Peer Review File
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Reviewer A

The paper titled “Corneal ulcer caused by sintilimab combined with anlotinib: a case report” is interesting. Sintilimab and anlotinib may be secreted into lacrimal fluid and thereby adversely affect the corneal epithelium. The development of corneal epithelial disorders in patients receiving these drugs may not be reversed by reducing its dose. The timely detection and intervention of adverse effects of anti-tumor drugs by oncologists and ophthalmologists is critical for rational prescription. However, there are several minor issues that if addressed would significantly improve the manuscript.
1) In the introduction of the manuscript, it is necessary to clearly indicate the knowledge gaps and limitations of prior study and the clinical significance of this study.
Reply 1：We have modified our text as advised. (See Page5, line127-128,133-135)

2) Only one case in this study is too limited. It is recommended to add a comparative analysis with other same or similar cases.
Reply 2：Relevant analysis has appeared in the Discussion. (See Page9, line257-269)

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.
Reply 3：We have modified our text as advised. (See Page4, line111-115)

4) What are the predictors of efficacy of immunotherapy? What is the application value of PD-1 inhibitors in neoadjuvant treatment of lung cancer? It is recommended that relevant information be added to the discussion.
Reply 4：We have modified our text as advised. (See Page4, line99-106)

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Efficacy, prognosis and safety analysis of anti-PD-1/PD-L1 inhibitor rechallenge in advanced lung cancer patients: a cohort study, Transl Lung Cancer Res, PMID: 35832441”. It is recommended to quote this article.
Reply 5：We have modified our text as advised，it has been added to the reference 10. (See Page4, line110)

6) What are the highlights and significance of this study? What is the author's next research plan? It is recommended to add relevant content to the discussion.
Reply 6：We have modified our text as advised. (See Page11, line322-328)

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.
Reply 7：We have modified our text as advised. (See Page10-11, line312-317)

Reviewer B

1) First, the title needs to specify the development of corneal ulcer from dry eye in both eyes.

Reply1：We have modified our text as advised. (See Page1, line4-5)

2) Second, the abstract needs some revisions. The background needs to explain the negative consequence of ocular adverse and what the uniqueness of this case report is. In the case presentation, please report the doses and duration of the administration of sintilimab combined with anlotinib and the eye disease history of this case, as well as time from treatment to dry eye and corneal ulcer. The sentence "Sintilimab and anlotinib may be secreted into lacrimal fluid and thereby adversely affect the corneal epithelium" should not be placed in the conclusion since this is not the finding of this study. The authors need to have comments on the prevention and early identification of dry eye and corneal ulcer in similar cases.

Reply 2：We have modified our text as advised. The sentence has been deleted. And the comments on the prevention and early identification of dry eye and corneal ulcer was mentioned in the abstract-conclusion. (See Page2， line38-45; Page2 line47-49;Page2-3 line48, 6;Page3 line 69-73)

3) Third, in the introduction of the main text, the authors need to briefly review what has been known about on the adverse events during the administration of ICIs and the negative clinical outcomes of these events. Please also review more on the ophthalmic adverse reactions since the argument "ophthalmic adverse reactions are less frequently reported" is unclear and not informative. The authors need to clearly the potential clinical contribution of this case and what the uniqueness of this case is.

Reply3：We have modified our text as advised. (See Page4-5, line111-120)

4) Fourth, the case presentation needs to report the survival time of this case and provide a timeline figure to briefly depict the whole diagnosis, treatment, and prognosis of this case.

Reply4：We have modified our text as advised. And we think that the timeline of the patient's development has been described in the report and does not need to be repeated.（See Page7，line195-196）

5) Fifth, in the discussion please have detailed comments on the early detection, prevention, and monitoring of ophthalmic adverse reactions.

Reply5：We have modified our text as advised. (See Page10-11, line312-317)

6) Finally, please consider to cite several related papers: 1. Yang S, Guo W, Gong Y, Wang J, Chen L, Zhao J, Guo X, Bai J, Song Y. Application of vitamin A palmitate eye gel and nurse value of Watson's theory of caring in children with dry eye after

strabismus surgery: a randomized trial. Transl Pediatr 2021;10(9):2335-2346. doi: 10.21037/tp-21-385. 2. Bai S, Tian T, Pacheco JM, Tachihara M, Hu P, Zhang J. Immune-related adverse event profile of combination treatment of PD-(L)1 checkpoint inhibitors and bevacizumab in non-small cell lung cancer patients: data from the FDA adverse event reporting system. Transl Lung Cancer Res 2021;10(6):2614-2624. doi: 10.21037/tlcr-21-464. 3. Huo GW, Zhu FY, Zuo R, Song Y, Chen WD, Chen WM, Zhang HM, Jia SS, Chen P. The incidence of gastrointestinal adverse events in patients with advanced non-small cell lung cancer (NSCLC) treated with PD-1 inhibitors: a meta-analysis. Transl Cancer Res 2021;10(7):3389-3403. doi: 10.21037/tcr-21-125. 4. Zhao H, Ning J, Gu Y, Zhang X, Yu W, Chen T, Luo Q. Consecutive severe immune-related adverse events after PD-1 inhibitor induction and surgery in locally advanced non-small cell lung cancer: a case report. Transl Lung Cancer Res 2021;10(8):3682-3688. doi: 10.21037/tlcr-21-603.

Reply6：We have modified our text as advised.(See Page12-13, line380-385)

Reviewer C

1. **References 18 and 38 are duplicated, please revise and update the ciations in the paper.**

18. Young L, Finnigan S, Streicher H, et al. Ocular adverse events in PD-1 and PD-L1 inhibitors. J Immunother Cancer 2021;9(7): e002119.

38. Young L, Finnigan S, Streicher H, et al. Ocular adverse events in PD-1 and PD-L1 inhibitors. J Immunother Cancer 2021;9:e002119.

Reply: We have modified our text as advised. (See Page15, line 453-454)

2. **Citation 60 was missing. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.**

256 optic neuropathy (11,38,54-59). Under physiological conditions, PD-L1 is highly
257 expressed in the corneal epithelium and negatively regulates the expression of
258 chemokines in the cornea to prevent the occurrence of autoimmunity. Studies have
259 shown that the downregulation of PD-L1 expression leads to an imbalance of the
260 immune system that regulates the corneal and conjunctival inflammatory
261 microenvironment, triggering dry eye, and further aggravates corneal inflammation in
262 patients with dry eye (40). It can even cause corneal perforation (61).

Reply: We have modified our text as advised. (See Page9, line 282)

3. **The authors mentioned "studies...", while only one reference was cited. Change "Studies" to "A study" or add more citations. Please revise. Please number references consecutively in the order in which they are first mentioned in the text.**

Studies have shown that angiogenesis is closely related to tumor immune microenvironment and vascular endothelial growth factor (VEGF) can block T cell infiltration, transport, and inhibit the induction, proliferation, and maturation of immune cells, so that the body can decrease tumor activity (31).
Reply: We have modified our text as advised. (See Page7, line 212)

However, studies have shown that anlotinib exerts anti-neovascular effects by blocking VEGFR and PDGFR as well as downstream signaling pathways, has a positive effect on regulating ischemia and hypoxia in ocular tissues, and has no obvious in vitro cytotoxicity or in vivo tissue toxicity (42).
Reply: We have modified our text as advised. (See Page9, line 255)

Studies have shown that the downregulation of PD-L1 expression leads to an imbalance of the immune system that regulates the corneal and conjunctival inflammatory microenvironment, triggering dry eye, and further aggravates corneal inflammation in patients with dry eye (40).
Reply: We have modified our text as advised. (See Page9, line 279)

4. Some references in the text are out of order. The references should be cited in order of their appearance in the text.

Please confirm where you would like to cite Ref. 38, for Ref. 38 should be cited between Ref. 37 and Ref. 39.
Reply: We have modified our text as advised. (See Page8 line 244-245)

5. There are 61 references in your list, while 62 references were cited in your main text. Please revise.

Reply: We have modified our text as advised. (See Page10, line 290)

6. Figure 3

Please explain the meaning of the arrow. Otherwise, please delete.

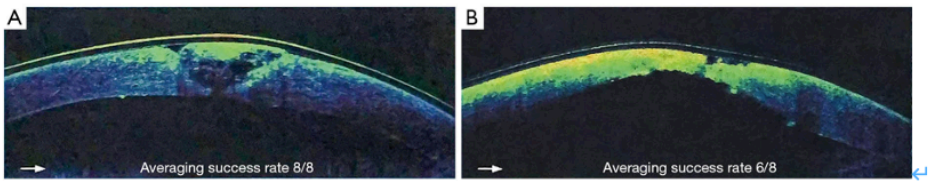

Figure 3 OCT images of the anterior segment of both eyes. (A) Left eye: corneal epithelial repair, subepithelial defect; (B) right eye: corneal stroma thinning, corneal subepithelial defect. OCT, optical coherence tomography.

Reply： We have modified our text as advised. (See Page18,line546）