Case Report

Lung adenocarcinoma patient with an *EGFR* kinase domain duplication (KDD) and the response to icotinib

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related morbidity and mortality worldwide (1). Epidermal growth factor receptor (*EGFR*) mutations, as driver oncogenes, were first identified in NSCLC in 2004 (2). Approximately 10% of Caucasian patients and 50% of Asian NSCLC patients have *EGFR* mutations (3,4). The most common *EGFR* mutations are deletions of exon 19, which account for 45% of all *EGFR* mutations, and the exon 21-point mutation, L858R, which accounts for 35% of all *EGFR* mutations) (5,6). Some clinical trials have demonstrated that most mutations involving exons 18, 19, and 21, especially for sensitive *EGFR* mutations, are considered predictive of the sensitivity response to EGFR tyrosine kinase inhibitor (TKI) therapy (5,7,8). Due to the limitations of first-generation testing techniques, uncommon *EGFR* mutations are not detected. It is our opinion that it is uncommon for these wild-type patients to have *EGFR* mutations. Moreover, these patients have poor survival because they do not receive EGFR-TKIs treatment. With the development of precise detection techniques, more and more rare or atypical *EGFR* mutations have been identified. Next generation sequencing (NGS) analyses are feasible in patients with NSCLC and identify notable proportions of patients who are potentially eligible for emerging molecular therapeutics, such as exons 18–25 kinase domain duplications (KDDs) and *EGFR* fusions (*EGFR-RAD51* or *EGFR-PURB*) (9,10). We know *EGFR*-KDD exists in NSCLC patients; however, the efficacy of EGFR-TKI treatment is still uncertain. We report the first case involving the presence of oncogenic *EGFR*-KDD in China. The patient had stable disease to treatment with an EGFR-TKI. In addition, we have summarized previous cases who had *EGFR*-KDD mutation NSCLC and whether or not EGFR-TKIs treatment was administered.

Case presentation

A 63-year-old Chinese female, who was a non-smoker, presented to our hospital for evaluation of a left lung mass on physical examination. A computed tomography (CT) scan showed a mass in the superior lobe of the left lung, and close to a pleural nodule (*Figure 1*). For staging purposes, surgery was performed. Hematoxylin and eosin staining of the surgical specimen showed a typical morphology for adenocarcinoma cells and surgical specimens from the left lobe tumor and pleural nodes (2.3 cm × 1.3 cm × 1.0 cm) showed lung adenocarcinoma (*Figure 2*). The immunohistochemical results [TTF-1 (+), NapsinA (+), CK7 (+)] According to the 7th edition of TNM staging, the patient was classified as stage IV (T1N0M1). The patient was wild-type for sensitive *EGFR* variants, including *EGFR*

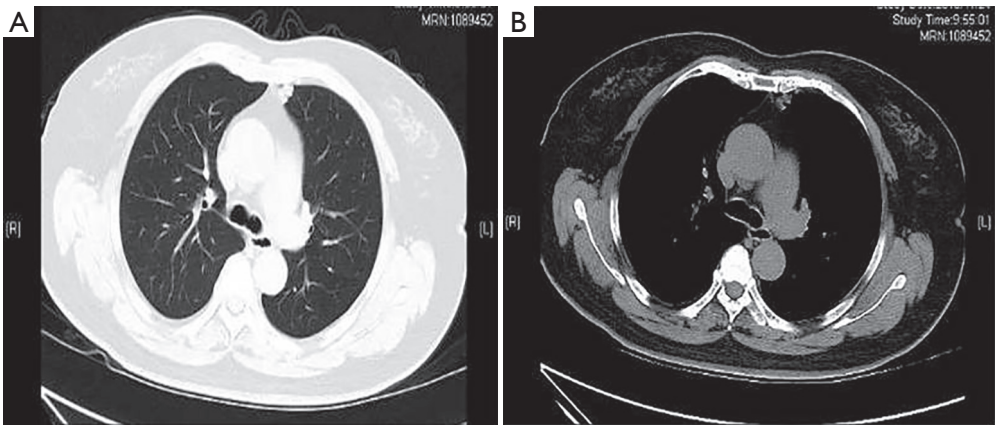

Figure 1 Computed tomography (CT) scans show: (A) lung window before surgery and (B) mediastinal window before surgery.

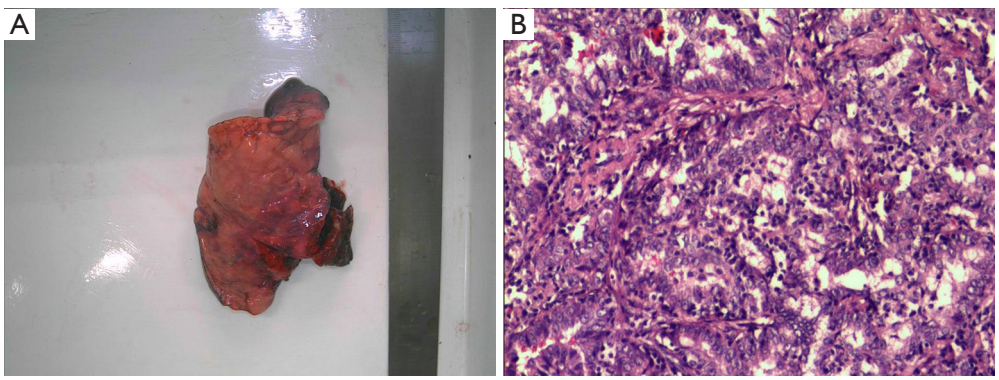

Figure 2 The gross morphology and microscopic morphology of lung tumor. (A) Surgery of left lung tumor; (B) hematoxylin and eosin (H&E) staining showed a typical morphology for adenocarcinoma cells (H&E, ×100).

18–21, by ARMS (AmoyDx, Xiamen, China) detection. Using an NGS assay (Illumina, San Diego, CA, USA), we found that the tumor had *EGFR*-KDD (3D Medicines, Shanghai, China) (*Figure 3*), and the most common types of *EGFR* mutations were wild. The patient received icotinib (125 mg/tid) treatment and showed a stable tumor response according to the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1). During treatment with icotinib, there were no treatment-related adverse events, including hepatic and renal function, gastrointestinal reactions, rashes, and cordis damage. To date, the disease is stable after 11 months and she is continuing treatment with icotinib. Our case is the first report of an *EGFR*-KDD mutation in the Asian population. Considering this rare *EGFR* mutation and response to TKI treatment, we conclude that the incidence of rare *EGFR* gene mutations in NSCLC patients should be studied.

Discussion

EGFR exons 18–25 KDDs were first described in a glioblastoma (11), and now are known to be a driver gene in lung cancer. In 2015, *EGFR*-KDD was first reported in a patient with lung adenocarcinoma (12). A female patient with metastatic adenocarcinoma, but without a known activating *EGFR* mutation based on initial polymerase chain reaction testing, underwent a repeat biopsy which was evaluated with a NGS platform. She was shown to have an *EGFR*-KDD mutation and demonstrated remarkable disease control with erlotinib therapy. In addition, Gallant *et al.* (9) reported a male patient with lung adenocarcinoma and an *EGFR*-KDD mutation detected with NGS. The patient had a partial response to afatinib therapy. These findings were studied *in vitro* and *EGFR*-KDD expression had significantly increased colony formation compared to

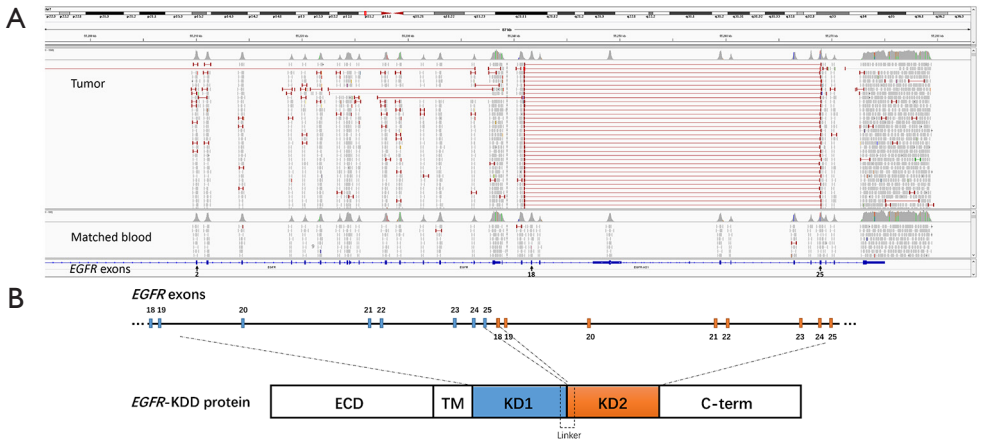

Figure 3 The *EGFR*-KDD is an oncogenic *EGFR* alteration. (A) the Integrative Genomics Viewer snapshot of paired NGS reads of tumor and matched blood; (B) schematic representation of *EGFR*-KDD depicting the genetic and protein domain structures. Blue, *EGFR* exons 18–25 #1; orange, *EGFR* exons 18–25 #2. *EGFR*, epidermal growth factor receptor; KDD, kinase domain duplication; ECD, extracellular domain; TM, transmembrane domain; KD1, first kinase domain; KD2, second kinase domain; C-term, carboxyl terminus.

the *EGFR* wild type and oncogenic *EGFR*-L858R mutation. Therefore, *EGFR*-KDD is an oncogenic alteration. Gallant *et al.* (9) also analyzed whether or not EGFR-TKIs is an effective therapeutic strategy for tumors harboring the *EGFR*-KDD mutation. Third-generation EGFR-TKIs (erlotinib, afatinib, and AZD9291) are able to inhibit *EGFR*-KDD tyrosine phosphorylation in a dose-dependent manner, albeit to different levels, and afatinib is the most potent inhibitor of *EGFR*-KDD autophosphorylation to decrease cell viability. The current report describes the first Asian patient with an *EGFR*-KDD mutation who derived a sustained anti-tumor response from treatment with the EGFR-TKI, icotinib. We have summarized the lung cancer patients who have been reported to have *EGFR*-KDD mutations in *Table 1*. Therefore, for this type mutation in NSCLC patients, EGFR inhibitors may be a first-line therapy, as in sensitive *EGFR* mutation patients.

A majority of patients ultimately develop acquired resistance to EGFR-TKI therapy and experience disease progression with a median progression-free survival of 9–13 months (5,7,8). With the in-depth study of resistance mechanisms, researchers have found various resistance mechanisms to first-generation EGFR-TKIs. The *EGFR* T790M mutation is regarded as the most common cause of acquired resistance, affecting 50% of patients (13). Other mechanisms include bypass signaling activation, such as *MET* gene amplification, *BRAF* (G469A and V600E) mutations, and *HER2* amplification and phenotype transition, including transition to small cell lung cancer and epithelial mesenchymal transition (14). Whether or not the acquired resistance mechanisms of EGFR-TKIs to uncommon EGFR mutation is similar to sensitive mutations is unclear. In the case described by Gallant *et al.* (9), the patient develop acquired resistance to afatinib after seven cycles of therapy. Molecular profiling was performed on the afatinib-resistant tumor biopsy sample, which showed significant amplification of the *EGFR*-KDD allele that differed from his pre-treatment tumor sample. Amplification of the mutant *EGFR* allele has been reported as a mechanism of acquired resistance in lung cancer patients with sensitive *EGFR* mutations (15). In addition, in the case reported by Christina S. Baik, the post-TKI resistance biopsy demonstrated a low level of T790M (12). Therefore, the acquired resistance of *EGFR*-KDD to EGFR-TKI may include the most common mechanisms of T790M mutation (a sensitive gene mutation, amplification of the *EGFR*-KDD mutation, and an EGFR-dependent mechanism of resistance). Due to the small number of cases, further exploring therapeutic targets in these patients and acquired resistance mechanisms are needed.

The polymerase chain reaction-based testing method is the standard assay routinely used clinically for NSCLC patients; however, some rare or uncommon types of *EGFR* gene alterations are not identified. Developments in multiple genome sequencing, such as NGS, is a more precise method for detecting a large number of gene alterations with known

Table 1 Clinical characteristics of patients with non-small cell lung cancer harboring *EGFR* KDD

Patient No.	Ethnicity	Age/gender	Smoking status	Diagnosis	EGFR TKI	Assessment
1	American	52/female	Never smoking	Adenocarcinoma	NA	NA
2	American	33/male	Never smoking	Adenocarcinoma	Afatinib	PR
3	American	53/female	Never smoking	Adenocarcinoma	NA	NA
4	American	57/female	Never smoking	Adenocarcinoma	NA	NA
5	American	29/female	Never smoking	Non-small cell lung cancer (NOS)	NA	NA
6	NA	69/male	NA	Adenocarcinoma	NA	NA
7	NA	33/male	NA	Adenocarcinoma	NA	NA
8	NA	68/female	NA	Adenocarcinoma	NA	NA
9	American	NA/female	Prev/curr smoking	Adenocarcinoma	NA	NA
10	American	NA/female	Never smoking	Adenocarcinoma	NA	NA
11	American	45/female	Prev/curr smoking	Adenocarcinoma	Gefitinib	PR
12	Asian	63/female	Never smoking	Adenocarcinoma	Icotinib	DFS did not reach

EGFR, epidermal growth factor receptor; KDD, kinase domain duplication; TKI, tyrosine kinase inhibitor; PR, partial response; DFS, disease-free survival.

and unknown gene mutations (16). Moreover, NGS can provide information for resistance mechanisms after disease progression on targeted therapy. For lung cancer patients to benefit from more personalized cancer treatment, clinical therapy should improve with clinical diagnostics through multi-gene assays to determine the actual clinical benefits.

This case report increases the evidence supporting EGFR-TKI treatment of *EGFR*-KDD mutations in NSCLC patients. In the future, we think it is possible to discover rare gene mutations during the routine use of multi-gene sequencing assays and explore differences in the acquired mechanism of 1st–3rd generation EGFR inhibitors between sensitive *EGFR* mutations and other uncommon mutations in NSCLC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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