

Osimertinib treatment response in a patient with lung adenocarcinoma harboring two rare EGFR mutations: A case report

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Abstract. Epidermal growth factor receptor (*EGFR*) mutations have emerged as the most well-studied oncogenic alterations in advanced non-small cell lung cancer. The presence of single common or rare *EGFR* mutations and extra complex *EGFR* mutations correlates with the response sensitivity to *EGFR* tyrosine kinase inhibitors. Therefore, given the lack of evidence for the emergence of rare *EGFR* mutation types, the pathogenic mechanisms of uncommon *EGFR* mutations and the optimal treatment strategies remain to be explored further. The present study describes the case of a patient diagnosed with lung adenocarcinoma (LUAD) carrying two rare *EGFR* exon 18 indel/G719C and exon 19 L747S mutations, in which persistent lesion shrinkage was exhibited within 16 months of osimertinib treatment. Given the paucity of clinical trials for the treatment of LUAD harboring complex *EGFR* mutations, the present detailed case description may provide clinicians with effective clinical experience in treating patients.

Introduction

Lung cancer remains a formidable global health challenge, claiming more lives than any other type of cancer. According

to the World Health Organization, lung cancer accounted for ~1.8 million deaths in 2020. This represents a significant burden on global health, particularly in developing countries. Despite advancements in prevention and treatment, the incidence of lung cancer continues to rise in many regions, underscoring the need for urgent action (1). Lung cancer bearing epidermal growth factor receptor (*EGFR*) mutations was originally discovered in 2004, and precise identification of the *EGFR* mutation type has laid the foundation for subdividing the clinically relevant molecular subtypes of non-small cell lung cancer (NSCLC) (2,3). Notably, *EGFR* mutations have mostly been found in lung adenocarcinoma (LUAD), which is the most classic histological form of NSCLC, and the prevalence of *EGFR*-mutated lung tumor is high in Asian populations, recorded at >40% (4). Clinically, patients with LUAD carrying *EGFR*-positive mutations have markedly inconsistent responses to *EGFR* tyrosine kinase inhibitors (TKIs) (5). Considering that clarifying whether a patient carries a driver gene is a prerequisite for predicting the clinical efficacy of molecularly targeted precision medicines, certain clinical practice guidelines recommend performing *EGFR* mutation testing in all lung cancer patients whose tumors contain adenocarcinoma components (6).

In total >30 types of *EGFR* mutations are scattered throughout the exon region encoding TK, of which deletion mutations in exon 19 and point mutations in exon 21 (L858R) are the most 'classic' (7,8). Patients with NSCLC harboring common *EGFR* mutations represent >85% of all *EGFR*-positive lung cancer cases. The remaining *EGFR*-positive cases (<15%) have uncommon mutations gathered within exons 18-21 (rare mutations: G719X, E709X or S768I) (9). With advances in precision detection technology, it appears that *EGFR* compound mutations (combinations of two or more unclassical mutations) are present in >1% of patients with NSCLC (3,9). Known mutation types help in selecting personalized effective treatment decisions. Information from a previous case report suggested that the combination of an *EGFR* TKI-sensitizing rare mutation with another resistant uncommon mutation diminished the patient's sensitivity to a TKI (10). However,

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rare *EGFR* mutations are characterized by high heterogeneity and low frequency, and combinations of duplex or even triple rare mutations need to be further explored.

The present study reports the case of a patient with LUAD carrying two rare *EGFR* mutations (a compound mutation in exon 18 indel/p.G719C and exon 19 p.L747S) who received osimertinib.

Case report

In October 2020, an 81-year-old man with a 68-year history of smoking was admitted to The Tenth Affiliated Hospital of Southern Medical University, Dongguan People's Hospital (Dongguan, China) suffering from persistent shortness of breath for 1-month. The patient developed a productive cough and worsened shortness of breath within the week prior to admission to the hospital. The chest radiograph presented a predominantly left-sided pleural effusion and no significant right-sided pleural effusion. After admission, the patient underwent thoracentesis catheter drainage guided by B-ultrasound. The pleural fluid was bloody and turbid, with lactate dehydrogenase (LDH) level of 1,028 U/l (normal range, 109-245 U/l). Hematoxylin and eosin staining identified a small number of atypical cells in the pleural fluid (Fig. 1A; Data S1). Immunohistochemical results also showed positive staining for cytokeratin (CK)7, thyroid transcription factor-1 and napsin A, while CK5/6 staining was negative (Fig. 1B-D; Data S1). The laboratory tests also revealed that the serum NSCLC-associated antigen (CK19 fragment antigen 21-1) level was 4.32 $\mu\text{g/ml}$ (normal level, 3.3 $\mu\text{g/ml}$), which was considered a more likely cause of LUAD. Further whole-body positron emission tomography/computed tomography (CT) examination revealed a lingual nodule in the upper lobe of the left lung, measuring 1.9x1.6 cm, with increased fluorodeoxyglucose metabolism, which was considered peripheral lung cancer (Fig. 2). In combination with the pathological findings, this confirmed that the patient had LUAD. Another whole-body scan imaging revealed multiple metastatic lesions involving the pleura, lymph nodes and bones. In order to find a reliable treatment strategy, in October 2020, the patient's chest fluid sediment biopsy tissue and plasma were submitted for next-generation sequencing (NGS) separately. DNA sequencing was performed by Geneseeq Technology, Inc., using a panel of 139 lung cancer-related genes. Briefly, the genomic DNA from FFPE sections, biopsy samples and whole blood control samples was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen, Inc.) and the DNeasy Blood and Tissue Kit (Qiagen, Inc.), respectively. Circulating cell-free DNA (cfDNA) from plasma was extracted using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Inc.). Sequencing libraries were prepared using the KAPA Hyper Prep Kit (Kapa Biosystems, Inc.) following the manufacturer's instructions. Customized xGen Lockdown probes (Integrated DNA Technologies, Inc.) targeting 139 cancer-relevant genes were used for hybridization enrichment. The capture reaction was performed with Dynabeads M-270 (Thermo Fisher Scientific, Inc.) and xGen Lockdown Hybridization and Wash Kit (Integrated DNA Technologies, Inc.). Captured libraries were PCR amplified on beads using Illumina p5 and p7 primers in KAPA HiFi HotStart ReadyMix (Kapa Biosystems, Inc.) and purified

with Agencourt AMPure XP beads. Libraries were quantified by qPCR using the KAPA Library Quantification Kit (Kapa Biosystems, Inc.), with a final loading concentration of 2.5 nM. The library fragment size was determined using a Bioanalyzer 2100 (Agilent Technologies, Inc.). The target-enriched library was sequenced on the HiSeq4000 NGS platform (Illumina, Inc.) using a paired-end 150 bp sequencing strategy. Data analysis involved quality control with Trimmomatic (version 0.39; <https://github.com/usadellab/Trimmomatic>), alignment using BWA (version 0.7.17; <https://github.com/lh3/bwa>), PCR deduplication with Picard (version 2.23.8; <https://github.com/broadinstitute/picard>), and variant calling using Mutect [version 1.1.7 (older version) or part of GATK 4.x series (current); <https://gatk.broadinstitute.org/hc/en-us/articles/360037593851-Mutect2>) and Scalpel (version 0.5.3; <https://github.com/lezonlab/scalpel>), followed by annotation with vcf2maf (version 1.6.19; <https://github.com/mskcc/vcf2maf>). The sequencing depth was 150X for whole blood control samples, 1500X for tumor tissues, and 5000X for cfDNA samples.

Two uncommon *EGFR* mutations [exon 18 c.2154_2155delinsTT (p.G719C) missense mutation and exon 19 c.2240T>C (p.L747S) missense mutation] were present (Table I). In addition, the tumor protein p53 (*TP53*) exon 4 c.228del (p.P77Qfs*46) frameshift mutation and the cyclin-dependent kinase 6 (*CDK6*) exon 2 c.112C>G (p.R38G) missense mutation were also identified as common mutations. In response to the *EGFR* mutation, the patient was administered osimertinib treatment orally (80 mg per day) from 1 week after admission (Fig. 3A), and evaluation of the tumor by CT scans displayed a persistent partial response to the disease for the next 2 months.

In December 2020, CT of the chest and upper abdomen showed that the focal nodule in the upper lobe of the left lung had regressed (Fig. 3B), with a size of 1.3x1.2 cm, that the number and size of pleural nodules were reduced compared with before, and that a small amount of effusion had appeared in the pericardial cavity and the left pleural cavity (Fig. 3C-E). The left-sided lung disease was in partial remission, which suggested that the osimertinib treatment strategy was effective. However, CT also revealed new lesions in the liver (S4) and thyroid gland. By February 2022, a repeat CT examination indicated that the patient's left lung lesion remained stable after 16 months of treatment with osimertinib. During the whole case period, the patient underwent monthly physical examinations and quarterly imaging studies.

Discussion

In recent years, NSCLC treatment has moved from histology-based therapy to molecularly targeted precision therapy for driver genes. In this therapeutic context, *EGFR* genotyping based on NGS technology has also become the preferred approach for assessing NSCLC (11,12). As an event usually excluded from clinical trials, the discovery of non-classical or complex *EGFR* mutations has opened up new opportunities for patients with NSCLC, especially for those with LUAD. However, there is a paucity of data obtained on rare *EGFR* mutations in the clinical setting. Given that *EGFR* mutations are highly heterogeneous genetic alterations that

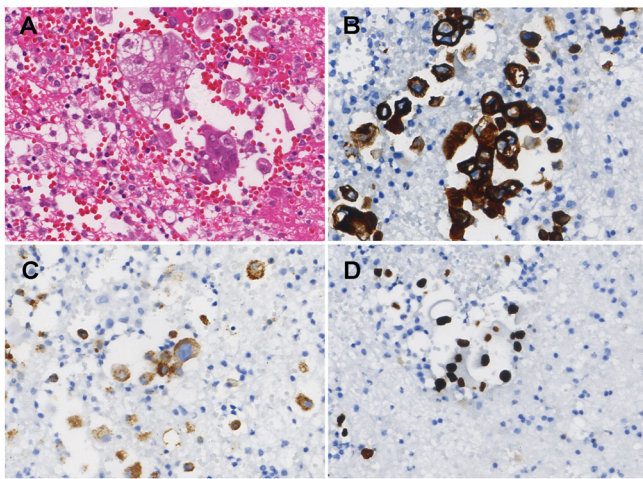


Figure 1. Histological and immunohistochemical findings. (A) Hematoxylin and eosin staining demonstrating the overall morphology of the tissue (x400 magnification). (B) Immunohistochemical staining for cytokeratin 7 highlighting epithelial cells (x400 magnification). (C) Immunohistochemical staining for napsin A, a marker for type II pneumocytes (x400 magnification). (D) Immunohistochemical staining for thyroid transcription factor-1, a marker for lung adenocarcinoma (x400 magnification). Scale bar, 50 μ m.

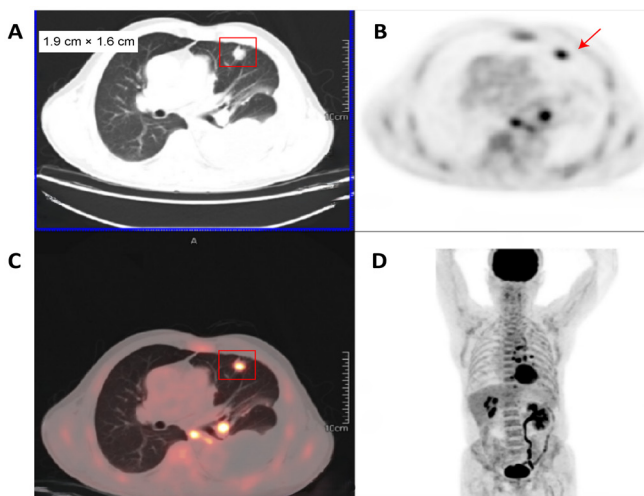


Figure 2. CT and PET/CT images of lung adenocarcinoma in an 81-year-old patient. (A) Pulmonary CT scan performed in October 2020 showing a nodule measuring 1.9x1.6 cm in the lingual segment of the upper lobe of the left lung, indicated by a red box. (B) PET scan indicating metabolic activity in the same area, marked by a red arrow. (C) Combined PET/CT scan corroborating the nodule's location, also indicated with a red box. (D) Whole-body PET scan revealing multiple pleural and lymph node metastases, as well as bone metastases. PET, positron emission tomography; CT, computed tomography.

occur within tumor lesions, and that rare *EGFR* mutations occur at a low frequency in LUAD tumors, there is a need to perform a more refined analysis of these patients. The present study reports the rare case of a patient in whom two non-classical *EGFR* mutations, indel/G719C (exon 18) and L747S (exon 19), were observed in the tumor tissue. Furthermore, a significantly better outcome in contrast to the typical outcome of patients with NSCLC, was observed in this patient, who responded well to osimertinib. Notably, the presence of *CDK6* and *TP53* mutations may be a key oncogenic event common to advanced *EGFR*-mutated LUAD. *CDK6* mutations have

been associated with tumorigenesis and progression in certain cancer types, such as breast (13), lung (14) and prostate (15) cancer. However, specific data on the prognostic impact in LUAD, particularly in the context of *TP53* mutations, may be limited (16). Numerous studies have, however, established a strong correlation between *TP53* mutations and a poor prognosis in various cancer types such as breast (17), lung (18) and colorectal (19) cancer, as well as LUAD. Patients with *TP53* mutations often exhibit advanced tumor stages, increased metastasis and reduced overall survival times (20).

EGFR exon 18 mutations have a low frequency, being observed in <4% of lung cancer patients with *EGFR* mutations (7). Among them, the G719X (X can be replaced by any base) point mutation is the predominant subtype among *EGFR* exon 18 mutations. To the best of our knowledge, the present case may be the first reported case on the application of the third-generation TKI osimertinib in a patient with LUAD carrying the *EGFR* exon 18 indel/G719C mutation. An encouraging efficacy of osimertinib has been reported in several case reports on LUAD with uncommon *EGFR* mutations. Fang and Liu (21) illustrated that patients with LUAD harboring *EGFR* T751_I759delinsS sustained a marked response to osimertinib for 16 months (21). In addition, a 2021 case report by Shan *et al* (22) also founded that high-dose osimertinib achieved great clinical benefit in a patient with metastatic lung cancer carrying two rare *EGFR* mutations (G719S and L861Q). Notably, the use of osimertinib was effective in extending the median overall survival time of the patients by >12 months. In a multicenter phase II study that included 36 patients with lung cancer, the objective response rate of osimertinib demonstrated in patients carrying the G719X mutation was ~50%, which was comparable to the response rate of a first-generation TKI (23). According to the present report, the patient was able to achieve a durable objective response with no adverse effects to osimertinib, suggesting a better efficacy of osimertinib against exon 18 indel compared with other treatment options.

Referring to previous datasets, more than three-quarters of G719X mutations are complex, that is, combinations of G719X with other rare or classical mutations. In one study, G719X and other mutations were present in 8 of 15 patients with lung cancer (24). In the present report, the patient carried the complex mutations of exon 18 indel/G719C + exon 19 L747S, which is a *de novo* compound mutation, before receiving TKI therapy. Considering that *EGFR* L747S is a crucial factor in the poor response to first-generation TKIs, the use of osimertinib may be feasible for patients with the aforementioned uncommon mutations. The G719C + L747S mutation was previously found in a female patient with LUAD whose symptoms of dyspnea and coughing disappeared within 1 month of osimertinib treatment, and a significant and sustained reduction in the lesion area was observed thereafter (25). The current case study is the first reported instance of a patient with *EGFR* L747S mutations responding positively to osimertinib treatment. The same appeared to be true for the exon 18 indel/G719C + exon 19 L747S mutations described in the present report and provided new clinical data for the treatment of patients with metastatic lung cancer harboring the G719C and L747S mutations.

The current study presents a detailed case report on a patient with LUAD carrying rare *EGFR* mutations and the response to osimertinib treatment. However, there

Table I. Patient tumor and plasma next-generation sequencing results.

Genes	Alterations	Nucleotide change	Plasma	Tissue
<i>EGFR</i>	p.G719C	c.2154_2155delinsTT	0.1%	31.4%
	p.L747S	c.2240T>C	0.2%	28.6%
<i>TP53</i>	p.P77Qfs*46	c.228del	-	18.1%
<i>CDK6</i>	p.R38G	c.112C>G	2.5%	-

EGFR, epidermal growth factor receptor; *TP53*, tumor protein p53; *CDK6*, cyclin-dependent kinase 6.

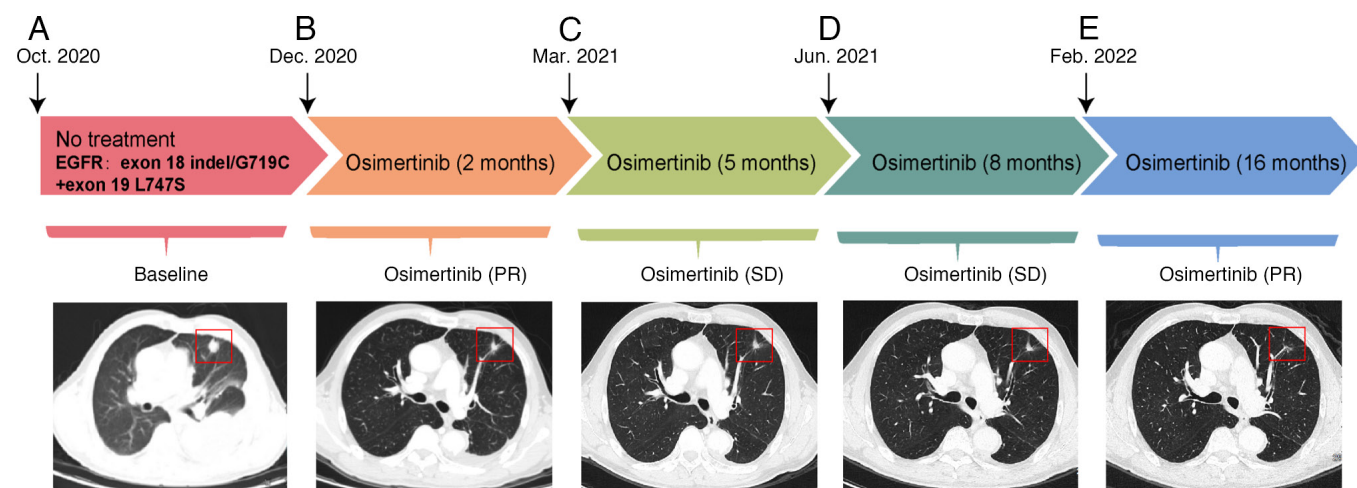


Figure 3. CT scan of the left upper lobe lung lesion before and after treatment. (A) The lesion in the left upper lobe of the patient's lung before osimertinib treatment. (B) Shrinkage of the lesion in the left upper lobe of the patient's lung after (B) 2, (C) 5, (D) 8 and (E) 16 months of treatment with osimertinib. The CT scan in February 2022 demonstrated significantly better outcomes than that in December 2020. PR, partial remission; SD, stable disease; CT, computed tomography; EGFR, epidermal growth factor receptor.

are several limitations and areas that could be improved. It is important to note that the study was restricted to a single patient, limiting the generalizability of the findings. Additionally, the lack of long-term follow-up data prevents a comprehensive understanding of the patient's overall survival and potential resistance development. The article also lacks detailed mechanistic insights into the efficacy of osimertinib for the specific EGFR mutations observed, and a more extensive review of comparative treatments would provide a broader context for evaluating the effectiveness of osimertinib.

In conclusion, the present study describes the case of a patient with LUAD carrying two rare *EGFR* mutations (exon 18 indel/G719C + exon 19 L747S) who responded well to osimertinib. This newly emerged complex mutation may be associated with a good progression-free survival time when using a third-generation TKI, but more convincing evidence is required to support this. To determine a more appropriate and comprehensive treatment strategy, a more extensive molecular analysis (e.g. NGS) is indispensable when dealing with lung cancer carrying *EGFR* mutations to maximize the identification of the complex genetic features of the cancer.

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Availability of data and materials

Due to the restrictions imposed by China's national legislation on patient privacy, the genome sequencing data generated and analyzed during the current study cannot be publicly shared. According to the Personal Information Protection Law and the Regulation on the Administration of Human Genetic Resources, the sharing of genetic data is strictly regulated to protect individual privacy and sensitive information. Researchers seeking access to this data for specific purposes may contact the corresponding author, subject to approval from relevant regulatory bodies.

Authors' contributions

All authors contributed to the manuscript. YL, LL, ZL and KL were responsible for the conception and design of the study. Data were collected and analyzed by YL, LL, CS and CL. ZL and KL confirm the authenticity of all the raw data. The manuscript was drafted by YL and LL, and was critically

revised by ZL and KL. The whole study was supervised by ZL and KL. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was performed according to institutional guidelines and was approved by Ethical Committee of The Tenth Affiliated Hospital of Southern Medical University, Dongguan People's Hospital (Dongguan, China; approval no. 2023KZPJ063), following the Declaration of Helsinki guidelines. Written informed consent was obtained from the patient for participation in this study.

Patient consent for publication

The patient provided written consent for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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