The *KIF5B-RET* Fusion Gene Mutation as a Novel Mechanism of Acquired EGFR Tyrosine Kinase Inhibitor Resistance in Lung Adenocarcinoma

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Clinical Practice Points

- Lung cancer is a common malignancy and a leading cause of cancer-related death worldwide. Non–small-cell lung cancer (NSCLC) is the most common type of lung cancer. The majority of patients with NSCLC with epidermal growth factor receptor (EGFR) mutations respond well to treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs); however, almost all patients undergoing EGFR-TKI therapy develop drug resistance within 1 year. The most common cause of acquired resistance to first-generation EGFR-TKI treatment is the T790M mutation in exon 20 of the *EGFR* gene, which occurs in approximately 50% of cases of acquired resistance.
- In this case report, we present a 72-year-old male nonsmoker with an *EGFR* exon 19 deletion who was diagnosed with lung adenocarcinoma and initially responded to first-generation EGFR-TKI treatment, later developing acquired resistance in association with the *KIF5B-RET* fusion gene.
- The present results suggested that the *KIF5B-RET* fusion gene is a possible novel cause of acquired resistance to first-generation EGFR-TKIs.

Clinical Lung Cancer, Vol. 20, No. 1, e73-6
Keywords: Acquired resistance, EGFR gene, KIF5B-RET, Lung adenocarcinoma, Novel mechanism

Introduction

Lung cancer is one of the major causes of cancer-related mortality worldwide and is classified into small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC); NSCLC is the most common tumor type.[1] NSCLC in nonsmokers tends to be driven by a single somatic mutation or a gene fusion, such as *EGFR* mutations, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) rearrangements, and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations.[2,3] Approximately 10% to 20% of Caucasian patients and 30% to 60% of Asians with NSCLC have somatic mutations in the *EGFR* gene.[4] Although the majority of patients with NSCLC with *EGFR* mutations initially respond well to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), a high percentage of patients develop drug resistance within 1 year.[5-7] Various mechanisms of acquired resistance to EGFR-TKIs have been reported, such as the T790M mutation in exon 20 of the *EGFR* gene, *HER2* amplification, *MET* amplification, *PIK3CA* mutation, epithelial-mesenchymal transition (EMT) changes, and SCLC cell transformation.[8] Here, we examined the involvement of the kinesin family member 5B (*KIF5B*)-rearranged during transfection (*RET*) fusion gene in disease progression in patients treated with first-generation EGFR-TKIs. The *KIF5B-RET* fusion gene was

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Submitted: Jun 3, 2018; Revised: Aug 11, 2018; Accepted: Sep 15, 2018; Epub: Sep 21, 2018

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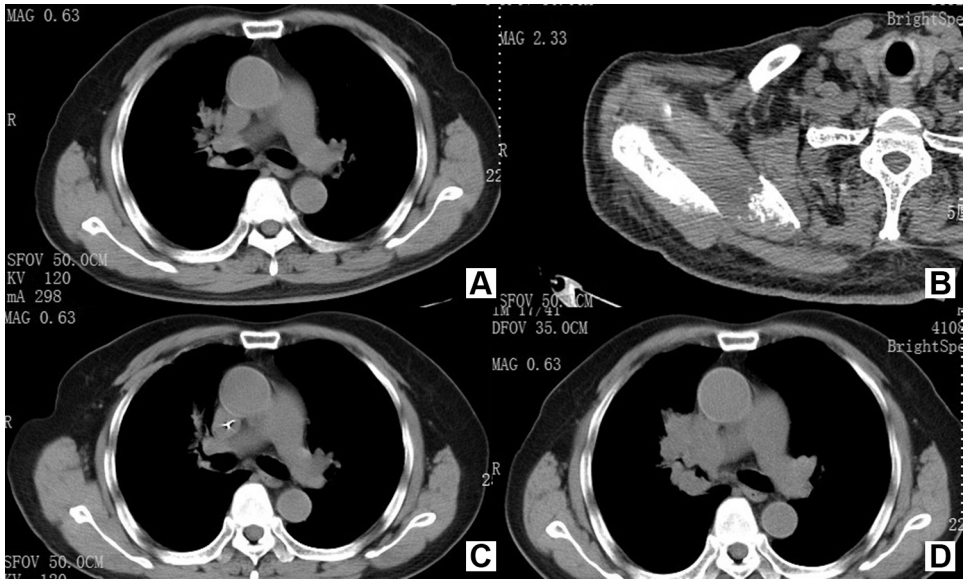
1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2018.09.011

Figure 1 Computed Tomography Scans Show: A, A Mass at the Superior Lobe of the Right Lung, and Local Invading Right-Hilar (March 2016); B, Bone Metastasis (March 2016); C, After Partial Response (May 2016); and D, After Progressive Disease (May 2017)



identified as a possible cause of acquired resistance to first-generation EGFR-TKIs in *EGFR*-mutant NSCLC.

Case Report

A 72-year-old male nonsmoker presented to our hospital in March 2016 with a 3-month history of coughing and sputum. Computed tomography (CT) scans revealed a mass in the superior lobe of the right lung, and locally invasive right-hilar and bone metastasis (Figure 1A, B). A pathologic diagnosis of adenocarcinoma was made using bronchoscope biopsy ($T_{2a}N_1M_1$, stage IV) (Figure 2). The amplification refractory mutation system method showed that the adenocarcinoma cells harbored an exon 19 deletion of the *EGFR* gene. We analyzed the initial tissue upon which was only found *EGFR* p. L747_A750insP by next-generation sequencing (3D Medicines, Shanghai, China). Because of the detection of an *EGFR* mutation (exon 19), treatment with icotinib (125 mg 3 times a day) was initiated in April 2016. Surveillance imaging examinations showed that partial response was achieved (Figure 1C). Considering the slow disease progression, icotinib therapy was continued for several months. Repeat liquid biopsy in March 2017 detected the *KIF5B-RET* fusion gene by next generation sequencing (Figure 3). Cabozantinib was added to the treatment, and stable disease was achieved. However, long-term effects were not achieved, and the progression-free survival was 2 months (Figure 1D). Subsequently, the patient was treated with chemotherapy (pemetrexed and lobaplatin) starting in May 2017, and Karnofsky Performance Status was 80 points at the time of discharge. Stable disease was achieved during the duration of therapy. The pulmonary lesions have rapidly progressed after 3.0 months, and the patient died in August 2017.

Discussion

Understanding the mechanisms of acquired resistance during cancer treatment is essential for the design of resistance mechanism-based therapies, which are becoming increasingly common and are often effective. Acquired resistance to EGFR-TKIs can be caused by the T790M mutation in exon 20 of the *EGFR* gene, *HER2* amplification, *MET* amplification, *PIK3CA* mutations, EMT changes, and SCLC transformation.[8] Here, we report a case of *KIF5B-RET* fusion gene detected by repeat liquid biopsy in a patient treated with EGFR-TKIs, which was previously an unknown

Figure 2 Hematoxylin and Eosin Staining Shows a Typical Morphology for Adenocarcinoma (× 100)

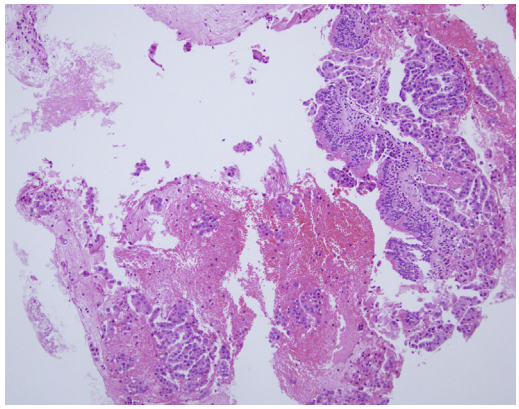
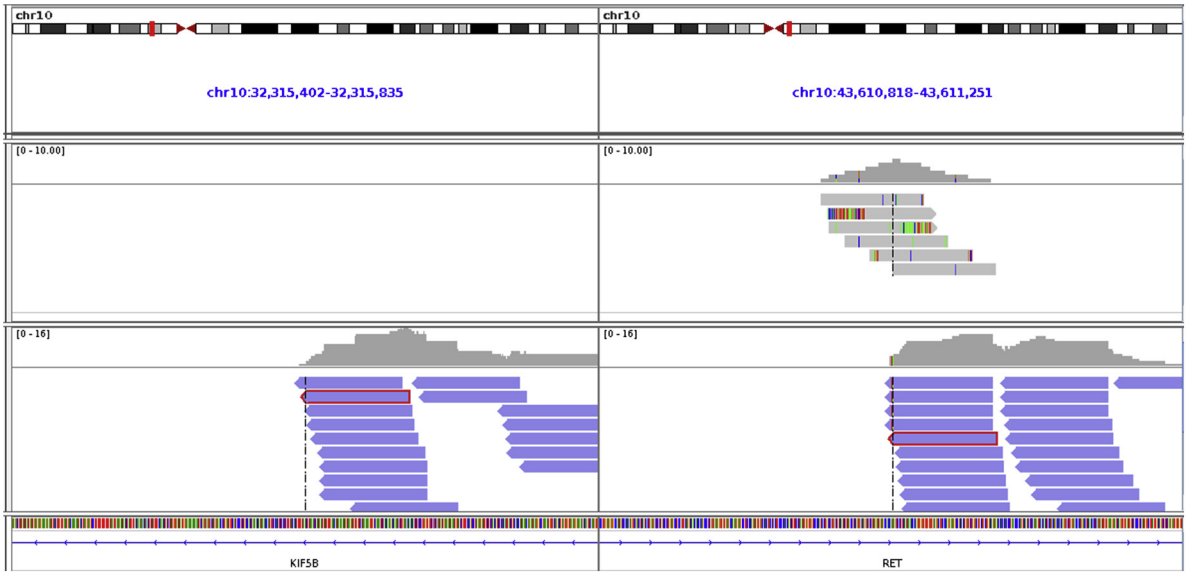


Figure 3 ***KIF5B-RET*** **Fusion Is Clinically Actionable. The Integrative Genomics Viewer Snapshot of** ***KIF5B-RET*** **Is Shown. Soft-Clipped Bases Can Match Each Other in Reverse Complementarity**



mechanism of EGFR-TKI resistance. We propose that this *KIF5B-RET* fusion gene could be a novel cause of acquired EGFR resistance.

Rearrangements in the *RET* gene, including inversions on chromosome 10 or translocations with other chromosomes involving different gene partners, have been reported in 30% of papillary thyroid carcinomas and 1% to 2% of NSCLCs.[9] At least 12 forms of *RET* rearrangement have been identified in NSCLC, including *KIF5B-*, *CCDC6-*, *NCOA4-*, *MYO5C-*, *EPHA5-*, *CLIP1-*, *ERC1-*, *PICALM-*, *FRMD4A-*, *RUFY2-*, *TRIM24-*, and *TRIM33-*. *KIF5B-* is the most common *RET* fusion partner (72%) identified to date.[10] A new chimeric fusion transcript of *KIF5B* and the *RET* oncogene, *KIF5B-RET*, was identified in 1% to 2% of lung adenocarcinomas (LADCs) in 2012.[11] The *KIF5B-RET* fusion gene can induce the abnormal proliferation and differentiation of tumor cells through the constitutional overexpression and activation of the *RET* proto-oncogene, ultimately leading to LADCs.[12] *KIF5B-RET* is a previously unidentified LADC driver mutation and rarely occurs simultaneously with other driver genes, such as *EGFR*, *ALK*, or *KRAS*, and is more frequent in nonsmokers.[13-15] Patients with NSCLC harboring the *KIF5B-RET* fusion gene can become sensitive to cytotoxic chemotherapies, including pemetrexed-based regimens, similar to *ALK-* or *ROS1*-rearranged lung cancers.[16] Although there are currently no clinically approved RET-selective inhibitors, several multi-targeted drugs with anti-RET activity, including cabozantinib, vandetanib, sunitinib, and sorafenib, have been evaluated in preclinical models and clinical trials.[10]

We analyzed previous reports based on histologic detection and found a case of LADC harboring a coexisting *KIF5B-RET* fusion gene and *EGFR* mutation. Hirai et al[17] reported a case of *EGFR* mutation in the primary lesion that showed a poor response to erlotinib, and repeat biopsy showed that both the primary lesion and metastatic lymph nodes harbored the *KIF5B-RET* fusion gene. Kim et al[18] indicated that the *KIF5B-RET* fusion gene may coexist with oncogenic mutations of the *EGFR* or *KRAS* gene in LADCs. When the response to molecular targeted therapy does not correlate with genetic information, oncologists should be aware of this novel molecular mechanism of resistance against EGFR-TKIs, or the possibility of other oncogenic driver mutations. Desai et al[19] reported the occurrence of a *CCDC6-RET* fusion gene along with the *EGFR* T790M mutation in association with disease progression after treatment with EGFR-TKIs. They suggested the emergence of the *CCDC6-RET* fusion gene as a possible mechanism of acquired resistance to EGFR-TKIs in *EGFR*-mutant NSCLC. Moreover, Schrock et al[20] analyzed 3505 unique *EGFR*-mutated (*EGFR*+) NSCLC to identify and characterize cases with co-occurring kinase fusions as potential resistance mechanisms to EGFR TKIs, and they found that a total of 31 *EGFR*+ cases had concurrent kinase fusions detected: 10 (32%) *BRAF*, 7 (23%) *ALK*, 6 (19%) *RET*, 6 (19%) *FGFR3*, 1 (3.2%) *EGFR*, and 1 (3.2%) *NTRK1*, including 2 novel fusions (SALL2-*BRAF* and PLEKHA7-*ALK*). Twenty-seven of 31 patients had either a known prior history of EGFR+ NSCLC diagnosis or prior treatment with an EGFR-TKI before the fusion+ sample was collected. The partner of *RET* fusions were *CCDC6-*, *NOCA4-*, and *TRIM24-*. In the present case, although partial response was achieved after treatment with first-generation EGFR-TKIs, the patient acquired resistance to first-generation EGFR-TKIs after almost 1 year. A repeat liquid biopsy identified the *KIF5B-RET* fusion gene. Hence, we propose that the emergence of the *KIF5B-RET* fusion gene may be a cause of acquired resistance to EGFR-TKIs in *EGFR*-mutant LADCs.

Repeat liquid biopsy of peripheral blood for circulating tumor DNA or circulating tumor cell analyses at clinical progression have become increasingly important, as the results may better predict the

prognosis of patients and guide treatment.[20-22] Furthermore, liquid biopsy approaches are noninvasive and can be used to overcome the problem of heterogeneity associated with acquired resistance to first-generation EGFR-TKIs.[21,23]

In conclusion, the present case indicated that the *KIF5B-RET* fusion gene may underlie the acquisition of resistance against EGFR-TKIs, and suggested that repeat liquid biopsy is necessary when the response to molecular targeted therapy is less than optimal. Further research is warranted to explore the mechanism underlying the resistance to EGFR-TKIs to develop targeted treatments against *KIF5B-RET* fusion gene-related resistance to EGFR-TKIs.

Acknowledgments

This study was supported in part by grants from the Science and Technology Planning Project of Zhejiang Province (2015C33194), the Medical Scientific Research Foundation of Zhejiang Province of China (2019RC027), the Technology Bureau of Jiaxing City of Zhejiang Province (2016AY23087, 2017BY18060), and the National Clinical Key Specialty Construction Program (2013) supported this work.

Disclosure

The authors have stated that they have no conflicts of interest.

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