Peer Review File

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Reviewer A

The paper titled "PD-1-induced encephalopathy: 2 case reports of neurological toxicities with immune checkpoint inhibitors" is interesting. These case reports show the difficulty in distinguishing PD-1-induced encephalopathy from other neurological disorders, especially paraneoplastic neurological syndromes. If not treated properly, patients' lives may be endangered. Thus, early identification and early treatment are very important. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What guidance can this research provide for the early identification and management of ir-AEs? How to provide treatment options for patients with advanced tumors? It is recommended to add relevant content.

R: Encephalitis caused by ICIs has diverse and atypical symptoms, and the diagnosis is difficult. These two cases are only to demonstrate the manifestations of immune encephalitis resulting from our clinical application of PD-1 therapy. For the time being, they cannot provide guideline recommendations for early diagnosis and treatment. The data statistics can be accumulated at a later stage. We believe that early diagnosis and treatment must be made at a specific time period after application of PD-1 therapy, with imaging and cerebrospinal fluid-specific changes, and also after multidisciplinary consultation to clarify the diagnosis. These have been mentioned in the discussion section.

2) What are the predictors of efficacy of immunotherapy? What is the application value of PD-1 inhibitors in neoadjuvant treatment of cancer? It is recommended that relevant information be added to the discussion.

R: I have added the above request on page 8, lines 7-10.

3) What is the tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors? It is recommended to add relevant content.

R: There is no specific pattern of immune-related adverse events due to immune checkpoint inhibitors, and as I have mentioned in the text, it may be that lung adenocarcinoma is more susceptible to immune encephalitis with the application of ICI, as detailed on page 8, line 17 and page 10, line 6-7.

4) In addition to those mentioned in this study, what other immune-related adverse events are associated with immune checkpoint inhibitors? Please give some examples to illustrate.

R: These case reports focus on PD-1-induced encephalopathy. I feel that any further reference to ICI-induced adverse events in other systems is too broad.

5) What are the characteristics and evaluation criteria of immunotherapy? What are the effects of immunotherapy on tumor micrometastasis? It is recommended to add relevant content.
R: (RECIST) 1.1 is commonly used in clinical practice to assess immunotherapy. Details have been added to this article, see page 8, line 10-12 in the text. As for the effect of immunotherapy on tumor metastasis, it is not the subject of this article.

6) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Prognostic Impact of Sarcopenia on Clinical Outcomes in Malignancies Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis, PMID: 34513704". It is recommended to quote the article.
R: Thank you very much for your advice! Although the introduction of PD1 and ICI-induced adverse events is not very comprehensive in the introduction part, this article is a case report and not a review. And sarcopenia is not the scope of this article, so I don't think it's appropriate to add this literature.

7) Does immune therapy have long-term effects on other normal tissues? How to monitor the adverse reactions in the follow-up course? It is recommended to add relevant content.
R: Thank you very much for your advice! The effects of immunotherapy on normal tissues are defined as immune-related adverse effects (irAEs), which usually occur early in the treatment, as detailed on page 3, lines 1-4. This part of the literature and research on long-term effects is also scarce. And the focus of this paper is not on the long-term effects of ICI therapy on normal tissues.

Reviewer B

1) First, the title needs to indicate epilepsy and headache possibly due to ICIs. The current title is not strict.

R: Thank you very much for your advice! Our team has discussed the title and agreed that "Immunotherapy-induced encephalitis" would be more appropriate.

2) Second, the abstract is not adequate. The background did not explain why the two cases are unique and what the potential clinical contribution is. The case presentation needs to provide the EEG and other laboratory findings for the epilepsy and the cognitive test results for the cognitive decline. It is also necessary to describe their past history of

epilepsy and cognitive disorders. The conclusion needs comment for how to early identify such cases with severe encephalopathy and effective treatment strategies.

R: Thank you very much for your advice! First, encephalitis caused by immunotherapy is a rare case, and these two case reports themselves is unique. The potential clinical contribution is to provide clinicians with a reference in the process of diagnosing immune encephalitis. Secondly, epilepsy and cognitive decline in the case reports are only clinical manifestations, and we believe that they can be described clearly. In the 1st case, epilepsy is a persistent state, and an EEG at this point is life threatening. And our EEG is short-range and can not capture epileptic discharges during non-seizure times. But clinical symptoms alone are sufficient for diagnosis. In addition, changes of cognitive scale scores in the 2st case are listed in Table 3 on page 20. Consequently, we believe that it is not necessary to provide EEG and cognitive function assessment. The real diagnosis is imaging and pathological examination.

3) Third, despite the rarity of related studies on irAE, it is still necessary to review the limited studies, including clinical presentations, treatment and prognosis, in particular to summarize the main clinical challenges and difficulties.

R: Thank you very much for your advice! The clinical symptoms of irAE lack specificity, and the clinical presentation is that of an autoimmune disease after the application of ICI. So this is not the focus of this article. And the clinical features and prognosis of irAE are also mentioned in the introductory part of this paper, see lines 3-6 on page 4. Also we have described in detail the incidence of irAE with the application of various ICIs, see page 4, lines 17-25 for details. In particular, on page 4, line 26 we mention that encephalitis after ICI treatment is a neurologic irAE.

4) Fourth, the authors need to report the psychiatric interview results of case 2 because of the psychotic symptoms. It is not adequate to describe as cognitive decline only.

R: Case 2 Cognitive functioning was assessed with the appropriate scores and listings as detailed in Table 3. we were not simply describing it as cognitive decline. In addition, the case has psychotic symptoms, which we described in detail inside the chart presentation, as detailed on page 7, lines 24-27. However, we really did not show the interview transcript. None of our previous case reports have shown interview transcripts because we are an oncology department but not a psychiatric department. The patient's clinical symptoms are described only, and the diagnosis and treatment are still based on pathologic findings and imaging.

5) Finally, please cite several related papers: 1. Rengarajan M, Gainor JF. Endocrine immune-related adverse events: a double-edged sword? Transl Lung Cancer Res 2021;10(1):13-17. doi: 10.21037/tlcr-2020-16. 2. Hara Y, Baba Y, Toihata T, Harada K,

Ogawa K, Iwatsuki M, Iwagami S, Miyamoto Y, Yoshida N, Baba H. Immune-related adverse events and prognosis in patients with upper gastrointestinal cancer treated with nivolumab. J Gastrointest Oncol 2022;13(6):2779-2788. doi: 10.21037/jgo-22-281. 3. Li S, Wang T, Lai W, Zhang M, Cheng B, Wang S, Tong G. Prognostic impact of sarcopenia on immune-related adverse events in malignancies received immune checkpoint inhibitors: a systematic review and meta-analysis. Transl Cancer Res 2021;10(12):5150-5158. doi: 10.21037/tcr-21-1470.

R: Thank you very much for your advice! I have included the literature you suggested at the appropriate places in this article. It does make this article a more compelling read.