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World J Clin Cases 2021 February 26; 9(6): 1247-1498



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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Quach is an Associate Professor of Gastroenterology at the University of Medicine and Pharmacy at Hochiminh City, Viet Nam, where he received his MD in 1997 and his PhD in 2011. Dr. Quach has published more than 100 reviews and original papers in local and international journals. He has received several awards, including Outstanding Presentation at the Biannual Scientific Congress of Vietnamese Nationwide Medical Schools, Medal of Creativeness from the Vietnamese Central Youth League, etc. Currently, he serves as a Vice President of the Vietnam Association of Gastroenterology and Secretary General of the Vietnam Federation for Digestive Endoscopy. (L-Editor: Filipodia)

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ji-Hong Liu*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lai Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

February 26, 2021

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<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

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<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Efficacy of afatinib in a patient with rare EGFR (G724S/R776H) mutations and amplification in lung adenocarcinoma: A case report

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Informed consent statement: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

Conflict-of-interest statement: Zhang JL is an employee of Shanghai 3D Medicines Inc. All other authors declare no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

The most common *EGFR* mutations are in-frame deletions in exon 19 and point mutations in exon 21. Cases with classical *EGFR* mutations show a good response to *EGFR* tyrosine kinase inhibitors (TKIs), the standard first-line treatment. With the development of next generation sequencing, some uncommon genomic mutations have been detected. However, the effect of TKIs on such uncommon *EGFR* mutations remains unclear.

CASE SUMMARY

Here, we report a case of rare *EGFR* co-mutation in non-small cell lung cancer and the efficacy of afatinib on this *EGFR* co-mutation. A 64-year-old woman was diagnosed with thoracolumbar and bilateral local rib bone metastases, bilateral pulmonary nodules, and pericardial and left pleural effusion. The pathological diagnosis was lung adenocarcinoma. To seek potential therapeutic regimens, rare co-mutation comprising rare *EGFR* G724S/R776H mutations and amplification were identified. The patient experienced a significant clinical response with a progression-free survival of 17 mo.

CONCLUSION

A case of non-small cell lung cancer with rare *EGFR* G724S/R776H mutations and *EGFR* amplification responds well to TKI treatment.

Key Words: *EGFR* G724S and R776H; Afatinib; Non-small cell lung cancer; Case report

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Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

Received: September 8, 2020

Peer-review started: September 8, 2020

First decision: November 20, 2020

Revised: December 3, 2020

Accepted: December 22, 2020

Article in press: December 22, 2020

Published online: February 26, 2021

P-Reviewer: Farshadpour F,

Higuera-de la Tijera F, Ishizawa K

S-Editor: Zhang H

L-Editor: Wang TQ

P-Editor: Zhang YL



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Core Tip: EGFR represents the first identified targetable oncogenic driver discovered in non-small cell lung cancer (NSCLC). The most common EGFR mutations are in-frame deletions in exon 19 and point mutations in exon 21. However, rare mutations were found in nearly 10%-15% of EGFR-positive NSCLC and NSCLC with rare co-mutations had significantly different responses to EGFR tyrosine kinase inhibitor. Herein, we describe a rare case of rare EGFR G724S/R776H mutations and amplification in a NSCLC responding to afatinib.

Citation: He SY, Lin QF, Chen J, Yu GP, Zhang JL, Shen D. Efficacy of afatinib in a patient with rare EGFR (G724S/R776H) mutations and amplification in lung adenocarcinoma: A case report. *World J Clin Cases* 2021; 9(6): 1329-1335

URL: <https://www.wjgnet.com/2307-8960/full/v9/i6/1329.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i6.1329>

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death, especially in developing countries such as China^[1]. A recent study shows that in 2015 there were about 733000 newly diagnosed cases of NSCLC in China, with approximately 610000 Chinese patients dying from the disease^[2]. NSCLC accounts for the majority (75%) of clinical lung cancer cases. Adenocarcinoma is the most common histological type of NSCLC and can be subdivided into different clinically relevant molecular subtypes according to the type of driver gene mutation.

EGFR was the first identified targetable oncogenic driver discovered in NSCLC^[3]. Approximately 40% of Asian patients with newly diagnosed metastatic NSCLC harbor a somatic mutation in the EGFR gene^[4]. The most common EGFR mutations are in-frame deletions in exon 19 and point mutations in exon 21. However, rare mutations were found in nearly 10%-15% of EGFR-positive NSCLC cases^[5,6]. Although it has been reported that afatinib is effective against rare EGFR mutations, there are significant differences in progression-free survival (PFS) and overall survival (OS) among patients with different rare EGFR mutations^[7]. Here, we describe a rare case of EGFR G724S/R776H mutations and EGFR amplification in an NSCLC patient responding to afatinib.

CASE PRESENTATION

Chief complaints

A 64-year-old nonsmoking woman visited our hospital on April 26, 2019 for further treatment because she could not tolerate the side effects of previous chemotherapy for lung adenocarcinoma, including myelosuppression and cardiac and renal insufficiency.

History of present illness

Chest computed tomography (CT) showed bone metastases in the thoracolumbar spine and bilateral local ribs, nodules in both lungs, and pericardial and left pleural effusion.

History of past illness

On September 10, 2014, the patient went to a local hospital because of sudden glossolalia with right lower limb numbness, and was diagnosed with stage IIIA lung adenocarcinoma, and then she underwent resection of the upper lobe on September 24, 2014 (Figure 1A). The patient received pemetrexed combined with carboplatin for four cycles of chemotherapy. In November 2015, the disease progressed. The patient was given paclitaxel plus cisplatin combined with bevacizumab for six cycles from November 11, 2015 to March 11, 2016. From April 1, 2016 to April 26, 2019, the patient received pemetrexed combined with bevacizumab, and his condition remained stable

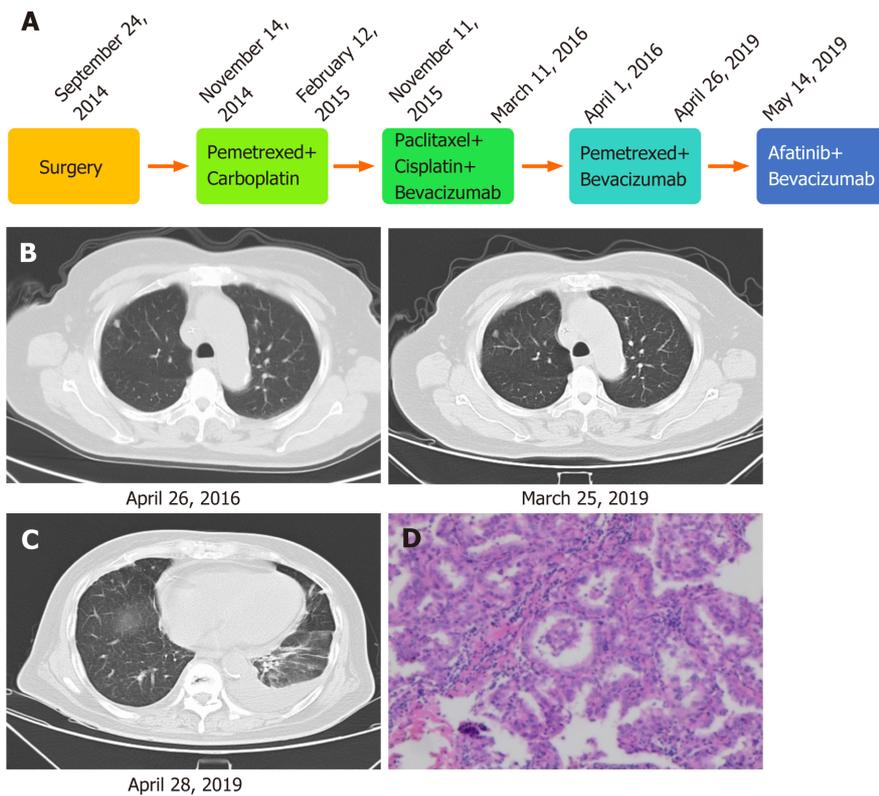


Figure 1 Diagnosis and treatment of the patient's disease. A: Treatment of lung adenocarcinoma using different regimens; B: Imaging diagnosis during pemetrexed plus bevacizumab treatment; C: Imaging diagnosis before afatinib therapy; D: Pathological diagnosis.

(Figure 1B). After the last cycle of treatment with pemetrexed plus bevacizumab, chest CT showed bone metastases in the thoracolumbar spine and bilateral local ribs, nodules in both lungs, and pericardial and left pleural effusion (Figure 1C).

Laboratory examinations

The previous pathological diagnosis was lung adenocarcinoma (Figure 1D).

Imaging examinations

After the last cycle of treatment with pemetrexed plus bevacizumab, CT showed bone metastases in the thoracolumbar spine and bilateral local ribs, nodules in both lungs, and pericardial and left pleural effusion (Figure 1C).

FINAL DIAGNOSIS

Because the patient could not tolerate the side effects of chemotherapy, potential therapeutic regimens were sought. Her blood was subjected to NGS analysis, and a rare *EGFR* G724S [mutant allele frequency (MAF): 67.59%] mutation in exon 18 and R776H (MAF: 40.54%) mutation in exon 20 as well as amplification was identified (Figure 2). Therefore, the patient was finally diagnosed with lung adenocarcinoma with rare *EGFR* G724S and R776H mutations and amplification.

TREATMENT

Based on the above findings, the patient was administered with afatinib (30 mg qd) combined with bevacizumab and followed regularly.

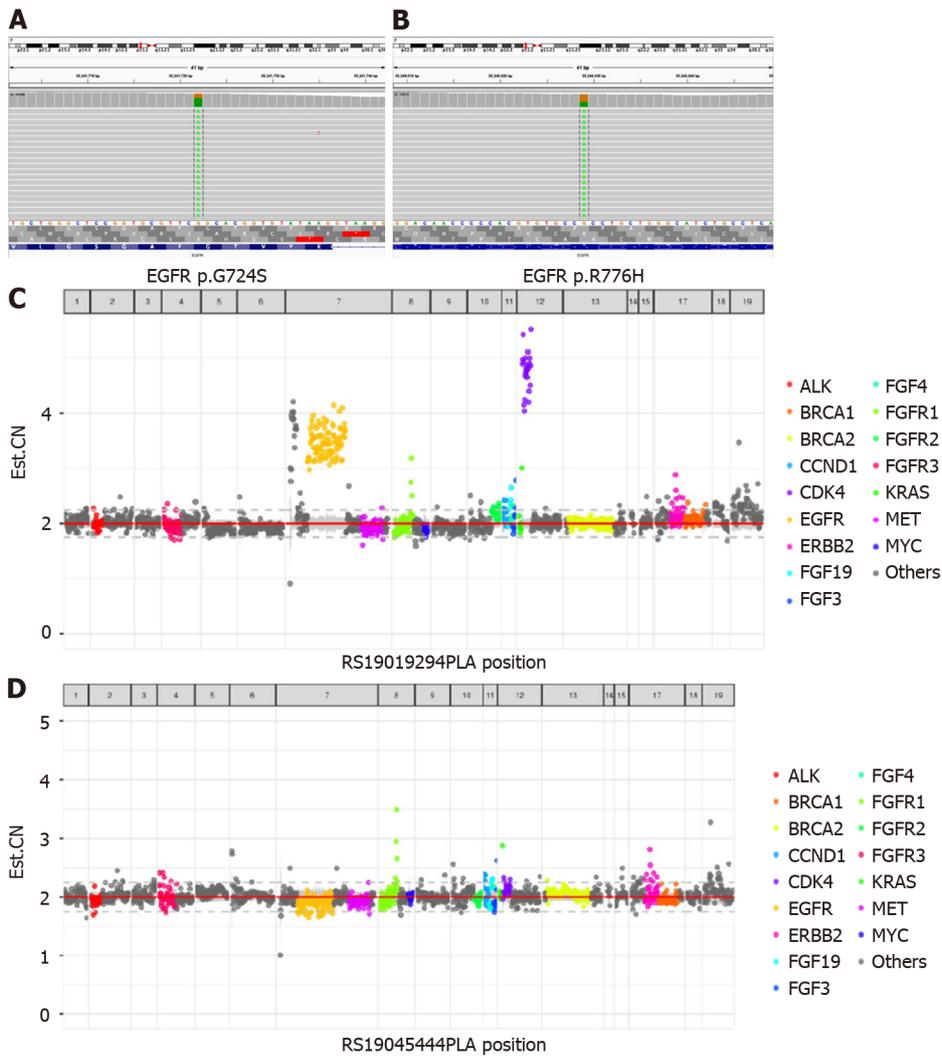


Figure 2 Next-generation sequencing results. A: Next-generation sequencing showed G724S in EGFR exon 18; B: Next-generation sequencing showed R776H in EGFR exon 20; C: Next-generation sequencing showed EGFR amplification before treatment; D: Next-generation sequencing showed EGFR amplification after treatment.

OUTCOME AND FOLLOW-UP

After 4 mo of treatment, the left pleural effusion and pericardial effusion were significantly reduced and the patient showed SD according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (Figure 3). The MAFs for both R776H and G724S were also decreased (R776H from 40.54% to 0.16% and G724S from 67.59% to undetected). During this period, zoledronic acid was irregularly given for anti-bone metastasis therapy. The patient was followed several times, and CT performed on July 10, 2020 showed that the tumor lesion of the right lung remained stable (Figure 3). However, the reexamination on October 25, 2020 revealed disease progression with multiple bone metastases (Figure 4). Imaging studies indicated progressive disease (PD), and the patient's final PFS was 17 mo. There were no obvious adverse reactions during the treatment.

DISCUSSION

In the era of precision medicine, EGFR genotyping has become the standard practice for NSCLC, but the identification of rare mutations does not necessarily imply clear targeted therapeutic action. Due to the small number and high heterogeneity of patients with rare mutations, the efficacy of EGFR TKIs in patients with rare EGFR mutations remains unclear. However, a large number of clinical studies have shown significant differences in the efficacy of EGFR TKIs in patients with rare mutations in

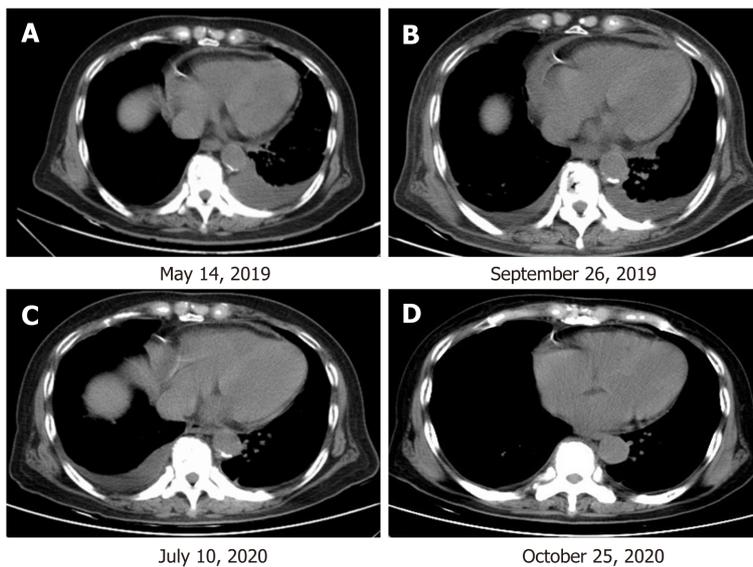


Figure 3 The patient's clinical course including treatment history and relevant imaging studies. A: At baseline before therapy with afatinib combined with bevacizumab; B: At 4 mo of therapy with afatinib combined with bevacizumab, with an SD response; C: At 14 mo of therapy with afatinib combined with bevacizumab, with an SD response. D: At 17 mo of therapy with afatinib combined with bevacizumab, with a progressive disease response.

EGFR. Therefore, these patients should be analyzed separately in clinical studies to provide them with more effective individualized treatment.

As a second-generation EGFR TKI, afatinib is more effective than chemotherapies and first-generation EGFR-TKIs^[8,9]. In LUX-Lung 7 and LUX-Lung 8 studies, it was found that patients treated with afatinib as both first-line treatment (compared with gefitinib) and second-line treatment (compared with erlotinib) resulted in a longer PFS or OS^[10,11]. However, most patients with rare or complex *EGFR* mutations had a shorter PFS than patients with exon 19 deletion (16.0 mo *vs* 9.0 mo; HR, 0.34; 95% CI, 0.13-0.94, $P = 0.037$)^[12]. In addition, it has been reported that patients aged ≥ 65 years with rare mutations have significantly longer PFS than patients aged < 65 years after receiving EGFR TKIs (median PFS: 10.5 mo *vs* 5.5 mo, $P = 0.0320$)^[13]. Patients with rare *EGFR* mutations are often excluded from clinical trials. However, these adverse characteristics are frequently encountered in clinical practice, and in particular, rare mutations of *EGFR* (two or more *EGFR* mutations at the same time) are generally considered a relatively rare event representing a unique and highly heterogeneous subset of NSCLC.

CONCLUSION

In summary, we report a rare case of NSCLC with *EGFR G724S/R776H* and amplification, which has never been reported before. The successful use of afatinib in this case may provide a new treatment option for this type of *EGFR* co-mutation, especially for patients who decline or are not suitable for chemotherapy. By deepening our understanding of functional and structural differences between rare subtypes of *EGFR* variation, the different responses to EGFR TKIs and overall survival rates of patients with these mutations need to be further studied. This case provides valuable insights for future clinical cancer treatment.

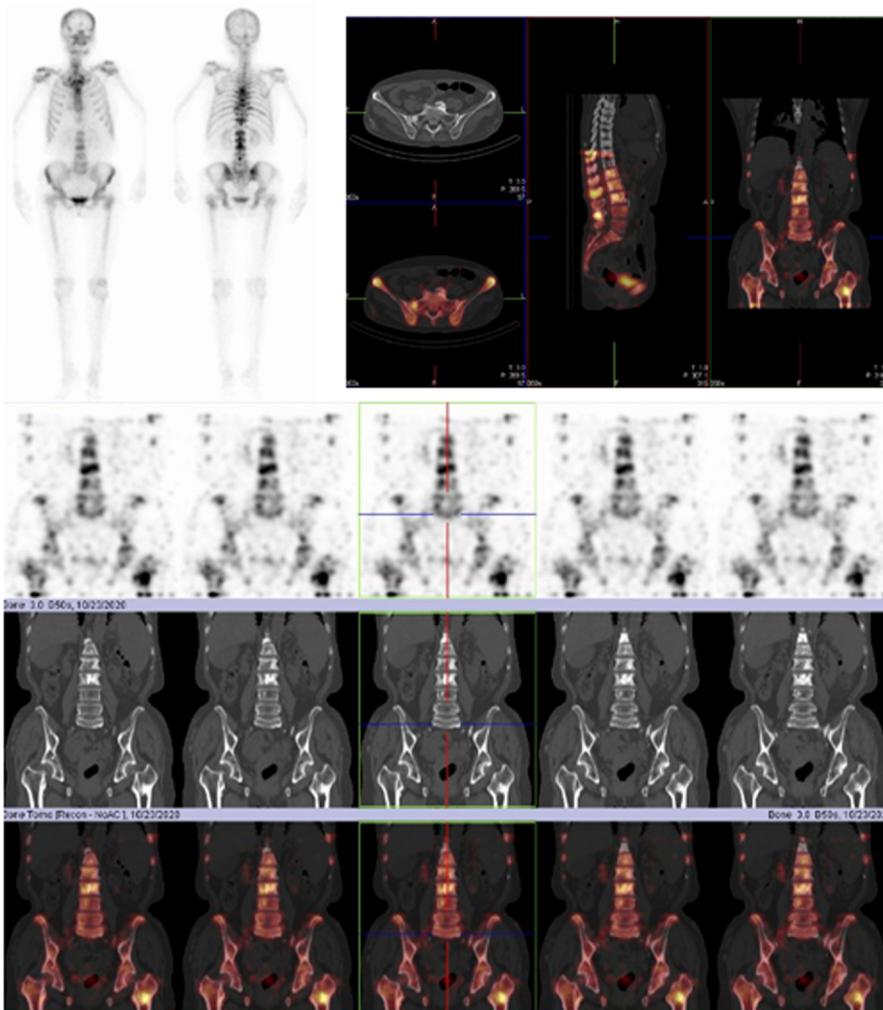


Figure 4 Diagnosis of disease progression in the patient. Whole-body bone scan and organ tomography revealed increased uptake of multiple imaging agents in the skull, spine, ribs on both sides, pelvis composition, and upper left femur, suggesting bone metastasis of the tumor.

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