Peer Review File

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Reviewer A

Comment 1: We hope that readers will find why the case report is unique and what it adds to existing literature in the Backgrounds of Abstract. So, please add more information about the uniqueness of this case, for example the co-mutation, discordant molecular pattern between plasmatic and cerebrospinal fluid.

Reply 1: We added in the section Background of Abstract "This case reported an acquired L718V *EGFR/TP53* resistance co-mutation of osimertinib with discordant molecular pattern between plasmatic and cerebral fluid in a leptomeningeal and bone metastatic L858R *EGFR* mutant NSCLC." (Page 1, line 20 to 22).

Comment 2: Authors stated "To our knowledge, this case is the first evaluating molecular pattern in plasmatic and CSF" in the Discussion. However, we find that CSF and paired plasma were tested by NGS in this article (PMID: 30659989). Would authors explain differences between this case and others? Or please be cautious about making conclusions regarding "the first time".

Reply 2: we deleted the sentence.

Comment 3: Please add medical, family, psycho-social history, and relevant past interventions with outcomes of patients. If there are no relevant information, please state it in the text also.

Reply 3: we added "without previous medical history" (page 3, line 2).

Comment 4: Could authors provide more specific analysis about this perspective in the Discussion: "In this reported patient, afatinib had no efficacy. This could be explained by the absence of EGFR L718V mutation in CSF tumor cells"? How afatinib effect with the presence of EGFR L718V? And please cite the corresponding references.

Reply 4: We added "As observed by Zheng *et al*. liquid biopsy in CSF is more sensitive than in plasma to detect resistance alterations in leptomeningeal metastatic NSCLC with oncogenic driver mutation. As reported by Aredo *et al*. afatinib had a limited activity after progression under osimertinib. Also, Tamiya *et al.* observed low efficacy of afatinib for leptomeningeal carcinomatosis with a median 2-month PFS (17). The same authors described a low CSF penetration rate (1.7% compared to blood concentration rate)." (see page 4, line 15 to 20).

Comment 5: A timeline is recommended, which enables the core elements of the case report alone. It ought to present relevant events in the patient's whole medical history chronologically.

Here is an example from our sister journal for authors' reference: https://tlcr.amegroups.com/article/view/35939/24197.

Reply 5: we added a timeline (see figure 1, page 7).

Comment 6: Clinical indices and therapeutic intervention should be presented specifically, such as dosage, strength, duration, etc. Please provide details of the use of gefitinib, the dosage of intrathecal methotrexate injections, of Osimertinib, etc.

Reply 6: we added details on the dosage and duration of the treatments (see page 3 line 4, 9, 11 and 22).

Comment 7: Of note, did the patient or her families provide informed consent, which should be identified in the text and confirmed in the CARE checklist?

Reply 7: we added "Oral consent was obtained from the patient for publication of this case report." (page 4, line 1).

Comment 8: Any Adverse and unanticipated events, like chemotherapy related toxicities and treatment, infective event, etc., should be clarified. If there were no related adverse events, please state it also.

Reply 8: we added tolerance data of the treatments (see page 3, line 4 and 11).

Comment 9: Key words should include the words "case report", and the number is limited within 3-5.

Reply 9: we added "case report" in the key words (page 2, line 9).

Comment 10: Is "8/5/22 11:14:00 AM" (Introduction) a typo? The correctness of writing needs to be noted. Please recheck the FULL text to ensure the accuracy.

Reply 10: we have checked our text as advised.

Comment 11: We recommend using a full name in the Title, without abbreviations.

Reply 11: we removed abbreviation in the title.

Reviewer B

Comment 12: You detected EGFR L718V mutation in the plasma but not in the CSF. You should at least speculate why this case did not respond to afatinib despite the lack of EGFR L718V mutation in CSF.

Reply 12: We added "As observed by Zheng *et al*. liquid biopsy in CSF is more sensitive than in plasma to detect resistance alterations in leptomeningeal metastatic NSCLC with oncogenic driver mutation. As reported by Aredo *et al*. afatinib had a limited activity after progression under osimertinib. Also, Tamiya *et al.* observed low efficacy of afatinib for leptomeningeal carcinomatosis with a median 2-month PFS (17). The same authors described a low CSF penetration rate (1.7% compared to blood concentration rate)." (see page 4, line 15 to 20).

Comment 13: You should at least show image findings of the patient.

Reply 13: we added CT scan images in the timeline (see figure 1, page 7)

Comment 14: You should discuss the clinical impact of the discordant EGFR L718V mutation on the clinical outcome.

Reply 14: we added "This case reported a rare resistance co-mutation *EGFR* L718V/*TP53* against osimertinib and a discordant molecular pattern between plasmatic and CSF fluid. It suggested that *EGFR* TKI induced a molecular heterogeneity on metastases and discordant clinical evolution. In routine practice, biopsies of the metastases that progressed should be performed to adapt the therapeutic strategy." (see page 5, line 1 to 5).