Peer Review File

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Reviewer A

This is a nice case report with a rather basic literature review. There are no new conclusions or novel perspectives on this issue, but it is another example of the Vismodegib treatment.

Response: We appreciate the reviewer for their input.

Line 50: Vismodegib is not the only neo-adjuvant option. There are different options (as you mentioned Sonidegib later).
Response: Thanks for the comment. We replaced "Vismodegib" with "neo-adjuvant therapies".

Line 83: I would expect a lacrimal system involvement description too.
Response: Thanks for the comment. "with no lacrimal system involvement" was added to line 83.

Line 107: What was the outcome of your patient? Did he go through another surgery?

Response: He underwent rotation flap, full thickness skin graft to anterior lamellar, and adjacent tissue trans (tenzel) to correct cicatricial ectropion and figure 1f is the last outcome with complete improvement of ectropion.

Lines 143-147- Please rephrase. This paragraph is unclear.

Response: Thanks for the comment. We changed the paragraph to "When any tumors regardless of their size invade the orbit, they might have worse outcomes compared to a larger tumor with no orbital invasion. Therefore, relying only on TNM staging for periorbital BCC lesions is not enough [12]. Invasion of the BCC and eyelid deformity should be considered in staging of the disease and the treatment plan.
."

Line 154- You did not conduct any study. This is only a review.
Response: Thanks for the point. We changed it to "The results of our literature review showed…"

Figure 2- There are a few misspelled names. Could you fix it? The lower graph is unclear.
There is one major paper on which most of your data is based (Ben Ishai, 2020) -This

point should be addressed too.

Response: Thanks for your input. We deleted the lower graph in figure 2 and corrected the misspelling. Thanks

Summery:
This is not a review of the literature. You did not address many points, and your conclusions and recommendations are unclear. Nevertheless, this is a nice case report, and I recommend changing this paper to a basic case report rather than a review.

Response: Thanks for your comment. This is a case report with review of literature and our main point for this study was to emphasize on the importance of Vismodegib on the shrinkage of periorbital BCCs.

Reviewer B

This article presents a patient with a recurrent basal cell carcinoma of the left lower eyelid that failed Mohs excision (i.e. recurred again). The case is compelling, but would benefit from tissue histology following vismodegib therapy. The description in lines 69-75 could also provide a much clearer outline of the original excision (when, how large), the nature of the reconstruction, the first recurrent tumor (when, how large), the number of Mohs micrographic excisions performed, the nature of the reconstruction, all leading up to this presentation of the twice-recurrent tumor.

Response: Thank you so much for your comment and for input. The BCC before the Vismodegib therapy was confirmed by pathology. We do not have any information on the original excision since patient had it done in other hospital. Based on the information that we have, the patient had recurrence after the Mohs excision. Only one Mohs micrographic excisions performed for the patient prior to this time's presentation.

The report does not describe any biopsy taken during the ectropion repair, lines 103-105, and figure. A key reference that was missed is:
Unsworth SP, Tingle CF, Heisel CJ, Eton EA, Andrews CA, Chan MP, Bresler SC, Kahana A. Analysis of residual disease in periocular basal cell carcinoma following hedgehog pathway inhibition: Follow up to the VISORB trial. PLoS One. 2022 Dec 1;17(12):e0265212. doi: 10.1371/journal.pone.0265212. PMID: 36455049; PMCID: PMC9714843.
This manuscript reveals that even after successful vismodegib therapy, residual cancer can be found, and that standard histologic techniques might miss the residual cluster of cancer cells. Further, many of the residual tumor cells harbored secondary mutations that conferred resistance to vismodegib, and complete molecular analysis of these mutations was performed. Hence, vismodegib is best used as a neoadjuvant for

advanced periocular BCC, to shrink the tumor (primarily in the deep margin), and then excise the residual.

Response: We appreciate the input and bringing this important point. We did monitor the lesion with the scouting biopsy as we mentioned in line 103 and we proceed with monitoring since the results of the histopathology did not show any residual cancerous tissue. We added a line: "The biopsy during ectropion repair was obtained to exclude the residual cancerous tissue.". We also mentioned this point in the discussion and added the reference that you kindly mentioned above.

The discussion inexplicably begins with a paragraph on radiation therapy. XRT is most useful as salvage palliative therapy meant to control symptoms, not to cure the BCC. And the author's entire case is an example of the maxim "you don't get a second chance to do it right the first time:" this patient would have benefited from Mohs surgery for the original tumor, rather than local excision with margin control that fails to control for deep margins.
The VISORB trial was the first prospective clinical trial to systematically study the role of vismodegib in locally advanced periorbital BCC, revealing no peripheral islands of tumor as the tumor shrank. This was confirmed in the VismoNeo trial:
Bertrand N, Guerreschi P, Basset-Seguin N, Saiag P, Dupuy A, Dalac-Rat S, Dziwniel V, Depoortère C, Duhamel A, Mortier L. Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study): Neoadjuvant Vismodegib in Locally Advanced Basal Cell Carcinoma. EClinicalMedicine. 2021 Apr 26;35:100844. doi: 10.1016/j.eclinm.2021.100844. PMID: 33997740; PMCID: PMC8093898.
This study is also not referenced.

Response: We appreciate you for mentioning this important point. We added a paragraph in line 160-165 and discussed about it. We cited the reference that you kindly mentioned too. Also, we made changes about radiation therapy in the discussion.

For a review of this nature to be helpful and informative, the discussion needs to take the existing knowledge and synthesize it in a manner that is more comprehensive and bolder. Their case demonstrates the risks of margin-control excision of periocular BCC, and the challenge of Mohs surgery after a reconstructive surgery had been performed in which residual cancer was likely seeded in surrounding non-contiguous areas. The synthesis of the literature should lead to an insightful conclusion that would add something new to the existing literature. As it stands, the discussion is neither comprehensive nor insightful. This needs to be addressed before publication.

Response: Thanks for the comment. We made changes in the discussion section and tried to include the new view about the importance of vismodegib and the failure of previous management options.

Minor:
Line 51: ‘preorbital’ should probably be ‘periorbital’
Response: Thanks for the point. We made changes as requested.