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Successful Treatment of Metastatic Lung Cancer with Fusion KIF RET Amplification Using Alectinib in the Absence of Selpercatinib and Pralsetinib: A Case Report and Literature Review

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Abstract

Background: The treatment landscape for advanced non-small cell lung cancer (NSCLC) has evolved significantly with the emergence of targeted therapies. Among these, tyrosine kinase inhibitors (TKIs) selective for the rearranged during transfection (RET) gene have shown promise. However, understanding resistance mechanisms and identifying effective treatments for patients progressing on RET-TKIs remains a challenge. **Case description:** we present a patient with metastatic lung cancer harboring a fusion involving KIF5B-RET amplification. Notably, this patient did not receive Selpercatinib or Pralsetinib, two RET-selective TKIs commonly used in RET-positive NSCLC. Instead, the patient was successfully treated with Alectinib, highlighting the potential efficacy of this alternative therapy. **Conclusion:** Our case report, provides a comprehensive overview of RET-positive advanced NSCLC, covering both therapeutic and molecular aspects. We compare clinical outcomes achieved with multikinase inhibitors (MKIs) and RET-selective TKIs, emphasizing the long-term resistance mechanisms. Additionally, we discuss unresolved issues and propose future pharmacological approaches.

Keywords: NSCLC, RET fusion, TKI, Drug resistance.

Introduction

Lung cancer continues to be the primary cause of cancer-related mortality globally, even with advancements in risk assessment, biological insights, immunological strategies, and the introduction of novel treatment modalities. Among lung cancers, non-small cell lung cancer (NSCLC) is the predominant type, constituting 84% of all lung cancer cases (1, 2).

The discovery of oncogenic activation in tyrosine kinases has revolutionized the treatment landscape for advanced non-small cell lung cancer (NSCLC). Significantly, mutations in the epidermal growth factor receptor (EGFR), rearrangements of the anaplastic lymphoma kinase (ALK) gene, and alterations in the c-ROS oncogene 1 (ROS1) gene have paved the way for targeted therapies in lung cancer.These findings have also prompted ongoing research to identify biomarkers and treatments applicable to other subsets of patients with advanced NSCLC (3).RET Gene fusions play a crucial role

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as oncogenic drivers in approximately 1% of non-small cell lung cancer (NSCLC) cases (4).

Recurrent rearrangements occur between RET and fusion partners such as CCDC6, KIF5B, and NCOA4. RET fusions account for about 1-2% of non-small cell lung cancer (NSCLC) cases and are more prevalent in younger patients and those who have never smoked. Overall, Brain metastases frequently occur in RET fusion-positive non-small cell lung cancers (NSCLC), with an approximate 46% prevalence. Break-apart FISH and NGS can identify RET rearrangements. Immunohistochemistry (IHC) is convenient but has poor sensitivity and specificity for RET detection in NSCLC. accurate identification of RET alterations is crucial for guiding treatment decisions in advanced patients (10- 12).

Patients with the KIF5B-RET genotype exhibit specific clinical features, showing that this fusion gene could serve as a more certain molecular marker in non-small cell lung cancer (NSCLC) (13).

The FDA has approved two RET inhibitors, Selpercatinib and Pralsetinib, for adult patients with advanced non-small cell lung cancer (NSCLC) harboring RET fusion-positive alterations. These agents are recommended as front-line treatment options for such patients, replacing immunotherapy or chemotherapy (14, 15).

Selpercatinib and Pralsetinib are FDA-approved RET-selective tyrosine kinase inhibitors (TKIs) with encouraging efficacy. In contrast, Cabozantinib, Vandetanib, Alectinib, and Sunitinib are multitargeted TKIs approved for other indications, but they are less potent than Selpercatinib and Pralsetinib (16- 22).

Immune checkpoint inhibitors (ICIs) have emerged as the standard treatment for patients with advanced non-small cell lung cancer (NSCLC) lacking driver mutations. Nevertheless, their effectiveness in treating advanced non-small cell lung cancer (NSCLC) with RET fusion remains a topic of debate. The IMMUNOTARGET trial published a modest response to ICIs in RET fusion-positive NSCLC, with an overall response rate (ORR) of 6.3% and a median progression-free survival (PFS) of 2.1 months. In contrast, real-world data from U.S. databases demonstrated favorable outcomes in patients with RET fusion-positive NSCLC who received ICI-based therapy, achieving a 53.8% ORR and a median PFS of 4.2 months. Given the limited and conflicting evidence, the use of ICIs in RET fusion-positive NSCLC remains uncertain (23- 27).

However, limited access to these drugs in certain clinical settings underscores the need to explore alternative treatment options. Here we present a case of successful management of metastatic lung cancer with fusion KIF-RET amplification using Alectinib as an alternative targeted therapy.

Case presentation

A 42-year-old nonsmoker woman presented with dyspnea, cough and weakness. In her chest CT scan, the mass lesion was reported in RLL and no evidence of metastasis on imaging's. In December 2023 she underwent CNB of the lung mass. The pathology showed necrosis and fibrosis and there was no evidence of malignant lesion. Based on the appearance of the lesion, the surgical team decided to perform resection and in January 2023 the patient underwent lobectomy. This time, the pathology was consistent with Adenosquamous carcinoma with necrosis. The subcarinal lymph node was also involved. The tumor was classified as pT2N2 (stage IIIA according to the TNM classification of the UICC). Imaging showed no evidence of metastatic disease. To decide on the treatment, the patient was subjected to the EGFR mutation panel test on a tissue sample. During this assessment, which was done by RT-PCR method, no mutation was detected. However, the evaluation of PDL1 expression with IHC showed 33%, which means significant PDL1 expression. Subsequently, the oncologist planned to treat her with a combination of pemetrexed and a platinum regimen. After 2 cycles of chemotherapy, in February 2023 the patient had a seizure. Brain MRI revealed a heterogeneous mass lesion in the frontal lobe (18*17*12 mm). Yet there was no evidence of other organ involvement. Due to the patient's lack of consent to surgery, we decided to do SRS. In this setting, the molecular profile of the patient was fully evaluated, which was positive for ROS1 amplification (20%) and RET rearrangement (67%) and negative for ALK gene rearrangement by FISH study and MET exon 14 by RT-PCR was also negative. Considering the unavailability of the medications and the inability of the patient to prepare the selected target drugs, as well as the suitable performance status and significant PDL1 expression, immunotherapy with pembrolizumab was added to the previous chemotherapy regimen which was continued up to a total of 6 cycles. Maintenance therapy with pembrolizumab was considered due to the lack of evidence for residual disease in the imaging. In July 2023, after receiving 4 cycles of pembrolizumab, evidence of disease progression was seen in the PET-CT scan in the form of mediastinal lymph node involvement and multiple brain lesions. The patient was a candidate for whole-brain radiotherapy. To choose the appropriate treatment plan, the patient's tissue sample was sent to another country (Turkey) for NGS. Regarding the NGS result that was positive only for fusion RET-KIF5b and negative for other biomarkers (such as ALK, ROS1, EGFR, BRAF, and HER2) it was decided to start RET inhibitor target therapy for the patient. It is noteworthy that the PDL1 expression was negative

in NGS despite being significantly positive in the patient's previous IHC test. Given the unavailability of Selpercatinib and pralsetinib due to logistical and financial constraints, the patient's treatment was initiated with Alectinib as a targeted therapy (1200 mg/day). After two weeks of treatment, she showed up with hemolytic anemia. Alectinib was temporarily stopped, and conservative treatment was performed. After a while, Alectinib started again with lower doses (600 mg/day) for 6months. Afterward, the patient underwent reevaluation with a PET scan. In the PET scan, the previous mediastinal lesions showed reduced uptake, with the only positive finding being increased uptake in the left humerus bone despite suboptimal dose administration of Alectinib (figure1). Furthermore the patient had no clinical symptoms. Overally, Considering that the patient's symptoms are controlled and imaging results was reasonable for this case, the decision was made to increase the Alectinib dose to 900 mg/day and for bone metastasis support, bisphosphonates were added to the patient's treatment.

Discussion

Fusion KIF RET amplification is a rare genetic alteration in lung cancer, occurring in approximately 1-2% of patients. (4) Based on LIBRETTO-431 and ARROW trial, first-line treatment with Selpercatinib and Pralsetinib has emerged as standard-of-care targeted therapies for this genetic alteration, demonstrating impressive response rates and prolonged progression-free survival in clinical trials (14, 28). However, access to these drugs may be limited in certain clinical settings (as was the case for this patient), necessitating the exploration of alternative treatment options. Alectinib, a potent and selective ALK inhibitor, demonestrates efficacy in treating ALK-positive non-small cell lung cancer and has also demonstrated activity against RET-altered tumors in preclinical studies. The successful outcome observed in this case highlights the potential efficacy of Alectinib as an alternative treatment for metastatic lung cancer with fusion KIF RET amplification when access to specific targeted therapies is limited. While Selpercatinib and Pralsetinib are considered standard-of-care options for this genetic alteration, the use of Alectinib in this context warrants further investigation and consideration as a viable treatment strategy (29).

Given the rarity of fusion KIF RET amplification, personalized treatment approaches tailored to individual patient needs and available resources are crucial in optimizing clinical outcomes. In addition to the high cost and lack of access to these medicines, the inconsistency of the results in the diagnostic modalities (ex NGS, FISH, PCR, etc.) renders it difficult to make an appropriate treatment decision (30).

In this case, the discrepancy between next-generation sequencing (NGS) and immune-histochemistry (IHC) results regarding PD-L1 expression influenced the treatment decision. Immunotherapy was chosen as the first-line treatment in the metastatic setting. Previous studies have highlighted the uncertainty surrounding immune checkpoint inhibitors (ICIs) in these patient subtypes. The efficacy of immune checkpoint inhibitors (ICIs) is notable, especially in patients with high PD-L1 and who have not undergone any prior therapy. Their effectiveness is comparable to that observed in unselected populations (23- 27).

The IMMUNOTARGET study reported a poor response of RET fusion-positive non-small cell lung cancer (NSCLC) to immune checkpoint inhibitors (ICIs). Before the approval of selective targeted agents, certain patients with RET fusion-positive lung cancer were treated with immune checkpoint inhibitors (ICIs)(31).

Conclusion

in the absence of access to Selpercatinib and Pralsetinib, Alectinib demonstrated remarkable efficacy in treating metastatic lung cancer with fusion KIF RET amplification. This case underscores the importance of exploring alternative therapeutic options and individualized treatment approaches to optimize patient outcomes, particularly in resource-constrained settings. Further research and clinical experience are warranted to validate the role of Alectinib in this context and inform treatment decisions for patients with similar genetic alterations. As precision medicine continues to evolve, the need for accessible and effective targeted therapies for rare genetic alterations remains a critical priority in improving outcomes for patients with metastatic lung cancer.

Statements and Declarations

Consent to participate and Publication

The patient provided informed consent for participation in this case report and publication. She understood the purpose, risks, and benefits of sharing her medical information for scientific and educational purposes. Confidentiality was maintained, and her initials were used to protect privacy.We seek to share this unique case to contribute to medical knowledge and improve patient care.

Availability of data and materials

availability of data and materials is subject to institutional policies, patient consent, and legal constraints. Researchers should follow established protocols and guidelines when requesting access to clinical information.

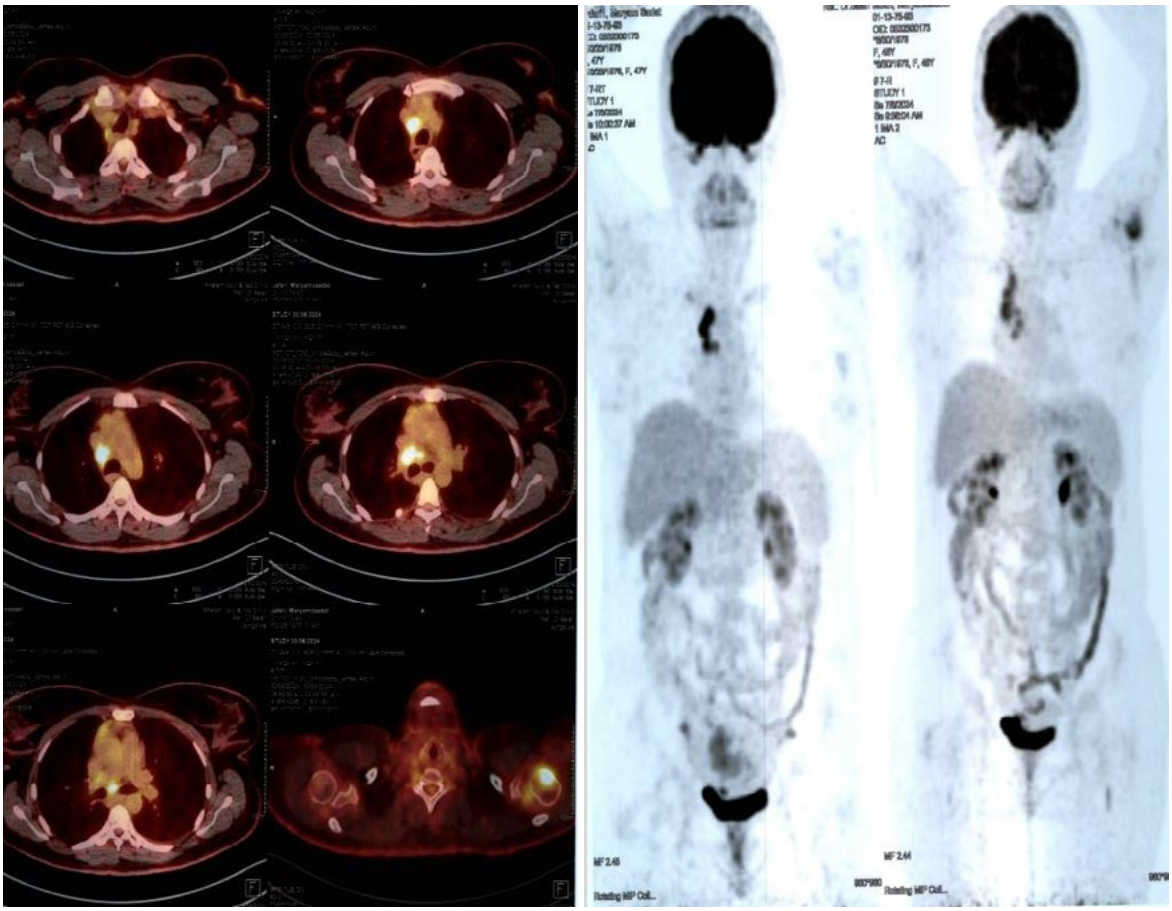

Fig 1. The patients PET scan rsult.

Ethics approval and consent to participate

Ethical considerations guided decision-making, ensuring patient autonomy, safety, and adherence to best practices.

Conflicts of Interest

The Authors affirm that they have no conflict of interest.

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Authors' contributions

Sina Salari: conceptualization; data curation; editing and review. Maedeh Mataji: investigation and writing. Soodeh Ramezaninejad: investigation and writing.

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