ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

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

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 9 Number 6 February 26, 2021

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 6 February 26, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 6 February 26, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 6 February 26, 2021

Contents

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)

AIMS AND SCOPE

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

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

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
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

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2021 February 26; 9(6): 1329-1335

DOI: 10.12998/wjcc.v9.i6.1329

ISSN 2307-8960 (online)

CASE REPORT

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

Shu-Yan He, Qing-Feng Lin, Jie Chen, Gui-Ping Yu, Jun-Ling Zhang, Dong Shen

ORCID number: Shu-Yan He 0000-0002-2975-5883; Qing-Feng Lin 0000-0003-1994-8945; Jie Chen 0000-0002-7536-8171; Gui-Ping Yu 0000-0002-9665-1225; Jun-Ling Zhang 0000-0002-8618-3471; Dong Shen 0000-0002-9665-1224.

Author contributions: He SY and Shen D contributed to the study concept and design and performed the statistical analysis; Lin QF, Chen J, and Yu GP contributed to the acquisition, analysis, or interpretation of the data; Zhang JL contributed to the drafting of the manuscript; Zhang JL and Shen D contributed to the critical revision of the manuscript for important intellectual content.

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).

Shu-Yan He, Qing-Feng Lin, Jie Chen, Dong Shen, Department of Medical Oncology, The Jiangyin Clinical College of Xuzhou Medical University, Jiangyin 214400, Jiangsu Province, China

Gui-Ping Yu, Department of Cardiothoracic Surgery, The Affiliated Jiangyin Hospital of Southeast University, Jiangyin 214400, Jiangsu Province, China

Jun-Ling Zhang, Medical Department, 3D Medicines Inc., Shanghai 201114, China

Corresponding author: Dong Shen, PhD, Chief Doctor, Professor, Department of Medical Oncology, The Jiangyin Clinical College of Xuzhou Medical University, No. 163 Shoushan Road, Jiangyin 214400, Jiangsu Province, China. sdshendong@126.com

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

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

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

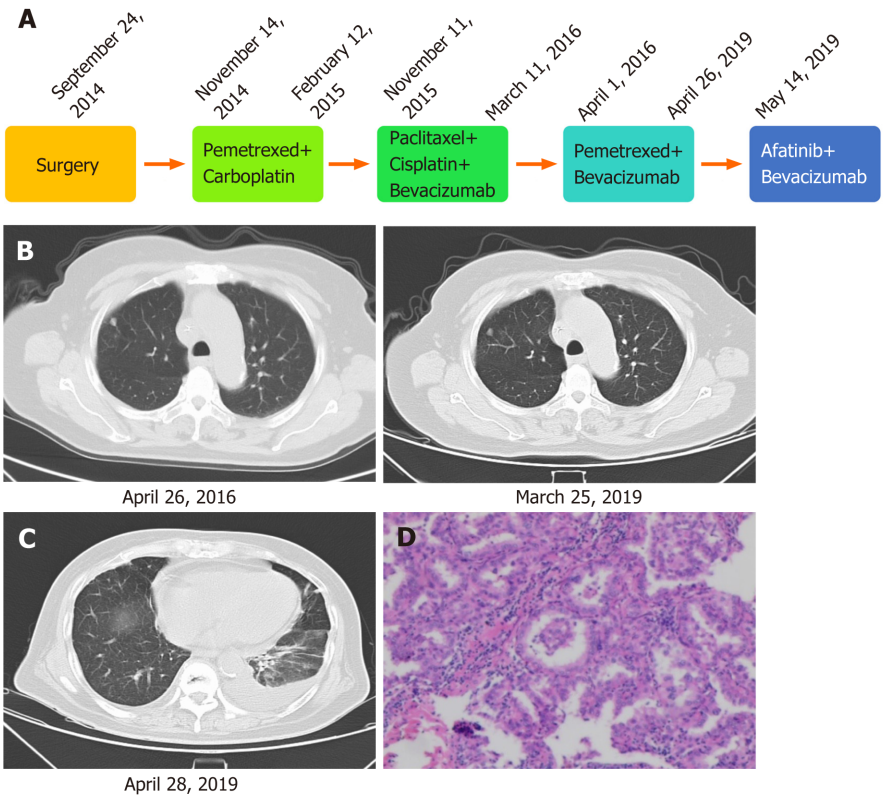

Figure 1 Diagnosis and treatment of the patient's disease. A: Treatment of lung adenocarcinoma using different regimens; B: Imaging diagnosis during pemetrexed plus bevacizumab treatment; C: Imaging diagnosis before afatinib therapy; D: Pathological diagnosis.

(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.

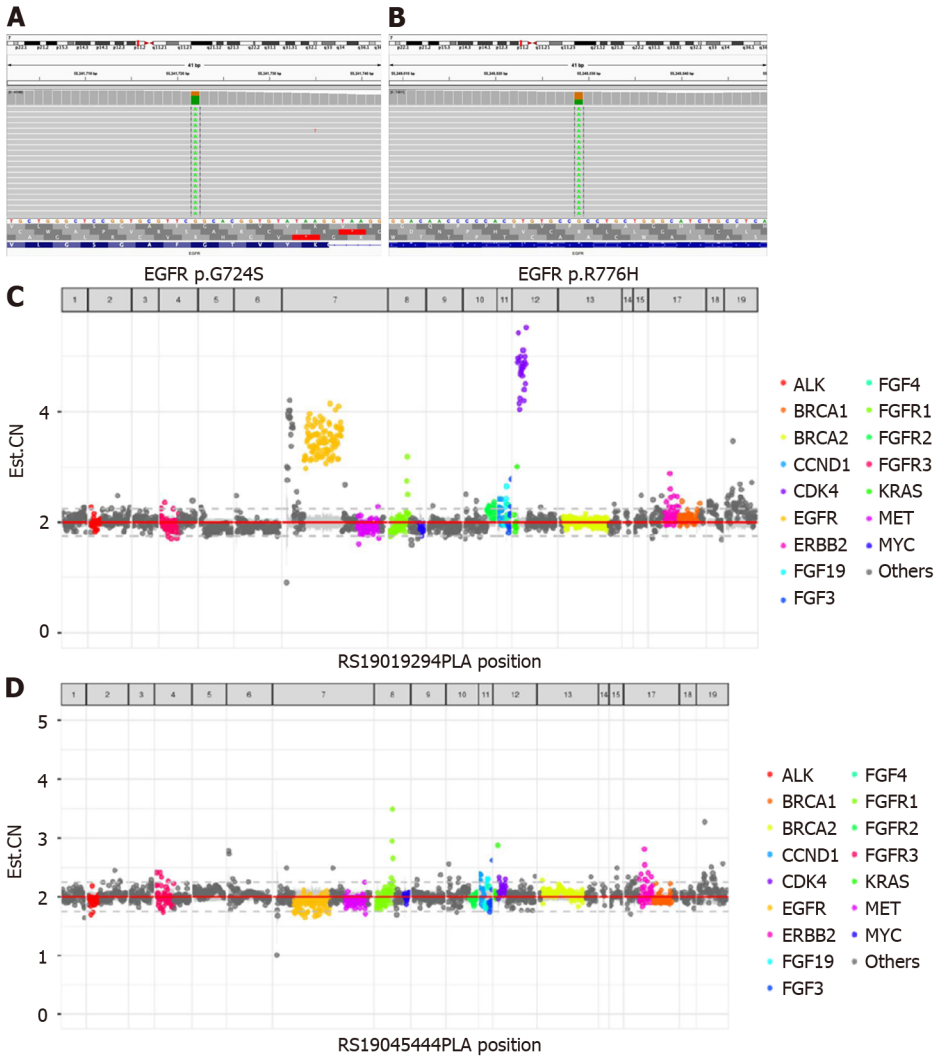

Figure 2 Next-generation sequencing results. A: Next-generation sequencing showed *G724S* in *EGFR* exon 18; B: Next-generation sequencing showed *R776H* in *EGFR* exon 20; C: Next-generation sequencing showed *EGFR* amplification before treatment; D: Next-generation sequencing showed *EGFR* amplification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

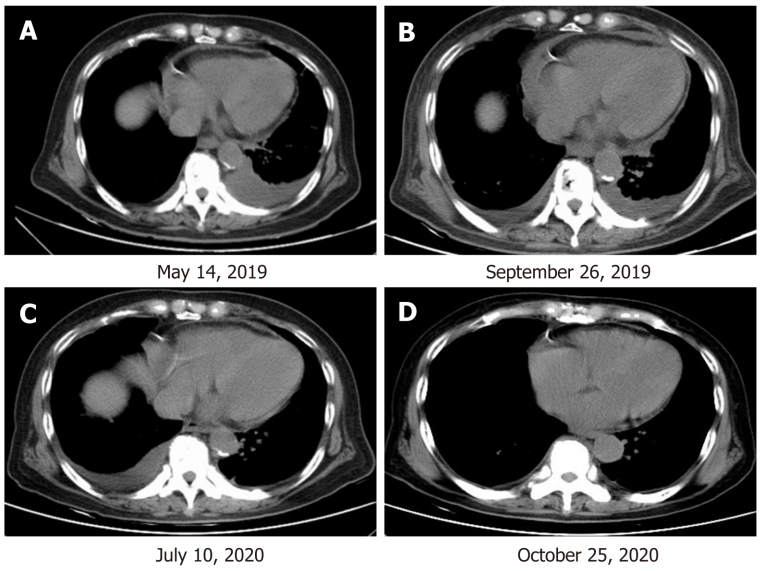

Figure 3 The patient's clinical course including treatment history and relevant imaging studies. A: At baseline before therapy with afatinib combined with bevacizumab; B: At 4 mo of therapy with afatinib combined with bevacizumab, with an SD response; C: At 14 mo of therapy with afatinib combined with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

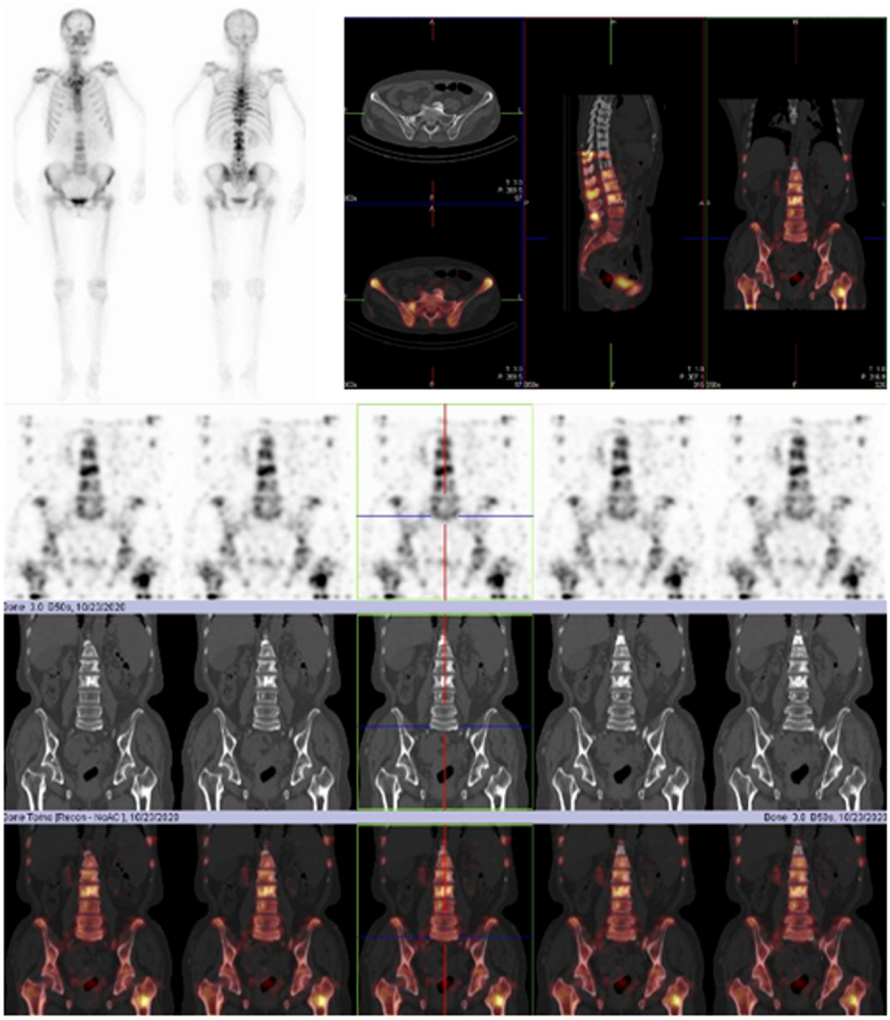

Figure 4 Diagnosis of disease progression in the patient. Whole-body bone scan and organ tomography revealed increased uptake of multiple imaging agents in the skull, spine, ribs on both sides, pelvis composition, and upper left femur, suggesting bone metastasis of the tumor.

REFERENCES

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]

2 **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]

3 **Baek JH**, Sun JM, Min YJ, Cho EK, Cho BC, Kim JH, Ahn MJ, Park K. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small cell lung cancer except both exon 19 deletion and exon 21 L858R: a retrospective analysis in Korea. *Lung Cancer* 2015; **87**: 148-154 [PMID: 25498243 DOI: 10.1016/j.lungcan.2014.11.013]

4 **Fogli S**, Polini B, Del Re M, Petrini I, Passaro A, Crucitta S, Rofi E, Danesi R. EGFR-TKIs in non-small-cell lung cancer: focus on clinical pharmacology and mechanisms of resistance. *Pharmacogenomics* 2018; **19**: 727-740 [PMID: 29785875 DOI: 10.2217/pgs-2018-0038]

5 **Tu HY**, Ke EE, Yang JJ, Sun YL, Yan HH, Zheng MY, Bai XY, Wang Z, Su J, Chen ZH, Zhang XC, Dong ZY, Wu SP, Jiang BY, Chen HJ, Wang BC, Xu CR, Zhou Q, Mei P, Luo DL, Zhong WZ, Yang XN, Wu YL. A comprehensive review of uncommon EGFR mutations in patients with non-small cell lung cancer. *Lung Cancer* 2017; **114**: 96-102 [PMID: 29173773 DOI: 10.1016/j.lungcan.2017.11.005]

6 **Wu JY**, Yu CJ, Chang YC, Yang CH, Shih JY, Yang PC. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res* 2011; **17**: 3812-3821 [PMID: 21531810 DOI: 10.1158/1078-0432.CCR-10-3408]

7 **Saxon JA**, Sholl LM, Jänne PA. EGFR L858M/L861Q cis Mutations Confer Selective Sensitivity to Afatinib. *J Thorac Oncol* 2017; **12**: 884-889 [PMID: 28088511 DOI: 10.1016/j.jtho.2017.01.006]

8 **Sequist LV**, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013; **31**: 3327-3334 [PMID:

23816960 DOI: 10.1200/JCO.2012.44.2806]

9 **Wu YL**, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 213-222 [PMID: 24439929 DOI: 10.1016/S1470-2045(13)70604-1]

10 **Park K**, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kölbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V, Paz-Ares L. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol* 2016; **17**: 577-589 [PMID: 27083334 DOI: 10.1016/S1470-2045(16)30033-X]

11 **Soria JC**, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, Göker E, Georgoulias V, Li W, Isla D, Guclu SZ, Morabito A, Min YJ, Ardizzoni A, Gadgeel SM, Wang B, Chand VK, Goss GD; LUX-Lung 8 Investigators. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2015; **16**: 897-907 [PMID: 26156651 DOI: 10.1016/S1470-2045(15)00006-6]

12 **Ho GF**, Chai CS, Alip A, Wahid MIA, Abdullah MM, Foo YC, How SH, Zaatar A, Lam KS, Leong KW, Low JS, Yusof MM, Lee EC, Toh YY, Liam CK. Real-world experience of first-line afatinib in patients with EGFR-mutant advanced NSCLC: a multicenter observational study. *BMC Cancer* 2019; **19**: 896 [PMID: 31500587 DOI: 10.1186/s12885-019-6107-1]

13 **Tsai MJ**, Hung JY, Lee MH, Kuo CY, Tsai YC, Tsai YM, Liu TC, Yang CJ, Huang MS, Chong IW. Better Progression-Free Survival in Elderly Patients with Stage IV Lung Adenocarcinoma Harboring Uncommon Epidermal Growth Factor Receptor Mutations Treated with the First-line Tyrosine Kinase Inhibitors. *Cancers (Basel)* 2018; **10** [PMID: 30428509 DOI: 10.3390/cancers10110434]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com