

Peer Review File

Article information: <https://dx.doi.org/10.21037/pcm-22-53>

Comments from Reviewer A

We appreciate your thorough review and detailed feedback on our manuscript. It helped us to improve the content and structure.

Comment 1: Due to the recently updated Author Instruction (<https://cdn.amegroups.cn/static/public/2.5-Structure%20of%20Case%20Reports-template-V2022.11.4.docx>), please kindly organize the structure of the manuscript.

Reply 1: We have reorganized the structure according to the last version of Authors Instruction.

Comment 2: (1) Please provide the “Highlight Box”, including key findings, what is known and what is new? what is the implication, and what should change now?

Reply 2: We have included the section “Highlight Box” in our manuscript.

Comment 3: (2) A separate background, rationale and knowledge gap, and objective section needed to be embedded in the Introduction.

Reply 3: We have reorganized the structure of Introduction.

Comment 4: (3) Similarly, the key findings, strengths and limitations, comparison with similar researches, explanations of findings, and implications and actions needed section should be clearly stated in the Discussion.

Reply 4: We have revised and modified the Discussion. We also added a phrase, covering side effects and increased risk of suicide among head and neck cancer survivors: “*Current standard of care CCRT for locally advanced OPSCC is associated with significant morbidity and long-term adverse effects influencing quality of life. Common side effects include mucositis, dysphagia, xerostomia, and dental problems. Additionally, there is an increased risk of death by suicide among head and neck cancer survivors*” with appropriate citation: Osazuwa-Peters N, Simpson MC, Zhao L, et al. Suicide risk among cancer survivors: Head and neck versus other cancers. *Cancer*. 2018 Oct 15;124(20):4072–9.

Comment 5: (1) Background: The authors must clearly analyze and clarify the internal clinical importance of the case report in the Abstract. The brief background statement about pembrolizumab for HNSCC should be provided. And highlight the unique point of this manuscript in the Abstract-Background (not just in the Conclusion).

Reply 5: Thank you for pointing this out. We have revised and added this information in the Abstract background.

Comment 6 : (2) Case Description: The vital detailed information about the case should be specified in the subsection. Please describe the patient’s demographic details and main history, the main diagnosis, interventions, outcomes and follow-ups.

Reply 6: Thank you. We have included all this information in the case description

Comment 7: (3) Conclusions: Please further summarize the main take-away lesson, clinical impact and potential implications from the case in the Conclusion. For the authors’ kind reference, what recommendations could be provided from the case for the clinical practice?

Reply 7: We have revised and edited conclusions in the Abstract

Comment 8: 3. Key words

We suggest the authors consider adding “pembrolizumab” as a key word.

Reply 8: The authors have added “*pembrolizumab*” as a key word

Comment 9: (1) Please kindly reorganize the content in the Introduction according to the “Structure of Case Reports-template” to provide a more informative Introduction. Please also highlight the unique point of this manuscript in the Introduction. This should be supported by evidence based on comparison with similar cases.

Reply 9: We have changed the structure of the Introduction and highlighted unique point.

Comment 10: (2) Lines 98-99: Please cite references for the sentence “Although initial studies of ICIs have shown a direct correlation between PD-L1 expression and objective response”.

Reply 10: Thank you for pointing this out. The citation that supports this sentence is “Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28;366(26):2443–54”. This is a highly cited paper with over 12 thousand citations. In the abstract in NEJM they have the following sentence “Preliminary data suggest a relationship between PD-L1 expression on tumor cells and objective response”.

Comment 11: (1) If available, please also provide the results of pathology biopsy.

Reply 11: The results of pathology biopsy are stated in the 4th and 7th sentences of Case Presentation. “*Pathology from the base of the tongue biopsy was consistent with p16 positive moderately differentiated squamous cell carcinoma*”. “*PD-L1 immunohistochemistry expression was performed and showed a tumor proportion score of 90%*”. Correction was made to TPS as it was initially written “95%”. Upon repeat review of pathology we realized that it was “90%”. There were less than 5% immune cells that were stained positive for PD-L1. Therefore, CPS score (which at this time is not feasible to obtain due to additional cost that may be associated with it and at this point is not going to change patient’s management) is likely 90-94% since it accounts for both tumor and immune cells in the numerator. CPS and TPS have the same denominator, which is the total number of viable tumor cells.

Comment 12 : (2) Did the case receive the same dosage and frequency of pembrolizumab –“200mg every 3 weeks” in the total of two and a half years of pembrolizumab therapy?

Reply 12: Yes. We added that information to the case presentation. “*Off-label treatment with pembrolizumab at a dose of 200mg every 21 days was started and in a year the patient achieved a complete response. Tracheostomy was reversed and the feeding tube was removed. The patient received a total of two and a half years of pembrolizumab therapy starting August 2018 and continuing until March 2021 and, as his multiple exams and scans were reassuring, pembrolizumab was discontinued in March 2021*”.

Comment 13: (3) We suggest the authors add a timeline. The timeline should present relevant events in the patient’s history in chronological order in a figure or table, enabling the core elements of the case report to stand alone. The authors are encouraged to merge the existing figures in the timeline too. Please see some examples from our sister journals:

<https://jgo.amegroups.com/article/view/50913/html>;

<https://tcr.amegroups.com/article/view/35939/24197>

Reply 13: Thank you for this suggestion. We have added a timeline using the examples you provided.

Comment 14: (1) It is great the authors specified the limitation of the study in the Discussion. We would suggest the authors further explicitly discuss the influence of the limitation on the outcome of the case. The authors should also transparently discuss the STRENGTHS of the study in the Discussion.

Reply 14: We have incorporated strengths and limitations in the Discussion.

Comment 15: (2) The authors should have discussed in-depth with comprehensive literature how such a finding would challenge clinical practice and provide hands-on recommendations in the Discussion.

Reply 15: We have added this information in the Discussion. We added two citations to support literature review.

Comment 16: Please provide the stand-alone footnote for the Figures.

Reply 16: We have added footnotes.

Comment 17: (1) The statements in the CARE checklist were inconsistent with the content in the manuscript. Please check: Item 4: the related content was provided in the Introduction on page 3, lines 80-105 not in the Discussion. Item 12: We failed to find the information about the patient perspective on page 4, lines 117-118. If it was not provided, please fill with “NA”.

Reply 17: We have completely revised and changed the CARE checklist after the major review was completed.

Comment 18: (2) The manuscript should also include a Reporting Checklist statement in the footnote: “The authors have completed the CARE reporting checklist.”

Reply 18: We have added a footnote with the checklist statement.

Comment 19: Similar to the points on Abstract-Conclusions, please provide the information that the primary “take-away” lessons of this case report (without references) in a one paragraph conclusions.

Reply 19: We appreciate this suggestion, we have added this section according to Structure of Case Reports.

Comments from Reviewer B

Comment 1: This is an interesting case report, even just the fact that pembrolizumab alone cured such a large oropharyngeal tumor. Unclear if the cannabis contributed or not.

Reply 1: Thank you for your review and feedback. Unfortunately, it remains unclear if cannabis had an influence on the therapy. We decided to include this information as we think there could be a relationship.

Minor concerns:

Comment 2: 1) Can the authors provide more info about what type of cannabis/CBD oil was used? Amount, formulation? This may be important as more people study cannabinoids.

Reply 2: Thank you for this question. The patient reported taking a liquid mixture of cannabidiol (CBD) and tetrahydrocannabinol (THC) oils, supplied by his family, that was 0.3% mixture of CBD and THC. He recalls taking 2 drops under the tongue once a day for about 9 months after the cancer diagnosis. We also added this information to the manuscript.

Comment 3: 2) TPS is given for PD-L1 staining, but CPS is more commonly used in HNSCC- can the authors replace with a CPS score if that information is available?

Reply 3: You have raised an important point here. However, the CPS is unavailable in the pathology report. Correction was made to TPS as it was initially written “95%”. Upon repeat review of pathology we realized that it was “90%”. There were less than 5% immune cells that were stained positive for PD-L1. Therefore, CPS score (which at this time is not feasible to obtain due to additional cost associated with it and at this point is not going to change patient’s management) is approximately 90-94% since it accounts for both tumor and immune cells in the numerator. CPS and TPS have the same denominator, which is the total number of viable tumor cells. We decided not to include CPS in the final version as this is just an approximation.

Comments from Reviewer C

Comment 1: The author describes the pathology results of a tonsil biopsy, but looking at Figure 1, this tumor is located in the Base of tongue, and it seems difficult to obtain a tumor specimen from the tonsil.

Reply 1: We appreciate the thorough review on the images. You are absolutely right, it was base of tongue mass, we verified this upon repeat review of the pathology report. We made the correction in the Case description. “Pathology from *the base of the tongue* biopsy was consistent with p16 positive moderately differentiated squamous cell carcinoma”.

Comment 2: It does not seem suitable for formal use of this drug. The author writes that it may be off-label. However, as a surgical oncologist, I would like to hear about this situation for inappropriate treatment decisions. In some cases of OPC, this simple use of ICI is good. I would recommend a more detailed description of the benefit of single agent use compared to FP combination therapy from a basic science perspective.

Reply 2: The patient in this manuscript has intentionally refused traditional treatment with chemotherapy and radiation due to concerns over side effects and total dental extraction that he would have to do prior to radiation. By “Off-label treatment with pembrolizumab” we meant that treatment was not approved (and is still not approved) for first line treatment of locally advanced HPV-positive OPSCC. As a matter of fact, we sent a request to his insurance company to approve the pembrolizumab off-label, but insurance refused to cover it. We then sent a request for pembrolizumab to the manufacturer (Merk company) and they provided the drug free of charge for two and half years.

Comment 3: I did not understand the indications for cannabinoids and the crosstalk with ICI.

Reply 3: Use of cannabinoids was not indicated for this patient and was not prescribed by physicians. The patient himself decided to start taking a liquid mixture of cannabidiol (CBD) and tetrahydrocannabinol (THC) oils on a daily basis for a total of 1 year after the cancer diagnosis. Unfortunately, it remains unclear if cannabis had any influence on the therapy and its outcome, but we felt it was important to report it in our manuscript as the patient had such an outstanding outcome and also since there is increased interest in use of cannabis in the last decade.