



A Rare Epidermal Growth Factor Receptor G735R Mutation in Advanced Non-Small-Cell Lung Cancer with Poor Response to Gefitinib

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Abstract

Background: Uncommon mutations account for 10% to 15% of Epidermal Growth Factor Receptor (EGFR) mutations in patients with Non-Small Cell Lung Cancer (NSCLC). However, limited clinical evidence is available on the efficacy of EGFR tyrosine kinase inhibitors in patients with NSCLC harboring these uncommon EGFR mutations.

Case Report: Here we report a 74-year-old man was diagnosed with stage IV lung adenocarcinoma by bronchoscopic biopsy to the left principal bronchus lung tumor. A novel EGFR p.G735R (c.2203G>C) mutation in exon 19 was detected by gene sequencing. The patient received first-line Gefitinib but primary resistance was noted with rapid tumor progression.

Conclusion: Our case suggests that G735R may be one of the EGFR TKI primary resistant rare EGFR mutations.

Keywords: NSCLC; EGFRG735R mutation; Gefitinib treatment; Primary resistance

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Abbreviations

EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-Smallcell Lung Cancer; TKI: Tyrosine Kinase Inhibitor; CT: Computed Tomography; EBUS-TBNA: Endobronchial Ultrasound Transbronchial Needle Aspiration; HE: Hematoxylin and Eosin; NGS: Next-Generation Sequencing; MAPK: Mitogen-Activated Protein Kinase; STAT3: Signal Transducer and Activator of Transcription 3

Introduction

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer-related death worldwide [1]. Mutation in Epidermal Growth Factor Receptor (EGFR) gene is one of the principal mechanisms leading to tumorigenesis of NSCLC and was found in up to 50% of Asian, female patients who never smoked [2]. EGFR mutation occurs mainly in exons 18 to 21, especially exon 19 deletion and exon 21 L858R covering about 85% of all EGFR mutations and resulting in a generally favorable response to Tyrosine Kinase Inhibitor (TKI) therapy [3]. The remaining 10% to 15% of EGFR mutations are regarded as “non-classical” or “uncommon” mutations and composed of a heterogeneous group of single or compound gene alterations within exons 18 to 21 [4]. However, the clinical significance and implications of uncommon mutations in EGFR are still unclear. Approximately 5% to 10% of TKI-treated patients exhibit primary resistance [5]. Here, we report a case of lung adenocarcinoma in which primary resistance to gefitinib treatment was caused by a novel G735R point mutation of EGFR exon 19.

Case Presentation

A 74-year-old man was admitted to our hospital in January 2019 due to a chronic cough. Computed Tomography (CT) scan showed a mass in the left upper lobe and enlarged multiple lymph nodes in the ipsilateral mediastinum and hilum (Figure 1A). An Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA) biopsy from the left principal bronchus was performed. The results of Hematoxylin and Eosin (HE) staining showed adenocarcinoma infiltration in the lung tissue, and poorly differentiated carcinoma was the dominant type. The

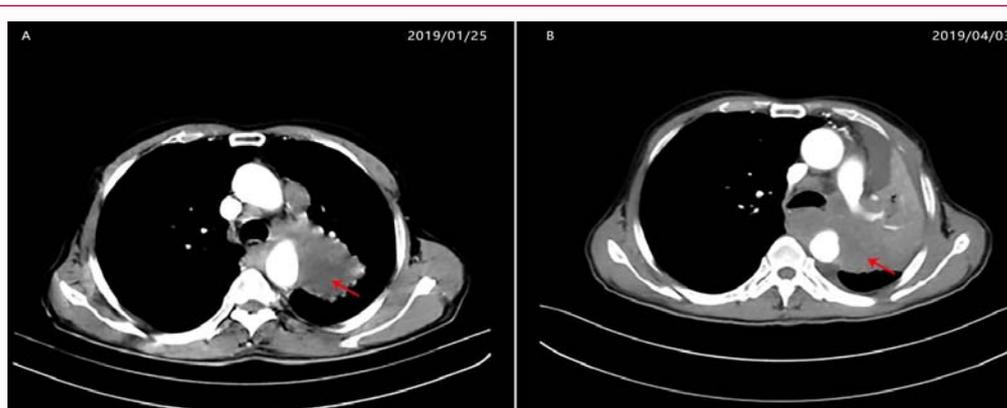


Figure 1: Chest CT scans showed the effects of different treatment stages of the patient's lung tumor. (A) Initial diagnosis revealed a space-occupying lesion in the left lung in January 2019. (B) Gefitinib treatment for 6 weeks in April 2019.

Table 1: Gene mutation lists for the NGS analysis.

Gene name	Mutation	Mutation abundance (%)
EGFR	NM_005228 exon19 c.2203G> Cp.G735R	17.62
TP53	NM_000546 exon5 c.537T>Ap.H179Q	81.16
ERBB2	Copy number gain	4.78

immunohistochemical markers were as follows: ALK-Lung (-), CD56 (-), CK (pan) (+), CK7 (+), TTF-1 (-), Napsin A (+), P63 (-), CK5/6 (-), Syn (-). Thus, the patient was diagnosed of stage IV (T4N3M1b) central lung adenocarcinoma with metastasis to mediastinal lymph node and right adrenal gland. The patients received one cycle of chemotherapy and subsequent standard follow-up. In February 2019, a follow-up thoracic CT performed after one month of chemotherapy, revealed the increase of lung lesions. A biopsy sample was subjected to 13-gene Next-Generation Sequencing (NGS) analysis. Genomic sequencing showed novel mutation of EGFR p.G735R in exon 19, ERBB2 copy number gain and TP53 p.H179Q mutation (Table 1). According to the result of EGFR G735R mutation, the oral administration of gefitinib was initiated on February 25th, 2019. Follow-up clinical and imaging examinations at 6 weeks of treatment showed rapid disease progression with enlargement of lung tumor (Figure 1B). Then the patient died in one month later, indicating a pattern of primary resistance.

Discussion

Resistance to EGFR-TKIs can be divided into primary or acquired resistance [6]. Primary resistance refers to the immediate inefficacy of EGFR-TKI in three months, while acquired resistance is progression of the disease after duration of clinical benefit [7]. Acquired resistance to TKI in patients with advanced NSCLC harboring sensitive EGFR mutations has been well documented, such as somatic T790M mutation and germline T790M polymorphism, or germline EGFR V843I mutation [8,9]. However, knowledge of primary TKI resistance is limited. In our case, the patient showed rapid resistance to gefitinib. None of the existing mechanisms for primary resistance was found. Instead, NGS revealed a rare primary EGFR mutation, G735R in exon 19 within the pretreatment tumor, implying close correlation with the rapid resistance to gefitinib. EGFR G735R point mutation in exon 19 in lung cancer has not been reported in the literature or databases and clinical significance is unknown [10]. However, a transition exon 19 c.2203G>A, p.G735R mutation at the same position has been observed [11,12]. This mutation has been described seven times in lung cancer

(COSMIC databank accessed 31.10.2019) with no data on response to EGFR-TKI therapy given in the literature. One research on prostate cancer *in vitro* revealed that [13], EGFRG735S may be a pathogenic mutation and is related to the occurrence and development of tumors. Western blot analysis showed that the EGFRG735S mutation enhanced cell growth and invasion *via* constitutive and hyperactive tyrosine phosphorylation and led to the activation of Mitogen-Activated Protein Kinase (MAPK), Signal Transducer and Activator of Transcription 3 (STAT3) and Akt pathways. In addition, a recent study has reported a case carrying G735S mutation [14]. The patient with adenocarcinoma stage IV showed progressive disease on 2nd line EGFR-TKI therapy with gefitinib, suggesting that this G735S mutation is associated with resistance to EGFR-TKI. The same finding in our case is that the EGFR G735R mutation was primary resistant to gefitinib treatment. To our knowledge, this is the first case to report the efficacy of the first generation TKI in an NSCLC patient harboring this rare mutation. The second-generation irreversible EGFR-TKI, afatinib, exhibits more convincing efficacy against non-classical EGFR mutations [15,16]. In addition to EGFR mutation, the patient in our case also harbored ERBB2 copy number variants and TP53 mutation. Genomic data suggest that afatinib combined with ERBB2 monoclonal antibody may be effective. Upon a comprehensive literature review, a recent case report from China presented a patient with advanced NSCLC harboring a rare EGFR L747P mutations in exon 19, who failed first-line gefitinib and the third generation TKI osimertinib but achieved sustained disease control to bevacizumab and erlotinib [17]. The possible reason is that the upregulation of the EGFR signaling pathway enhances the production of angiogenic factors, including VEGF, and dual blockade of VEGF and EGFR, resulting in additive anti-tumor activity, and may prove to be an alternative treatment in advanced NSCLC with resistance [18,19]. In our case, the patient died before being treated for gefitinib resistance and the efficacy of subsequent second generation TKI cannot be evaluated. Based on *in vitro* testing, we wondered whether afatinib or bevacizumab were a clinically beneficial regimen for NSCLC patients with the EGFR G735R mutation, but to date, no case reports have been verified.

Conclusion

In conclusion, the results of this case suggest that the rare EGFR G735R mutation in exon 19 confers primary resistance to the first generation TKI gefitinib. Because of the rarity of this mutation, the relationship between G735R mutation and gefitinib resistance

requires further study. Moreover, it is necessary to seek strategies to overcome G735R associated TKI resistance.

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