Received: 5 October 2021 | Accepted: 18 October 2021

DOI: 10.1111/1759-7714.14215

CASE REPORT

WILEY

Afatinib and osimertinib in lung adenocarcinoma harbored *EGFR* T751_I759delinsS mutation: A case report

Yueh-Fu Fang[1,2] | **Ping-Chi Liu**[3]

[1]Department of Thoracic Medicine, Chang Gung Foundation, Chang Gung Memorial Hospital, Taoyuan, Taiwan

[2]College of Medicine, Chang Gung University, Taoyuan, Taiwan

[3]Divison of Pulmonary, Critical Care, and Sleep Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan

Correspondence
Yueh-Fu Fang, Department of Thoracic Medicine, Chang Gung Memorial Hospital, 199 Tun-Hwa N. Rd., Taipei, Taiwan.
Email: dr.fang.yf@gmail.com

Abstract

Tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) are the standard treatment for lung cancer patients with activating *EGFR* mutation. The traditional direct polymerase chain reaction (PCR) has lower sensitivity in the detection of *EGFR* mutations in patient tissue samples. Whilst PCR amplification kits increase the sensitivity in detecting some types of *EGFR* mutations, not many types of rare mutations are found. Here, we report a patient who had lung adenocarcinoma harboring *EGFR* T751_I759delinsS mutation and had good response to afatinib initially and osimertinib after developing resistance to afatinib. This rare *EGFR* mutation was not detected by Scorpion and ARMS method but was found using the next-generation sequencing method. There are less prospective trials in the treatment of lung adenocarcinoma with very rare *EGFR* mutations. Our case report could therefore provide clinical experience to the clinicians in the management of their patients.

KEYWORDS
afatinib, EGFR, Osimertinib, T751_I759insdelS

INTRODUCTION

Lung adenocarcinoma patients diagnosed with mutant *EGFR* usually have a good response to EGFR tyrosine kinase inhibitors (TKIs). Complex mutation patterns can be detected by traditional direct polymerase chain reaction (PCR).[1] Direct PCR showed a lower sensitivity in patient samples which had a lower proportion of cancer cells. Some *EGFR* PCR kits increase the sensitivity but can only detect some specific mutations. The Scorpion and amplification refractory mutation system (ARMS) can detect several types of point mutations (G719X, S768I, T790M, L858R, L861Q), three subtypes of exon 20 insertion and 25 subtypes of exon 19 deletions. Many subtypes of rare *EGFR* mutations cannot be detected by PCR kits.[2] In these patients, next-generation sequencing (NGS) is a good method to find the rare *EGFR* mutations and other oncogenic mutations or amplifications.

There have been fewer prospective trials in the treatment of rare *EGFR* mutations.[3,4] Retrospective studies of real-world data in lung cancer patients have reported the outcome of EGFR TKIs treatments in lung cancer patients.[5,6] Some case reports of vary rare *EGFR* mutations provide details of clinical experience and suggestions for clinicians for patient treatment.[1,7,8] Deletion in exon 19 of *EGFR* has been found in many lung adenocarcinomas, but insertion in exon 19 of *EGFR* is less commonly reported in lung cancer patients. Here, we report the case of a lung adenocarcinoma patient who was found to have *EGFR* exon 19 insertion and achieved a good response to EGFR TKIs.

CASE REPORT

In March 2019, a 58-year-old male presented to our clinic with a cough and chest X-ray revealed a mass in the right lung. Following biopsy, the pathology confirmed that the patient had pulmonary adenocarcinoma. Positron emission tomography (PET-CT) showed a positive uptake in the right lung mass and bilateral mediastinal lymph nodes but there was no distal metastasis. Brain magnetic resonance imaging (MRI) with contrast showed no brain metastasis. The Scorpion and ARMS method showed no detectable *EGFR*

mutation. Immunohistochemistry staining of anaplastic lymphoma kinase (*ALK*) was negative. Programmed-death 1 ligand staining was 10%. He received concurrent chemoradiotherapy (CCRT) with docetaxel and cisplatin from April 9 to May 13 for stage III lung cancer. Chest computed tomography (CT) showed a partial response after CCRT. The patient received immunotherapy with durvalumab on June 19 and July 7 and had progressive

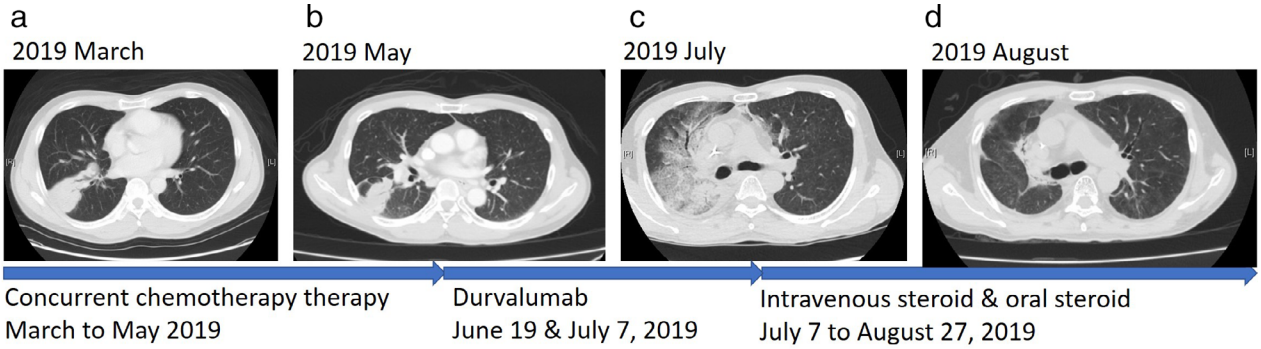

FIGURE 1 The patient was diagnosed with adenocarcinoma stage III (a) and received concurrent chemoradiotherapy (CCRT). Regression of the tumor (b) was noted and the patient subsequently received durvalumab after CCRT. The patient had pneumonitis after two cycles of durvalumab (c) but his pneumonitis improved after steroid treatment (d)

VARIANT(S) WITH CLINICAL RELEVANCE

Only variant(s) with clinical significance are listed. See the "DETAILED TEST RESULTS" section for full details.

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
EGFR	T751_I759delinsS	3893	95.6%	COSM1667027

COPY NUMBER VARIANTS (CNVS)

Amplification (Observed Copy Number ≥ 4)

Chr	Gene	Observed Copy Number
chr7	*EGFR*	23.5

Heterozygous / Homozygous deletion (Observed Copy Number < 2)

Chr	Gene	Observed Copy Number
ND	ND	ND

ND, Not Detected

FIGURE 2 Next-generation sequencing of the patient's tissue showed *EGFR* mutation with T751_I759delinsS and amplification (copy number 23.5)

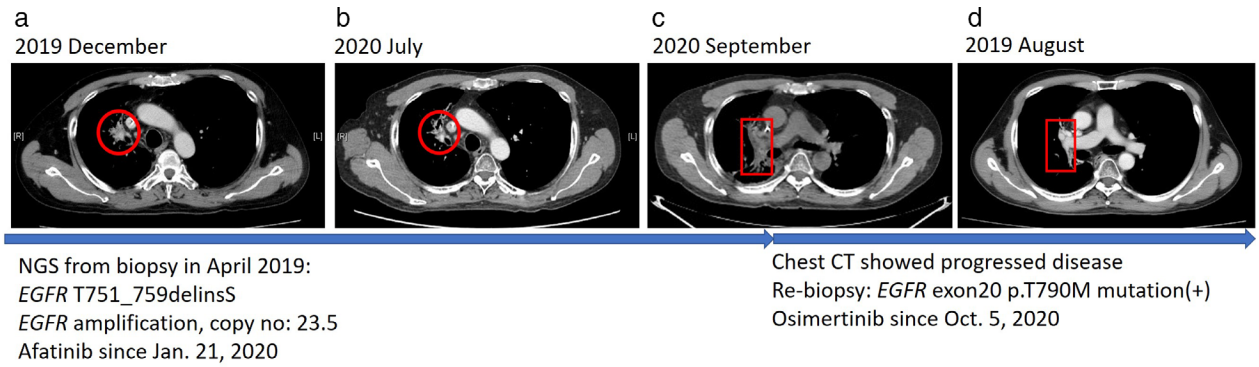

FIGURE 3 The patient received afatinib for recurrent lung cancer (a) and had a partial response (b). The patient had progressive disease (c) and rebiopsy of the lung tumor showed positive *EGFR* exon 20 p.T790M mutation. He had a partial response to osimertinib treatment (d)

dyspnea and grade 3 pneumonitis which was diagnosed on July 15. He was treated with steroids and had no further immunotherapy after his recovery from pneumonitis (Figure 1).

However, chest CT and brain MRI showed disease progression in the right lung with lymphangitic carcinomatosis and brain metastases in December 2019. Brain radiotherapy was performed for brain metastases. The NGS panel ACTDrug+ (ACT Genomics) showed *EGFR* T751_I759delinsS and *EGFR* amplification (copy number 23.5). The patient subsequently received afatinib on January 21, 2020 and brain MRI and chest CT showed a partial response. However, grade 1 skin rash and paronychia were reported. Chest CT showed progressed lymphangitic carcinomatosis of the right lung after treatment with afatinib for 9 months. The pathology of rebiopsy of the lung tumor confirmed a positive *EGFR* exon 20 p.T790M mutation by the Scorpion and ARMS method. We subsequently prescribed osimertinib for the patient commencing on October 5, 2020 and his chest CT and brain MRI have revealed a partial response. Our report showed *EGFR* T751_I759delinsS and *EGFR* amplification are sensitive to afatinib. Progression-free survival was 9 months for the patient in our study. Osimertinib was effective for this rare mutation after the patient was found to be resistant to afatinib because of *EGFR* exon 20 p.T790M mutation (Figure 2).

DISCUSSION

Here, we present the report of a patient who was found to harbor *EGFR* T751_I759delinsS and amplification of *EGFR* and had a good response to afatinib and osimertinib. Deletion from E746 or L747 of exon 19 are common mutations of *EGFR* and have shown a good response to EGFR TKIs. A study of 195 patients with exon 19 deletion showed shorter progression-free survival (PFS) 2.9 months of first-generation EGFR TKIs in the patients who had deletion from T751 or S752. The lower detection rate (16.7%) of *EGFR* exon 20 p.T790M may have resulted in shorter PFS in a previously reported study.[9] A case report showed a patient had PFS 7.0 months to icotinib and had resistant mutation T751_I759delinsS after icotinib treatment.[10] The patient had no response to three combinations with chemotherapy, bevacizumab and erlotinib but had a good response to osimertinib for 16 months. The *EGFR* T751_I759delinsS should be sensitive osimertinib depended on our report (Figure 3).

EGFR amplification has been reported as one resistant mechanism to *EGFR* TKIs.[11,12] Our patient had coexisting *EGFR* T751_I759delinsS mutation and *EGFR* amplification and received 9 months PFS following afatinib treatment. The 9-months PFS was shorter than in those patients who receive first-line treatment with afatinib for common *EGFR* exon 19 deletions. In patients with other uncommon *EGFR* mutations, PFS was less than 9 months and depended on retrospective analysis of clinical trial and real-world evidence.[4]

The T751_I759delinsS in *EGFR* exon 19 could not be detected by several commercial PCR kits. NGS should be a better method to detect complex variants of *EGFR* mutations. Half lung adenocarcinoma patients had common *EGFR* mutations or expression of *ALK* in Asia. For economic reasons, NGS is often only performed in patients who have been confirmed to ahve negative *EGFR* mutations by PCR kits and low expression of *ALK* in Asia. In a subgroup of patients who had a lower ratio of *EGFR* mutation, NGS was reported to be the better method of detecting driver genes.[13]

In summary, we report a case of lung adenocarcinoma with T751_I759delinsS in *EGFR* exon 19 which may be a predictive factor of poor response to first generation TKIs as reported in a previous study.[14] Our case showed acceptable PFS to afatinib after CCRT and checkpoint immunotherapy. This rare mutation may indicate good PFS to osimertinib but more real-world data is needed to support our findings.

CONFLICT OF INTEREST

The authors do not report any conflicts of interest.

ORCID

Yueh-Fu Fang https://orcid.org/0000-0003-2211-3076

REFERENCES

1. Hsieh MH, Fang YF, Chang WC, Kuo HP, Lin SY, Liu HP, et al. Complex mutation patterns of epidermal growth factor receptor gene associated with variable responses to gefitinib treatment in patients with non-small cell lung cancer. Lung Cancer. 2006;53:311–22.
2. Qin L, Zhong W, Zhang L, Li LY, Wang MZ. Comparison of three methods for detecting epidermal growth factor receptor mutations in plasma DNA samples of Chinese patients with advanced non-small cell lung cancer. Chin Med J (Engl). 2011;124:887–91.
3. Cho JH, Lim SH, An HJ, Kim KH, Park KU, Kang EJ, et al. Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09). J Clin Oncol. 2020;38:488–95.
4. 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.
5. Brindel A, Althakfi W, Barritault M, Watkin E, Maury JM, Bringuier PP, et al. Uncommon EGFR mutations in lung adenocarcinoma: features and response to tyrosine kinase inhibitors. J Thorac Dis. 2020;12:4643–50.
6. Chantharasamee J, Poungvarin N, Danchaivijitr P, Techawatanawanna S. Clinical outcome of treatment of metastatic non-small cell lung cancer in patients harboring uncommon EGFR mutation. BMC Cancer. 2019;19:701.
7. Ibrahim U, Saqib A, Atallah JP. EGFR exon 18 delE709_T710insD mutated stage IV lung adenocarcinoma with response to afatinib. Lung Cancer. 2017;108:45–7.
8. Xia P, Liu E, Li P, Li W, Jiang G. A case of primary resistance to Ge fi tinib due to novel deletion-insertion mutation of EGFR exon 19 in NSCLC. J Thorac Oncol. 2019;14:e117–e9.
9. Xu H, Li W, Yang G, Li J, Yang L, Xu F, et al. Heterogeneous response to first-generation tyrosine kinase inhibitors in non-small-cell lung cancers with different EGFR exon 19 mutations. Target Oncol. 2020; 15:357–64.
10. Li H, Yu T, Lin Y, Xie Y, Feng J, Huang M, et al. Three novel EGFR mutations (750_758del, I759S, T751_I759delinsS) in one patient with

metastatic non-small cell lung cancer responding to Osimertinib: a case report. Onco Targets Ther. 2020;13:7941–8.
11. Lin L, Lu Q, Cao R, Ou Q, Ma Y, Bao H, et al. Acquired rare recurrent EGFR mutations as mechanisms of resistance to Osimertinib in lung cancer and in silico structural modelling. Am J Cancer Res. 2020;10:4005–15.
12. Lee PC, Fang YF, Yamaguchi H, Wang WJ, Chen TC, Hong X, et al. Targeting PKCdelta as a therapeutic strategy against heterogeneous mechanisms of EGFR inhibitor resistance in EGFR-mutant lung cancer. Cancer Cell. 2018;34:954–69. e4.
13. Guo G, Li G, Liu Y, Li H, Guo Q, Liu J, et al. Next-generation sequencing reveals high uncommon EGFR mutations and tumour mutation burden in a subgroup of lung cancer patients. Front Oncol. 2021;11:621422.
14. Xu CW, Lei L, Wang WX, Lin L, Zhu YC, Wang H, et al. Molecular characteristics and clinical outcomes of EGFR exon 19 C-helix deletion in non-small cell lung cancer and response to EGFR TKIs. Transl Oncol. 2020;13:100791.

How to cite this article: Fang Y-F, Liu P-C. Afatinib and osimertinib in lung adenocarcinoma harbored *EGFR* T751_I759delinsS mutation: A case report. Thorac Cancer. 2021;12:3429–32. https://doi.org/10.1111/1759-7714.14215