CASE REPORT

A Naive Lung Adenocarcinoma Harboring G1269A *ALK* Resistance Mutation

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Received 12 March 2020; revised 19 April 2020; accepted 22 April 2020
Available online - 28 April 2020

Introduction

ALK gene rearrangement in NSCLC results from fusion with another partner gene, mainly *EML4* gene, and is observed in less than 5% of adenocarcinoma tumors. Patients usually manifest a response to ALK tyrosine kinase inhibitors. Unfortunately, acquired resistance ineluctably occurs and has been associated with the emergence of secondary mutations.[1] Here, we report the identification of an *ALK* resistance mutation in a patient with ALK tyrosine kinase inhibitor–naive multimetastatic NSCLC.

Case Presentation

A 49-year-old man with a smoking history presented with a visual loss. Brain computed tomography scan result revealed a single occipital secondary lesion. Chest computed tomography scan result revealed a right lung mass.

The biopsy result of the lung mass revealed a bronchial mucosa with massive infiltration by poorly differentiated adenocarcinoma (Fig. 1). Immunohistochemistry test result revealed a diffuse positivity of the tumor cells for the antibody thyroid transcription factor-1, confirming its primary pulmonary origin. The ALK protein was not expressed by immunohistochemistry, and no *EML4–ALK* gene rearrangement was found by fluorescence in situ hybridization (Fig. 2). Several metastatic lesions were identified, such as hepatic, skeletal, cerebral, muscular, and other sites.

Next-generation sequencing (NGS) revealed *ALK* pathogenic variant c.3806G>C;p(Gly1269Ala) in the following three different sites: lung biopsy specimen, muscular biopsy specimen of a secondary nodule with about 8% of allelic frequency (Fig. 3), and blood circulating tumor DNA. The somatic nature of this mutation was confirmed using nontumoral tissue. c.469G>T;p.(Val157Phe) *TP53* mutation was also identified in both the circulating tumor DNA and bronchial biopsy specimen. The patient did not receive ALK tyrosine kinase inhibitor (TKI) given the absence of rearrangement as per treatment guidelines. He received platinum-based chemotherapy and immunotherapy as second line. He died after 4 months.

Discussion

ALK–rearranged NSCLCs are driven by a constitutively active fusion protein that confers marked sensitivity to ALK TKIs. Gly1269Ala is one of secondary resistance mutations previously described in tumor specimens collected after previous exposure to TKI therapy.[1]

This point mutation located in ALK tyrosine kinase domain coding sequence is positioned in direct contact with crizotinib, a first-generation ALK inhibitor molecule. The mutation of glycine to the larger alanine may

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Disclosure: Dr. Girard reports grants, personal fees, and nonfinancial support from Roche Holdings AG and Pfizer, outside the submitted work. The remaining authors declare no conflict of interest.

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Cite this article as: Trabelsi-Grati O, et al. A Naive Lung Adenocarcinoma Harboring G1269A *ALK* Resistance Mutation. JTO Clin Res Rep 1:100047

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2020.100047

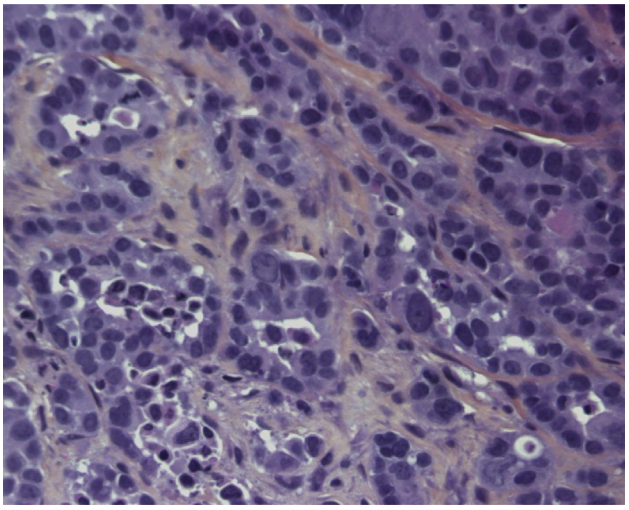

Figure 1. Hematoxylin and eosin section (×400) of poorly differentiated carcinoma of the bronchial mucosa.

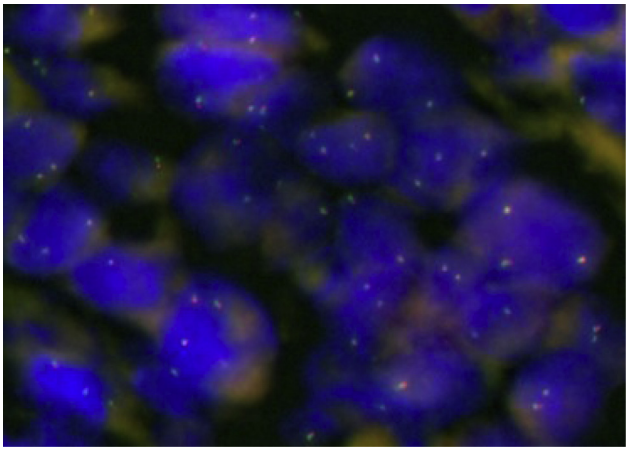

Figure 2. Fluorescence in situ hybridization (Vysis ALK break apart probe) result revealing normal (fused) ALK signals.

block crizotinib binding directly without affecting the adenosine triphosphate binding site or destabilizing the protein structure.[2]

Gly1269Ala mutation is described as a resistance mutation after progression on crizotinib therapy in NSCLC, epithelioid inflammatory myofibroblastic sarcoma,[3] and *ALK*–positive anaplastic large cell lymphoma.[4]

The tumor of this patient was aggressive and multisite metastatic at diagnosis. This uncommon clinical presentation in NSCLC may be linked to the presence of Gly1269Ala mutation.

The allelic frequencies of less than 10% in three different sites suggest the presence of aggressive somatic-mutated subclones, detected thanks to the upfront NGS analysis. To highlight unusual mutations and to better characterize primary and acquired resistance mutations, NGS analysis in naive tumors is essential. To our knowledge, this is the first report of a classical secondary resistance mutation in an ALK TKI–naive NSCLC.

Conclusions

ALK secondary resistance mutations can be present in naive tumors and may be associated with aggressive presentation. Baseline NGS screening is very important to identify uncommon mutations and improve first-line targeted therapeutic strategies.

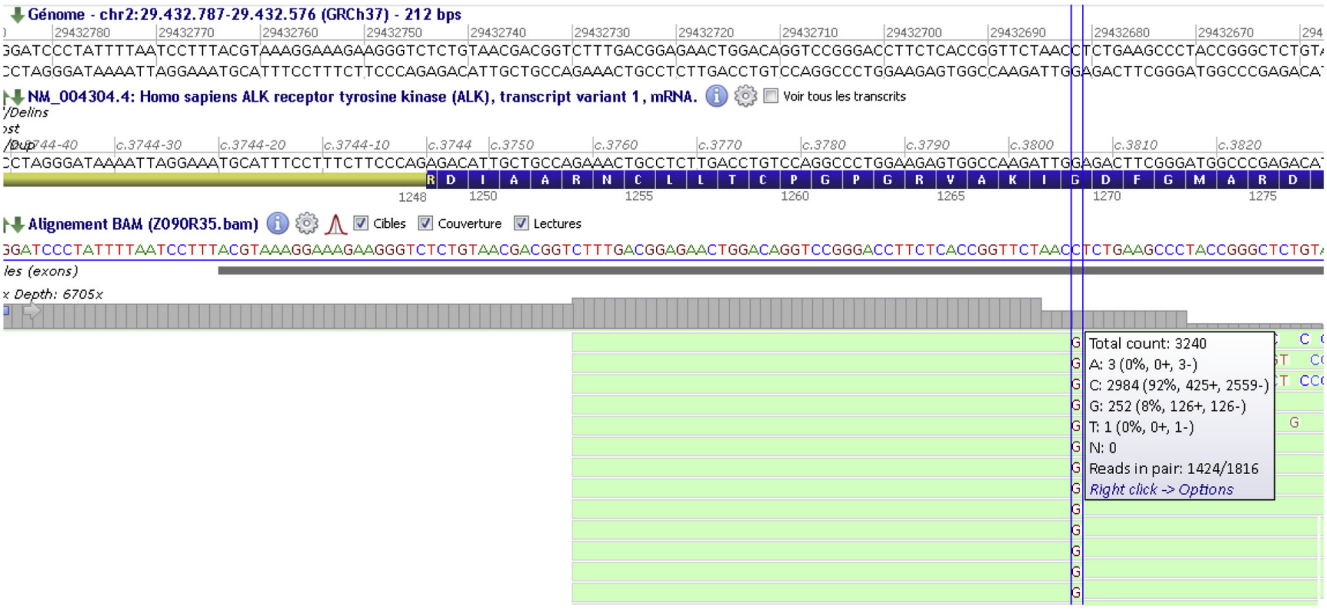

Figure 3. Binary alignment mapping data (.bam) revealing next-generation sequencing results from secondary metastatic site c.3806G>C/p.(Gly1269Ala) (8%; 3240X) mutation in *ALK* gene.

Acknowledgments

The authors thank all the following laboratory technicians: P. Portois, C. Derouet, E. Hua, A. Margogne, M. Sene, A. Curto Taribo, F. Maraone, S. Antonio, and C. Franck. Dr. Trabelsi-Grati has contributed in conceptualization, writing of the original draft, formal analysis, visualization, and final approval of the version to be submitted. Dr. El-Alam has contributed in conceptualization, writing—review and editing, visualization, and final approval of the version to be submitted. Drs. Melaabi and Allory have contributed in acquisition and interpretation of data, writing—review and editing, and final approval of the version to be submitted. Dr. Bièche has contributed in supervision, acquisition and interpretation of data, writing—review and editing, and final approval of the version to be submitted. Dr. Girard has contributed in resources, writing—review and editing, and final approval of the version to be submitted. Dr. Callens has contributed in validation, acquisition and interpretation of data, writing—review and editing, and final approval of the version to be submitted.

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