Dear Editor

Thank you for your letter and considering our manuscript to publish in *World J of Clinical Cases*. Before we address the specific remarks raised by the reviewers and editors, we would also like to thank them for the positive support and constructive remarks that help us to improve the manuscript. We have addressed their concerns and taken their suggestions. Corresponding changes are also made in the revised manuscript. We hope the reviewers and you will now agree that our manuscript merits for publication.

Sincerely,

Jialei Wang MD

Department of Medical Oncology, Fudan University Shanghai Cancer Center
Department of Oncology, Shanghai Medical College, Fudan University
Shanghai, China.
Email: m18017312369@163.com.

Authors' response

Reviewer 1:

Specific Comments to Authors:

1. This article is an original article describing a very rare case of NSCLC with multiple genetic mutations. Abstracts, introductions, case presentations, and discussions are very well discussed.

Authors' response: Thanks for the positive comment.

2. Please explain the biopsy technique that was first performed on line 73 of the statement

Authors' response: Thanks for comment. A percutaneous puncture biopsy of the lung lesion was performed. We have added the corresponding part in the "FINAL DIAGNOSIS" section, paragraph 1, line 1.

3. Please clarify that the word "Brian" on line 74 is correct or incorrect

Authors' response: Thanks for pointing out the typo. We have corrected it into "Brain" in the revised manuscript.

4. Please clarify the statements on lines 74-75 regarding metastases in the brain, is it one lesion or many lesions? This contrasts with the explanation in Figure 2 which only shows 1 metastatic lesion.

Authors' response: Thanks for comment. The patient had multiple brain metastatic lesions. The statements on lines 74-75 are correct. However, instead of showing all brain lesions, Figure 2A only shows the target lesion that progressed after afatinib treatment. The citation of Figure 2A in lines 74-75 was inappropriate. In the revised manuscript, we have deleted the citation and also clarify this in the legend of Figure 2A (now is Figure 1A).

5. Please attach the Response Evaluation Criteria in Solid Tumors 1.1 form and explain how to determine "Partial Respone" in this patient.

Authors' response: Thanks for comment. We have attached the forms. A 30% decrease in the sum of diameter of the lung lesion was observed (from 4cm to 2.8cm in diameter) which indicated partial response. The part had been added in line the "TREATMENT" section, paragraph 1, line 3.

6. Please explain in the discussion section why the NGS examination can reveal complex genetic mutations compared to the PCR examination. Is there any suggestion to the reader when the NGS examination should be used to improve patient outcomes?

Authors' response: Thanks for comment. We have add "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 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 strong recommend if conventional methods fail to detect any actionable alterations." In the discussion section

Reviewer 2

Specific Comments to Authors: Zhang and colleagues report a case report of a stage IV NSCLC patient harboring EGFR L861Q-L833F compound mutations benefits from both afatinib and osimertinib.I have few comments.
The authors use the phrase "our study" in the conclusion section and the core tip section, but this is only a case report. Please revise the description.
Authors' response: Thanks for the correction. We have revised it into "our case" in the revised manuscript.

The authors reported that they detected the compound mutation by NGS, but please provide more details about the NGS method.
Authors' response: Thanks for the comment. We have added the detail information in the "TREATMENT" section, paragraph 1, line 12-13 in the revised manuscript.

In the discussion section, the authors only mention the effect of osimertinib on compound mutation. However, there is a report that afatinib is more effective in the treatment of compound mutation (Kohsaka, et al. Sci Transl Med 2017), and in this case, afatinib actually had a better long-term response than osimertinib. Please add a discussion on the effect of afatinib on compound mutation.
Authors' response: Thanks for the comment. We have added a paragraph "Our case demonstrated a durable response of 10 months to 1st-line treatment with afatinib suggesting the clinical activity of this TKI against the rare compound mutations L833F-L861Q. In line with our observation, a pooled analysis revealed that afatinib resulted in an ORR of 77.1% and a median time to treatment failure (TTF) of 14.7 months [95% confidence interval (CI): 6.8-18.5 months] in EGFR TKI–naive patients harboring compound mutations. A recent retrospective study also shows that afatinib is associated with 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. 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 significant longer PFS (afatinib vs. gefitinib vs. erlotinib: 10.5 months vs. 3.0 months vs.0.9 months)." in the discussion section.

EDITORIAL OFFICE'S COMMENTS

(1) Science editor: 5 Issues raised:
(1) The title is too long, and it should be no more than 18 words;
Authors' response: We have shorten the title as "Non-small-cell lung cancer with EGFR L861Q-L833F benefits from both afatinib and osimertinib: a case report".

(2) The "Author Contributions" section is missing. Please provide the author contributions;
Authors' response: We have added the "Author Contributions" section.

(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;
Authors' response: We have uploaded the PPT version of figures.

(4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;
Authors' response: We have revised throughout the references except for Ref 9 and 10 that do not have PMID.

(5) The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

Authors' response: We have revised the manuscript according to the requirements.