

Response letter

Dear Editors and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made a correction which we hope meet with approval. The changed portion is marked in red font in our revised manuscript. The main corrections in the paper and the response to the reviewer's comments are as flowing.

Reviewer 1

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

1. Do PD-1 inhibitors cause easy infection?

Response: Sorry for the impoliteness, does the infection refer to the hypophysitis? In clinical practice, the occurrence rate of hypophysitis caused by PD-1 inhibitors was not high. The reported frequency is between 0.5 and 1.1% for PD1 inhibitors. Related information can be found in the second paragraph of the Introduction section.

2. Are inflammatory cytokines involved?

Response: In this study, we did not detect the inflammatory cytokines. In the published papers about PD-1 inhibitors and hypophysitis, related inflammatory cytokines were not reported too. But the clinical significance of PD-1 immune check point molecule and expression of inflammatory cytokines have been revealed in other diseases. We have added related description in the Discussion section. The detection of inflammatory cytokines might be a valuable point for monitoring hypophysitis caused by PD-1 inhibitors. Thanks for the Reviewer's precious suggestions again.

3. Do PD-L1 inhibitors cause similar side effects? Please discuss citing the following article. (2021). Characterization of PD-1/PD-L1 immune checkpoint expression in soft tissue sarcomas. European journal of histochemistry : EJH, 65(3), 3203. <https://doi.org/10.4081/ejh.2021.3203>

Response: The side effects caused by PD-L1 inhibitors was similar with that of PD-1 inhibitors. We have cited the article in our revised manuscript (Discussion section).

4. Were there any side effects other than hypophysitis?

Response: Besides the nausea, vomit, and hypophysitis, the case 1 and case 2 in this study also developed a mild skin rash. We found no any other symptoms in this study.

4. Please describe preventive measures.

Response: At present, there are no effective preventive measures in clinic. For the patients receiving the PD-1/PD-L1 inhibitor treatment, the critical monitoring on patients is crucial. We detected the cortisol and ACTH levels at the baseline, gave periodical monitoring, and focused on dynamic changes. In addition, we also paid close attention to several symptoms such as fatigue, nausea, and vomiting and performed pituitary MRI if necessary, so that we can diagnose the hypophysitis, ceased medicines, and gave the patients positive treatments timely. The symptoms related to hypophysitis can be quickly relieved and patients generally presented a favorable prognosis.

Reviewer 2

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Grammar: Need Some revision. (Check The Paper Comments).

Please provide the following information in the Paper

1. Conflict of Interest

2. Source of Funding

Finally, this was an appealing article, in its current state it adds much new insightful information to the field. Therefore, I accept that paper to be published in your journal

Response: We have described the Conflict of Interest and Source of Funding after Conclusion section.

ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

Response: All the abbreviations have been defined upon first appearance.