CASE REPORT

Unusual Resistance Mechanisms in a Case of *ROS1*-Rearranged NSCLC: A Case Report

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ABSTRACT

The unprecedented growth of the high-throughput next-generation sequencing has facilitated the identification of rare oncogene fusions such as *ROS1* for NSCLC. *ROS1* rearrangement has been observed in only 2% of cases of NSCLC and has been successfully targeted using various tyrosine kinase inhibitors including crizotinib. However, the on-target and off-target mechanisms of the resistance are still vague. Here, we report a case of a patient with *ROS1* rearranged NSCLC presenting primary resistance to crizotinib.

Keywords: ROS1; Crizotinib; Non–small cell lung cancer; Case report

Introduction

ROS1-rearranged NSCLC is rare,[1] yet actionable, and is treated with tyrosine kinase inhibitors (TKIs). However, similar to other TKIs, resistance often ensues—the mechanisms of which are still unclear with both on-target and off-target mechanisms reported (Table 1). This case depicts unusual primary resistance mechanisms to crizotinib in a patient with *ROS1*-rearranged NSCLC.

Case Presentation

A 42-year-old man, ex-smoker, presented with cough and neck swelling and was diagnosed with *ROS1*-rearranged (detected by fluorescence in situ hybridization) stage IV NSCLC adenocarcinoma with metastases to lymph nodes and bone. Magnetic resonance imaging of the brain was normal. He was initially treated with crizotinib 250 mg twice daily. The patient tolerated the treatment well without any treatment delays. Positron emission tomography–computed tomography re-evaluation revealed progressive disease in bones and lymph nodes after 3 months. Repeat biopsy from the new metastatic node was subjected to next-generation sequencing (Supplementary Data), which revealed *SDC4-ROS1* fusion along with new subclonal variants in *RET* (p.C634Y) and *HRAS* (p.G12S). The same subclones were tracked in two-fortnightly–spaced blood samples using liquid biopsy and revealed increased allele frequency of the *RET* subclone, with persistent *ROS1* fusion and *HRAS* alteration. The patient was treated with lorlatinib 100 mg per day, to which he exhibited partial response in lung and lymph nodes. He is currently on lorlatinib for 6 months with grade 2 hypercholesterolemia. To determine the primary versus secondary mode of resistance, next-generation sequencing was done on diagnostic tumor block, which revealed the same *RET* subclone, although *HRAS* was not detected.

The evolution of clones is depicted in Figure 1.

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Table 1. Various Resistance Mechanisms (On-Target and Off-Target Mechanisms) in ROS1-Rearranged NSCLC

On-Target Resistance Mechanisms	Off-Target Mechanisms
G2032R	*EGFR*
D2033N	*HER2*
L2026M	*KIT*
S1986F/Y	*KRAS*
	BRAF
	MEK
	MET

Discussion

ROS1-rearranged NSCLC is known to respond to TKI therapy including crizotinib, as reported in PROFILE 1001 (disease control rate: ∼90% and progression-free survival: ∼19.2 mo).[2] However, in our case, there was rapid progression and resistance ensued. On-target kinase domain mutations[3] G2032R and D2033N, and off-target activation of the bypass *EGFR*, *KIT* signaling are well-known mechanisms of resistance to crizotinib.[3]

Activation of the RAS pathway (*KRAS* or *NRAS* mutations) has been described *in vitro* as both primary and secondary *ROS1* resistance mechanisms[4]; however, the same has not been studied for *HRAS*. *HRAS* is more frequently found in NSCLC cases with squamous morphology,[5] and in anecdotal case reports of adenocarcinoma portending an aggressive disease course, distinct from this case.[6]

In this patient, a subclonal variant in the intracellular domain of *RET* gene (p.C634Y) was detected, which has been proven oncogenic in medullary thyroid cancers as germline and also in a few sporadic cases.[5] In a study, one patient with *ROS1*-rearranged NSCLC was detected to have a copy number gain in *RET* posttherapy; however, the same was not seen in our case. The possibility of contamination from germline DNA was ruled out orthogonally from DNA extracted from the cell pellet of the blood sample. The same has not been reported in cases of NSCLC as *ROS1* fusions are mutually exclusive with *RET* alterations.

A thorough literature search for *RET* as a resistance mechanism to crizotinib revealed no reports, hence, this requires functional and *in vitro* studies for the lucid understanding of the biological processes.

Conclusion

The patient exhibits a primary resistance to crizotinib with unusual mechanisms not reported in the literature. Further elucidation for both *RET* and *HRAS* is needed to better understand the biology to institute appropriate therapy.

CRediT Authorship Contribution Statement

Ullas Batra: Conceptualization, Methodology, Software, Writing - reviewing and editing of the article.

Shrinidhi Nathany, Mansi Sharma: Data curation, Writing and preparation of the original draft, Software, Data validation.

Sakshi Mattoo, Joslia T. Jose: Laboratory techniques.

Anurag Mehta: Supervision.

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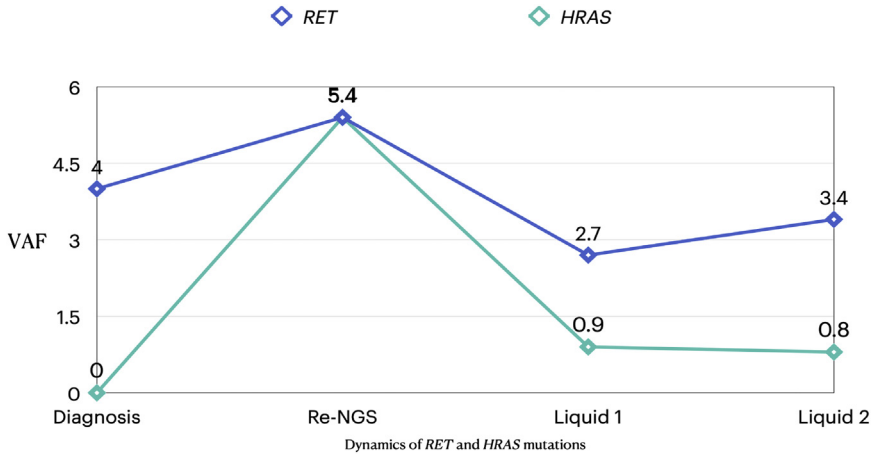

Figure 1. Graph illustrating evolution of the *RET* and *HRAS* clones along with their respective variant allele frequencies. Liquid 1 and liquid 2 were done fortnightly after disease progression on crizotinib. NGS, next-generation sequencing; VAF, variant allele frequency.

Supplementary data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100286.

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