SDK1-ALK Fusion in a Lung Adenocarcinoma Patient With Excellent Response to ALK Inhibitor Treatment: A Case Report

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Background: Rearrangements of Anaplastic lymphoma kinase (ALK) have been discovered as a novel driver mutation in patients with non–small-cell lung cancer (NSCLC). Patients’ responses to ALK tyrosine kinase inhibitors (TKIs) may vary depending on the variations of ALK rearrangements they have. It is imperative for clinicians to identify druggable ALK fusions in routine practice.

Case Presentation: In this study, we discovered a rare ALK rearrangement type (SDK1–ALK) in a Chinese lung adenocarcinoma patient who responded well to ALK inhibitor SAF-189s. The positive expression of ALK in lung biopsy tissue was verified by IHC analysis. A new SDK1-ALK fusion was discovered using NGS. The patient was treated with SAF-189s (160 mg per day) as a first-line therapy and went into continuous remission, with a 12 months progression-free survival at the last follow-up.

Conclusion: This is the first case of SDK1-ALK fusion with an excellent response to an ALK inhibitor, which will provide better understanding of ALK-TKI applications for NSCLC patients with ALK fusion in the future.

Keywords: non–small-cell lung cancer, ALK rearrangement, ALK inhibitor, SAF-189s, SDK1-ALK

INTRODUCTION

Anaplastic lymphoma kinase (ALK) rearrangements account for approximately 5% of patients with non–small-cell lung cancer (NSCLC) and represent as a critical therapeutic target in clinical practice (1). Patients with ALK rearrangements in NSCLC are usually younger and light smokers. ALK tyrosine kinase inhibitors (TKIs) provide a marked objective response rate (ORR) and impressive clinical benefit for patients with ALK-rearranged lung cancer. The first-generation ALK inhibitor was crizotinib, developed after the discovery of chromosomal rearrangement involving the ALK and echinoderm microtubule-associated protein like 4 (EML4) genes in NSCLC in 2007. Second-generation inhibitors including ceritinib, alectinib, and brigatinib, were authorized for treatment in ALK-positive patients after then. As third-generation inhibitors, lorlatinib and ensartinib have been developed for the treatment of NSCLC patients who have acquired resistance to prior ALK inhibitor
treatment (2). In 2021, the FDA has expanded the approval for lorlatinib to include an new indication for the first-line treatment of patients with ALK-positive NSCLC (3). In our case, SAF-189s is a new ALK inhibitor that has the ability to overcome various resistance mutations.

Numerous ALK fusion partner genes, such as EML4 (94%), KIF5B (1.6%), and other variants (4.7%), have been identified with the rapid development and application of next-generation sequencing (NGS) (4). For patients who are using ALK inhibitors, distinct fusion patterns are linked to varying clinical outcomes (5). It is imperative for clinicians to delineate a “response diagram” of patients with unknown ALK fusion variants treated with ALK inhibitors. Here, we describe an undocumented ALK rearrangement (SDK1-ALK fusion) in a lung adenocarcinoma patient who exhibited a remarkable response to SAF-189s.

CASE PRESENTATION

In December 2020, a 47-year-old man with a history of smoking came to our hospital with a paroxysmal dry cough that had lasted about a year and left subcostal pain for two months, which aggravated after deep inhalation. A computed tomography (CT) scan revealed a mass in the left lower lobe measuring 8.1 × 6.1 cm, multiple enlarged lymph nodes in left hilum and mediastinum, obstructive pneumonia in the left lung, and left pleural effusion. Radionuclide bone scan and magnetic resonance imaging revealed no evidence of bone or brain metastasis. His medical history was not remarkable. The pathology of this patient’s lung cancer was verified through a CT-guided percutaneous fine-needle lung biopsy. According to the American Joint Committee on Cancer Staging Manual, 8th edition, he was finally diagnosed with stage IV lung adenocarcinoma (cT4N2M1). The biopsy specimen was subjected to next-generation sequencing (NGS), which revealed a hitherto unknown SDK1 Exon36-ALK Exon20 fusion variant (abundance: 9.2%) (Figure 1A). Further immunohistochemical (IHC) analysis indicated the positive expression of ALK protein (clone D5F3, Ventana) (Figure 1B).

It is well known that ALK inhibitors, such as Crizotinib and alectinib, are price. If the patient had maintained his treatment, he would have been in serious financial trouble. SAF-189s is a new selective ALK inhibitor, and the patient satisfied all of the criteria for clinical trial inclusion. He provided informed permission. On January 13, 2021, the patient was then enrolled onto a phase I/II clinical trial evaluating SAF-189s in NSCLC (Clinical Trials.gov number, NCT00585195) after a thorough enrollment assessment and began with oral administration of SAF-189s at a dose of 160 mg per day. After 10 days of medication, his symptoms considerably improved. On February, 2021, done 2 months after treatment initiation, a chest CT scan revealed a partial response (42 percent reduction in the sum of the target lesion’s longest diameters per RECIST 1.1) (Figure 1C), and further radiological assessments confirmed his continuing tumor response to this ALK inhibitor. At the time of the latest follow-up, he tolerated well with only grade 1 rash and had a 12-month progression-free survival (Figure 1D). Now he continues to be in partial response and keeps on SAF-189s treatment.

DISCUSSION

ALK fusions are more common in patient with younger age and light or never smoking history. Like epidermal growth factor receptor (EGFR) mutations that were frequently found in female and adenocarcinoma patients, ALK gene aberrations are routinely found in patients with adenocarcinoma histological subtype. Remarkably, brain metastases are more likely to be found in this subset of patients (6). Many researchers focused on the heterogeneous response mechanism of EGFR-mutated NSCLC patients during EGFR-TKI treatment as the significant proportion of EGFR-positive cases in NSCLC. In patients with ALK-rearranged lung cancer, little is known regarding the effectiveness and relevant mechanism of ALK-TKIs. Firstly, different ALK fusion partners resulted in different levels of ALK expression and protein stabilities, which may be interpreted as different ALK-TKI sensitivities in individuals (7, 8). Secondly, the signaling networks activated by ALK are intricate due to the various alterations found in individuals. Phosphorylated ERK and STAT3 levels were found to be upregulated in EML4-ALK-positive cell lines. Delineation of the extensive ALK signaling network is critical for the development of ALK inhibitor-based combination therapies.

A number of biomarkers should be tested on account of the incredible accomplishment of precision medicine improving NSCLC patients’ outcomes significantly. Patients with advanced-stage NSCLC always have a limited amount of tissue for molecular analysis. NGS is a valid approach able to detect sufficient gene alterations simultaneously, and it can be started with nucleic acids recovered from patients’ cancer tissues in situ or liquid biopsy samples. According to the KWAY Italian multicenter cost evaluation research, the implementation of NGS saves personnel time spent to testing activities and lowers the overall cost of testing per patient (9, 10). Fluorescence in situ hybridization and IHC are gold standards for ALK mutation testing, NGS further identify the complex ALK rearrangement in NSCLC, which can be an effective complement in clinical decision-making and an efficient approach to find novel variants and fusion partners (11).

In this case, NGS was used for the identification of an uncommon SDK1-ALK fusion in a patient with lung adenocarcinoma for the first time. SDK, encoded by the Sidekick gene was initially discovered in Drosophila, which is one of the largest members in immunoglobulin superfamily (12). Sidk1 and Sidk2 are vertebrate ortholog of Sidk. Genome-wide studies revealed that SDK1 polymorphism is related to neurological disorders (13, 14). Reports clarified that the SDK gene is extremely fragile, and that SDK mutations can be found in a variety of human cancers (15, 16). Ren et al. found that SDK1-AMACR fusion might be a crucial factor in progression of
A Chinese patient with adenocarcinoma harboring a novel SDK1-ALK fusion variant exhibited excellent response to ALK inhibition. (A) The schematic diagram. (B) IHC showed the positive expression of ALK protein. Cancer cells showed an uneven stippled cytoplasmic and perimembranous staining pattern. (C) Compared with the baseline images, the size of the lesion in the left lower lobe, as well as lymph nodes in left hilum and mediastinum was significantly reduced after this patient was treated with SAF-189s for 1 month, 2 months, and 4 months. (D) The timeline diagram of this case. At the time of the latest follow-up, he tolerated well with only grade 1 rash and had a 12-month progression-free survival. Now he continues to be in partial response and keeps on SAF-189s treatment.

FIGURE 1 | A Chinese patient with adenocarcinoma harboring a novel SDK1-ALK fusion variant exhibited excellent response to ALK inhibition. (A) The schematic diagram. (B) IHC showed the positive expression of ALK protein. Cancer cells showed an uneven stippled cytoplasmic and perimembranous staining pattern. (C) Compared with the baseline images, the size of the lesion in the left lower lobe, as well as lymph nodes in left hilum and mediastinum was significantly reduced after this patient was treated with SAF-189s for 1 month, 2 months, and 4 months. (D) The timeline diagram of this case. At the time of the latest follow-up, he tolerated well with only grade 1 rash and had a 12-month progression-free survival. Now he continues to be in partial response and keeps on SAF-189s treatment.
prostate cancer (17). The specific function of SDK1 in NSCLC
still needs further study. The homophilic binding of Sdk1
ectodomain regions is required for cell-cell aggregation (18).
Mutations in SDK1 gene have been found in the lung tissue of
asbestos-exposed patients and cancer specimens of stage I lung
adenocarcinoma, which may be responsible for dysfunction of
cell adhesion in tumor progression (19, 20). In our case, the
SDK1 Exon36-ALK Exon20 fusion protein contained Sdk1
ectodomain regions and the ALK kinase domain, which might
have resulted in ligand-independent dimerization and hence
continuous activation of ALK.

Targeted therapy has brought notable clinical benefits to ALK
positive NSCLC patients. Crizotinib has become the standard
first-line oral TKI therapy in patients with ALK-positive metastatic
NSCLC based on the outcomes of the PROFILE 1007 trial and the phase III PROFILE 1014 clinical study. The
second-generation ALK TKIs ceritinib and alectinib obtained
expedited approval as first-line medications based on the clinical
trials ASCEND-4 and ALEX. Another second-generation TKI
brigatinib exhibited a 71% ORR in the phase 3 ALTA-1L trial,
making it the new first-line medication for advanced-stage
NSCLC patients. Lorlatinib, a third-generation ALK TKI,
achieved a 72% improvement in PFS compared with crizotinib
as a first-line therapy in the phase III CROWN trial (3, 21).
Secondary mutations in the ALK tyrosine kinase domain, such as
L1196M, C1156Y, G1202R, and G1269A, are the most common
cause of ALK-targeted therapeutic resistance, termed as ALK-
dependent resistance. ALK gene amplification and activation of
alternative pathways, including epidermal growth factor receptor
(EGFR), hepatocyte growth factor receptor, and insulin-like
growth factor 1 receptor, represent other resistance mechanisms (2).

SAF-189s is a novel selective ALK inhibitor and can overcome
multiple resistance mutation. In a multicenter I/II study, all
enrolled 34 ALK-positive patients responded well to SAF-189s
treatment, with a confirmed PR of 50% and an unconfirmed PR
of 11.7%. In 24 patients who progressed on previous first-line crizotinib or ceritinib treatment, a confirmed PR was 47.6% (22).
In the nude mice xenograft model of SDC4-ROS1 fusion NSCLC,
SAF-189s induced tumor regression and exhibited notable
prolonged and durable efficacy and was more potent than
crizotinib and comparable to lorlatinib against G2032R
mutant-driven tumors (23). The present untreated lung cancer
patient exhibited excellent response to SAF-189s treatment with
manageable toxicities.

Immune checkpoint inhibitors, which can modulate tumoral
imunosuppression and reactive host immunity, promising
long-term disease control in a segment of patients with
advanced NSCLC. As a result, increasing emphasis is being
placed on the combination strategies of immunotherapy and
targeted therapy. However, the present research findings on ALK
TKIs in combination with immunotherapy are still ambiguous.
The CheckMate 370 phase 1/2 study and TATTON trial, for
example, had halted their enrolments due to severe intolerant
toxicities. Conversely, research of alectinib plus atezolizumab
showed a manageable side-effects profile with excellent
antitumor activity (ORR 85%). The understanding of biological
mechanisms underlying immune-targeted combinations still
need further clinical investigations and NGS will be a valid
tool in future decision-making (24).

CONCLUSION
In summary, this is the first case report involving SDK1-ALK
fusion detected in a Chinese patient with advanced lung
adenocarcinoma by using NGS-based cancer genomic DNA
profiling in the clinic. In this case, the SDK1-ALK-rearranged
lung cancer in this patient is susceptible to treatment with a new
ALK inhibitor SAF-189s, which is now being studied in a clinical
trial. Thus, our study provides a new druggable target for NSCLC
driver mutation in routine practice.

DATA AVAILABILITY STATEMENT
The datasets for this article are not publicly available due to
concerns regarding participant/patient anonymity. Requests to
access the datasets should be directed to the corresponding author.

ETHICS STATEMENT
The studies involving human participants were reviewed and
approved by Ethics Committee of The First Affiliated Hospital of
Shandong First Medical University. The patients/participants
provided their written informed consent to participate in this
study. Written informed consent was obtained from the
individual(s) for the publication of any potentially identifiable
images or data included in this article.

AUTHOR CONTRIBUTIONS
LM: Data curation, Writing- Original draft preparation. JX:
Writing - review & editing. TG: Visualization, Investigation.
DW: Software. JW: Supervision. All authors contributed to the
article and approved the submitted version.

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Conflict of Interest: DW and TG are employees of YuceBio Technology Co., Ltd. Shenzhen.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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