Int J Clin Exp Med 2018;11(5):5212-5216
www.ijcem.com /ISSN:1940-5901/IJCEM0067567

Case Report

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

Youcai Zhu[1], Xinghui Liao[2], Wenxian Wang[3], Chunwei Xu[4], Wu Zhuang[5], Kaiqi Du[1]

Departments of [1]Chest Disease Diagnosis and Treatment Center, [2]Tumor Molecular Laboratory, Zhejiang Rongjun Hospital, Jiaxing, P.R. China; [3]Department of Chemotherapy, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang, P.R. China; Departments of [4]Pathology, [5]Medical Thoracic Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou 350014, Fujian, P.R. China

Received October 19, 2017; Accepted March 1, 2018; Epub May 15, 2018; Published May 30, 2018

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.

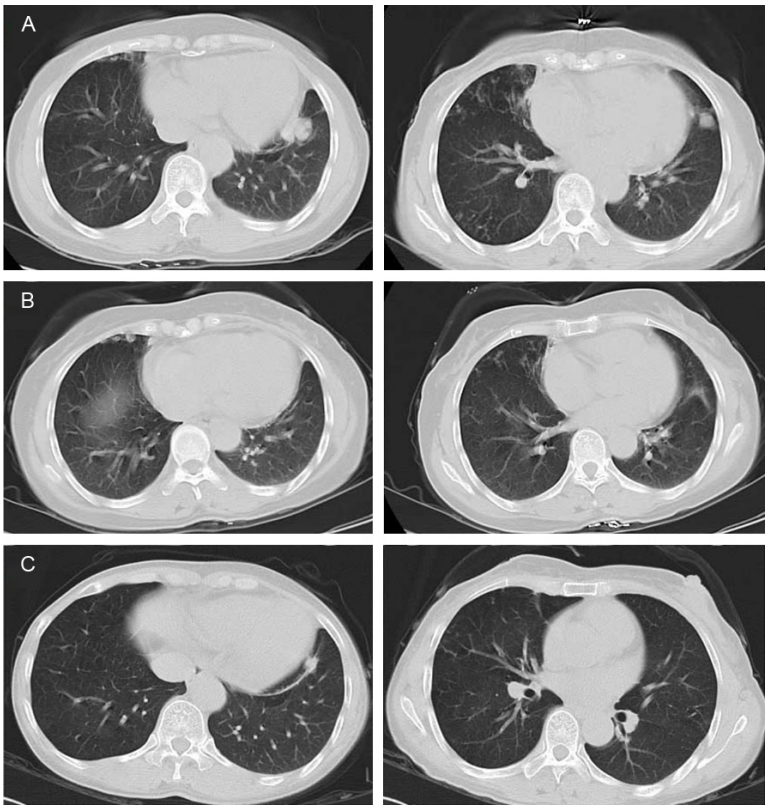

Figure 1. Computed tomography (CT) scans show: before crizotinib therapy (A); CT of the chest showed partial response after one months of crizotinib (B); CT of the chest revealed disease progression after thirty-four month treatment (C).

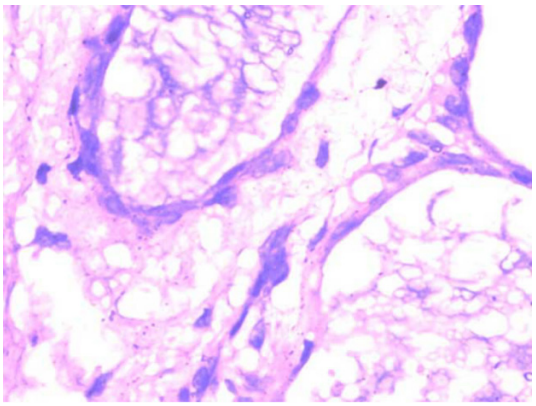

Figure 2. Thoracoscopy of left pulmonary showed adenocarcinoma cell lung cancer (HE × 400).

Case report

A 56-year old woman, who was never a smoker, presented to our hospital with a one-month history of cough and a little phlegm with blood. Computed tomography (CT) scan revealed a 2.6 × 2.0 cm mass at inferior lobe of the left lung and multiple pulmonary and pleural nodules (T1N0M1a, stage IV A) (**Figure 1A**). Because the tumor was close to the heart, thoracentesis of lung tumor was risky. Therefore, we performed a thoracoscopy 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 cordis 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 HiSEquation 4000 (Illumina).

Discussion

HIP1-ALK fusion in lung cancer has been reported in some cases [6, 12, 13]. Huntingtin

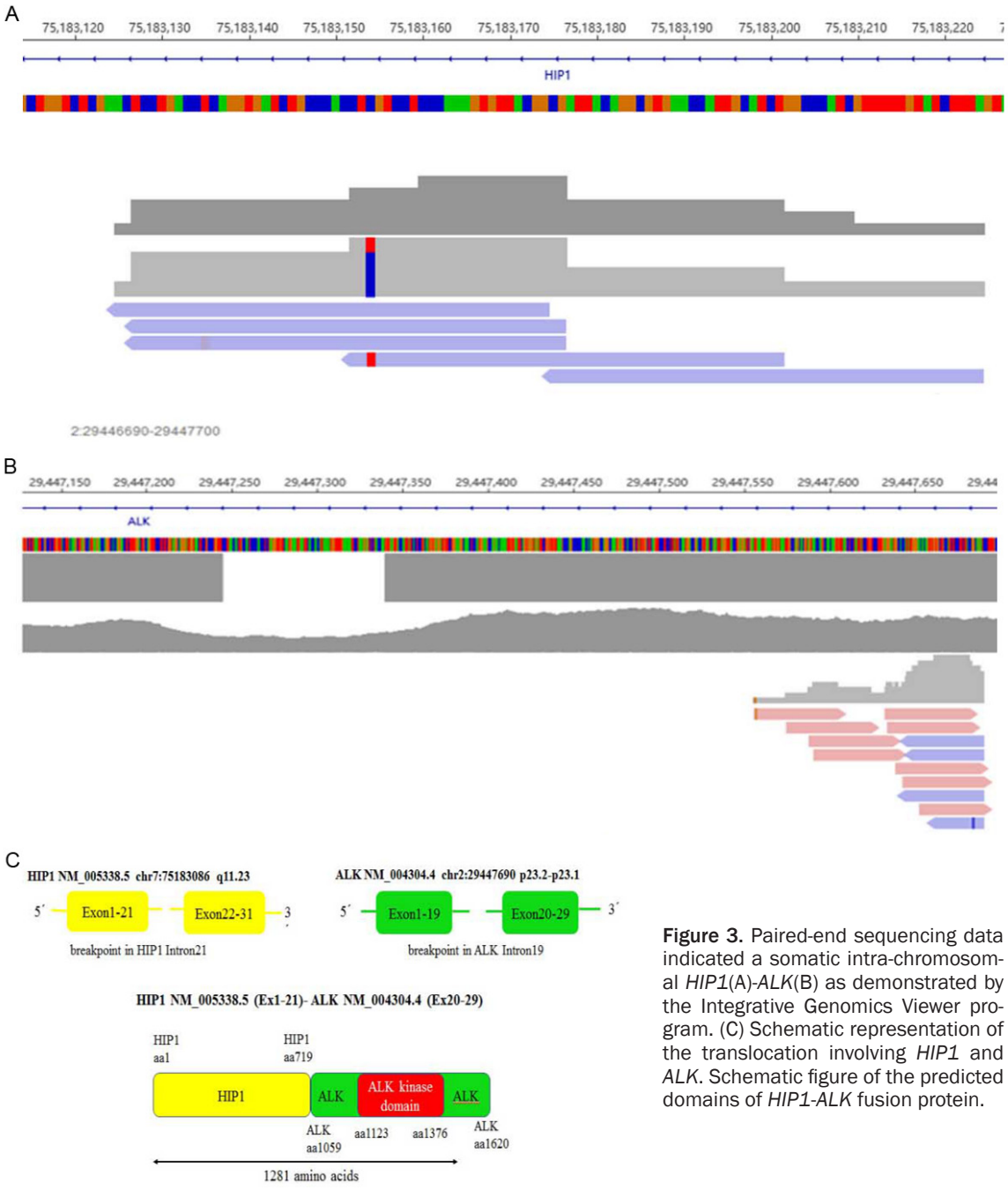

Figure 3. Paired-end sequencing data indicated a somatic intra-chromosomal *HIP1*(A)-*ALK*(B) as demonstrated by the Integrative Genomics Viewer program. (C) Schematic representation of the translocation involving *HIP1* and *ALK*. Schematic figure of the predicted domains of *HIP1-ALK* fusion protein.

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

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.

Acknowledgements

This work was supported by Zhejiang Province of China (2013KYB051); Zhejiang Administration of Traditional Chinese Medicine Foundation (2013ZQ005); Science and Technology Planning project of Zhejiang Province (2015C33194) and National Clinical Key Specialty Construction Program (2013).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wenxian Wang, Department of Chemotherapy, Zhejiang Cancer Hospital. 1 Banshan East Street, Gongshu District, Hangzhou 310022, Zhejiang, P.R. China. Tel: 0086-10-88122188; Fax: 0086-10-88122004; E-mail: helen-0407@163.com; Dr. Chunwei Xu, Department of Pathology, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital; 420, Fuma Road, Fuzhou 350014, Fujian Province, P.R. China. Tel: 0086-591-83660063; Fax: 0086-591-62752890; E-mail: xuchunweibbb@163.com

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.

[3] Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the college of American pathologists, international association for the study of lung cancer, and association for molecular pathology. J Thorac Oncol 2013; 8: 823-859.

[4] Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F; PROFILE 1014 Investigators. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014; 371: 2167-2177.

[5] Sasaki T, Rodig SJ, Chirieac LR, J?nne PA. The biology and treatment of EML4-ALK non-small cell lung cancer. Eur J Cancer 2010; 46: 1773-1780.

[6] Hong M, Kim RN, Song JY, Choi SJ, Oh E, Lira ME, Mao M, Takeuchi K, Han J, Kim J, Choi YL. HIP1-ALK, a novel fusion protein identified in lung adenocarcinoma. J Thorac Oncol 2014; 9: 419-422.

[7] Ou SH, Bartlett CH, Mino-Kenudson M, Cui J, Iafrate AJ. Crizotinib for the treatment of ALK-

rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. Oncologist 2012; 17: 1351-1375.

[8] Takeuchi K, Choi YL, Togashi Y, Soda M, Hatano S, Inamura K, Takada S, Ueno T, Yamashita Y, Satoh Y, Okumura S, Nakagawa K, Ishikawa Y, Mano H. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 2009; 15: 3143-3149.

[9] Togashi Y, Soda M, Sakata S, Sugawara E, Hatano S, Asaka R, Nakajima T, Mano H, Takeuchi K. KLC1-ALK: a novel fusion in lung cancer identified using a formalin-fixed paraffin-embedded tissue only. PLoS One 2012; 7: e31323.

[10] Jung Y, Kim P, Jung Y, Keum J, Kim SN, Choi YS, Do IG, Lee J, Choi SJ, Kim S, Lee JE, Kim J, Lee S, Kim J. A Discovery of ALK-PTPN3 gene fusion from human non-small cell lung carcinoma cell line using next generation RNA sequencing. Genes Chromosomes Cancer 2012; 51: 590-597.

[11] Drilon A, Wang L, Arcila ME, Balasubramanian S, Greenbowe JR, Ross JS, Stephens P, Lipson D, Miller VA, Kris MG, Ladanyi M, Rizvi NA. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. Clin Cancer Res 2015; 21: 3631-3639.

[12] Fang DD, Zhang B, Gu Q, Lira M, Xu Q, Sun H, Qian M, Sheng W, Ozeck M, Wang Z, Zhang C, Chen X, Chen KX, Li J, Chen SH, Christensen J, Mao M, Chan CC. HIP1-ALK, a novel ALK fusion variant that responds to crizotinib. J Thorac Oncol 2014; 9: 285-294.

[13] Ou SH, Klempner SJ, Greenbowe JR, Azada M, Schrock AB, Ali SM, Ross JS, Stephens PJ, Miller VA. Identification of a novel HIP1-ALK fusion variant in non-small-cell lung cancer (NSCLC) and discovery of ALK I1171 (I1171N/S) mutations in two ALK-rearranged NSCLC patients with resistance to Alectinib. J Thorac Oncol 2014; 9: 1821-1825.

[14] Waelter S, Scherzinger E, Hasenbank R, Nordhoff E, Lurz R, Goehler H, Gauss C, Sathasivam K, Bates GP, Lehrach H, Wanker EE. The huntingtin interacting protein HIP1 is a clathrin and alpha-adaptin-binding protein involved in receptor-mediated endocytosis. Hum Mol Genet 2001; 10: 1807-1817.

[15] Wilbur JD, Chen CY, Manalo V, Hwang PK, Fletterick RJ, Brodsky FM. Actin binding by Hip1 (huntingtin-interacting protein 1) and Hip1R (Hip1-related protein) is regulated by clathrin light chain. J Biol Chem 2008; 283: 32870-32879.

[16] Bradley SV, Holland EC, Liu GY, Thomas D, Hyun TS, Ross TS. Huntingtin interacting protein 1 is a novel brain tumor marker that associates with epidermal growth factor receptor? Cancer Res 2007; 67: 3609-3615.

[17] Ross TS, Bernard OA, Berger R, Gilliland DG. Fusion of Huntingtin interacting protein 1 to platelet-derived growth factor beta receptor (PDGFbetaR) in chronic myelomonocytic leukemia with t (5;7) (q33;q11.2). Blood 1998; 91: 4419-4426.

[18] Wynes MW, Sholl LM, Dietel M, Schuuring E, Tsao MS, Yatabe Y, Tubbs RR, Hirsch FR. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. J Thorac Oncol 2014; 9: 631-638.

[19] Pekar-Zlotin M, Hirsch FR, Soussan-Gutman L, Ilouze M, Dvir A, Boyle T, Wynes M, Miller VA, Lipson D, Palmer GA, Ali SM, Dekel S, Brenner R, Bunn PA Jr, Peled N. Fluorescence in situ hybridization, immunohistochemistry, and next-generation sequencing for detection of EML4-ALK rearrangement in lung cancer. Oncologist 2015; 20: 316-322.

[20] Gao X, Sholl LM, Nishino M, Heng JC, J?nne PA, Oxnard GR. Clinical implications of variant ALK FISH rearrangement patterns. J Thorac Oncol 2015; 10: 1648-1652.