Durable response to afatinib in an advanced lung adenocarcinoma patient with an EGFR L858R/G729A compound mutation: a case report

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Abstract: Of the epidermal growth factor receptor (*EGFR*) mutations in patients with non-small cell lung cancer (NSCLC), 10–15% are uncommon mutations. Most of the *EGFR* "major" uncommon mutations have shown responses to EGFR-tyrosine kinase inhibitors (TKIs). However, there is a lack of clinical data for other less common types of EGFR mutations and the response to EGFR-TKIs, occurring either alone or in combination with *EGFR* sensitizing mutations. We reported a 70-year-old Chinese man with no smoking history who was diagnosed with stage IVA lung adenocarcinoma. An exceptionally uncommon *EGFR* G729A mutation in *EGFR* exon 19 was detected concomitantly with *EGFR* L858R in exon 21 in tumor specimens by next generation sequencing (NGS). This patient obtained limited benefit from icotinib and the increase in symptoms of cough and chest tightness, so we decided to switch the treatment to afatinib. Our patient exhibited partial response to afatinib with progression-free survival of 10 months. Subsequently, an *EGFR* T790M mutation was detected in the second lung biopsy. Then, osimertinib was administered and the symptoms improved significantly and the progress-free survival was nearly 16 months. Our data suggests that patients with NSCLC who are positive for uncommon *EGFR* G729A mutations may benefit from treatment with afatinib.

Keywords: Non-small cell lung cancer (NSCLC); uncommon mutation; afatinib; *EGFR* G729A; case report

Submitted Nov 09, 2021. Accepted for publication Jan 13, 2022.

doi: 10.21037/atm-22-95

View this article at: https://dx.doi.org/10.21037/atm-22-95

Introduction

Genetic alterations in epidermal growth factor receptor (*EGFR*) constitute a major oncogenic mechanism in non-small cell lung cancer (NSCLC) (1). The frequency of EGFR-positive mutations is approximately 10% to 15% among Caucasians and 30% to 50% among Asians with NSCLC (2). Patients with common *EGFR*-mutant NSCLC, including deletions in exon 19 (19del) and Leu858Arg (L858R), account for 85–90% of the *EGFR* mutations (3). The remaining 10–15% *EGFR* mutations are composed of a heterogeneous group of "major" rare mutations (i.e., G719X, S768I, L861Q), very rare mutations (major rare mutations negative), and compound gene alterations within exons 18–21 (4). Given the significant heterogeneity among uncommon *EGFR* mutations, their responses to EGFR-tyrosine kinase inhibitors (TKIs) are also different. Thus, individualized treatment for each case is strongly recommended. Afatinib is the second-generation EGFR-TKI, which block ErbB family receptors irreversible. Previous study indicated that afatinib

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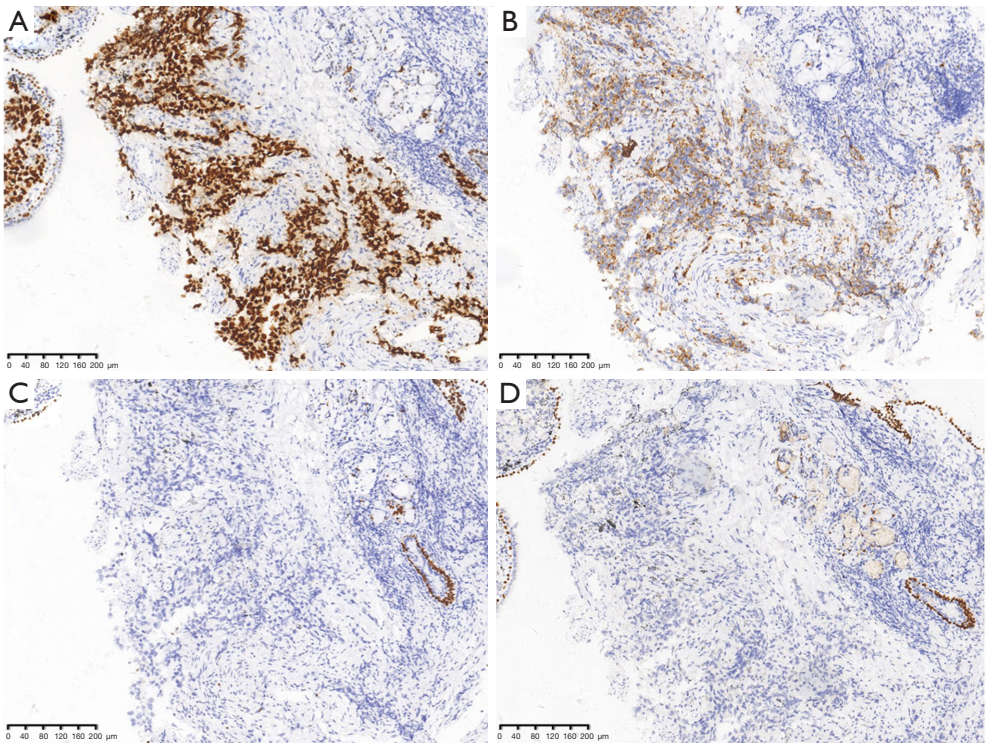

Figure 1 Pathological examination of lung biopsies revealed metastatic lung adenocarcinoma. Immunostaining of TTF1 (A), Napsin A (B), P40 (C) and P63 (D) in tissues.

combined with bevacizumab had good effects on NSCLC patient with brain metastasis and *EGFR* del 18 mutation; but the effect of bevacizumab cannot be eliminated (5). In this study, we reported a case of a patient with advanced stage NSCLC harboring a rare *EGFR* L858R/G729A compound mutation, in which the second-generation EGFR-TKI afatinib monotherapy elicited more durable responses than the initial icotinib treatment. We present the following case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-95/rc).

Case presentation

A 70-year-old Chinese man with no smoking history presented to our hospital with 1 month of intermittent coughing. A contrast-enhanced computed tomography (CT) scan revealed a 5 cm × 4.1 cm mass located in the left upper lung lobe. A bone scan showed ilium metastasis. Immunohistochemistry (IHC) indicated that most of the tumor cells were positive for thyroid transcription factor-1 (TTF-1) and Napsin A (*Figure 1*). After comprehensive evaluation, the patient was diagnosed with stage IVA (cT2bN0M1b) lung adenocarcinoma with bone metastasis. Capture-based targeted sequencing performed on formalin-fixed paraffin-embedded (FFPE) samples of lung lesions indicated the presence of complex mutations: *EGFR* L858R in exon 21 and G729A in exon 19, with mutation frequencies of 16.77% and 12.48%, respectively (*Figure 2*).

The patient was administered with icotinib as a first-line treatment at 125 mg orally TID from Nov 2018. From a CT scan in Mar 2019, the patient was assessed as stable disease (SD) based on the Response Evaluation Criteria on Solid Tumors version (RECIST) version 1.1 (*Figure 3*). Because of inadequate treatment response, the dosage of icotinib was increased to 250 mg orally TID from Jun 2019. After another 3 months of treatment, the patient developed severe clinical symptoms including worsening cough and shortness of breath. Follow-up CT scans revealed slight enlargement of the primary lesion (5.4 cm × 4.9 cm) and mediastinal lymph nodes compared with previous images (*Figure 3A*,*3B*). Although an assessment of progressive disease (PD) could not be made based on the CT scans, the physician decided to switch the treatment to afatinib

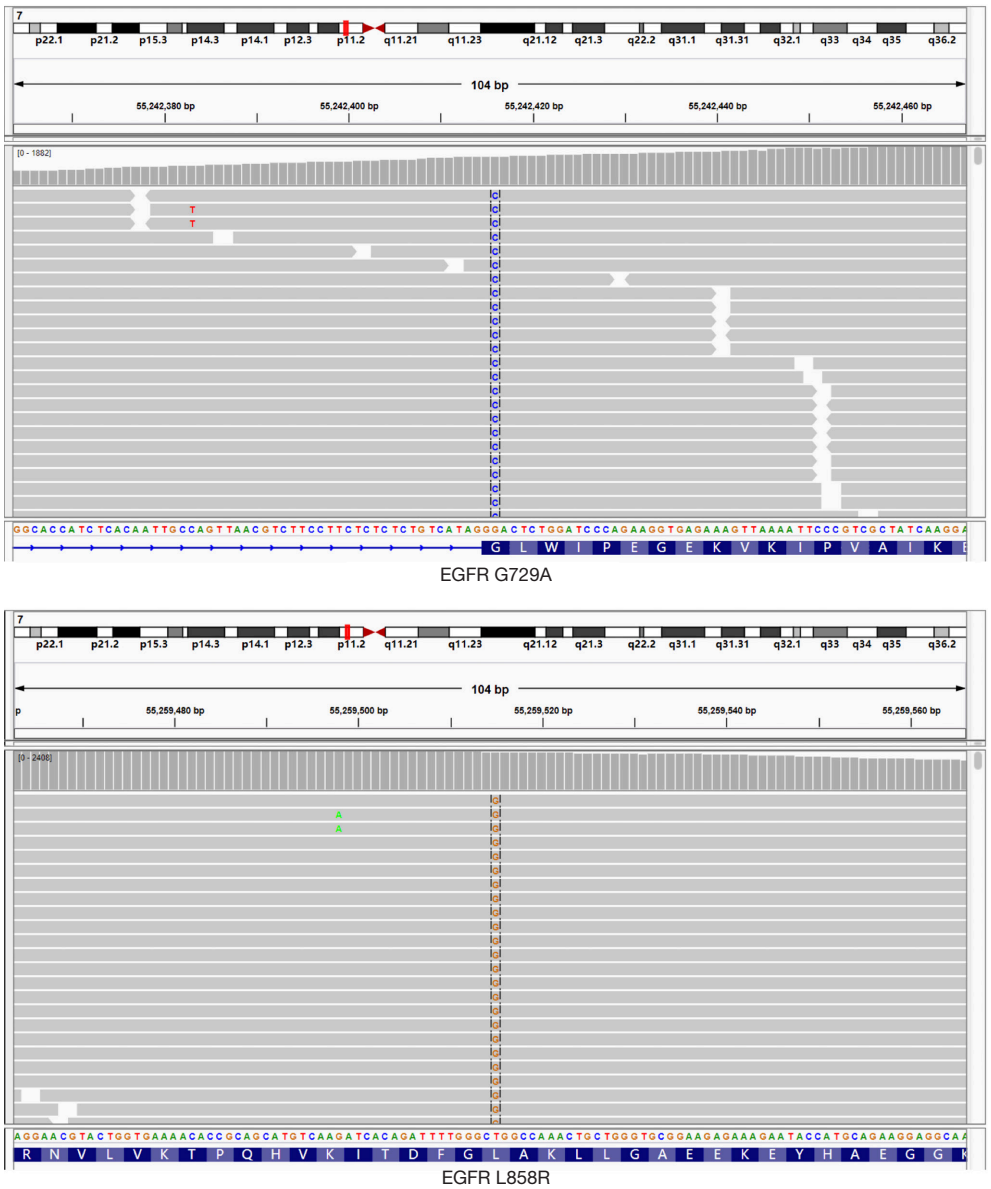

Figure 2 The IGV images representing the EGFR compound mutation consisting of L858R and G729A in the lung lesion samples. IGV, integrative genomics viewer; EGFR, epidermal growth factor receptor.

due to the limited benefit from icotinib and the increase in symptoms of cough and chest tightness. The total treatment duration of icotinib was 10 months.

Subsequently, the patient was placed on afatinib at 40 mg once daily from Sep 2019. Four weeks after the initiation of afatinib, CT scans revealed remarkable tumor shrinkage of the left lung mass (3 cm × 3 cm; *Figure 3C*). The patient achieved partial response (PR). CT scans 5 months later showed further shrinkage in the primary pulmonary lesion (2.8 cm × 2.6 cm; *Figure 3D*). There was no serious adverse effect during the course of afatinib therapy. The patient's clinical symptoms were also alleviated.

After 10 months of afatinib treatment in total, chest CT scans revealed a marked increase in tumor size that led to PD (5.2 cm × 3.7 cm). *EGFR* T790M mutation was detected in the second lung biopsy. The progression-free survival (PFS) of afatinib was 10 months. The treatment was switched to osimertinib at 80 mg once daily from Jul 2020,

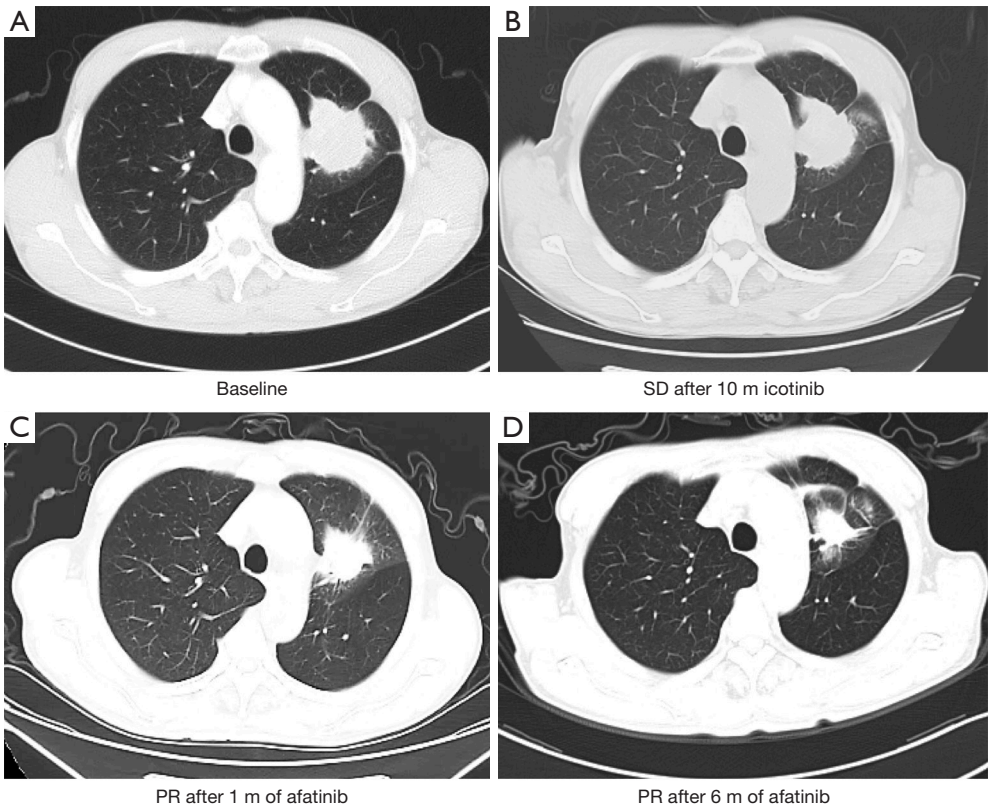

Figure 3 The CT images of the primary lung mass at baseline (A), at the evaluation of SD after 10 months of icotinib treatment (B), at the evaluation of PR after 1 month of afatinib treatment (C), and at the evaluation of PR after 6 months of afatinib treatment (D). SD, stable disease; PR, partial response.

with the patient's disease remaining stable for 16 months as of his last follow-up in October 2021. Timeline of the patient's treatment history was presented in *Figure 4*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This case reported the enhanced clinical efficacy of afatinib compared to icotinib in a patient with metastatic NSCLC carrying an *EGFR* L858R/G729A compound mutation. Although the patient achieved SD and never progressed radiologically during the course of icotinib treatment, his primary tumor was enlarging slowly with the exacerbation of clinical symptoms. After switching to afatinib, the patient achieved PR as evidenced by the alleviation of clinical symptoms as well as shrinkage of the primary lung lesion. This patient harboring a rare *EGFR* L858R/G729A compound mutation did not achieve an objective response to icotinib but appeared to be sensitive to afatinib, suggesting that G729A may contribute to the lack of response to first-generation EGFR-TKIs.

The uncommon G729A mutation has rarely been reported in NSCLC. Only one patient with quadruple mutations of L861Q, L858R, E745_A750del, and G729A has been reported (6). Like the *EGFR* G719X (where X represents A, S, C, or D) mutation, the Gly729 mutation site is also predicted to be part of the phosphate-binding "P-loop" of the EGFR tyrosine kinase domain, which contributes to the hydrophobic cluster surrounding L858 in the inactive state (7). Substitution of the Gly729 amino acid residue with alanine may potentially "tweak" the P-loop and

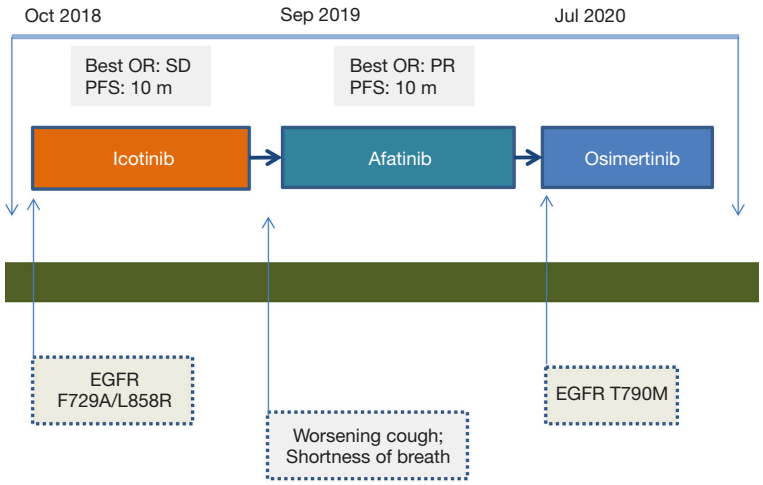

Figure 4 Timeline of the patient's treatment history. OR, best overall response; PFS, progression-free survival; SD, stable disease; PR, partial response; EGFR, epidermal growth factor receptor.

positively regulate the ATP binding affinity to EGFR-TKIs, which suggests that the G729A mutation might be a TKI sensitizing mutation. Although there is limited published research regarding the point mutations in the P-loop, most of the mutations are reported to be sensitive to TKIs including S720P/F, P699S, N700D, E709Q, G721A, and L718P (7). However, one study reported that none of the tumors with the *EGFR* E709A/G mutation associated with L858R responded to EGFR-TKIs (8). *EGFR* uncommon mutations showed divergent sensitivities to EGFR-TKIs, making it difficult to predict suitable TKIs for patients harboring uncommon *EGFR* mutations. This highlights the importance of assessing uncommon *EGFR* mutations not as a whole group but independently.

Afatinib has generally been shown to exhibit broad activity across *EGFR* rare mutations (9). Study showed that afatinib was active in patients with certain types of uncommon *EGFR* mutations, especially G719X, but less active in other uncommon *EGFR* mutation types because of significant heterogeneity among *EGFR* mutations (10). An *in vitro* study showed that *Ba/F3* cells expressing the G719X *EGFR* mutation were sensitive to irreversible inhibitors, especially the second-generation EGFR-TKI afatinib, but resistant to first-generation reversible EGFR-TKIs (8). In our study, we demonstrated that a patient with metastatic NSCLC harboring a L858R/G729A compound mutation showed a more favorable response to afatinib than to icotinib. This provides clinical evidence supporting that patients with NSCLC carrying "less" uncommon *EGFR* mutations may derive a greater benefit from afatinib. Further studies are warranted to examine the efficacy of different EGFR-TKIs in various rare *EGFR* mutations occurring alone or concomitantly with *EGFR* sensitizing mutations.

In conclusion, we showed the significant clinical efficacy of the second-generation EGFR-TKI afatinib in a patient with advanced stage NSCLC harboring an exceptionally rare compound *EGFR* L858R/G729A mutation. This is the first report of a durable response to afatinib in a patient with NSCLC harboring the *EGFR* G729A mutation. Our data suggests that patients with NSCLC who are positive for uncommon *EGFR* mutations may benefit from treatment with afatinib. However, as a high degree of molecular heterogeneity is present in the uncommon *EGFR* mutation population, individualized treatment should be recommended based on existing data for each case in clinical practice.

Acknowledgments

Funding: This study was supported by the Science and Technology Project for Youth Talent of Changzhou Health Commission (QN201703, QN201722), Young Talent Development Plan of Changzhou Health Commission (CZQM2020024), Major Science and Technology Project of Changzhou Health Commission (ZD202004, ZD202007), and China Postdoctoral Science Foundation (2020M670064ZX).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-95/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-95/coif). XL is from Burning Rock Biotech. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Yatabe Y, Kerr KM, Utomo A, et al. EGFR mutation testing practices within the Asia Pacific region: results of a multicenter diagnostic survey. J Thorac Oncol 2015;10:438-45.
2. Passaro A, Mok T, Peters S, et al. Recent Advances on the Role of EGFR Tyrosine Kinase Inhibitors in the Management of NSCLC With Uncommon, Non Exon 20 Insertions, EGFR Mutations. J Thorac Oncol 2021;16:764-73.
3. Li WQ, Cui JW. Non-small cell lung cancer patients with ex19del or exon 21 L858R mutation: distinct mechanisms, different efficacies to treatments. J Cancer Res Clin Oncol 2020;146:2329-38.
4. Graham RP, Treece AL, Lindeman NI, et al. Worldwide Frequency of Commonly Detected EGFR Mutations. Arch Pathol Lab Med 2018;142:163-7.
5. An N, Wang H, Zhu H, et al. Great efficacy of afatinib on a patient with lung adenocarcinoma harboring uncommon EGFR delE709_T710insD mutations: a case report. Onco Targets Ther 2019;12:7399-404.
6. Jing C, Mao X, Wang Z, et al. Next-generation sequencing-based detection of EGFR, KRAS, BRAF, NRAS, PIK3CA, Her-2 and TP53 mutations in patients with non-small cell lung cancer. Mol Med Rep 2018;18:2191-7.
7. Massarelli E, Johnson FM, Erickson HS, et al. Uncommon epidermal growth factor receptor mutations in non-small cell lung cancer and their mechanisms of EGFR tyrosine kinase inhibitors sensitivity and resistance. Lung Cancer 2013;80:235-41.
8. Kohsaka S, Nagano M, Ueno T, et al. A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer. Sci Transl Med 2017;9:eaan6566.
9. Yang JC, Schuler M, Popat S, et al. Afatinib for the Treatment of NSCLC Harboring Uncommon EGFR Mutations: A Database of 693 Cases. J Thorac Oncol 2020;15:803-15.
10. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 2015;16:830-8.

(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Wu L, Fang C, Zhao W, Li D, Tang S, Li X, Ji M. Durable response to afatinib in an advanced lung adenocarcinoma patient with an EGFR L858R/G729A compound mutation: a case report. Ann Transl Med 2022;10(2):116. doi: 10.21037/atm-22-95