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The clinical responses of *TNIP2-ALK* fusion variants to crizotinib in *ALK*-rearranged lung adenocarcinoma

Tingting Feng[a,1], Zhongzhong Chen[a,1], Jianjun Gu[b], Yuxiu Wang[a], Jun Zhang[b], Lingfeng Min[a,*]

[a] *Department of Respiratory and Critical Care Medicine, Northern Jiangsu People's Hospital, The First Clinical College of Dalian Medical University, Yangzhou 225001, Jiangsu, China*

[b] *Department of Respiratory and Critical Care Medicine, Northern Jiangsu People's Hospital, Clinical Medical College of Yangzhou University, Yangzhou 225001, Jiangsu, China*

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ABSTRACT

Objectives: Anaplastic lymphoma kinase (*ALK*) has been proven to be another driver oncogene that accounts for 3%–7% of non-small-cell lung cancer, and it is more common in young patients and nonsmokers. *ALK* rearrangements have been previously identified in about 5.1% of lung adenocarcinoma, including *EML4-ALK* fusion variants, *KIF5B-ALK* and *TFG-ALK*. However, a *TNIP2-ALK* fusion has not been reported in lung adenocarcinoma. Herein, we described a rare case of *ALK*-rearranged lung adenocarcinoma responding to crizotinib.

Materials and methods: Immunohistochemistry (IHC) assay and comprehensive next-generation sequencing (NGS) were performed on the aspirated biopsied tumor tissue.

Results: The IHC analysis revealed an *ALK*-positive tumor, while NGS detected a *TNIP2-ALK* fusion. The patient achieved continuous remission after treatment with crizotinib (250 mg, twice a day).

Conclusion: This case provides valuable information on the response to crizotinib of patients with *TNIP2-ALK* fusion and better understanding of ALK-TKI applications in the future. NGS is a new method that can offer effective detection of gene fusion and gene mutations.

1. Introduction

Lung cancer is the leading cause of cancer deaths; its incidence and mortality is increasing rapidly. Non-small-lung-cancer (NSCLC) accounts for about 85% of all lung carcinomas, and the five-year survival rate is extremely low [1]. With the rapid development of molecular targeted therapy, anaplastic lymphoma kinase (*ALK*) was proven to be another main oncogene-driven gene after the epidermal growth factor receptor (EGFR). *ALK* fusions account for approximately 2%–7% of patients with lung adenocarcinoma [2]. However, a *TNIP2-ALK* fusion has not been reported in lung adenocarcinoma. Herein, we describe a rare case of *ALK*-rearranged lung adenocarcinoma responding to crizotinib.

2. Case report

A 49-year-old female non-smoker who had no personal history of hypertension, diabetes mellitus, heart disease, nor cancer was presented to our hospital with a 3-month history of chest pain and symptoms that worsened after 10-day. Chest computed tomography (CT) scan images showed a 1.2 cm mass in the lower lobe of the right lung and enlargement of hilar and mediastinal lymph nodes (larger lesion: 2.6 cm in size) and a small pleural effusion (T1N3M1a, stage IV; Fig. 1A and B). The patient completed the CT-guided percutaneous transthoracic needle aspiration biopsy, and immunohistochemical (IHC) analysis was positive for *CKpan*, *TTF-1*, and *NapsinA* and negative for *P63* and *P40* (Fig. 2A–F). Combining with the IHC analysis, the pathologic diagnosis was lung adenocarcinoma. We further performed next-generation sequencing (NGS, at Nanjing Geneseeq Technology, Jiangsu, China) assay on blood and aspiration biopsy and observed that the tumor contained concomitant *TNIP2-ALK* fusion (abundance: 0.1% and 3.3%; Fig. 3A). The patient underwent crizotinib treatment (250 mg, twice a day) in March 2019. After 2 months, chest CT scan images obtained during crizotinib treatment demonstrated a reduced tumor volume (lesion: 0.9 cm in size) and significantly smaller hilar/mediastinal lymph nodes compared with previous measurements (larger lesion: 1.3 cm in size, Fig. 1C and D). We have not detected brain metastasis in the clinical process of diagnosis and treatment of this patient by brain magnetic

* Corresponding author.
E-mail address: minlingfeng@126.com (L. Min).
[1] These authors contributed equally to this work.

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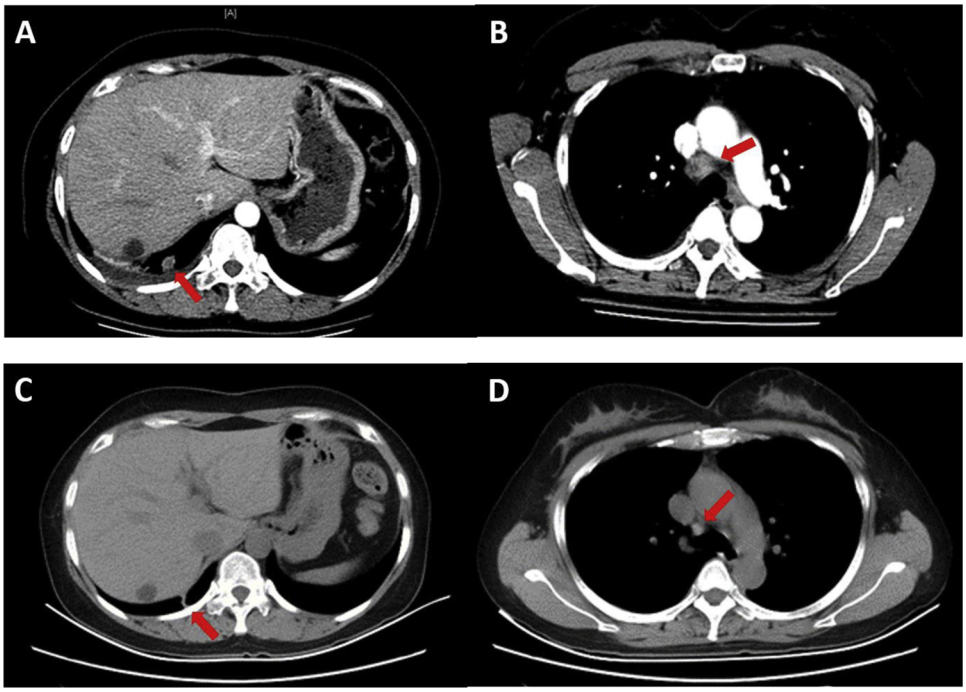

Fig. 1. CT scans before crizotinib therapy (A and B). CT of the chest showing partial response after two months of crizotinib treatment (C and D).

resonance imaging scanning. During treatment with crizotinib, the hepatic and renal functions were normal. No chemotherapy-induced events, including visual exceptions and gastrointestinal reactions, were observed. After two months, the disease was stabilized, and the patient continued taking crizotinib.

To further explore how *TNIP2-ALK* may function as a pathogenic driver and the potential role of the dimerization domain in *TNIP2*, we determined the exact fusion pattern of *TNIP2-ALK* by RNA-sequence. However, the RNA acquisition for the rest of biopsy specimen was below the testing requirements. After treatment, the CT scan revealed a significant decrease in the size of lesions, and these minor lesions cannot be used to perform a new biopsy. Additionally, performing another new biopsy is unethical. The NGS results of liquid biopsy and biopsy specimen support the occurrence of *TNIP2-ALK* fusion. Therefore, we deduced that *TNIP2-ALK* is likely underwent fusion, as expected based on the NGS results. Fig. 3B shows the diagram of the hypothetical *TNIP2-ALK* fusion. The patient was followed-up until death or for at least 12 months. We will perform a new biopsy if the patient presents disease recurrence or progress, as necessary.

3. Disscusion

In recent years, *ALK* has been proven to be another driver oncogene accounting for 3%–7% of NSCLC; it is more common in young patients [3] and nonsmokers [4]. *ALK* rearrangements have previously been identified in about 5.1% of lung adenocarcinoma, including *EML4-ALK* fusion variants, *KIF5B-ALK,* and *TFG-ALK*. Crizotinib, a small molecule targeting the receptor tyrosine kinase activity of *ALK*, is recognized worldwide as the first-line treatment for advanced NSCLC. This drug features a reported response rate of over 70% and a disease control rate of up to 90% [5]. Furthermore, its median progression-free survival is 11 months [6].

Several researchers have reported the primary resistance or the heterogeneity of EGFR-TKIs for *EGFR*-mutation positive NSCLC patients [7,8], but similar studies on ALK-TKIs are limited. The most important mechanism of heterogeneity of ALK-TKIs response includes the diverse *ALK* rearrangements caused by different protein stabilities and expression levels. The specific gene fusion cannot be identified by fluorescence in situ hybridization and IHC method [9]. As the different gene fusions respond in various ways to the same medication, the identification of mutations to achieve personalized and precision medicine becomes more important. Thus, NGS would complement the detection of gene rearrangements [2,10]. NGS is a new method that can offer effective detection of gene fusion and gene mutations. This method benefits clinical patients with gene mutation or gene fusion during treatment.

In this case report, a new fusion form of *ALK* rearrangement (*TNIP2-ALK*) was identified. *TNIP2* (also known as *ABIN2*) contains a CC2-LZ domain, which is a leucine-zipper domain associated with the CC2 coiled-coil region of nuclear factor-kappa B essential modulator [11]. The coiled-coil structure in CC2-LZ domain is considered to drive the dimerization of the *ALK* fusion protein, which activates the self-

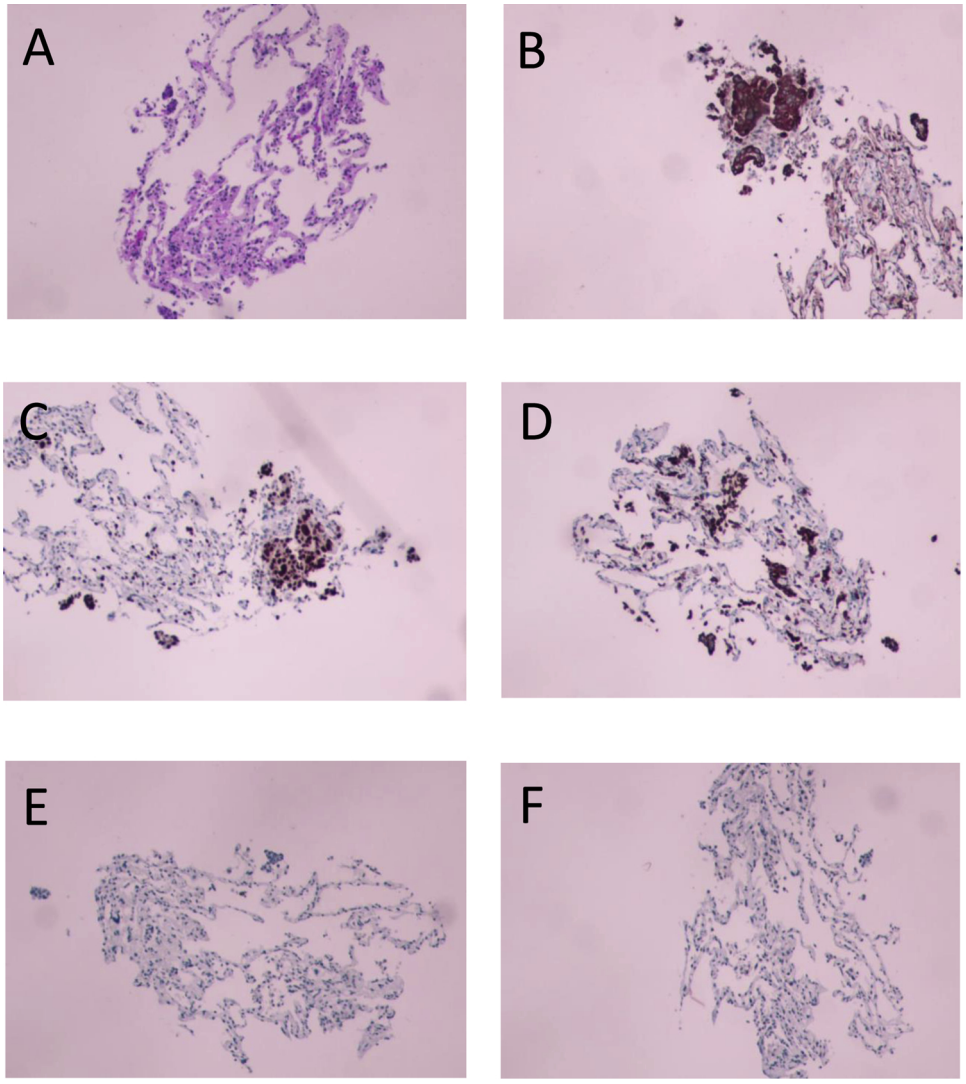

Fig. 2. (A) Needle aspiration biopsy showing adenocarcinoma lung cancer (HE × 100); (B) IHC analysis showed that the lung tumor cells were positive for *CKpan* (×100); (C) IHC analysis showed that the lung tumor cells were positive for *TTF-1* (×100); (D) IHC analysis showed that the lung tumor cells were positive for *Napsin A* (×100); (E) IHC analysis revealed that the lung tumor cells were negative for *P63* (×100); (F) IHC analysis revealed that the lung tumor cells were negative for *P40* (×100).

phosphorylation of *ALK* kinase domain in the fusion protein and triggers the *ALK* downstream signaling pathways. *TNIP2-ALK* fusion contains the inversion of *TNIP2* exon 5 and *ALK* exon 20. This fusion gene retains the complete domain of *ALK*, which is a critical region for *ALK* activity. Furthermore, *TNIP2-ALK* fusion may be involved in the period of pathogenesis and development of lung adenocarcinoma and increase the sensitivity of *ALK* inhibitors. The disease was stabilized after the patient was treated with crizotinib for 2 months. We will continue to follow-up on this patient. The patient's positive response to crizotinib has provided valuable information on *TNIP2-ALK* fusion and better understanding of ALK-TKI applications in the future.

4. Conclusion

The discovery of *TNIP2-ALK* fusion of *ALK* in lung adenocarcinoma is a novel finding. In addition, the *TNIP2-ALK*-rearranged tumor is sensitive to treatment with crizotinib therapy, implying that *TNIP2-ALK* acts as an oncogenic driver of lung tumorigenesis. In general, our case indicated that *TNIP2-ALK*-positive NSCLC may benefit from clinical applications of crizotinib.

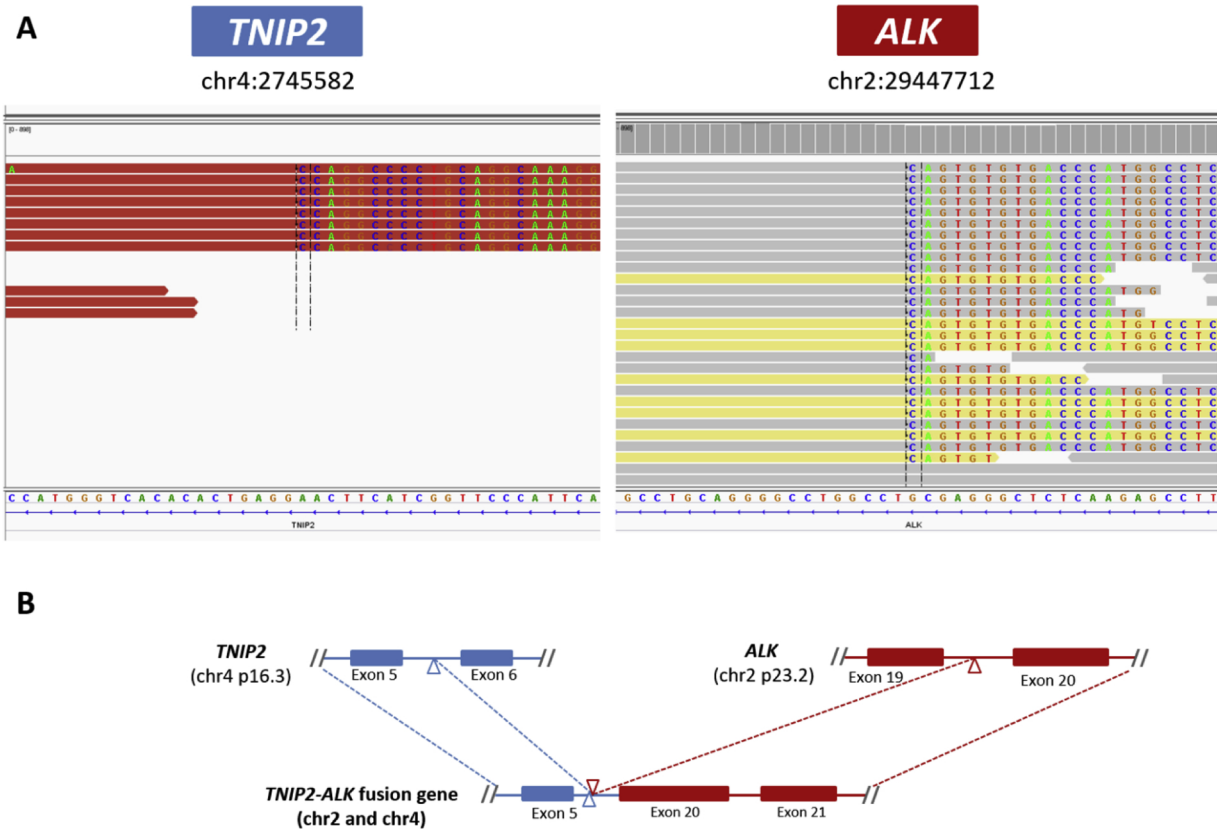

Fig. 3. *TNIP2-ALK* fusion is clinically actionable in a lung adenocarcinoma patient. The Integrative Genomics Viewer snapshot of *TNIP2-ALK*. A portion of *TNIP2* exon 5 fused to *ALK* exon 20. The exact breakpoints in the Fig. 3A. A diagram of hypothetical *TNIP2-ALK* fusion is shown in the Fig. 3B.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.08.032.

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