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Case Report

Advanced lung adenocarcinoma with rare *EGFR* exon 21 T854A mutation: a case report on increased dose osimertinib following resistance

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Abstract: *EGFR* T854A mutation, a rare genetic alteration, presents challenges in the treatment of lung adenocarcinoma due to its potential role in drug resistance. This case describes a 67-year-old male patient who was diagnosed with advanced left lower lobe adenocarcinoma with *EGFR* exon 21 L858R mutation and *EGFR* amplification in January 2018. Subsequently, the patient started gefitinib treatment, and 3 months later, the treatment effect assessment showed a partial response (PR) at regular follow-up according to RECIST evaluation criteria. Efficacy was maintained as PR/SD up to January 2021 until disease progression (PD). At the same time, the second genetic test showed that in addition to *EGFR* exon 21 L858R, there was also a new and rare *EGFR* exon 21 T854A mutation. In response, Osimertinib treatment was started in February 2021, and 3 months later, CT scans showed tumor shrinkage and stable disease (SD) that continued until September 2022. However, in December 2022, the enlargement of the primary tumor and the emergence of new metastases once again suggested disease progression after drug resistance. We implemented a double dose of Osimertinib treatment strategy for the patient. The patient achieved disease control and maintained progression-free survival for nearly 9 months without exhibiting any dose-related hematological or other systemic toxicities. Another progression of the disease occurred in September 2023, and newer drug-resistant mutations such as *EGFR* exon 20 C797S and exon 21 V834L appeared. Furthermore, we adopted double Osimertinib combined with Cabozantinib therapy. Two months later, imaging examination showed that the lesions in various parts of the body were stable. Except for dryness of oral and nasal mucosa, the patient did not experience other serious adverse reactions.

Keywords: Case report, advanced lung adenocarcinoma, epidermal growth factor receptor, T854A mutation, osimertinib

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, with adenocarcinoma being the most common histological subtype [1]. Epidermal growth factor receptor (*EGFR*) mutations have emerged as a significant predictive biomarker for the efficacy of *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs) in patients with NSCLC [2]. Among the common *EGFR* mutations, exon 19 deletions and exon 21 L858R point mutations are most prevalent, accounting for 85-90% of all *EGFR* mutations found in NSCLC patients [3].

While the treatment landscape for *EGFR*-mutant NSCLC has significantly evolved with the development of first, second, and third-generation *EGFR*-TKIs, resistance to these therapies invariably occurs. Resistance mechanisms are multifactorial, ranging from the development of secondary *EGFR* mutations, like T790M, to bypass signaling pathways and histologic transformation [4].

The *EGFR* exon 21 T854A mutation is a rare resistant mutation that has been scarcely reported in the literature. Understanding the clinical significance, the biological behavior of tumors harboring this mutation, and potential therapeutic strategies is essential for optimal

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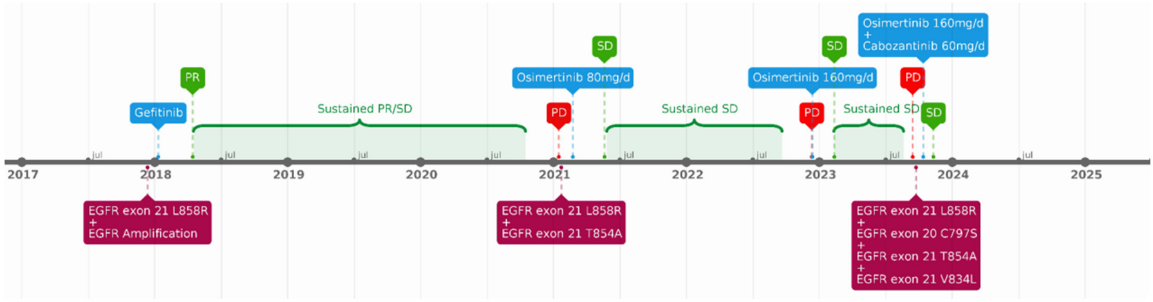

Figure 1. Treatment timeline chart. PR: partial response. SD: stable disease. PD: progressive disease.

patient management. In this case report, we present a patient with advanced lung adenocarcinoma harboring the *EGFR* exon 21 T854A mutation and review existing literature on this rare mutation.

Case report

This case concerns a 67-year-old male patient who experienced dyspnea, marked weight loss, fatigue, and decreased exercise tolerance in November 2017. Laboratory tests revealed hypoalbuminemia with serum albumin levels at 23 g/L and elevated lactate dehydrogenase (LDH) at 320 U/L. Additionally, the serum carcinoembryonic antigen (CEA) level was found to be five times above the upper limit of normal. These findings indicated a systemic impact of the malignant disease. In December 2017, further ultrasound examination of the chest revealed a large amount of pleural effusion, which was consistent with the patient's symptoms of dyspnea. Thoracentesis was performed for fluid examination and treatment, with pathological analysis of the pleural fluid confirming adenocarcinoma. In January 2018, the patient was hospitalized for further diagnostic assessments. A CT scan revealed adenocarcinoma in the lower lobe of the left lung, with metastases to the upper lobe of the right lung, bilateral hilar lymph nodes, mediastinal lymph nodes, and pleura. The definitive clinical diagnosis was stage IV adenocarcinoma of the left lung lower lobe. Genetic profiling identified an *EGFR* exon 21 L858R mutation (mutation abundance: 58.61%) and *EGFR* amplification (mutation abundance: 4.07%). Given the presence of pleural metastasis and the patient's significant systemic symptoms, the patient was deemed to have lost the opportunity for radical surgical intervention. Therefore, surgical treatment was not considered, and the patient primarily received drug therapy. Subsequently, the patient commenced gefitinib treatment in January 2018, with regular follow-ups indicating well-controlled pleural effusion. At three months, treatment evaluation, based on RECIST criteria, showed a partial response (PR). From April 2018 to October 2020, he maintained PR/SD status during routine outpatient follow-ups every three months. The various event diagrams of the patient throughout the course of the disease are shown in **Figure 1**.

However, imaging in January 2021 revealed an increase in the number of lesions in the left lung, enlarged bilateral hilar and mediastinal lymph nodes, and persistent bilateral pleural effusions, indicating progressive disease (PD). A second genetic test displayed a continued presence of *EGFR* exon 21 L858R (mutation abundance: 23.03%) and a new mutation, *EGFR* exon 21 T854A (mutation abundance: 23.55%). In response, Osimertinib treatment was initiated in February 2021, and after three months, a CT scan demonstrated tumor reduction, maintaining stable disease (SD). This stability persisted through his medication period until September 2022.

Nevertheless, in December 2022, imaging showed lesion progression in the lower lobe of the left lung and new metastases in the greater omentum and peritoneum, fulfilling the criteria for PD. The patient's Osimertinib dosage was doubled, and after three months, both the pulmonary and peritoneal lesions showed regression, achieving a controlled condition with evaluations indicating sustained SD. At the same time, the patient did not exhibit any dose-related hematological or other systemic toxic side effects.

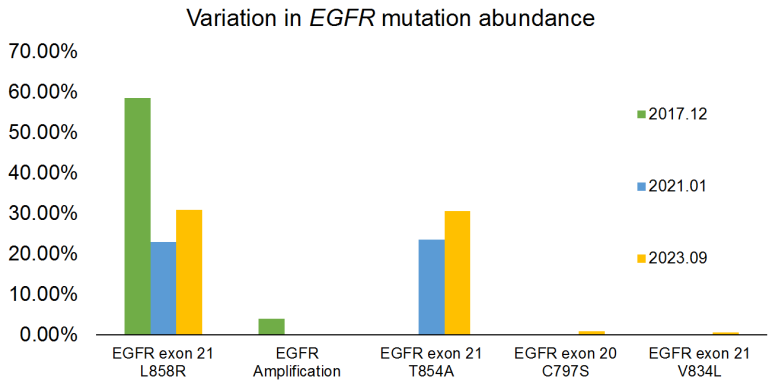

Figure 2. *EGFR* gene mutation and its abundance change chart.

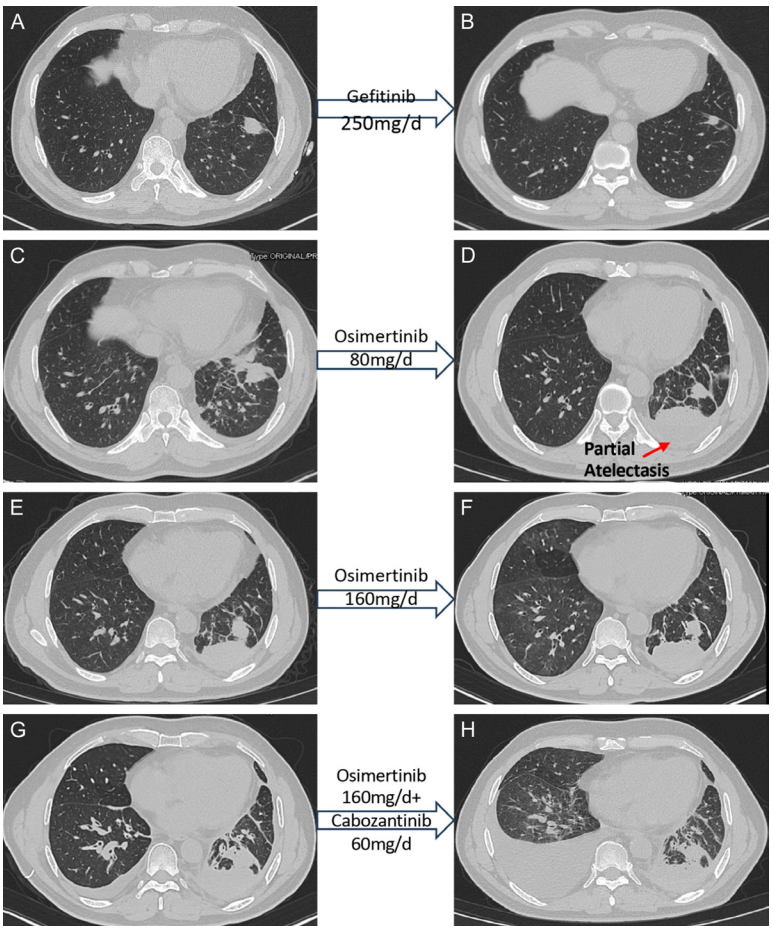

Figure 3. CT imaging changes of the primary lesion in the left lower lobe following treatment strategy modifications. A. CT image of the patient at the initial diagnosis. B. CT image after 3 months of treatment with gefitinib. C. CT image of the first disease progression. D. CT image after 3 months of osimertinib treatment. E. CT image of the second disease progression. F. CT image after more than 2 months of double-dose osimertinib treatment. G. CT image of the third disease progression. H. CT image after more than 1 month of double dose osimertinib combined with cabozantinib treatment.

Regrettably, a CT re-examination in September 2023 revealed an increase in the left lung lesions, substantial pleural effusion, and new liver and peritoneal metastases. Multiple thoracenteses and intrapleural cisplatin infusions were administered, yet the pleural fluid's pathology continued to indicate metastatic pulmonary adenocarcinoma. The third gene testing showed mutations in *EGFR* exon 21 L858R (mutation abundance: 30.9%), exon 20 C797S (mutation abundance: 0.9%), exon 21 T854A (mutation abundance: 30.7%), and exon 21 V834L (mutation abundance: 0.7%). The statistical graph of *EGFR* gene mutations during disease progression is shown in **Figure 2**. Owing to the patient's chronic renal dysfunction (creatinine clearance rate below 45 ml/min) and the high risk of chemotherapy-induced nephrotoxicity, systemic intravenous chemotherapy was not pursued. Considering potential alternative driver mutations, a double-dose therapy comprising Osimertinib and Cabozantinib was administered. Two months later, the patient's reexamination imaging results showed that except for the increase in contralateral pleural effusion, the lesions in the lungs and body had not increased compared with before, and the efficacy evaluation was SD. Imaging changes of representative primary left lower lobe lesions after each change in treatment strategy are shown in **Figure 3**. Apart from dryness of the oral and nasal mucosa, the patient did not experience any other serious adverse reactions. As of this report's drafting, the patient's overall condition is favorable, and pleural effusion is satisfactorily managed; ongoing monitoring of his condition is planned.

Discussion

Resistance to TKIs, whether primary or acquired, poses a significant clinical challenge in the management of NSCLC. The emergence of resistance can be attributed to several mechanisms, including the acquisition of secondary mutations in the *EGFR* gene or activation of bypass signaling pathways [5, 6]. Bean and colleagues first reported the association between the T854A mutation and acquired resistance [7]. This finding underscores the importance of conducting molecular typing and regularly monitoring *EGFR* mutation status to adjust treatment plans in a timely manner. The *EGFR* T854A mutation in exon 21, while less common compared to other *EGFR* mutations like L858R or exon 19 deletions, has also been identified as a potential mechanism of resistance to tyrosine kinase inhibitors (TKIs) in a larger population sample [4]. The precise mechanism by which this mutation confers resistance is still under active investigation, but structural analyses suggest that the substitution at this position might alter the binding affinity of TKIs to the receptor [8, 9]. Furthermore, by integrating computational analysis and kinase assays, the researchers found that the gain-of-function mutation T854A significantly reduces inhibitory activity by disrupting geometrically perfect hydrogen bonds [10]. In terms of understanding the molecular mechanism of the T854A mutation, Goyal et al. identified new *EGFR* inhibitors targeting the T854A mutation through structure-activity relationship studies, providing important information for the design of more effective drugs [11].

Interestingly, some reports have found the T854A mutation concurrently with other *EGFR* mutations. This coexistence can further complicate the therapeutic approach, as the presence of multiple mutations might synergistically influence resistance patterns [12]. The intricacies of such co-mutations underscore the importance of comprehensive genomic profiling in NSCLC patients, which can offer a more detailed view of the mutational landscape and help in tailoring personalized treatment strategies.

Regarding treatment strategies, Avizienyte et al. compared the spectrum of resistance mutations generated by different *EGFR* TKIs and the potential effect of drug combination therapy and affirmed the status of first-line TKIs in the treatment of NSCLC with rare *EGFR* mutations especially in the case of dual uncommon mutations [13]. The second generation TKI-Afatinib exhibited clinically activity and benefited many TKI-pretreated NSCLC patients harboring uncommon *EGFR* mutations [14]. However, in the experiments of drug screening in vitro, researchers found that Ba/F3 cells carrying the C797S mutation exhibited resistance to afatinib after acquiring the T854A mutation [15]. Besides, reports showed that some patients harboring the T854A mutation have shown partial responses to the third generation TKI, Osimertinib, and others have shown resistance [16, 17]. This highlights the heterogeneity of responses, even within the subset of patients with this specific mutation, emphasizing the need for combination therapies or alternative approaches. In our case, the patient had multiple drug resistance mutations, highlighting the complexity of the disease and the challenges in selecting an effective treatment strategy. Emerging preclinical data suggest that certain combination therapies might be effective in overcoming resistance conferred by T854A and potentially other co-existing mutations. For instance, the combination of *EGFR* inhibitors with agents targeting other pathways, like *MET* or *BRAF*, could provide a more comprehensive blockade of tumor growth signals [18]. Cabozantinib, one of likehood inhibitor, has demonstrated activity in various tumors, including NSCLC [19]. The rationale for combining Osimertinib with Cabozantinib might be to simultaneously target multiple pathways and overcome the resistance mediated by the rare T854A mutation and other co-existing resistance mechanisms. Emerging strategies to overcome resistance include the development of newer TKIs, combination therapies, and immunotherapies. The case of our patient, treated with the combination of double dosage Osimertinib and Cabozantinib, offers a unique perspective and insight into the potential benefits of combination therapy in patients with rare *EGFR* mutations.

The patient in our case developed a rare mutation of *EFGR* T854A and obtained a survival benefit from Osimertinib, which has a low level of clinical evidence. When drug-resistant disease progresses, it is reasonable to consider changing medications or participating in drug

clinical trials for treatment. Surprisingly, we achieved disease control by increasing the dosage of medication, increasing the patient's PFS by nearly 9 months. Zhao et al. previously reported a case of a patient with T854A mutation who maintained a PFS survival of 8 months on second line Osimertinib treatment [20]. When the disease progressed again, genetic testing revealed multiple *EGFR*-TKI resistance mutations as well as some mutations with unclear clinical significance. At this time, we added a multi-target inhibitor to the original double dose of Osimertinib for combined treatment, and the patient once again achieved short-term progression-free survival benefit without significant toxic side effects.

The successful management of drug-resistant disease in this patient highlights the importance of personalized treatment strategies based on comprehensive genomic profiling. The emergence of multiple resistance mutations, including the rare EGFR exon 21 T854A mutation, underscores the complexity of treating advanced lung adenocarcinoma. Our findings suggest that doubling the dose of osimertinib can overcome initial resistance, while the addition of cabozantinib may provide further disease control. This case supports the potential benefits of combination therapies in managing complex cases with rare EGFR mutations. The T854A mutation in EGFR exon 21 has been identified as a potential resistance mechanism to EGFR-TKIs. Structural studies suggest that this mutation may alter the binding affinity of TKIs to the receptor, thereby reducing their inhibitory activity [8, 9]. Additionally, computational analyses have shown that the T854A mutation disrupts hydrogen bonds, leading to decreased sensitivity to irreversible pyrimidine-based inhibitors [10]. This highlights the need for alternative therapeutic approaches, especially in cases where multiple resistance mutations are present.

Combination therapies have emerged as a potential solution to overcome resistance in EGFR-mutant NSCLC. For instance, the combination of EGFR-TKIs with multi-targeted inhibitors like cabozantinib has shown promise in preclinical studies. Cabozantinib, a potent inhibitor of multiple receptor tyrosine kinases, including MET and AXL, has demonstrated activity in various solid tumors, including NSCLC [19]. The rationale for combining osimertinib with cabozantinib is to simultaneously target multiple pathways involved in tumor growth and survival, thereby overcoming resistance mediated by rare mutations like T854A [18].

In our case, the patient initially responded well to double-dose osimertinib, achieving nearly 9 months of progression-free survival (PFS). However, subsequent disease progression led to the identification of additional resistance mutations, including EGFR exon 20 C797S and exon 21 V834L. The addition of cabozantinib to the treatment regimen resulted in stable disease, further supporting the potential benefits of combination therapy in managing complex resistance patterns. The novelty of this case report lies in the comprehensive documentation of the clinical course of a patient harboring the rare EGFR exon 21 T854A mutation and the successful management of multiple drug-resistant mutations through a combination therapy approach. Specifically, the use of double-dose osimertinib and its subsequent combination with cabozantinib provided significant disease control and prolonged progression-free survival, which has not been extensively reported in the literature. This case highlights the potential benefits of such a treatment strategy in managing complex cases of advanced lung adenocarcinoma with rare EGFR mutations.

While our case demonstrates the potential efficacy of combination therapies, further clinical trials are needed to confirm their safety and efficacy in patients with rare EGFR mutations. Emerging strategies include the development of next-generation EGFR-TKIs, such as those targeting the C797S mutation, as well as the integration of immunotherapy into treatment paradigms [21]. Additionally, the use of liquid biopsies and real-time monitoring of genetic changes may help in the early detection of resistance mutations and guide personalized treatment strategies [22].

In conclusion, the treatment of advanced lung adenocarcinoma with rare *EGFR* mutations like T854A in exon 21 requires a comprehensive understanding of the molecular mechanisms underlying resistance and the exploration of novel therapeutic strategies. The combination of *EGFR*-TKIs and Muti-target inhibitors might provide a promising approach for such challenging cases, but further clinical trials and

research are needed to confirm its efficacy and safety.

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Disclosure of conflict of interest

None.

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