Case Reports

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A novel *GHR-ALK* fusion gene in a patient with metastatic lung adenocarcinoma and its response to crizotinib: a case report

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Abstract

Anaplastic lymphoma kinase (*ALK*) rearrangement occurs in approximately 5% of non-small cell lung cancers (NSCLCS), and *EML4-ALK* is the most commonly observed ALK fusion variant in NSCLC. However, growth hormone receptor (*GHR*) as the fusion partner for *ALK* and the clinical response to ALK tyrosine kinase inhibitors in patients with metastatic lung adenocarcinoma (LUAD) who carry the *GHR-ALK* variant have not been documented. This case describes a 63-year-old woman diagnosed with metastatic LUAD. Immunohistochemistry revealed positive *ALK* expression, and the patient was treated with crizotinib. After 3 weeks of treatment, the patient had a partial response. Because of treatment-related adverse events, the dose of crizotinib was reduced. After 3.7 months, computed tomography uncovered disease progression. Next-generation sequencing identified a novel *GHR-ALK* fusion in the plasma of the patient. The patient was treated again with crizotinib, but the disease progressed again 2 months later. Then, the patient received chemotherapy. She succumbed to her disease 11 months after the initial diagnosis. Our work provides evidence supporting the use of crizotinib in patients with metastatic LUAD harboring *GHR-ALK*.

Keywords

GHR-ALK, lung cancer, crizotinib, case report, metastasis, fusion gene, tyrosine kinase inhibitor

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Introduction

Anaplastic lymphoma kinase (*ALK*) rearrangement occurs in 5% of all non-small-cell lung cancers (NSCLCs).[1] The ALK tyrosine kinase inhibitor (TKI) crizotinib has been approved for the treatment of patients with *ALK* rearrangement-positive NSCLC. *EML4* is the most common fusion partner for ALK.[1] Approximately 20 *ALK* fusion partners have been reported in NSCLCs, such as *EML4*, *KIF5B*, *HIP1*, *STRN*, and *SQSTM1*.[2] Previous studies demonstrated that most of these *ALK* fusion variants in NSCLCs respond to crizotinib. A prior study indicated that *CMTR1-ALK* does not respond to crizotinib.[3] In this study, we presented growth hormone receptor (*GHR*) as a novel *ALK* fusion partner in a patient with NSCLC and described her response to crizotinib.

Case report

This case report was prepared according to the CARE Guidelines,[4] and the protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University. A 63-year-old woman presented with cough, chest tightness, and hemoptysis on April 17, 2018. The treatment history of the patient is summarized in Figure 1. Chest computed tomography (CT) revealed a mass located in the lower lobe of the left lung, enlarged mediastinal lymph nodes, and the emergence of bilateral pleural effusion (Figure 2a). In addition, she underwent lung biopsy during fiberoptic bronchoscopy. Transbronchial biopsy revealed *ALK* immunohistochemistry-positive LUAD (Figure 3a). Whole-body positron emission tomography combined with bone CT disclosed multiple metastases to bone, and abdominal ultrasound identified suspected liver metastases. The patient was newly diagnosed with *ALK*-positive stage IVB (cT4N3M1c) LUAD on April 28, 2018.

The patient was initially treated with crizotinib at a dose of 250 mg twice daily starting on April 28, 2018. Chest CT revealed regression of the left lung lesion and mediastinal lymph nodes, and complete remission based on an analysis of bilateral pleural effusion was achieved after 3 weeks of crizotinib treatment (Figure 2b). The efficacy was evaluated as a partial response (PR). She presented with treatment-related adverse events, including grade 2 nausea, emesis, and diarrhea. The dosage of

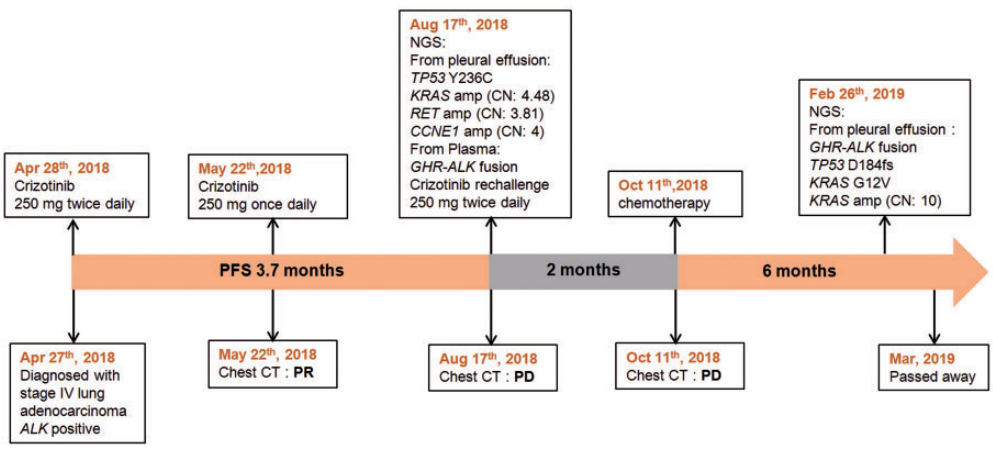

Figure 1. Diagram of the course of disease management.

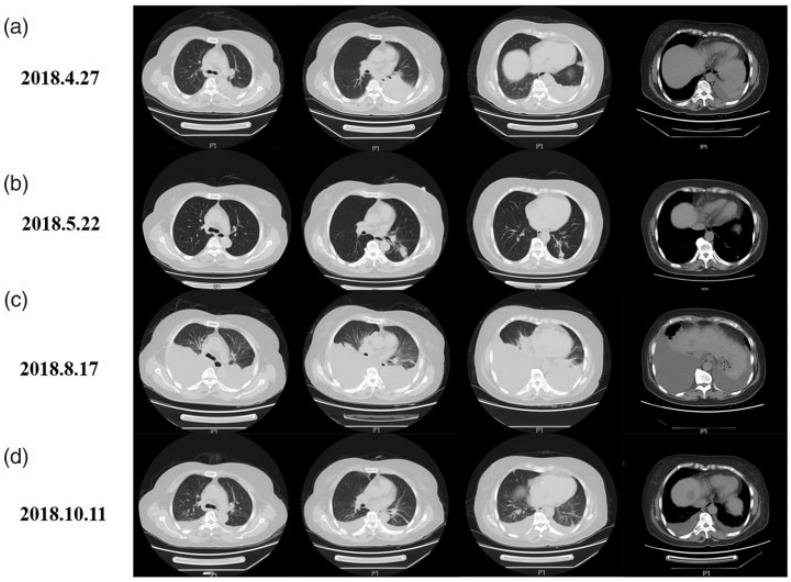

Figure 2. CT findings of the patient before and after therapy. (a) Baseline CT at diagnosis. (b) CT after 3 weeks of crizotinib treatment. (c) CT revealed progress disease after 3 months of reduced-dose crizotinib treatment. (d) CT after 2 months of crizotinib rechallenge.
CT, computed tomography.

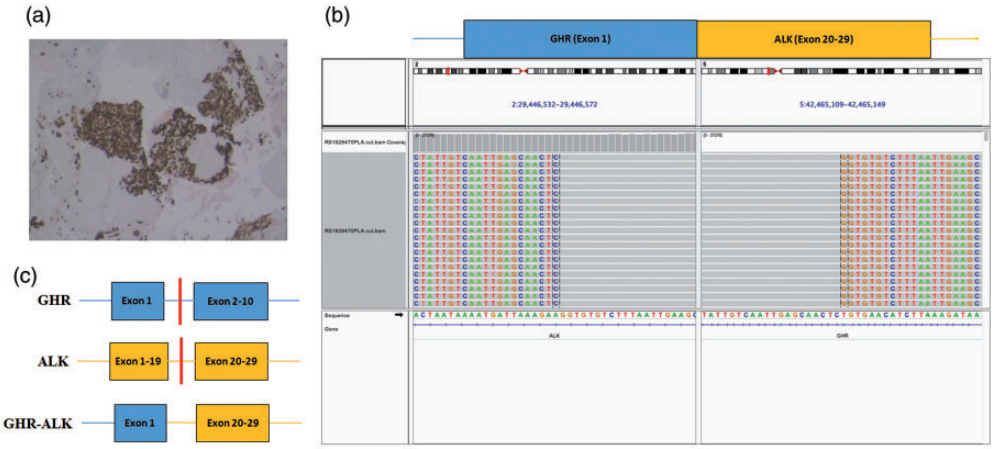

Figure 3. (a) Immunohistochemical analysis revealing *ALK*-positive cells. (b) The fusion pattern of *GHR-ALK*. (c) *GHR-ALK* fusion pattern identified by targeted next-generation sequencing.
ALK, anaplastic lymphoma kinase; GHR, growth hormone receptor.

crizotinib was subsequently reduced to 250 mg once daily on May 22, 2018. Chest CT revealed an enlarged left lung lesion and recurrent massive bilateral pleural effusion, and progressive disease (PD) was identified (Figure 2c) on August 17, 2018 (progression-free survival [PFS] = 3.7 months). Follow-up capture-based next-generation

sequencing (NGS) was performed on pleural effusion and plasma using a panel covering 168 cancer-related genes (Burning Rock Biotech, Guangzhou, China). The NGS results revealed the emergence of the *GHR-ALK* fusion in plasma. *TP53* mutation, *KRAS* amplification, *RET* amplification, and *CCNE1* amplification were detected in pleural effusion (Table 1). The *GHR-ALK* fusion transcript was generated by exon 1 of *GHR* and exons 20 to 29 of *ALK*, the latter of which encodes the entire tyrosine kinase domain of *ALK* (Figure 3b and 3c). She was treated again with crizotinib at a dose of 250 mg twice daily starting on August 17, 2018. Chest and abdominal CT revealed contralateral lung metastasis and enlarged metastatic liver tumors after another 2 months of crizotinib treatment (Figure 2d). The response assessment was PD. Crizotinib was discontinued and switched to platinum-based doublet chemotherapy in combination with bevacizumab. When the patient displayed PD despite chemotherapy on February 26, 2019, her pleural effusion was subjected to NGS. The result confirmed the uncommon *GHR-ALK* fusion in this patient (Table 1). She died 11 months after the primary diagnosis.

Written informed consent for treatment was obtained from the patient. Written informed consent for publication of this case was obtained from a relative of the patient. All patient details have been de-identified.

Discussion

Our work identified *GHR* as a novel *ALK* fusion partner in a patient with NSCLC. This study also presented the first clinical evidence of a patient with metastatic LUAD harboring the *GRH-ALK* variant who benefited from crizotinib.

ALK rearrangements have been discovered in a variety of human cancers, such as diffuse large B cell lymphoma, inflammatory myofibroblastic tumor, and NSCLC.[5] *ALK* fusion leads to the constitutive activation of ALK and downstream signaling pathways that drive tumorigenesis.[6] A series of ALK inhibitors such as crizotinib, alectinib, brigatinib, ceritinib, and lorlatinib have been developed to target ALK and prolong the survival of patients with *ALK* fusion-positive NSCLC.[7] *EML4-ALK* is the most common *ALK* rearrangement in NSCLC,[1] and a variety of *ALK* fusion partners have been identified.[8]

Table 1. Next-generation sequencing targeting 168 cancer-related genes using plasma and pleural effusion samples from the patient.

Gene alteration	8-23-2018 Plasma allele frequencies	8-23-2018 Pleural effusion allele frequencies	2-26-2019 Pleural effusion allele frequencies
GHR-ALK fusion	0.38%	–	5.21%
KRAS amplification	–	Copy number = 4.48	Copy number = 10.0
TP53 p.Y236C	–	91.94%	–
RET amplification	–	Copy number = 3.81	–
CCNE1 amplification	–	Copy number = 4	–
KRAS p.G12V	–	–	5.57%
TP53 p.D184fs	–	–	3.98%

–, tested negative for the indicated alteration.

GHR, growth hormone receptor; *ALK*, anaplastic lymphoma kinase; *KRAS*, KRAS proto-oncogene, GTPase; *TP53*, tumor protein p53; *RET*, RET proto-oncogene; *CCNE1*, cyclin E1.

High-throughput sequencing technology increases the ability to identify new *ALK* fusion partners. We identified a novel *GHR-ALK* fusion in a patient with LUAD using capture-based targeted NGS. Previous studies demonstrated the benefits of crizotinib in both *EML4-ALK* fusion and non-*EML4-ALK* fusion-positive NSCLC populations, and there were no statistically significant differences in PFS and overall survival between these two groups.[9] A PR was achieved in the present case after 3 weeks of crizotinib treatment, and PFS was 3.7 months, which was much shorter than the median PFS of 10.9 months reported in *ALK*-positive NSCLC.[10] The shorter PFS might be attributable to several factors. First, dosage of crizotinib was reduced because of intolerant crizotinib-related adverse events. Second, *KRAS* amplification was detected in pleural effusion after the failure of crizotinib treatment, which might have contributed to the mechanism of acquired crizotinib resistance.[11] Moreover, concomitant *TP53* mutation may also lead to reduced responses and worse prognosis to crizotinib in *ALK* rearrangement-positive NSCLC.[12]

There were some limitations associated with our study. Because of sample contamination with diagnostic tissue, we could not validate the existence of the *GHR-ALK* fusion in the primary tumor tissue through NGS. However, according to the positive *ALK* expression in the diagnostic tumor tissue detected by immunohistochemistry and the detection of the *GHR-ALK* fusion in plasma and pleural effusion by NGS, we speculate that *GHR-ALK* was a primary fusion in this patient. Clinical trials are also needed to validate the efficacy of crizotinib for patients with metastatic LUAD harboring *GHR-ALK*.

In summary, we reported a novel *GHR-ALK* fusion in a patient with metastatic NSCLC. We also demonstrated a clinical benefit from crizotinib as the first-line treatment. Our work provided clinical options for the treatment of *GHR-ALK* rearrangement-positive metastatic NSCLC.

Ethics statement

Written informed consent was obtained for publication of this case report and any accompanying images in an anonymized manner.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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