Case Report

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A rare epidermal growth factor receptor T790M/cis-C797S/L718Q compound mutation in a lung adenocarcinoma patient who did not derive any benefit from combination therapy with afatinib and bevacizumab

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Abstract

The most common mutations in epidermal growth factor receptor (*EGFR*) are exon 19 deletions and exon 21 L858R mutations, both of which respond effectively to *EGFR* tyrosine kinase inhibitors. However, the efficacy of *EGFR* tyrosine kinase inhibitors against rare *EGFR* mutations remains controversial. Many patients eventually develop resistance to *EGFR* tyrosine kinase inhibitors. Here, we encountered the case of a 62-year-old male with lung adenocarcinoma and a history of hypertension, who harbored a rare *EGFR* L858R/T790M/cis-C797S/L718Q compound mutation and showed resistance to osimertinib. The patient showed a partial response to treatment with a combination of afatinib and bevacizumab lasting 2 months. Although this case did not demonstrate a clear benefit from dual therapy with afatinib and bevacizumab, it provides a valuable therapeutic reference for patients with rare compound *EGFR* mutations and offers insights for future studies.

Keywords

Rare compound mutation, lung adenocarcinoma, afatinib, bevacizumab

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Introduction

Patients with non-small cell lung cancer (NSCLC) carrying common epidermal growth factor receptor (*EGFR*) mutations, such as L858R and exon 19 deletions, are effectively treated with *EGFR* tyrosine kinase inhibitors (TKIs).[1] However, a subset of patients with rare *EGFR* mutations, accounting for 10%–15%, often develop resistance to third-generation TKIs.[2,3] Various responses to different *EGFR* TKIs have been reported for rare *EGFR* mutations, emphasizing the importance of individualized treatment strategies. Afatinib, a second-generation *EGFR* TKI, is an irreversible inhibitor that offers more potent and prolonged inhibition of ErbB family receptors than first-generation *EGFR* TKIs.[2,4] Many attempts have been made to explore the potential of afatinib in combination with bevacizumab as a promising treatment for *EGFR*-mutated NSCLC. A Phase II ABCD study revealed clinical benefits from the combination of afatinib and bevacizumab after osimertinib resistance in some cases with advanced NSCLC harboring uncommon *EGFR* and C797S mutations.[5] Another study also supported that afatinib and bevacizumab combination treatment in chemo-naïve patients with advanced NSCLC harboring *EGFR* mutations exhibited good tolerability and favorable disease control.[6] In addition, in some early phase clinical trials, manageable adverse events and promising efficacy have been observed.[7,8] However, the efficacy of afatinib and bevacizumab in uncommon *EGFR* compound mutations remains under exploration. We encountered a case of lung adenocarcinoma harboring a rare *EGFR* L858R/T790M/cis-C797S/L718Q compound mutation, for whom afatinib

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treatment combined with bevacizumab proved ineffective. In accordance with the CARE reporting checklist, we report the following case.

Case report

A 62-year-old, never-smoking Chinese male with a history of hypertension was admitted to our hospital with a 2-year history of cough and expectoration. Chest computed tomography (CT) revealed a neoplasm in the right lung. In December 2017, the patient underwent a right lower lobectomy to remove the primary tumor, along with systemic lymph node dissection after confirming he had no surgical contraindications (Supplemental Figure A). Postoperative pathology results indicated a peripherally located, moderately to poorly differentiated adenocarcinoma, with a postoperative staging of pT2bN2M0 IIIA, according to the eighth edition of the American Joint Committee on Cancer.[9] Standard chemotherapy, consisting of four cycles of carboplatin and pemetrexed, was initiated in January 2018. Due to grade 3 myelosuppression during chemotherapy, granulocyte colony-stimulating factor treatment was administered. Unfortunately, in October 2018, the patient experienced disease progression (PD), with multiple metastatic nodules in both lungs as observed on chest CT (Figure 1(a)).

Real-time polymerase chain reaction (PCR) was performed on tumor tissue paraffin sections, revealing that PD-L1 mRNA expression was below 5% and detecting an *EGFR* L858R mutation, which is sensitive to first-generation *EGFR* TKIs. During treatment with gefitinib (250 mg qd) (Figure 1(b)), a grade I adverse event (rash) occurred. However, in June 2019, PD was confirmed by CT, showing new lymph nodes in the lungs and increasing serum concentrations of carcinoembryonic antigen (CEA) (Figures 1(b) and 2). Droplet digital PCR detected an *EGFR* T790M mutation rate of 1.45% in the serum. In June 2019, osimertinib therapy (80 mg qd) was initiated, achieving a prolonged partial response, with a reduced number of lung metastatic nodules observed by December 2019. However, in October 2020, the patient developed further disease progression, marked by widespread metastatic lung nodules (Figure 1(c)). In November 2020, next-generation sequencing was conducted using panels covering 95 lung cancer-related genes (Shanghai Biotecan Pharmaceuticals Co., Ltd., Shanghai, China), revealing a complex mutation: *EGFR* L858R (abundance: 47.13%), *EGFR* T790M (abundance: 15.06%), *EGFR* cis-C797S (abundance: 6.90%), and *EGFR* L718Q (abundance: 8.58%) (Figure 3).

Literature evidence indicates that afatinib is effective in patients with uncommon mutations who develop resistance to osimertinib.[10,11] Studies have also shown that combining *EGFR* TKIs with bevacizumab is one of the main approaches to enhance the efficacy of *EGFR* TKIs.[12,13] Therefore, combination therapy with afatinib (30 mg qd) and bevacizumab (400 mg) was initiated on November 6, 2020. Chest CT on December 22, 2020, showed a marked decrease and shrinkage of multiple diffuse nodules in both lungs. However, magnetic resonance imaging on January 11, 2021, revealed bone metastases in the cervical vertebra (Figure 1(d)). Unfortunately, the patient declined radiotherapy and opted to continue the afatinib and bevacizumab treatment. During this regimen, the serum CEA level decreased from 10.52 to 5.67 ng/mL. The patient achieved a partial response lasting approximately 2 months on combination therapy. Tragically, the patient died from respiratory failure in March 2021 (Supplemental Figure A). Overall survival exceeded 38 months from the initial pathological diagnosis. Previous studies have shown the efficacy of afatinib in patients with the *EGFR* L858R/L718V double mutation (Supplemental Table 1); however, there is currently no clinical evidence to support its effectiveness in patients with a triple-resistant mutation (T790M/cis-C797S/L718Q). Although the combination treatment has not proven to be effective, dual therapy provides a reference for future treatment options for this specific pattern of genetic alterations.

Discussion

EGFR TKIs are the recommended first-line therapy for NSCLC patients with activating *EGFR* mutations. Although the initial response rates to first- and second-generation *EGFR* TKIs are high, most NSCLC patients eventually develop "on-target" resistance, primarily through secondary *EGFR* mutations, notably T790M. Acquired *EGFR* T790M mutations are typically not identified in NSCLC patients receiving first-line osimertinib, while resistance to osimertinib in later-line treatment has been associated with the loss of *EGFR* T790M in certain cases.[14–16] Compound *EGFR* TKI-resistant mutations, such as T790M/C797S, have emerged as subsequent events during second-line osimertinib therapy.[16,17] In addition to *EGFR* T790M/C797S, other resistance mutations to osimertinib, particularly uncommon mutations like L718X, D585Y, and E709K, have also been observed.[18,19] In the present study evaluating afatinib combined with bevacizumab, dual therapy has not proven to be effective in a case harboring a rare *EGFR* L858R/T790M/cis-C797S/L718Q mutation.

Research on the *EGFR* L718X mutation and its resistance to osimertinib is limited. The L718 residue is located in the ATP binding site of the *EGFR* kinase domain, and in silico models suggest that a substitution at this residue may impede osimertinib binding to *EGFR* due to spatial constraints.[20] The drug-resistant *EGFR* L718Q mutation, first identified in Ba/F3 cells in 2015, has since been validated both in vitro and in vivo studies.[21–23] Several reported cases have shown that patients with osimertinib-resistant *EGFR* L718X mutations achieved stable disease or partial response with the second-generation inhibitor afatinib (Supplemental Table 1).[10,11,19,24,25] Notably, afatinib remains effective in patients with the L718X mutation, especially in scenarios where L718X is acquired or T790M is lost.[11,19,24,25] For example, a patient with an acquired L718Q

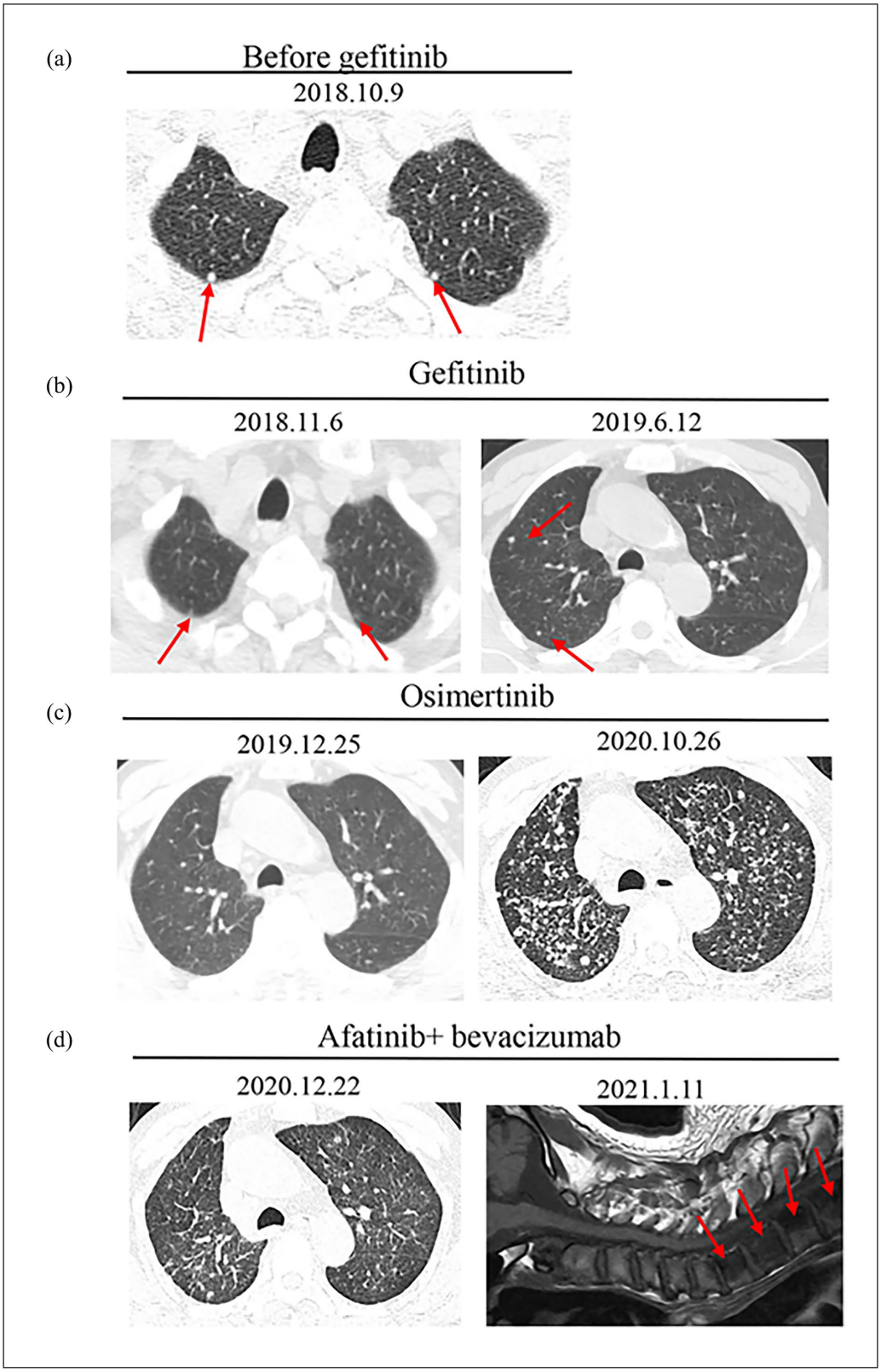

Figure 1. Representative clinical images. (a) October 2018: baseline imaging before starting gefitinib. Red arrows indicate double lung nodules. (b) November 2018: one month after starting gefitinib; June 2019: PD confirmed by CT. Red arrows indicate the resolution of lung nodule and new nodules, respectively. (c) December 2019: six months after starting osimertinib; October 2020: PD confirmed by CT. (d) December 2020: one and a half months after initiating the combination treatment of afatinib and bevacizumab; January 2021: Bone metastases detected by magnetic resonance imaging. Red arrows indicate the bony destruction to cervical vertebra and thoracic vertebrae. PD: progressive disease; CT: computed tomography.

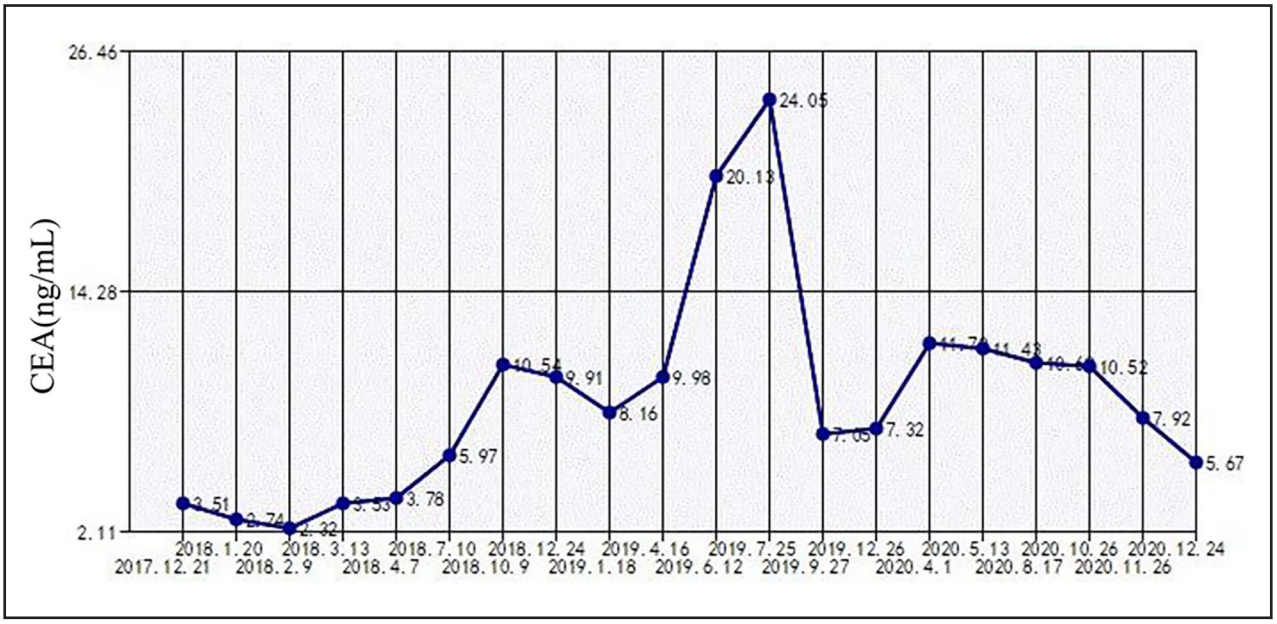

Figure 2. Line chart showed changes in the level of serum CEA from December 21, 2017 to December 24, 2020. Tumor biomarker: CEA.
CEA: carcinoembryonic antigen.

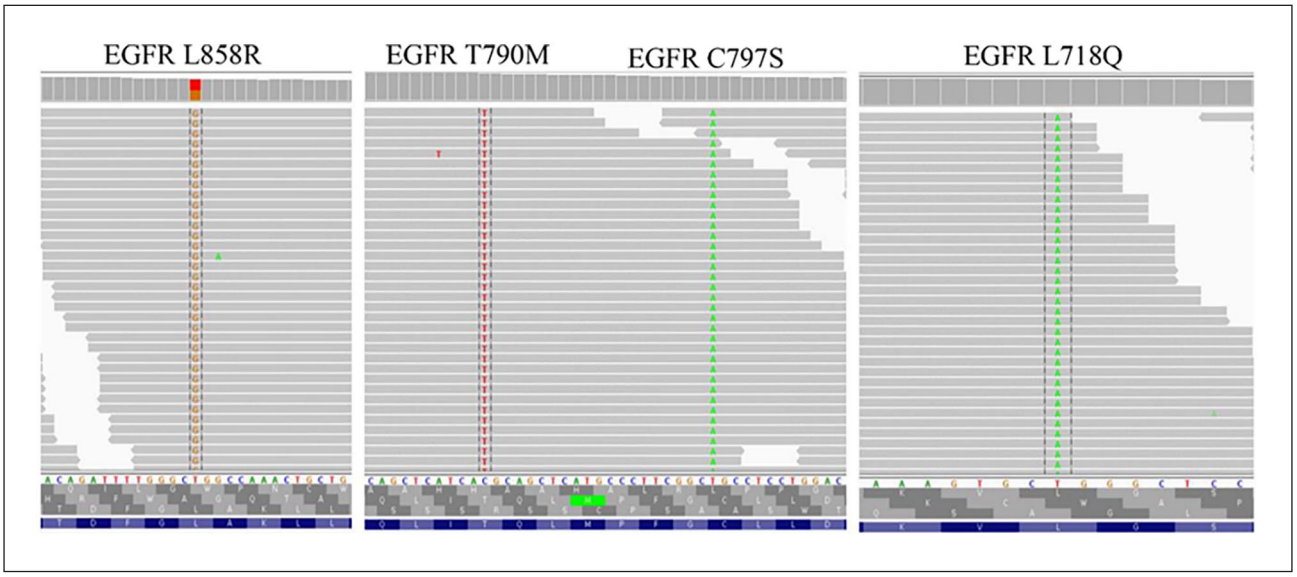

Figure 3. Integrated genomics viewer snapshots illustrating the detected L858R, T790M, cis-C797S, and L718Q mutations in the lung adenocarcinoma tumor of the patient.

mutation overcame resistance to almonertinib and achieved a progression-free survival of 7 months with combination therapy of afatinib and cetuximab.[19] In contrast, patients with *EGFR* L858R/L718X double mutation showed limited benefits from the second-generation inhibitor dacomitinib,[26] suggesting that afatinib offers superior efficacy over dacomitinib in treating patients with the L718X mutation.

First-generation inhibitors, such as erlotinib and icotinib, may not show efficacy in treating NSCLC patients with low sensitivity to osimertinib. A study has demonstrated primary resistance to icotinib in 21.7% of NSCLC patients, including those with uncommon *EGFR* mutations.[27] Reports have indicated primary and acquired resistance rates in patients with uncommon *EGFR* mutations, emphasizing poor responsiveness to first-generation TKIs, particularly in cases harboring G719X, S768I, and L861Q mutations.[28,29] While *EGFR* L718V confers resistance to first-generation TKIs such as erlotinib and gefitinib in Ba/F3 cells, it retains sensitivity to

afatinib,[29] indicating greater responsiveness to second-generation TKIs than to first-generation TKIs.

Evidence suggests an obvious association between *EGFR* mutation status and varying responses to *EGFR* TKIs for rare mutations.[3,30,31] Noteworthy cases include patients with *EGFR* L858R/L718V/amplification who achieved a 6-month progression-free survival with afatinib[10] and another patient with *EGFR* L858R/L718Q/amplification and *BRAF* G466R mutation, who showed good sensitivity to afatinib with a 4-month partial response.[11] In addition, stable disease was observed in three patients with *EGFR* L858R/L718V mutations.[24,25] Changes in *EGFR* mutation status from *EGFR* L858R/L718Q/amplification to L858R/T790M after personalized chemotherapy resulted in a patient benefit from osimertinib therapy, achieving progression-free survival of 4.7 months.[32] In Ba/F3 cells, Del19/T790M/L718Q mutations demonstrated slightly lower resistance to osimertinib than L858R/T790M/L718Q mutations,[33] though this finding was not consistently replicated.[23]

Anti-angiogenic agents, such as bevacizumab, show promise in combination with *EGFR* TKIs, yielding a synergistic effect against tumors. Clinical trials have reported favorable outcomes in NSCLC patients with *EGFR* 19del or L858R mutations receiving afatinib combined with bevacizumab.[8] Additional studies have shown that adding atezolizumab to bevacizumab and chemotherapy yields significant benefits in metastatic nonsquamous NSCLC patients, especially those previously treated with *EGFR* TKIs.[34] Preclinical experiments also support the efficacy of afatinib combined with bevacizumab in inhibiting tumors with *EGFR* 19del/T790M and L858R/T790M mutations, showing superior results compared to *EGFR* TKI monotherapy.[35] In our study, we provide evidence that the combination of afatinib and bevacizumab is a viable approach for managing patients with the L718Q mutation following progression on osimertinib.

Conclusion

Although our study did not demonstrate any explicit benefit from afatinib and bevacizumab, this case in particular could shed light on future studies. Moreover, this finding underscores the importance of continuous genetic monitoring to guide therapeutic decisions in managing NSCLC with complex mutation profiles.

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Author contributions

Conceptualization by X.P.M. and P.P.; X.P.M. performed pathological imaging. J.Y.L., X.H.W., and P.P. participated in data collection. P.P. Writing-original draft preparation. All authors contributed to the article and approved the submission of the manuscript.

Data availability

The gene detection dataset and original contributions presented in this study will be available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Pei Peng, Jingyi Liu, and Xiaohui Wu were employed by Shanghai Biotecan Pharmaceuticals Co. Ltd. (Shanghai, China). The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Ethics approval

Written informed consent was obtained from the patient's legally authorized representative for their anonymized information to be published in this article.

Informed consent

Our institution does not require ethical approval for reporting individual cases or case series.

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Supplemental material

Supplemental material for this article is available online.

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