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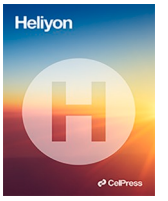

Case report

Coexistence of a novel SRBD1-ALK, ALK-CACNA1D double-fusion in a lung adenocarcinoma patient and response to alectinib: A case report

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A B S T R A C T

A Chinese male patient with advanced lung adenocarcinoma experienced disease progression one and a half years after receiving first-line immunochemotherapy. The second biopsy was performed and tissue immunohistochemistry revealed Anaplastic lymphoma kinase (ALK) expression in the cytoplasm of tumor cells, so he began to receive Alectinib treatment. Then the next generation sequencing found double fusion variants of S1 RNA binding domain 1 (SRBD1)- ALK and ALK- Calcium voltage-gated channel subunit alpha1 D (CACNA1D). After continuous Alectinib treatment for 7 months, almost complete response (CR) was achieved. The patient is currently taking Alectinib for 13 months, the condition is stable, and is waiting for the next cycle of efficacy evaluation.

1. Introduction

Anaplastic lymphoma kinase (ALK) is a member of the insulin receptor protein-tyrosine kinase superfamily, and is not expressed in normal lymphoid tissue and lung. When ALK gene recombination, mutation or amplification occurs, it causes the activation of downstream signaling pathway, leading to the occurrence, proliferation and invasion of tumors. In advanced non-small cell lung cancer (NSCLC), ALK fusion mutations are important mutations therapeutic targets, with an incidence of approximately 3–7% [1], of which echinoderm microtubule associated protein-like 4 (EML4)-ALK is the most common fusion variant. With the increasing coverage of gene testing, more than 90 rare ALK fusion subtypes have been discovered in NSCLC currently, such as kinesin family member 5B

Abbreviations: ALK, Anaplastic lymphoma kinase; CACNA1D, Calcium voltage-gated channel subunit alpha1D; CR, Complete response; EML4, Echinoderm microtubule associated protein-like 4; KIF5B, Kinesin family member 5B; MDR, Multidrug resistance; NSCLC, Non-small cell lung cancer; P-gp, P-glycoprotein; PRKCB, Protein kinase C beta; SRBD1, S1 RNA binding domain 1; STRN, Striatin gene; TKI, Tyrosine kinase inhibitors.

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(KIF5B)-ALK, striatin gene (STRN)-ALK, etc., and there are also double fusion variants, such as protein kinase C beta (PRKCB)-ALK, EML4-ALK double-fusion. First-to third-generation ALK-tyrosine kinase inhibitors (TKI) have brought significant benefits to patients. But for the newly discovered fusion variants, especially the missing EML4-ALK fusion mutations, the clinical efficacy of ALK-TKI in its first line or even the posterior line needs to be further evaluated. In addition, in the face of new complex and diverse rare fusion targets, individual responses to TKI may help to infer new therapeutic mechanisms and interventions. SRBD1-ALK has been reported in a few cases, but ALK-CACNA1D has not been reported. An advanced lung adenocarcinoma patient with the above double fusion mutation responsed to Alectinib was first reported here, and the literature was studied to analyze their roles in the case.

2. Case presentation

A 38-year-old Chinese man with no family history or smoking history developed cough and shortness of breath and was pathologically diagnosed with left upper lobe adenocarcinoma with pericardial and bone metastasis (cT1N3M1c, stage IVB) in local hospital three years ago. Since only TP53p.v73G mutation was found and PD-L1 staining (tumor proportion score) was 2%, he received Tislelizumab (200mg every 3 weeks) combined with or without chemotherapy for 15 cycles in a year and a half (discontinuation due to grade 4 myelosuppression and multiple skin rashes). Follow-up of chest CT showed that the lung lesions increased and enlarged (Fig. 1A).

The tumor tissue acquired during biopsy was sent for immunohistochemistry with the Ventana D5F3, revealing the diffuse expression of ALK in the cytoplasm of tumor cells (Fig. 2). Therefore, based on guidelines and clinical studies, combined with the patient's wishes, he received Alectinib (600 mg twice daily) as second-line treatment after disease progression. At the same time, genomic testing by next-generation sequencing based on a pan-cancer 1021-gene panel was performed. Soon after, SRBD1-ALK (SRBD1(END..IVS16)_ALK(IVS19.END)) and ALK-CACNA1D (ALK(PMT..IVS19)_CACNA1D (IVS2.END)) double fusion variant was identified with mutant frequencies of 21.2% and 16.9% (Fig. 3A & Fig. 3B). Tumor protein 53 (TP53) mutation, CDK4 amplification, MYC amplification and RAD21 mutation(EX14) were found at the same time.

After 7 months of Alectinib therapy, a follow-up computed tomography scan found that the lesions in the lung shrank and unmeasured (Fig. 1B), thus achieving a complete response, and at the cut-off date of this study the patient had been receiving Alectinib for 13 months with no complaints of discomfort and no adverse effects, and remained in follow-up for progression.

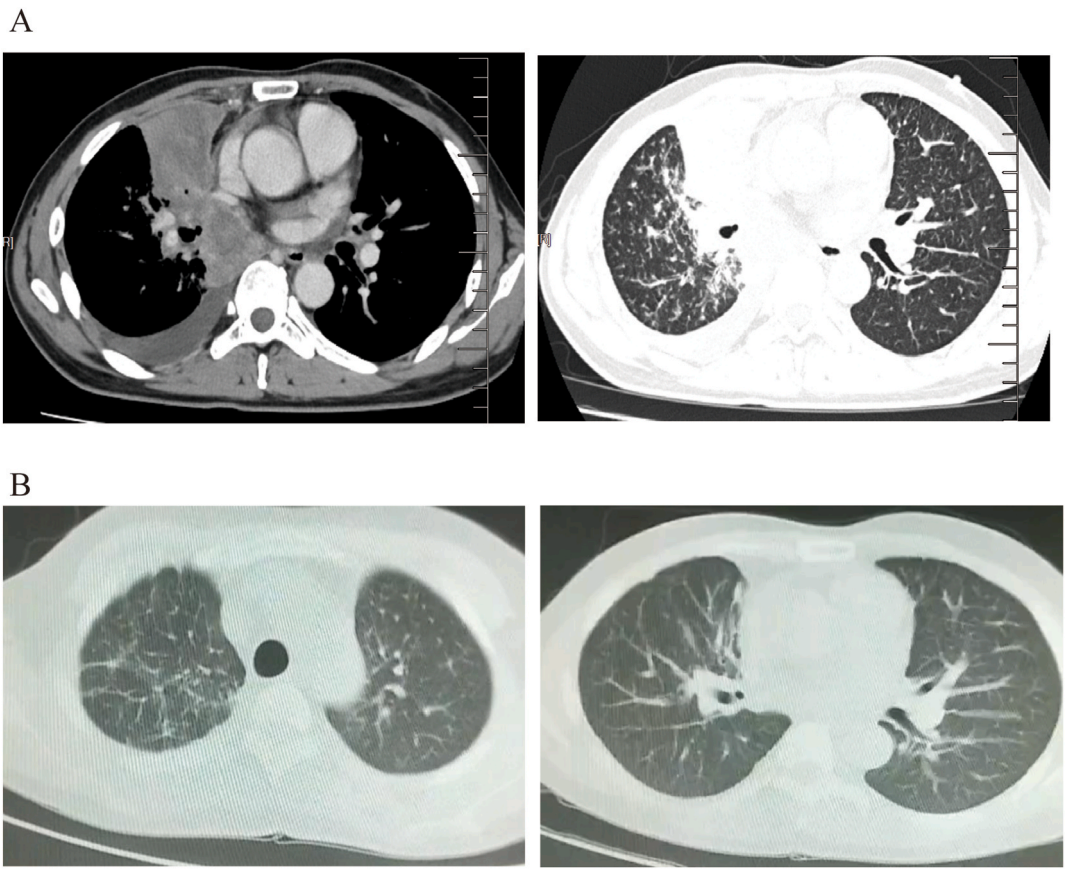

Fig. 1. Dynamic imaging of lung lesions at different stages of treatment. (A) Lung lesions increased after approximately 18 months of immunotherapy. (B) After targeted therapy with Alectinib for 7 months, resulting in almost completed response (CR).

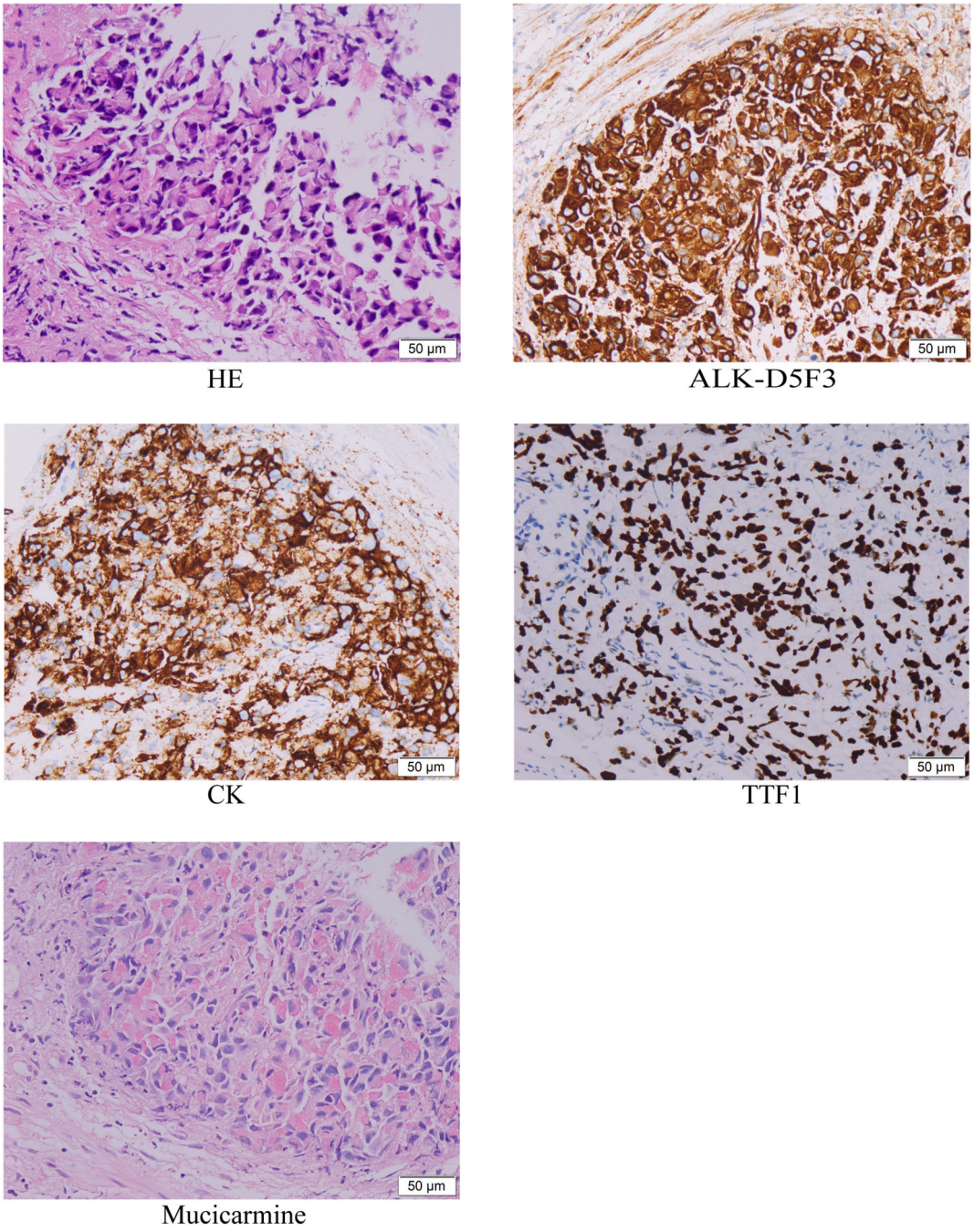

Fig. 2. Pathological examination of the patient. Hematoxylin and eosin staining of the biopsy specimen showed poorly differentiated NSCLC. IHC showed positive expression for TTF-1, CK, Muc and negative expression for P40, revealing an adenocarcinoma of lung origin(×100).

3. Discussion

In summary, this is the first case to describe a novel SRBD1-ALK, ALK-CACNA1D double-fusion lung adenocarcinoma patient who is sensitive to Alectinib. The SRBD1-ALK fusion gene was first identified by Xue Hou [2] and they found the fusion transcript was generated from a fusion of SRBD1 exon 20 and ALK exon 20 (S20: A20 PMT-END), while Yao Chen [3] found another fusion of SRBD1 exon 6 and ALK exon 20 (S6: A20), and the patient responsed to Crizotinib, which was different from what we detected in our case SRBD1(END..IVS16)_ALK(IVS19.END), demonstrating a significant response to Alectinib. Zhang [4] found that SRBD1 were specifically expressed in non-small cell lung cancer tissue, and silencing of SRBD1 inhibits cell growth and promotes cell apoptosis in non-small cell lung cancer cells, and suppresses tumorigenesis in vivo, suggesting that SRBD1 may be a new diagnostic indicator and

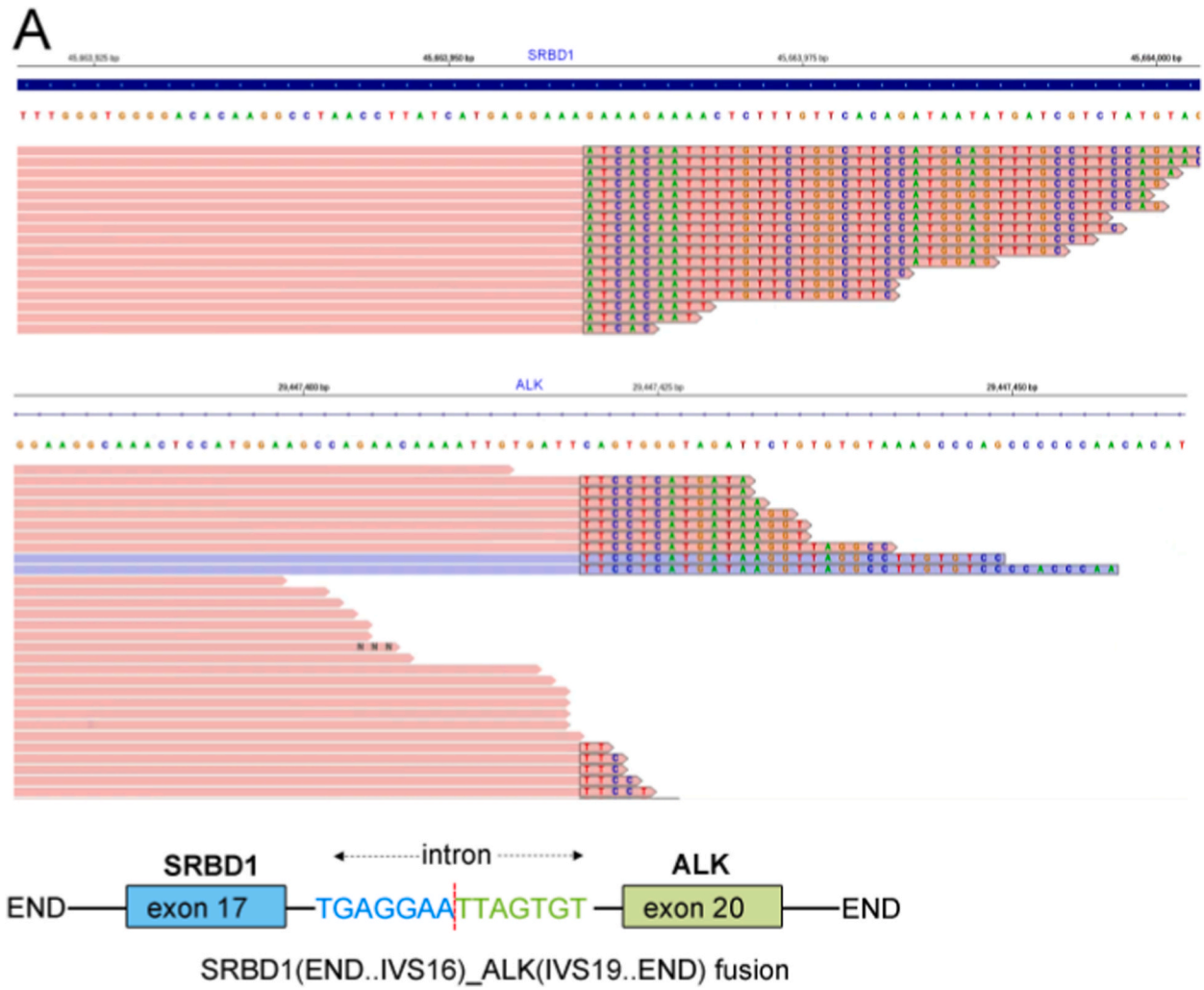

Fig. 3a. Identification of SRBD1-ALK and ALK-CACNA1D double fusion variant in a NSCLC patient. (A) Sequencing reads of SRBD1-ALK was visualized by the Integrative Genomics Viewer (IGV).

therapeutic target of non-small cell lung cancer.

As far as we know, ALK-CACNA1D fusion has not been reported in lung cancer before. CACNA1D is a calcium related transporter gene that encodes L-type voltage-gated calcium channels. Calcium ion channels have confirmed roles in cellular functions, including mitogenesis, proliferation, differentiation, apoptosis and metastasis. No direct link between CACNA1D and lung cancer has been reported present in the literature, but bioinformatics analysis revealed that CACNA1D was abundantly expressed in normal lung tissue, but significantly decreased in lung squamous cell carcinoma and lung adenocarcinoma and up-regulated in lung carcinoid tumors datasets [5,6]. P-glycoprotein (P-gp) is an ATP-dependent transporter encoded by multidrug resistance 1 (MDR1). The overexpression of P-gp in tumor cells increases the efflux of anticancer drugs, which is the main mechanism of multidrug resistance (MDR) in tumor cells. Previous studies have also found that under hypoxia, the up-regulation of HIF-1 α will promote the expression of MDR gene, which in turn mediates the intracellular expression of P-gp. Liu found that inducing Ca2+ to accumulate specifically in mitochondria, suppressing cell respiration and intracellular ATP production, relieving tumor hypoxia, down-regulating the expression of HIF-1 α to inhibit P-gp biosynthesis and decrease function, so as to reverse drug resistance [7]. Based on the above literature research, we boldly speculate that ALK-CACNA1D fusion may lead to abnormal conformation of calcium channels and ion pumps in lung tumor cells, resulting in abnormal distribution of intracellular and extracellular calcium ions, changes in cell membrane potential activity, and further affect the function of p-gp, or calcium ions directly affect cell proliferation, migration and apoptosis, etc., but Alatinib is not the substrate of p-gp, so patients get ideal curative effect.

We speculate that the SRBD1-ALK fusion is the driving mutation of lung cancer in the case. According to previous reports, they speculated that the N- terminal of the fusion partner provided a promoter, which led to the constitutive expression of ALK fusion protein, and the activated ALK fusion protein induced cancer by acting on the downstream signal pathway. The fusion breakpoint of SRBD1-ALK reported by us falls into intron 19 of ALK, retaining its entire intracellular kinase domain. The ALK fusion fragment of the

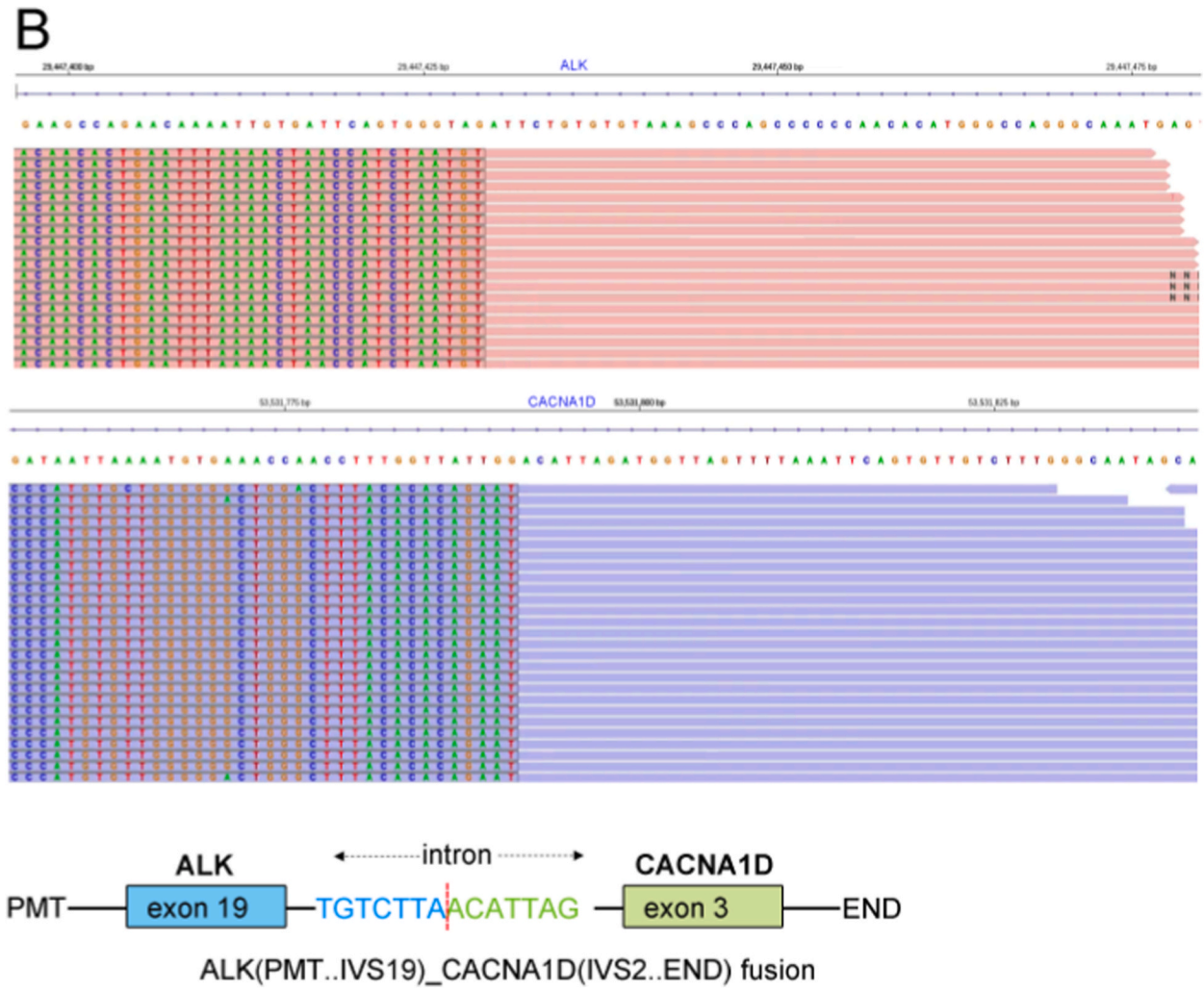

Fig. 3b. (B) Sequencing reads of ALK-CACNA1D was visualized by the IGV.

ALK-CACNA1D fusion gene is a previous fragment containing intron 19, and the intracellular kinase domain of ALK is not preserved. Therefore, it may be inferred that SRBD1-ALK fusion is the driving mutation of lung cancer, but the SRBD1-ALK gene of this patient is fused from head to head, which is different from previous reports, we speculate that there are fragments in the reversed SRBD1 that can activate ALK, but the exact mechanism is unknown.

In addition, a retrospective study by Kang et al. found that patients with complex ALK fusions (with coexisting canonical and non-canonical alk fusions) were likely to have better OS than patients with pure uncommon ALK fusion and pure canonical EML4-ALK fusion in the context of crizotinib treatment [8]. Patient in the case can be included in the pure uncommon ALK fusion group but benefit significantly from Alectinib, perhaps by conducting a study similar to Professor Kang's to further explore the association between ALK fusion patterns and Alectinib treatment outcomes can inform clinical treatment strategies. Some literature mentions that the gene fusion of the double fusion gene will disappear or the abundance will change after treatment, resulting in poor efficacy, disease progression, or liver metastases [9–11]. Despite the moderate outcome of this patient, vigilance and dynamic assessment are required. The patient trusts us and approves of our diagnosis and treatment.

4. Conclusion

The function of the fusion gene largely depends on the fusion partner, and the type of fusion partner has a vital impact on the efficacy of targeted therapy. According to literature studies and our case, the rare new SRBD1-ALK and ALK-CACNA1D double fusion mutation sensitive to Alectinib, even after progression of first-line immunotherapy. However, due to individual differences, this study has limitations and needs larger sample size verification.

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Ethics statement

The authors report no conflicts of interest in this work.

Author contributions

Haiyi Deng: Writing – review & editing, Writing – original draft, Supervision, Methodology. Huixin Jiang: Writing – review & editing, Writing – original draft, Investigation. Yijia Li: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. Chengzhi Zhou: Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization. Ming Liu: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Conceptualization. Wenhui Guan: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation, Conceptualization. Xiaohong Xie: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Investigation, Conceptualization. Juhong Jiang: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources. Wenting Huang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Xiaohong Xie reports financial support was provided by Wu Jieping Medical Foundation (320.6750.2021-17-7). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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