Case Report

Ling Deng, Panwen Tian, Zhixin Qiu, Ke Wang*, Yalun Li*

A novel SLC8A1-ALK fusion in lung adenocarcinoma confers sensitivity to alectinib: A case report

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Abstract: ALK fusion genes are diverse. Approximately 30 different ALK fusion protein partners have been described previously, and some of these fusion proteins have been reported to be effective against ALK-tyrosine kinase inhibitor (TKI). ALK rearrangements often occur at a common breakpoint in exon 20 of the genome. SLC8A1-ALK, a novel fusion protein partner, comes from exon 2 of the SLC8A1 gene rearranged with exon 20 of the ALK gene. Here, we reported a patient with advanced lung adenocarcinoma harboring a SLC8A1-ALK fusion who benefited from first-line treatment with alectinib. After 2 months of taking alectinib, the targeted lung lesions and intrahepatic metastases regressed significantly. To date, the patient has achieved nearly 1 year of progression-free survival while taking the drug. Given the diversity of ALK fusion genes and the different efficacy of ALK-TKIs, we believe that this case report has an important clinical reference.

Keywords: lung adenocarcinoma, SLC8A1-ALK, ALK fusion protein partners, alectinib

1 Introduction

The anaplastic lymphoma kinase (ALK) gene is located on the short arm of chromosome 2 (2p23), and it is a member of the insulin receptor superfamily that encodes the ALK protein. ALK gene rearrangement is a driver mutation underlying the development of non-small-cell lung cancer (NSCLC) that has been identified in 5–6% of cases [1]. ALK rearrangements are more prevalent in Asian populations of female nonsmokers [2]. Although the incidence of ALK rearrangement is low, 60% of patients respond well to ALK-tyrosine kinase inhibitors (TKIs). The most common ALK fusion partner in NSCLC is EML4-like 4 (EML4)-ALK (88.9%). ALK fusion with some rare genes has also been reported [3,4]. Although ALK fusion genes have a high response rate to ALK-TKIs in patients with NSCLC, some patients with rare ALK fusions have been reported to be non-responders to ALK-TKIs [5]. Zhu and He [6] reported a case of a nonsmoking male with lung adenocarcinoma who was found to be SLC8A1-ALK fusion gene positive and developed resistance to treatment with crizotinib for 9 months. Given the differences in patient response to targeted ALK inhibitors for the treatment of lung adenocarcinoma, the genomic heterogeneity of ALK rearrangements has received considerable attention in recent years. So, the exploration of novel forms of ALK fusion and their association with tumor sensitivity to drugs remains essential. Here, we described a patient with advanced lung adenocarcinoma with a rare ALK gene fusion, SLC8A1-ALK, which was sensitive to alectinib.

2 Case report

A 41-year-old Chinese female nonsmoker presented to our hospital with hoarseness that had persisted for 2 months. The chest computed tomography (CT) scan showed a 5.3 cm × 5.1 cm mass in the left upper lobe with metastases
to the left pulmonary artery, bilateral intrapulmonary, mediastinal, and bilateral cervical lymph nodes, liver, and multiple bones. The patient underwent fibreoptic bronchoscopy and received a pathological diagnosis of stage IVB adenocarcinoma. The immunohistochemical analysis revealed positive expression for CK7, thyroid transcription factor 1 (TTF-1), and negative expression of P63, CK5/6, indicating an adenocarcinoma origin of the lung tumor. Besides, there was a positive staining for ALK-V and a negative staining for ROS-1 expression (Figure 1). The patient’s tumor tissues were subjected to next-generation sequencing at the DNA level based on 61 genetic panels on biopsy specimens (Nova-Seq 6000, Illumina Corporation), which revealed a rare ALK rearrangement, SLC8A1-ALK (allele frequency = 10.39%) (Figure 2a and b). Treatment with alectinib (600 mg twice daily) was initiated in February 2021. After 2 months of this therapy, CT scans were repeated, and the images showed that the lesions had obviously decreased in size to 1.9 cm × 1.7 cm (Figure 3). The tumor invasion of the left pulmonary artery and the intrahepatic metastatic lesions were also reduced. The patient was considered to have achieved partial remission (PR) according to the Response Evaluation Criteria in Solid Tumours 1.1. Patient maintains PR efficacy for 1 year after taking the drug. To date, the patient continues to take alectinib and no serious adverse effects have been observed.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations and institutional policies and in accordance with the tenets of the Declaration of Helsinki and has been approved by the Ethics Committee of West China Hospital.

### Discussion

Approximately 30 different ALK fusion protein partners have been described, and SLC8A1 is a rare partner for ALK. So far, Zhu and He. [6] reported a case of a non-smoking male with lung adenocarcinoma who was found to be SLC8A1-ALK fusion gene positive by second-generation gene sequencing. This patient was selected for crizotinib as a first-line treatment option and achieved a progression-free survival (PFS) of 9 months. Following the development of resistance to crizotinib, treatment with alectinib was initiated. It can be boldly speculated that not only does the ALK fusion pattern affect the response to ALK-TKI treatment, but the same ALK fusion pattern may respond very differently to different types of

![Figure 1: Histological findings (40× magnification). (a) Hematoxylin and eosin-stained biopsy specimen reveals adenocarcinoma; (b) immunohistochemical analysis showing ALK-positive staining; (c) keratin 7 (CK7)-positive staining; and (d) thyroid transcription factor-1 (TTF-1)-positive staining. Scale bars represent 50 μm.](image)
Figure 2: (a) Sequencing reads of ALK and SLC8A1 are shown by the Integrative Genomics Viewer. SLC8A1 and ALK both located on chromosome 2, the two genes translocation leading to a new fusion oncogene SLC8A1-ALK. (b) Schematic structure of the genomic DNA sequence shows fusion points for the SLC8A1-ALK fusion gene. Exon 2 of the SLC8A1 gene rearranged with exon 20 of the ALK gene.

Figure 3: Lung adenocarcinoma shown by radiologic. Dynamic imaging of CT scan of patients treated with alectinib showing target lesions, mass invasion of the left pulmonary artery and response of liver metastases at baseline, 2 and 4 months of treatment.
### Table 1: The clinical characteristics of patients with NSCLC harboring rare ALK fusions

| Article | Age/gender | Smoking status | Histologic type | ALK fusion gene | Rebiopsy specimen | Technique | ALK TKIs | Response |
|---------|------------|----------------|----------------|-----------------|-------------------|-----------|----------|----------|
| Hao Lin, et al., 2018 | 56/M | Never | AC | ALK, FBXO11-ALK | Lung | NGS | Crizotinib | PR |
| SLMAP, ALK | Lung | NGS | Crizotinib, alectinib | PR |
| Jing Luo, et al., 2019 | 44/M | Former | AC | EML4, PRKCB-ALK | Lung | NGS | Crizotinib | PR |
| Tingting Feng, et al., 2019 | 49/F | Never | AC | TNIP2-ALK | Lung | NGS | Crizotinib | PR |
| Bao-Dong Qin, et al., 2019 | 29/M | Former | AC | ALK, BCL11A-ALK | Bronchial | NGS | Crizotinib | PR |
| Chunhua Zhou, et al., 2019 | 43/M | Former | AC | STRN-ALK | Liver | NGS | Geftinib, crizotinib | PR |
| Jiang, EML4 | Lung | NGS | Crizotinib | PR |
| Ming Zhong, et al., 2020 | 60/M | Unknown | AC | ALK, BIRC6-ALK | Lung | NGS | Alectinib | PR |
| Hua, SOS1 | Lung | NGS | Crizotinib | PR |
| fei Chen, et al., 2020 | 52/M | Unknown | AC | ALK | Lung | NGS | Crizotinib | PR |
| Xingyu Zhu and He, 2021 | 62/M | Never | AC | SLC8A1-ALK | Lung | NGS | Crizotinib, alectinib | PR |
| Hao Zeng, et al., 2021 | 70/M | Never | AC | KIF5B-ALK | Lung | NGS | Crizotinib, alectinib | PR |
| Present patient | 41/F | Never | AC | SLC8A1-ALK | Lung | NGS | Alectinib | PR |

**Notes:**
- ALK fusion in lung adenocarcinoma confers sensitivity to alectinib.
- ALK-TKI therapy. Of course, this requires more clinical data to discover and summarize the patterns.
- Both alectinib and crizotinib were recommended as category 1 agents for first-line therapy in patients with ALK-positive NSCLC in the National Comprehensive Cancer Network (NCCN) guidelines, version 5. 2018 [7], but alectinib is preferred [7]. Alectinib is a highly selective ALK inhibitor that inhibits the activation of ALK fusion proteins and thus acts as an anti-tumor agent. The treatment with alectinib showed a survival benefit in terms of both the median PFS rate and safety compared with crizotinib in three randomized phase III studies [8]. It has also been previously reported in the literature that crizotinib is highly effective for treating typical or atypical ALK gene fusion positive for advanced NSCLC; however, few cases of observed efficacy with aletinib have been reported. We administered aletinib to the patient and so far have achieved 1 year of sustained remission. Compared with the report by Zhu and He., this suggests that PFS with first-line treatment with aletinib may be superior to crizotinib in patients with SLC8A1-ALK fusion lung adenocarcinoma.

The most common form of mutation in the ALK gene is gene translocation with another partner gene, which results in a fusion oncogene. ALK rearrangement produces ALK tyrosine kinase, which activates downstream signaling pathways and the underexpression of the SLC8A1 gene, which leads to the dysregulation of calcium-dependent signaling pathways that promote cell proliferation and migration and inhibit cell death [8,9]. In the current case, exon 2 of the SLC8A1 gene rearranged with exon 20 of the ALK gene to form a new fusion gene, SLC8A1-ALK. Novel ALK fusion proteins promote cell proliferation by activating the RAS-MAPK and JAK-STAT downstream signaling pathways through dimerization [10]. Based on the results of available studies, the SLC8A1-ALK fusion is considered to be tumorigenic. Our patient with this newly identified SLC8A1-ALK fusion benefited from alectinib treatment. We summarized the clinical characteristics of patients with NSCLC harboring rare ALK fusions in Table 1.

### 4 Conclusion

The significance of this case report is to report not only a novel SLC8A1-ALK fusion in a lung adenocarcinoma patient but also the follow-up of this patient’s treatment with alectinib. It can provide a useful reference for the treatment of patients with ALK driver-positive lung adenocarcinoma.
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Conflict of interest: Authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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