

A Case of Crizotinib-Resistant Lung Adenocarcinoma Harboring a KRAS Mutation and an EML4-ALK Fusion Gene

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Abstract

Here, we report a case of lung adenocarcinoma resistant to crizotinib harboring *KRAS* mutation and the echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) fusion gene. Our case suggests that *KRAS* mutation in addition to *EML4-ALK* fusion gene may cause the resistance to crizotinib.

Keywords: *EML4-ALK* fusion gene; *KRAS* gene mutation; Crizotinib

Introduction

The echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) fusion gene in lung cancer is mutually exclusive with epidermal growth factor receptor (*EGFR*) and *KRAS* mutations. If *EGFR* or *KRAS* gene mutations have been detected, it is unlikely that *EML4-ALK* fusion gene will be present in the same patient. Here, we describe a case of lung adenocarcinoma resistant to crizotinib harboring *KRAS* mutation and the *EML4-ALK* fusion gene.

Case Report

A 54-year-old female non-smoker underwent right middle and lower lobectomy for stage IIIA lung adenocarcinoma in Janu-

ary 2006 (Fig. 1A). The pathological diagnosis was invasive mucinous adenocarcinoma (Fig. 1B), and the patient received four cycles of platinum-based adjuvant chemotherapy. Peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method performed on formalin-fixed paraffin-embedded (FFPE) resected tumor tissue showed that the sample was negative for epidermal growth factor receptor (*EGFR*) gene mutation. However, the mutant *KRAS* codon 12 (c. 35G > A, p.Gly12Asp) was identified using direct sequencing (Fig. 2) of tissue from the same tissue block.

The patient relapsed in January 2007, presenting with multiple lung metastases, and was treated with gefitinib, docetaxel, erlotinib, S-1 and pemetrexed. Among these chemotherapies, she responded to S-1 for 6 months and to pemetrexed for 18 months. The patient requested crizotinib treatment, and we therefore assessed the presence of the *EML4-ALK* fusion gene using the same FFPE tissue block. Fluorescence *in situ* hybridization (FISH) for *ALK* rearrangements and immunohistochemistry (IHC) for *ALK* expression were both negative, but reverse transcription-polymerase chain reaction (RT-PCR) and sequencing identified variant 1 of the *EML4-ALK* fusion gene (Fig. 2). The patient received crizotinib treatment, but her disease was found to have progressed after 42 days of therapy (Fig. 3).

Discussion

EML4-ALK gene translocation was initially reported in 2007 [1]. *ALK*-positive lung cancers account for roughly 2-5% of all non-small-cell lung cancer cases [1]. The frequency of *EML4-ALK* translocation variant 1 is approximately 30% [1]. Comparison of FISH, IHC, and RT-PCR methodologies for detecting *EML4-ALK* translocation variant 1 showed RT-PCR to be the most sensitive [2], as in the current case. The presence of the *EML4-ALK* fusion gene in lung cancer is mutually exclusive with *EGFR* and *KRAS* mutations [1], and patients with *EGFR* or *KRAS* gene mutations are unlikely to also harbor the *EML4-ALK* fusion gene. However, some patients with lung adenocarcinoma with both the *KRAS* mutation and *EML4-ALK* fusion gene were reported by Martelli et al [3] and Doebele et al [4].

Although the PROFILE 1007 study reported higher response rates (65%) to crizotinib than to standard chemothera-

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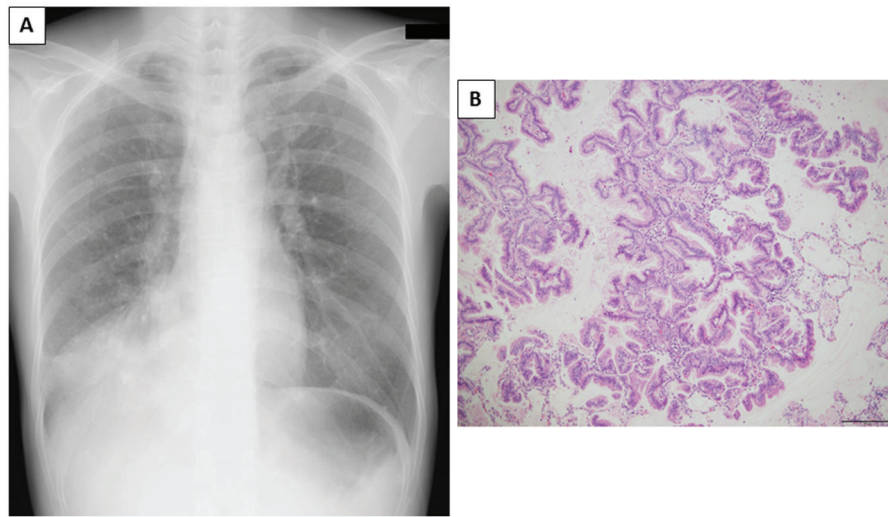


Figure 1. Chest radiography revealed a mass shadow in the right lower lung field (A). Histology of the primary tumor showed an invasive mucinous adenocarcinoma (hematoxylin and eosin stain, × 100 magnification, internal scale bar = 200 μm) (B).

py in patients with *ALK*-positive lung cancer who had received one prior platinum-based regimen [5], the current case was intrinsically refractory to crizotinib. It has been suggested that, in cases with concomitant presence of the *EML4-ALK* fusion gene and the *KRAS* mutation prior to crizotinib administration, the *KRAS* mutation might serve as a driver of crizotinib resistance [4], and cytotoxic chemotherapies may be more effective in such cases [4]. Indeed, the current patient experienced longer progression-free survival times with chemotherapies such as S-1 and pemetrexed, compared with crizotinib. This study suggests that the detection of a single driver gene mu-

tation is inadequate for patient selection, and comprehensive examination of driver gene mutations may be needed to allow personalized cancer treatment.

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Conflict of Interest

The authors have declared no conflicts of interest.

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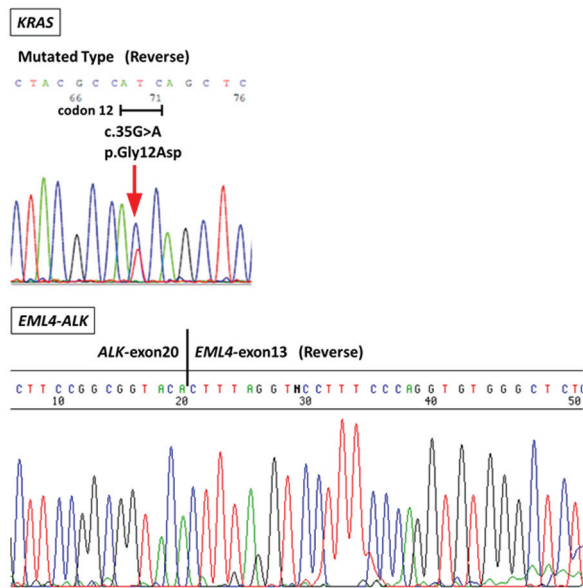


Figure 2. *KRAS* mutation of codon 12 was positive. Variant 1 of the *EML4-ALK* translocation was identified by RT-PCR and sequencing assays.

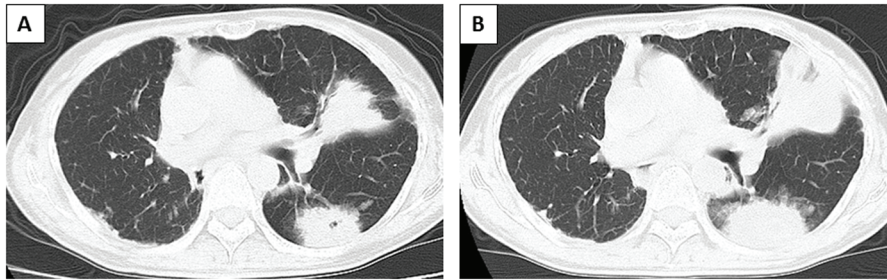


Figure 3. Comparison of computed tomography scans of the thorax before crizotinib (A), and 42 days after crizotinib treatment (B) showed tumor enlargement.

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