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 January 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-
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 mutation 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.

References

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