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# Non-small-cell lung cancer with epidermal growth factor receptor L861Q-L833F compound mutation benefits from both afatinib and osimertinib: A case report

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## Abstract

### BACKGROUND

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been adopted as the standard of care for non-small cell lung cancer (NSCLC) patients harboring *EGFR* sensitizing mutations. Besides the two common mutations exon 19 deletion and L858R, which together comprise approximately 85% of *EGFR* mutations in NSCLC, rare *EGFR* mutations also exist, including point mutations, deletions, and insertions spanning *EGFR* exons 18-25. However, the responsiveness of uncommon *EGFR* mutations to EGFR TKIs remains elusive and attracts increasing interest.

### CASE SUMMARY

Herein, we report a 55-year-old male patient with stage IV NSCLC harboring a rare *EGFR* L833F-L861Q compound mutation *in cis*. The patient achieved a partial response to first-line treatment with afatinib and a progression-free survival of 10 mo. After afatinib failure, the patient received multiple line treatments with chemotherapy. Upon disease progression, the heavily pretreated patient was treated with osimertinib and bevacizumab, and both lung lesion and brain metastases were stable for more than 3 mo. He had an overall survival of 25 mo.

### CONCLUSION

Checklist (2016).

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Our case revealed that both afatinib and the osimertinib + bevacizumab combination demonstrated clinical efficacy in NSCLC harboring an *EGFR* L833F-L861Q compound mutation. The results provide more therapeutic options for patients with rare compound mutations.

**Key Words:** Afatinib; Osimertinib; Epidermal growth factor receptor; L861Q-L833F; Non-small cell lung cancer; Case report

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**Core Tip:** Our case revealed that both afatinib and the osimertinib + bevacizumab combination demonstrated clinical efficacy in a non-small cell lung cancer patient harboring a rare epidermal growth factor receptor (*EGFR*) L833F-L861Q compound mutation. The results provide more options for the clinical management of patients with rare *EGFR* compound mutations.

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## INTRODUCTION

Epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) have been adopted as the standard of care for non-small cell lung cancer (NSCLC) patients harboring *EGFR* sensitizing mutations. Besides the two common mutations exon 19 deletion and L858R, which together comprise approximately 85% of *EGFR* mutations in NSCLC[1], rare *EGFR* mutations also exist, including point mutations, deletions, and insertions spanning *EGFR* exons 18-25. However, the responsiveness of these uncommon mutations to *EGFR* TKIs has not been well elucidated and attracts increasing interest.

Located within *EGFR* exon 21, L861Q accounts for approximately 3% of *EGFR* mutations in NSCLC[2]. L861Q often exists as a single mutation, while under rare circumstances, it occurs concomitantly with other *EGFR* mutations (mostly with G719X)[3]. *Post hoc* analysis of LUX lung trials showed a response rate of 56% and a median progression-free survival (PFS) of 8.2 mo for afatinib treatment in L861Q mutant positive patients[4], which ultimately drove the Food and Drug Administration approval for afatinib for NSCLC harboring this mutation. L833F, a more rare *EGFR* mutation, has only been reported in a few cases[5]. The therapeutic relevance of L833F remains largely unknown.

In the present study, we describe a stage IV NSCLC patient harboring a rare *EGFR* L833F-L861Q compound mutation *in cis*, who benefited from osimertinib after progressing on afatinib treatment and multiple lines of chemotherapy.

## CASE PRESENTATION

### Chief complaints

A 55-year-old man with a 30-year smoking history (1 pack/d) was admitted to our hospital with the chief complaint of a hoarse voice.

### History of present illness

The patient's symptoms started 3 mo ago.

### History of past illness

The patient denied any history of present illness.

### **Personal and family history**

No personal or family history was reported.

### **Physical examination**

Physical examination indicated a performance status score of 1.

### **Laboratory examinations**

Laboratory examinations revealed elevated serum carcinoembryonic antigen (CEA) and soluble fragment of cytokeratin 19 (CYFRA21-1) levels.

### **Imaging examinations**

A chest computerized tomography (CT) scan detected a space-occupying lesion on the left lung (Figure 1A) in September 2018. Brain magnetic resonance imaging (MRI) suggested multiple brain metastases. Bone metastasis was not detected.

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## **FINAL DIAGNOSIS**

Histopathological test of the percutaneous lung puncture biopsy specimen indicated adenocarcinoma. Amplification refractory mutation system polymerase chain reaction (ARMS-PCR) with the biopsied tissue identified an *EGFR* L861Q mutation. The patient was diagnosed with stage IV (T1N2M1c) lung adenocarcinoma.

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## **TREATMENT**

The patient's treatment history is summarized in Figure 2A. The patient started first-line treatment with afatinib (40 mg qd) in October 2018. Three months later, a chest CT scan showed shrinkage of the lung lesion (from 4 cm to 2.8 cm in diameter, Figure 1B) and a partial response (PR) was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). In August 2019, the lung lesion remained as PR but brain MRI revealed a progressive disease (PD) on the right occipital lobe lesion (Figure 1C). The patient received MRI-guided brain stereotactic radiosurgery in August and September 2019. Disease progression was observed on brain lesions in October 2019 when the lung lesion remained stable. He subsequently underwent a combined treatment of afatinib (40 mg qd) and bevacizumab (15 mg/kg) but brain metastases progressed rapidly. Next-generation sequencing (NGS) was performed with the re-biopsy of lung lesion at PD using a capture-based panel including 168-cancer related genes (Burning Rock Biotech, Guangzhou, Guangdong Province, China) and identified *EGFR* L833F (allele frequency: 43.02%) *in cis* with L861Q (allele frequency: 40.77%) (Figure 2B). *TP53* L194\_I195delinsV and *CCNE1* amplification (copy number: 9.2) were also detected. From December 2019, the patient received six cycles of bevacizumab + pemetrexed + carboplatin (BAC) chemotherapy and achieved stable disease (SD) with a PFS of 4 mo. After PD, he was switched to docetaxel for four cycles (cycle 1: 140 mg d1; cycles 2-4: 110 mg d1 q3w) and brain lesions progressed. In May 2020, a regimen of docetaxel (110 mg d1) and bevacizumab (15 mg/kg) was administered and a PD was observed (Figure 3A). Starting from June 2020, the patient received the combinatorial treatment of osimertinib (160 mg, qd) and bevacizumab (15 mg/kg).

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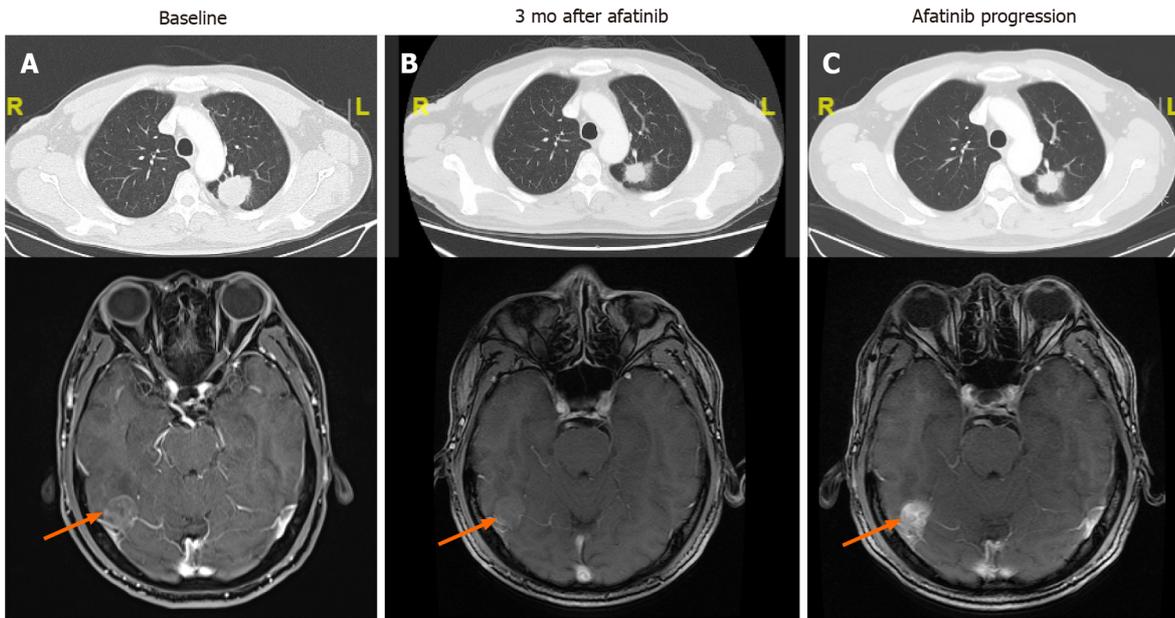
## **OUTCOME AND FOLLOW-UP**

After two cycles of treatment, the patient achieved shrinkage on the lung lesion which was evaluated as SD and brain lesions were stable (Figure 3B). The disease remained stable until the last flow-up in September 2020 (Figure 3C). The patient passed away in October 2020. He achieved a PFS of more than 3 mo and an overall survival of 25 mo.

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## **DISCUSSION**

In the present case, NGS detected an L833F-L861Q compound mutation *in cis* after afatinib failure. However, according to the two allele frequencies (Figure 2B), it is

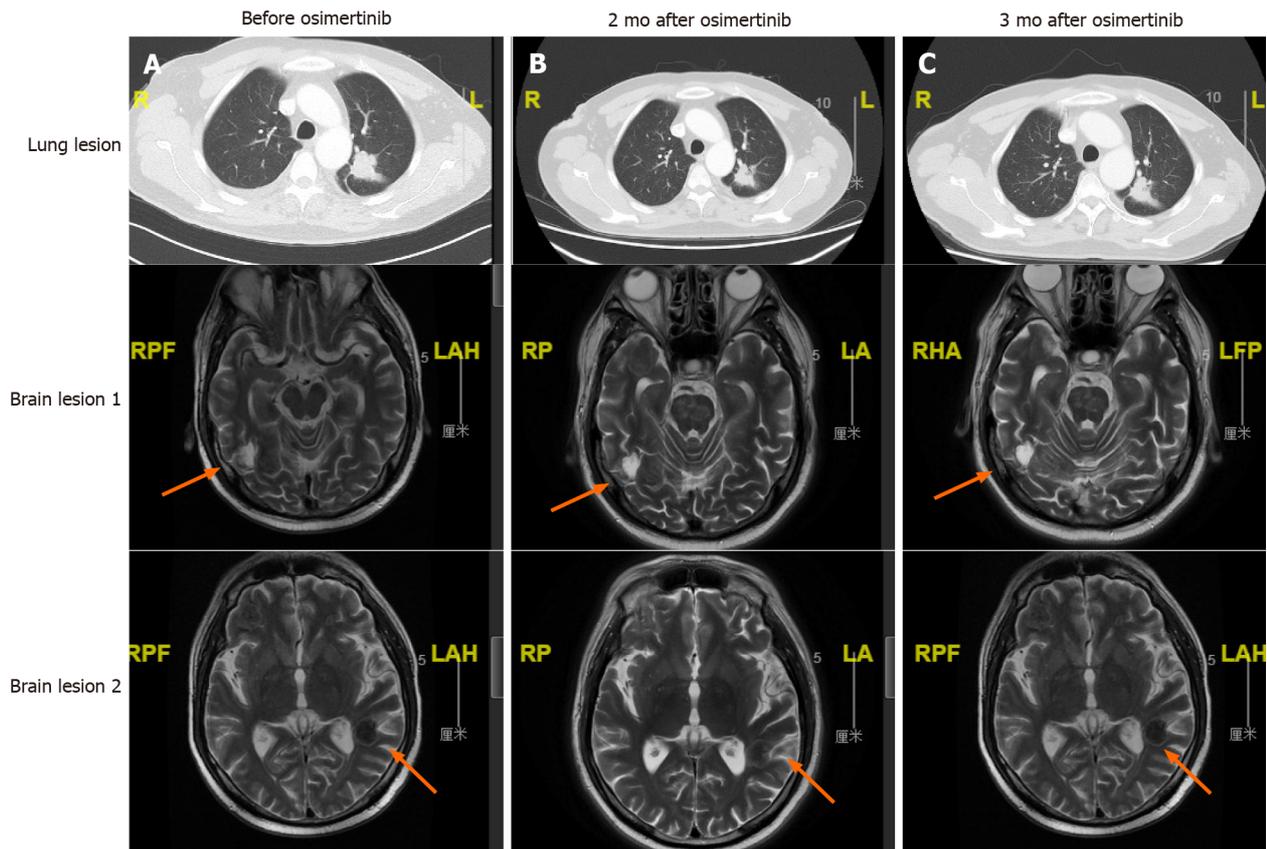


**Figure 1 Responses of lung and brain lesions to afatinib.** A: Baseline before treatment; B: After 3 mo of afatinib treatment: Lung lesion responded partially and brain lesion was stable; C: After 10 mo of afatinib treatment: Lung lesion remained stable and brain lesion progressed. Only the target brain metastatic lesion was displayed and indicated by the orange arrow.



**Figure 2 Treatment history and timeline of the patient's best objective response.** A: Treatment history and timeline; B: Illustration of epidermal growth factor receptor L833F mutation *in cis* with L861Q mutation. BAC: Bevacizumab + pemetrexed + carboplatin; ARMS PCR: Amplification refractory mutation system polymerase chain reaction; NGS: Next generation sequencing; PFS: Progression-free survival; OS: Overall survival; EGFR: Epidermal growth factor receptor; SD: Stable disease; PD: Progressive disease.

deduced that this compound mutation actually presented at baseline before afatinib treatment, which ARMS-PCR failed to detect. The results support the advantage of NGS over PCR-based methods for detecting more complex mutations. PCR can only detect known mutations and those for which the PCR primers are designed, while NGS is able to simultaneously identify multiple mutations including unknown ones



**Figure 3 Responses of lung and brain lesions to osimertinib + bevacizumab regimen.** A: At docetaxel + bevacizumab failure, before osimertinib treatment; B: 2 mo after treatment initiation, both lung and brain lesions were stable; C: 3 mo after treatment, both lesions remained stable. RAH: Right/anterior/head; RPF: Right/posterior/feet; RP: Right/posterior; LA: Left/anterior; RHA: Right/head/anterior; LFP: Left/feet/posterior.

and reveal the configuration in the case that mutations are present within one sequencing read. NGS can also detect some structure rearrangements that might also serve as therapeutic targets for patients (ALK, RET fusion, *etc.*). Therefore, NGS is strongly recommended if conventional methods fail to detect any actionable alterations.

Our case demonstrated a durable response of 10 mo to first-line treatment with afatinib, suggesting the clinical activity of this TKI against the rare compound mutation L833F-L861Q. In line with our observation, a pooled analysis revealed that afatinib resulted in an objective response rate (ORR) of 77.1% and a median time to treatment failure (TTF) of 14.7 mo [95% confidence interval (CI): 6.8-18.5 mo] in EGFR TKI-naïve patients harboring compound mutations[6]. A recent retrospective study also shows that afatinib is associated with a more favorable PFS compared with gefitinib [hazard ratio (HR) = 2.01; 95%CI: 1.11-3.62] and erlotinib [HR = 2.61; 95%CI: 1.31-5.22] in patients with EGFR compound mutations[7]. Especially in those with uncommon patterns (without 19 deletion and L858R), afatinib yielded a higher response rate (afatinib *vs* gefitinib *vs* erlotinib: 78.9% *vs* 38.9% *vs* 20.0%,  $P = 0.013$ ) and significantly longer PFS (afatinib *vs* gefitinib *vs* erlotinib: 10.5 mo *vs* 3.0 mo *vs* 0.9 mo).

Li *et al*[5] reported a stage IV lung adenocarcinoma patient harboring EGFR L833F-L861R compound mutation, who achieved a PFS of 193 d to gefitinib treatment. In another study, icotinib resulted in a 0% response rate and a 100% disease control rate in L833F positive NSCLC patients with a median PFS of 4.2 mo[8]. An *in vivo* study has shown that L861Q retains sensitivity to both afatinib and osimertinib[2]. In a phase II trial (KCSG-LU15-09) to investigate osimertinib efficacy in NSCLCs with uncommon EGFR mutations, the ORR and median PFS were 78% and 15.2 mo, respectively, in the nine L861Q-positive patients (7 with L861Q single mutation and 2 with L861Q-G719X compound mutation)

A recent retrospective study recruiting 51 NSCLC patients with uncommon EGFR mutations (including 2 with L833F-L861Q) showed a median time of 7.1 mo on osimertinib treatment. However, the detailed clinical outcomes of the two L833F-L861Q positive patients were not described[9]. In our case, the L833F-L861Q mutant patient achieved SD on the osimertinib + bevacizumab regimen. Of note, our case had

brain metastases and was heavily pre-treated. This might in part explain the short duration of effectiveness of the osimertinib regimen.

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## CONCLUSION

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In conclusion, our case revealed that both afatinib and the osimertinib + bevacizumab combination demonstrated clinical efficacy in NSCLC harboring an *EGFR* L833F-L861Q compound mutation. The results provide more options for the clinical management of patients with rare compound mutations.

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