionally, the efficacy of immunotherapy positively correlates with high PD-L1 expression, irrespective of the specific KRAS mutation subtype.[29] Therefore, the Chinese Society of Clinical Oncology (CSCO) recommends a first-line treatment strategy combining immunotherapy with chemotherapy for locally advanced NSCLC patients harboring KRAS mutations.[30]

The combination of EGFR-TKIs with KRAS inhibitors holds promise but remains underexplored in clinical trials. A Phase II study demonstrated that the novel KRAS G12C-targeted agent, garsorasib, exhibits a high response rate, prolonged duration of response, and an acceptable safety profile in patients with previously treated KRAS G12C-mutated NSCLC.[31] These findings highlight the potential of combined targeted therapies for dual EGFR/KRAS-mutant NSCLC. Notably, a Phase II trial presented at the 2024 ASCO Annual Meeting evaluated the KRAS G12C inhibitor fulzerasib combined with the EGFR inhibitor cetuximab as first-line therapy in advanced KRAS G12C-mutated NSCLC, reporting an 80% objective response rate (ORR) and a 100% disease control rate (DCR).[32] This suggests that dual KRAS/EGFR inhibition may be a viable strategy for co-mutated NSCLC. However, the efficacy and safety of combining EGFR-TKIs with KRAS inhibitors in dual EGFR/KRAS-mutant NSCLC remain undetermined due to limited clinical data.

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This study has several limitations that warrant acknowledgment. First, as a single case report, the findings lack generalizability and cannot establish causal relationships. Second, the patient received only two cycles of systemic chemotherapy combined with localized radiotherapy during first-line treatment and did not undergo ICIs therapy. This limited treatment exposure may have influenced the observed outcomes and precluded a comprehensive evaluation of the potential benefits of ICIs in this setting. Third, there are currently no approved targeted therapies for KRAS G12A mutations, and the high cost of KRAS G12C inhibitors rendered them inaccessible for this patient. Consequently, the patient was treated solely with EGFR TKIs, which may have contributed to the rapid disease progression observed. Further research is needed to explore optimal therapeutic strategies for NSCLC patients with concurrent EGFR and KRAS mutations, particularly in resource-limited settings.

In conclusion, this rare case of LUAD with concurrent EGFR and KRAS mutations highlights the challenges in managing dual-driver mutations. Relying solely on EGFR-TKIs is insufficient; a multidisciplinary approach integrating KRAS inhibitors, immunotherapy, and chemotherapy may offer a more effective strategy. Future research should focus on elucidating the molecular mechanisms underlying dual mutations and exploring novel therapeutic combinations. Large-scale, multi-center clinical trials are essential to optimize treatment strategies and improve outcomes for patients with this challenging molecular profile.

Data Sharing Statement

The data is available from upon request from the two corresponding authors.

Ethics Committee Approval

This study was approved by the Ethics and Scientific Committee of Hubei University of Medicine (XYYYE20240074) and was performed according to the Good Clinical Practice Guidelines and the Helsinki Declaration. Institutional approval was obtained from Xiangyang No.1 hospital for the publication of the case detail.

Consent for Publication

Informed consent for the publication of identifying information/images in an online open-access publication was obtained from the patient'.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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