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). 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. Approximately 20 ALK fusion partners have been reported in NSCLCs, such as EML4, KIF5B, HIP1, STRN, and SQSTM1. 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. 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, 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.
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 (progression-free survival \( \text{PFS} = 3.7 \) 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 GHR-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. 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. 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. Moreover, concomitant TP53 mutation may also lead to reduced responses and worse prognosis to crizotinib in ALK rearrangement-positive NSCLC.

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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