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Case Report
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A Novel ME1-ALK Fusion Identified in an Invasive Lung Adenocarcinoma Patient with Micropapillary and Solid Patterns: Case Report

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Abstract

Background: Anaplastic Lymphoma Kinase (*ALK*) re arrangement is observed in about 3% to 7% lung Adenocarcinoma (ADC). With the development of Next-Generation Sequencing (NGS) technology, more novel *ALK* fusions have been discovered, which can provide patients more opportunities to receive target therapies and achieve clinical effects.

Case Report: A case of an invasive lung ADC patient with micropapillary and solid patterns harboring a novel *ALK* fusion (*ME1-ALK*) was reported. Then, thoracoscopic resection of right upper lung and cautery division of pleural adhesions were performed with general anesthesia. Considering that solid and micropapillary components accounted for 50%, nedaplatin plus pemetrexed were administrated for 4 cycles after operation with the patient's consent. The patient had no recurrence and the Disease Free Survival (DFS) was 10 months by May 17th, 2021.

Conclusion: This case highlights that NGS profiling can identify more novel fusions and help solid/micropapillary-lung ADC patients find more opportunities to receive target therapies if the patient recurrence.

Keywords: Invasive lung adenocarcinoma; Solid/micropapillary components; *ME1-ALK* fusion

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Introduction

Lung ADC is the main histological phenotypes of Non-Small Cell Lung Cancer (NSCLC), accounting for about 48% of all NSCLC [1]. Studies have shown that the pathological subtypes of lung ADCs were related to prognosis and adjuvant therapy response [2]. Notably, solid/micropapillary predominant lung ADC patients often have a high risk of recurrence compared with other sub types [2-4]. However, the mechanism between the subtypes and prognosis remains unknown.

ALK fusion is observed in about 3% to 7% lung ADC [5]. Studies have shown that *ALK* fusions in patients with lung ADC are significantly related to pathological stage, age or histology subtype [6]. Remarkably, *ALK* fusions are frequently detected in solid/micropapillary-based lung ADC patients (up to 7%) compared with other subtypes, indicating that these patients may have the opportunity to receive and benefit from targeted therapy of *ALK* Tyrosine Kinase Inhibitors (TKIs) [6-8]. Herein, we firstly identified a novel *ME1-ALK* fusion in an invasive lung ADC patient with solid (45%), micropapillary (5%), acinar (40%) and papillary (10%) patterns, who might benefit from ALK-TKIs.

Case Presentation

A 64-year-old Chinese man, having a 30-year history of smoking and quitting for 12 years, was admitted to our hospital due to pain and tightness in the left chest for more than 3 days on July 13th, 2020. A chest Computed Tomography (CT) scan revealed a 2.1 cm × 1.7 cm mass with uneven density at the apex of the right lung (Figure 1A). Then, thoracoscopic resection of right upper lung and cautery division of pleural adhesions were performed with general anesthesia. After 3 months of postoperative, the re-examination result revealed that the patient was in SD (Figure 1B).

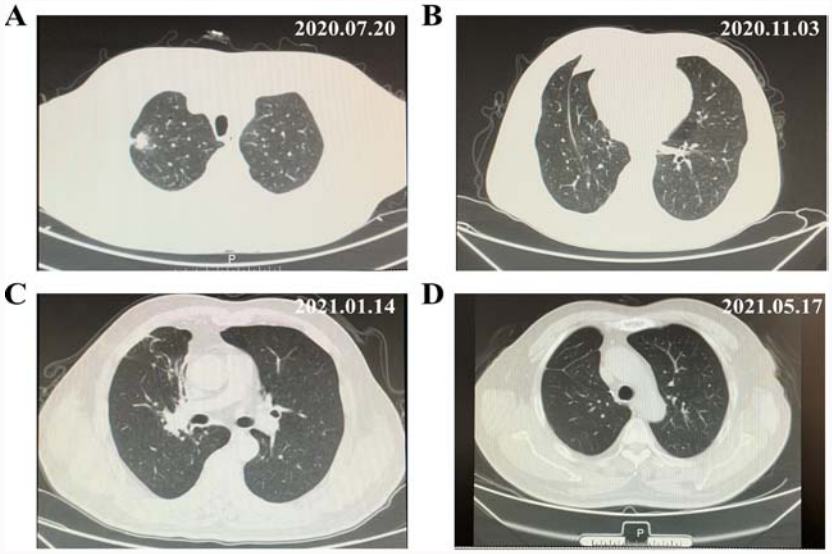

Figure 1: The chest computed tomography (CT) scan. (A) Before surgery. (B) After 3 months of postoperative. (C) After 4 months of chemotherapy. (D) After 10 months of postoperative.

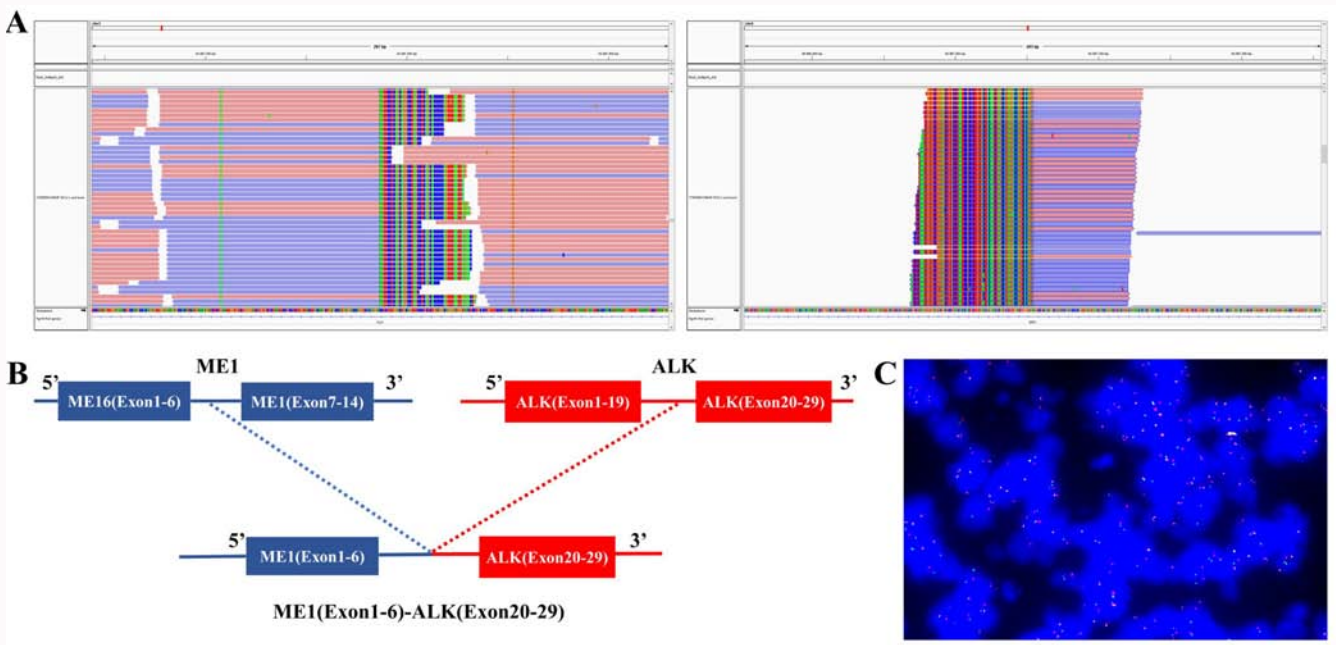

Figure 2: *ME1-ALK* fusion detected by DNA-based NGS and FISH. (A) The integrative genomics viewer snapshot of *MEI-ALK*. (B) Schematic representation of the *ME1-ALK* fusion. (C) The FISH staining of *ME1-ALK* fusion (original magnification x1000).

Postoperative Immunohistochemistry (IHC) analysis showed CK (+), Vimentin (-), TTF-1 (+), Napsin A (+), CK5/6 (-), P40 (-), Syn (weakly +), CgA (-) and Ki67 (60%). Tumor thrombus is seen in the vessel and IHC in vessel showed CD34 (+), D2-40 (+). Invasive lung ADC was diagnosed and consisted of solid (45%), micropapillary (5%), acinar (40%) and papillary (10%).

NGS was performed using postoperative tissue by 539-gene panel (Simceredx), and *ME1* (Exon1-6)-*ALK* (Exon 20-29) fusion (allele frequency, AF 36.99%), copy number variation (CNV) of *CDK4* (n=4.21), *DDR2* (n=3.89), *CDKN2A* (n=1.12) were identified. On September 15th, 2020, nedaplatin (20 mg, day 1 to 3 every 4 weeks) plus pemetrexed (600 mg day 1) were administrated for 4 cycles. CT scan showed the patient had no recurrence after 4 months of adjuvant chemotherapy (Figure 1C) and 10 months after operative (Figure 1D). The Disease Free Survival (DFS) of the patient is 10 months by May 17th, 2021.

Discussion

In our case, a novel *ME1-ALK* fusion was found by DNA-based NGS. The *ME1-ALK* fusion comprised exons 1 to 6 of *ME1* and exons 20 to 29 of *ALK* (Figure 2A, 2B). The complete kinase domain was retained. The partner gene, Malic Enzyme Gene (*ME1*), is a protein coding gene which encodes NADP-dependent enzyme and generates NADPH for fatty acid biosynthesis [9]. *ME1* contains coiled_ coil domain, which makes *ME1-ALK* fusion as a plausible functional fusion. Fluorescence in Situ Hybridization (FISH) was performed to verify *ALK* fusion and the result was positive (Figure 2C).

Studies have shown that the pathological subtypes of lung ADCs were related to prognosis and adjuvant therapy response [2-4]. Notably, the solid/micropapillary predominant lung ADC is associated with poor prognosis even if they were not predominant, and adjuvant chemotherapy after surgery can prolong the survival of these patients according to many studies [10,11]. In thislung ADC patient with solid and micropapillary patterns, postoperative pathology revealed vessel-positive and ki-67-positive (the proportion up to 60%), indicating that this patient had a risk of distant metastasis and a poor prognosis.

The lung ADC patient with solid and micropapillary patterns in our case might have a poor prognosis and might benefit from ALK-TKIs when the patient relapsed. Notably, *ALK* fusion is significantly associated with solid/micropapillary patterns lung ADC [6]. For patients with solid/micropapillary patterns lung ADC harboring *ALK*-positive, ALK-TKIs are a good choice of treatment. With the development of NGS technology, more novel *ALK* fusions have been reported in clinical practices. NGS can detect and distinguish *ALK* fusions with complete kinase domain, which have the worth of guiding clinical medication [12,13].

Conclusion

In conclusion, we firstly reported a novel *ME1-ALK* fusion in a patient with invasive lung ADC including solid and micropapillary components, which enriched the spectrum of *ALK* fusions and can seek more opportunities for invasive lung ADC patients harboring *ALK* fusions.

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