**Case Report**

**HIP1-ALK** fusion variant in non-small-cell lung cancer and response to crizotinib: a case report and review of the literature

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**Abstract:** Several fusion partners of ALK have been reported in patients with non-small cell lung cancer (NSCLC). Huntingtin interacting protein 1 (HIP1)-ALK is one kind of ALK fusion. We report a case of HIP1-ALK fusion variant in non-small-cell lung cancer and further review the clinical characteristics and efficacy of crizotinib to this type of fusion in NSCLC patients. The case involved a 56-year-old Chinese woman with multiple lung metastases NSCLC (T1N0M1, stage IV). Histological examination of the tumor showed lung adenocarcinoma. Ventana (D5F3) ALK IHC assay (Ventana Medical Systems, Roche, Inc) analysis of the left lung tissue revealed the presence of an ALK rearrangement. The patient then experienced a remarkable tumor response to crizotinib. By using next generation sequencing, we found that the tumor had HIP1-ALK (H21; A20) rather than the most common kind of Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK). Considering this rare ALK fusion and remarkable response to crizotinib treatment, we conclude that the incidence of HIP1-ALK in NSCLC patients with ALK rearrangement should be attentive. NSCLC patients with HIP1-ALK fusion gene respond to treatment with ALK inhibitors. With the guidance of a precise diagnosis, attention to other rare ALK fusions could lead to novel diagnostic methods.

**Keywords:** Lung cancer, HIP1, anaplastic lymphoma kinase, crizotinib

**Introduction**

Morbidity and mortality of lung cancer is increasing in both developed and developing countries worldwide [1, 2]. Anaplastic lymphoma kinase (ALK) positive is found in 2% to 7% of non-small cell lung cancer (NSCLC) patients [3]. ALK-rearranged NSCLC patients are highly sensitive to ALK kinase inhibitors. Crizotinib is the first small molecule tyrosine kinase inhibitor to ALK genes and it has been recommended as the first line treatment of ALK-rearranged NSCLC patients. Compared with first-line standard chemotherapy, the objective response rate to crizotinib is about 70% and its median progression free survival is 10 months [4]. Echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene is the common fusion type in ALK-rearranged NSCLC patients [5] and due to precise detection assays, such as next generation sequencing (NGS), more and more novel ALK fusion partner genes have been identified. To date, Huntingtin-interacting protein-1 (HIP1) [6], TRK-fused gene (TFG) [7], kinesin family member 5B (KIF5B) [8], kinesin light chain 1 (KLC1) [9], tyrosine-phosphatase, and non-receptor type 3 (PTPN3) [10] have been identified and CLIP4-ALK and SOCS5-ALK [11] have been found in lung cancer. However, the clinical significance of these variants requires further investigation. Not all of the above mentioned ALK rearrangements have reported efficacy during crizotinib treatment.

Therefore, we report here a HIP1-ALK fusion associated with NSCLC and demonstrate sensitivity to treatment with crizotinib. We also overview reported cases involving HIP1-ALK fusion patients in lung cancer.
HIP1-ALK fusion in lung cancer has been reported in some cases [6, 12, 13]. 

Because the tumor was close to the heart, thoracentesis of lung tumor was risky. Therefore, we performed a thoracoscopcy of left pulmonary wedge resection. Hematoxylin and eosin (H&E) staining showed a typical morphology of adenocarcinoma cell (Figure 2). Immunohistochemistry (IHC) analysis demonstrated positivity in TTF-1 and Napsin A and negativity in cytokeratin (CK) 5/6 and P63. Tumor tissue was used to detect wild-type of epidermal growth factor receptor variants by ARMS (AmoyDx, Xiamen China) but ALK protein expression was shown by VENTANA ALK IHC assay (VENTANA Medical Systems, Roche, Inc). The patient then underwent crizotinib treatment (250 mg/bid, orally) in September 2014. After one month, chest CT scan images demonstrated a decrease in tumor size (Figure 1B). According to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1), this patient was considered as partial response (PR) to crizotinib. During treatment of crizotinib, abnormal hepatic and renal function after administration were not found. There were no treatment-related adverse events including gastrointestinal reaction, flickering vision, and corneal damage. So far, after thirty-four months, the disease has shown slow progression of the left mass which is close to the heart (Figure 1C), too dangerous to re-biopsy. Currently, she is still undergoing crizotinib treatment. Due to the development of NGS, we wanted to analyze the initial tissue by NGS (Geneplus, Beijing China) and found HIP1-ALK fusion (H21:A20) (Figure 3A-C) and other mutations that were harbored such as ROS1 C.4058A>C, ALK C.3454C>G, and ALK C.3436C>A. The NGS assay used HiSEQe4000 (Illumina).

**Discussion**

HIP1-ALK fusion in lung cancer has been reported in some cases [6, 12, 13]. Huntington...
interacting protein family includes HIP1 and HIP1R in mammals and Sla2p in yeast, which plays a role in clathrin-mediated endocytosis and receptor trafficking [14-16]. For HIP1 protein, there is a pseudo dia-autoregulatory domain (pDAD) that may mediate apoptosis within the coiled-coil domain. One report has demonstrated that HIP1 is rearranged to kinases leading to aberrant signaling and malignant transformation [17].

Fang et al. [12] has found HIP1-ALK fusion gene and performed in patient-derived Xenograft (PDX) models to demonstrate that HIP1-ALK (H28; A20) is responsive to crizotinib in vitro. The elevated ALK mRNA and in vivo efficacy caused by ALK inhibition suggest that HIP1-ALK fusion, as does the EML4-ALK fusion gene in NSCLC, results in activation of ALK and triggers oncogenic cascade. Hong et al. [6] also found a HIP1-ALK (H21; A20) NSCLC patient...
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treated with adjuvant crizotinib after complete surgical resection with no recurrence at the time of their report (15 months). Ou et al. [13] described that a patient with NSCLC harboring the HIP1-ALK (H30; A20) fusion variant was responsive to ALK inhibitors inducing 5 months crizotinib treatment (PR) and then 12 months Alectinib treatment (CR). However, efficacy of crizotinib to HIP1-ALK fusion patients was undefined. In our current study, we identified the aberrant expression of interacting protein 1 (HIP1)-ALK (H21; A20) and showed a positive response to crizotinib treatment (PR) for the patient. PFS was about three years. Therefore, for this fusion type NSCLC patient, ALK inhibitors are the first line of therapy as with EML4-ALK patients.

VENTANA immunohistochemistry (IHC) detects ALK expression for ALK fusion genes regardless of variant and fusion partner. Therefore, in our report, the tissue of the patient first showed ALK positive by IHC. IHC has been demonstrated to be a reliable prescreening test for detecting lung cancer in clinical practice [18]. Currently, in the era of personalized medicine, accurate multi-gene diagnostics are crucial. Developments in next-generation sequencing (NGS) have created a new method for simultaneous detection of a large number of gene fusions with known and unknown genes and gene mutations [19, 20]. We thought the types of ALK fusion were many and IHC assay could be a pre-screening test. In addition, NGS could identify novel fusions and increase the list of actionable variants for patients. In particular, for long-term or short-term response to TKI treatment, we could use NGS assays in the future to explore gene differential expression.

This case report may increase the evidence in favor of crizotinib treatment to HIP1-ALK translocation NSCLC patients. Patients with HIP1-ALK fusion may respond to treatment with the first generation ALK inhibitor. NGS assays could provide a novel diagnostic. In the future, we should explore differences of the acquired mechanism in ALK inhibitors between HIP-ALK1, EML4-ALK rearrangement and other fusion variants of NSCLC patients.

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Disclosure of conflict of interest

None.

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