

Peer review file

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Round 1

Review Comments:

An interesting case. Always exciting to see a new possibility when multiple therapies have failed. It is happy to see the five months PFS after applying the combination of pembrolizumab and bevacizumab with the addition of nab-paclitaxel. Overall, this case report is in line with APM. Some concerns are listed below.

1. Highlight the most significant findings in this case in the title, abstract, introduction, discussion and conclusion. At present, such a highlight is not enough.

For example, “immunotherapy” in the title is too obscure. Replace it with “pembrolizumab plus nab-paclitaxel/bevacizumab”; in the abstract, immunotherapy is also not focused enough. Besides, authors should highlight the five months PFS result and how such findings are different (most prolonged PFS in such cases?) from other cases; issues are similar in the discussion and conclusion too.

Reply 1: We would like to thank the reviewer for this valuable comment. Immunotherapy is not recommended for patients with EGFR-mutated patients due to lack of efficacy. At the same time, we currently don't have enough data of the patients with uncommon EGFR mutations. The most significant finding in this case is that patient harboring EGFRex20ins mutation failed with multi-line treatments, but on the other hand, responded to pembrolizumab plus nab-paclitaxel/bevacizumab. It identifies a clinically meaningful therapeutic option.

Changes in the text: We have devoted significant effort in revising the paper to address the

issue, as listed below:

Title: We have replaced “immunotherapy” with “pembrolizumab”.

Abstract: We have added a brief discussion about the data obtained during the treatment of immunotherapy (refer to Page 1, lines 24-28).

Discussion: We further provided detailed discussions about the data obtained during the treatment of immunotherapy (refer to Page 5, lines 4-7, lines 21-27; Page 6, lines 5-10).

2. **Figures.** Figure 1 is quite informative. However, there is a barrier to the presentation to understand it better. It is suggested to draw a timeline (a figure) to outline the whole procedure and critical information, including key findings, important manifestations, therapies, CT images, and prognosis etc. The entire picture should be organized and presented in a clear time-based way. Here is an example for your reference:
<http://apm.amegroups.com/article/view/37579/29305>

Reply 2: Thanks for the suggestion. We have completely re-drawn Figure 1, which is now organized as a timeline of the whole procedure. We have also changed the title of the figure to reflect the changes made to the figure.

Changes in the text: Please refer to Figure 1 to check the changes.

3. **Accuracy.** The “still” on line 59 is improper as this is the very first place where EGFRex20ins is mentioned in the case presentation. Double-check the manuscript thoroughly, and please make sure all display is accurate.

Reply 3: We regret the confusion, and have changed the sentence in the paper.

Changes in the text: EGFRex20ins is now introduced in the first paragraph of case presentation to avoid the confusion (refer to Page 3, line 15). We have also gone through the paper to ensure the accuracy of descriptions.

4. In the abstract, information regarding the CARE checklist item 3a, 3b, 3c and 3d are all missing.

Reply 4: Thanks a lot for the suggestion. We have revised the abstract to address the issue.

Changes in the text: We have provided more details about the patient's information and the unique findings in the abstract. 3a, 3b, 3c, and 3d were respectively reported on Page 1, lines

24-28, on Page 1, lines 28-29, on Page 2, lines 1-6, and on Page 2, lines 8-10.

5. In the introduction, WHY this case is unique is not well presented.

Reply 5: Sorry about the confusion. We have clarified the significance of the case in the introduction.

Changes in the text: We added further discussions about the unique findings from the case in the introduction (refer to Page 2, lines 24-30)

6. In the case presentation, patient history information is missing.

Reply 6: We regret the confusion, and have added the missed information.

Changes in the text: We added the patient history information in the case presentation. (refer to Page 3, line 7)

7. In the case presentation, the rationale for changes in therapeutic interventions is missing. This is critical.

Reply 7: The missed information has been added.

Changes in the text: We discuss the reason for changes in therapeutic interventions in the case presentation. (refer to Page 3, lines 18-19, 22-24, 27-28)

8. The discussion is superficial. There should have an in-depth comparison between this case report with similar ones (EGFRex20ins). Comparisons should include the difference in therapies, adverse events and the outcomes (DFS, OS, etc.).

Reply 8: Thanks for the suggestion. We have added comparisons between our case and existing ones in the discussion, and rewritten most paragraphs of the discussion to emphasize the significance of our case.

Changes in the text: We have compared the treatment of EGFRex20ins mutations with several approaches. Our results are quite different compared to existing reports. In the first paragraph of this section, we added a discussion that although previous research show the effectiveness of combination of cetuximab and afatinib, such a treatment does not work in our case (refer to Page 4, lines 24-28). Generally, whether the uncommon EGFR mutants respond to immunotherapy remains unknown. Currently only a few researches have suggested the

feasibility of immunotherapy towards EGFRex20ins mutations. In the second and third paragraphs, we compared our case with existing reports (Page 5, lines 21-27; Page 6, lines 1-2, 6-9). Our report further confirms that combining chemotherapy with immunotherapy can prolong PFS to more than five months.

9. Please add one separate paragraph to list both strengths and limitations of this case report.

Reply 9: Thanks for the suggestion. We added one separate paragraph to list both strengths and limitations of this case report.

Changes in the text: Please refer to Page 6, lines 16-25 to see the changes.

Round 2

Review Comments:

Timeline: Please clarify the precise time at each point.

Reply: Thanks for the suggestion. We have provided precise time at each point in Figure 1.

Changes in the text: Please refer to Figure 1 to see the changes.