Case Report

Next-generation Sequencing Identified a Novel WDPCP-ALK Fusion Sensitive to Crizotinib in Lung Adenocarcinoma

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Clinical Practice Points

- Lung cancer is the leading cause of cancer-related death worldwide. Over 85% of lung cancers are classified as non–small-cell lung cancer (NSCLC), and identification of oncogenic alterations in subsets of patients with NSCLC is transforming clinical care. The majority of patients with NSCLC with an anaplastic lymphoma kinase (ALK) fusion respond well to ALK tyrosine kinase inhibitors (ALK-TKIs).
- In this case report, we present a 52-year-old female nonsmoker carrying a WD (Trp-Asp) planar cell polarity (PCP) effector gene (WDPCP)-ALK fusion who was diagnosed with lung adenocarcinoma and initially responded to first-generation ALK-TKI but later developed disease progression in association with WDPCP-ALK and C1156Y.
- The results suggest that WDPCP-ALK acts as an oncogenic driver.

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Keywords: C1156Y, Crizotinib, Next-generation sequencing, Sensitivity, WDPCP-ALK

Introduction

Anaplastic lymphoma kinase (ALK) fusion has been identified in 3% to 7% of patients with non–small-cell lung cancer (NSCLC), and such patients benefit greatly from ALK tyrosine kinase inhibitors (ALK-TKIs). The most common ALK fusion is echinoderm microtubule-associated protein-like 4 (EML4)-ALK, and several variants that are generally sensitive to crizotinib exist.[1] In recent years, other fusion types sensitive to crizotinib, such as DYSF&ITGAV-ALK, BCL11A-ALK, and BIRC6-ALK, have been discovered by next-generation sequencing (NGS).[2-6] However, a WD (Trp-Asp) planar cell polarity (PCP) effector gene (WDPCP)-ALK fusion has not been previously published. Here, we report this novel WDPCP-ALK fusion, which is sensitive to crizotinib, in a patient with lung adenocarcinoma.

Case Report

A 52-year-old woman was admitted to our hospital for a medical examination in February 2016. Computed tomography (CT) scan showed a right-lobe lung lesion in the inferior lobe. Video-assisted thoracoscopic surgery and systemic lymph node dissection were conducted to remove the primary tumor. The margin was negative, and no metastasis in the lymph nodes was found. Surgical pathology indicated an invasive adenocarcinoma, mainly belonging to the micropapillary type, and pleural invasion. The pathologic stage was pT2aN0M0, stage IB. In March 2017, CT scans showed a mass in the inferior lobe of the right lung (Figure 1A). Ultrasound-guided core needle biopsy of the right supraclavicular lymph node demonstrated lung adenocarcinoma, pathologically confirming disease recurrence. Immunohistochemistry revealed abnormal ALK protein positivity, and fluorescence in situ hybridization showed a split signal for ALK (Figure 2). Capture-based NGS (Gene Detection Panel for Target Drug of Lung Cancer, Burning Rock, Guangzhou, China) was performed on biopsy samples using a gene panel comprising 8 lung cancer-related genes (epidermal growth factor

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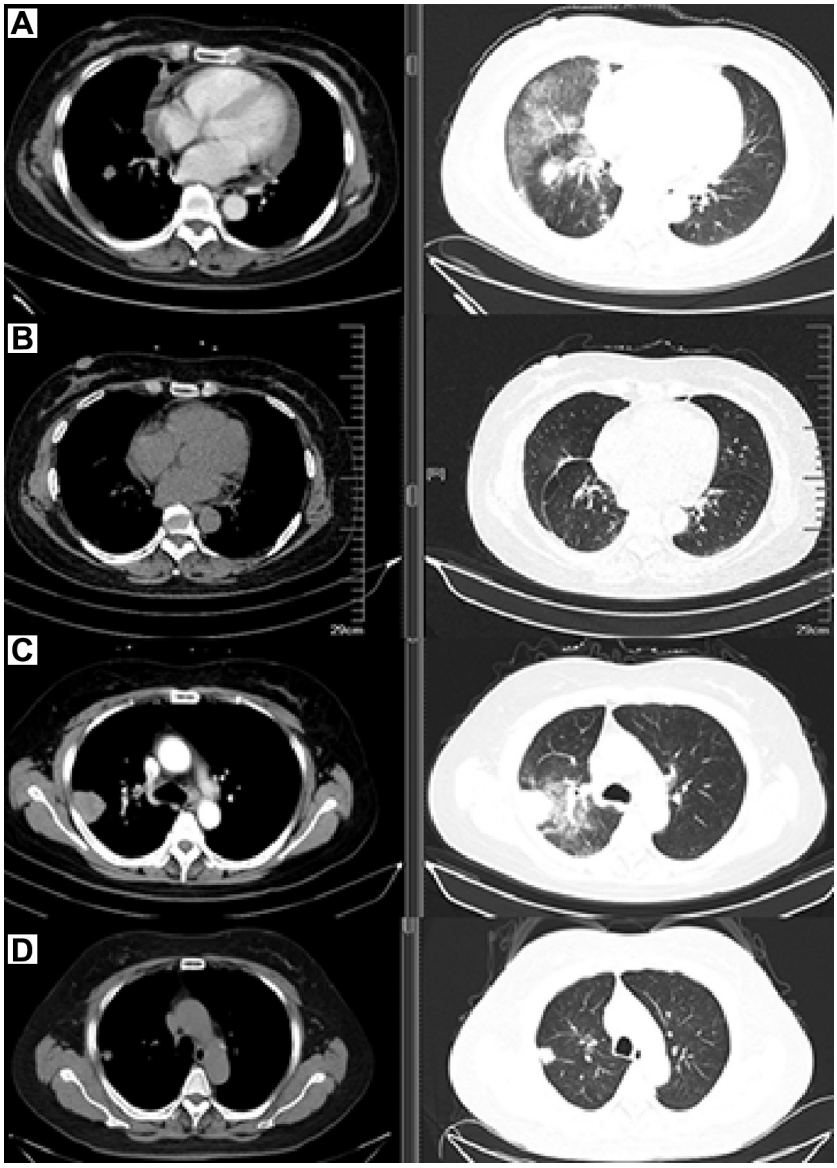
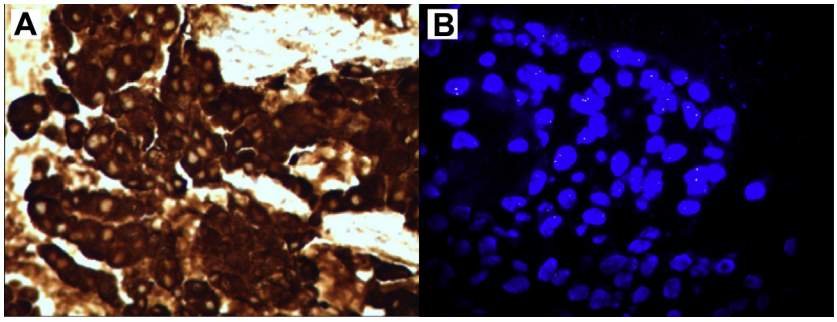
Figure 1 A, Computed Tomography (CT) Scan Showed Tumors Reproduced in the Inferior Lobe of the Right Lung. B, CT Scan After 2 Months of Crizotinib Treatment. C, CT Scan Showed a Progression of Cancer (2.5 × 3.0 cm). D, CT Scan After 4 Cycles of Pemetrexed Plus Bevacizumab



receptor [EGFR], ALK, erb-b2 receptor tyrosine kinase 2 gene [ERBB2], serine-threonine protein kinase B-RAF [BRAF], MNNG HOS transforming gene [MET], proto-oncogene 1, receptor tyrosine kinase [ROS1], ret proto-oncogene [RET], and Kirsten rat sarcoma viral oncogene [KRAS]). A novel WDPCP-ALK fusion (W17:A20) (with an abundance of 61.94%) was identified, whereby the 17th intron of WDPCP and the 19th intron of ALK were broken and rearranged (Figure 3). The fusion sequence is GGTGGAAGCATGTGGGAGCTA-GAAGTGACGTCTAGGGGTGGGGGCGAGCT<>GGGAT TACGTTAAACAACCAAACTTAAGAATAATCAGTGTTCC TGAGGAA. This ALK fusion has not been reported in tumors, and the significance of this specific mutation is not clear. Regardless, as the fusion results in an intact ALK protein tyrosine kinase domain, stimulation of ALK kinase activity may lead to sensitivity to ALK inhibitors such as crizotinib.[7]

In April 2017, the patient began crizotinib treatment (250 mg, twice daily, oral), which resulted in a partial response and an 11-month long progression-free survival (Figure 1B). However, follow-up CT scans showed that the tumor continued to grow to a maximum diameter of 30 mm (Figure 1C). Considering the possibility of drug resistance mutations, we examined the lung biopsy sample using NGS and identified both WDPCP-ALK (with an abundance of 52.6%) and C1156Y (with an abundance of 38.64%)

Figure 2 Positive Anaplastic Lymphoma Kinase Protein With Immunohistochemistry (A) and Anaplastic Lymphoma Kinase Split Signal With Fluorescence in Situ Hybridization (B)



(Figure 4). The C1156Y mutation confers resistance to crizotinib, which is the main cause of disease progression.[8]

From March to June 2018, the patient received 6 cycles of pemetrexed (500 mg/m^2 once every 3 weeks) plus bevacizumab (7.5 mg/kg once every 3 weeks) and achieved a partial response (Figure 1D). There was no significant cancer progression until November 2018.

Discussion

Tumor targeting has become a common modality in the field of cancer treatment. Identifying biomarkers for selecting patients who may benefit from a targeted drug is key to such treatment. NGS is increasingly being applied for analyzing tumor biopsy samples, and a wide range of potential targeted mutations have been identified. These rare mutations characterize NSCLC and may represent vital oncogenic drivers.

To the best of our knowledge, this is the first report of this rare somatic WDPCP-ALK fusion. WDPCP (WD planar cell polarity), the gene for which is located on human chromosome 2, is known to play essential roles in organogenesis during embryonic development through regulation of collective cell movement; WDPCP also functions in ciliogenesis. The patient with NSCLC harboring this WDPCP-ALK fusion showed a partial response to the ALK inhibitor crizotinib. WDPCP-ALK may be considered an oncogenic fusion gene, and it should be added to the list of ALK fusion genes.

An increasing number of ALK alteration rearrangements, including point mutations and genomic amplification, have been detected using NGS-based techniques, and preclinical and early clinical trials are constantly exploring potential targets and new treatment options. Individualized and precise treatment based on molecular biology will be the target and direction of future treatments.[9,10]

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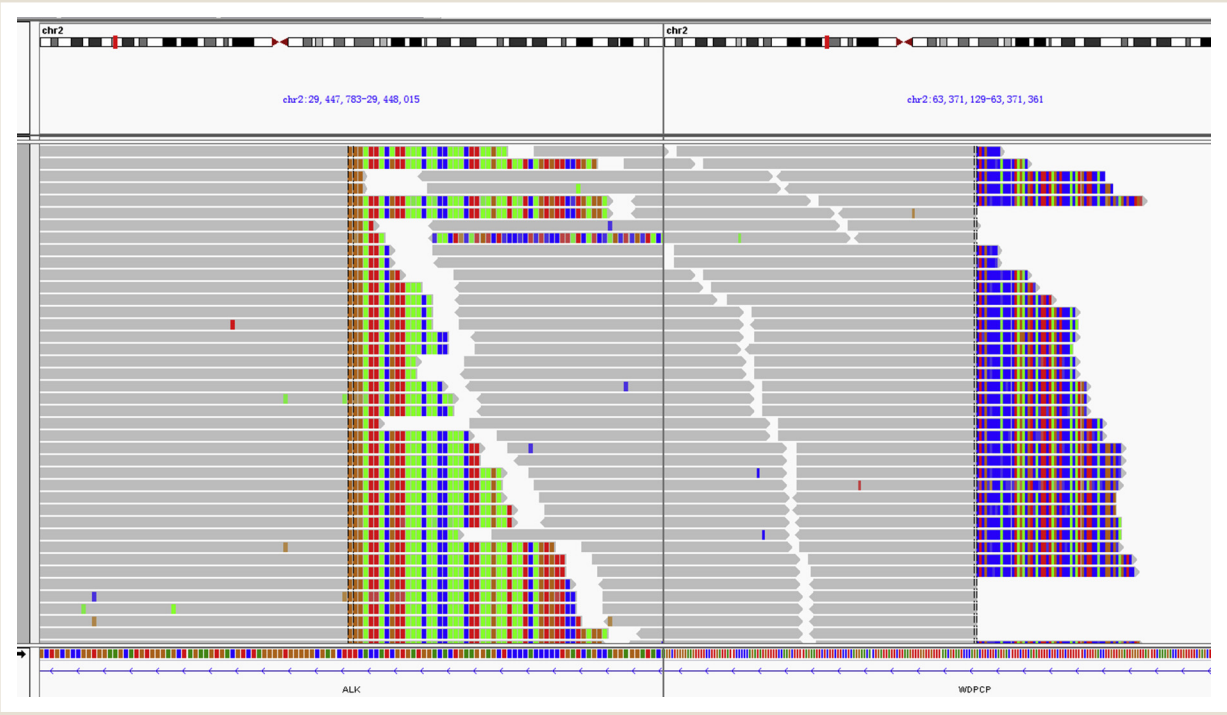
Figure 3 A Novel WDPCP-ALK Fusion Was Identified by Next-generation Sequencing

Abbreviations: ALK = anaplastic lymphoma kinase; WDPCP = WD planar cell polarity effector gene.

Figure 4 WDPCP-ALK Fusion and C1156Y-ALK Were Identified by Next-generation Sequencing



Abbreviations: ALK = anaplastic lymphoma kinase; WDPCP = WD planar cell polarity effector gene.

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Disclosure

The authors have stated that they have no conflicts of interest.

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