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Peer Review File

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Reviewer A:

Congratulations to the authors on this case report of two cases and also completing a very thorough systematic review. There is certainly precedent here, with the two most recent case reports having 4 cases and completing a systematic review (Carlson et al 2015) and a single case report and review (Metz et al 2019. Each of these studies detailed a total of 32 and 26 cases published respectively. Although these reviews were fairly recent, they clearly weren't as thorough on their search or adherence to the established guidelines - and this doesn't seem to be from a more detailed coverage of SIPTB as defined by the authors.

Reviewer B:

This paper presents an excellent overview of a rare surgical entity together with two additional cases. Given the limited literature, the authors have attempted to summarise the key findings.

However, there are some issues which need to be clarified in the manuscript before publication can proceed:

Comment 1:

Case 1 - The case has some aspects missing. At first an MRI scan showed tissue in the paranasal sinuses but it is not clear why it was biopsied a year later. It is not clear when the mass in the middle ear was diagnosed and to what extent it was prior to mastoidectomy. It is not clear what multiple debulking procedures were performed and in what location

Reply 1:

The case was summarized for brevity due to the length of the history relating to this condition. It has now been expanded to add further details as requested by the reviewer. In particular:

- Timeline between MRI and biopsy
- Diagnosis of middle ear mass
- Extent of disease prior to mastoidectomy
- Description of debulking procedures

Changes in the text:

The reviewer's queries have been addressed in line 137-168.

Comment 2:

Case 2 - Similarly, it is not clear what the clinical findings of the middle ear were and when they arose. What was the cause of the facial nerve palsy if there was no

peri neural tumour spread.

Reply 2:

- *Part 1*

The case was summarized for brevity due to the length of the treatment history related to this condition. It has now been expanded to add further details as requested by the reviewer. In particular:
- More detailed timeline
- Clinical details regarding the middle ear findings and the timeline

Changes in the text:
The reviewer's queries have been addressed in line 172-201.

- *Part 2*

The cause of the facial nerve palsy is uncertain. The MRI showed no obvious features consistent with perineural spread along the facial nerve. The facial nerve was not sacrificed and so no pathologic assessment could be made to determine if there was perineural tumor spread. However, there could have been perineural spread but not below the resolution of the MRI. Other possible causes could have been facial nerve palsy due to extrinsic compression from the tumor or secondary to chronic inflammation / infection as the ear was chronically infected and discharging as a result of the tumor.

Changes in the text:
Lines 193-195 - "Repeat MRI was performed and this showed no significant interval change in disease or radiologic evidence of perineural tumour spread."

Comment 3:
Could the authors please clarify the multitude of different surgical procedures which are used in throughout manuscript as there are at least 8 terms used - what is "conservative" surgery, "simple excision", "debulking", "radical" surgery, "salvage" surgery, or "incomplete" excision, "complete" surgery or "curative" resection. This is especially important when attempting to determine the effectiveness of surgery. For example, how did the authors arrive at the figure that the failure of "conservative" surgery was 50% and "radical surgery" was 22.2%?
Recurrence rates - could the authors comment on when did the recurrences occur after treatment (eg. Line 205, Line 230)
Is there a staging system for IPTB?

Reply 3:

- *Part 1*

We have further clarified the descriptors of the surgical procedures. See lines 112-120. Simple excision has been removed. These clarifications have been incorporated into the entire manuscript.

Changes in the text:
Lines 112-120 - "Surgery with a curative intent, aiming for an R0 or R1 resection, was classified broadly as conservative or radical. Conservative surgery we defined as any resection less extensive than a modified radical mastoidectomy, while radical surgery was defined as a modified radical mastoidectomy or more extensive ablation. We defined tumor debulking as surgery where the incomplete removal was the likely and intended outcome, resulting in an R2 resection. Typically, tumor debulking was a limited procedure where only gross disease was extirpated. We defined salvage surgery (either conservative or radical) as revision surgery performed with curative intent after failed initial conservative or radical surgery."

- *Part 2*

The estimate of failure of surgery or disease recurrence are calculated by only including those cases with reported outcomes and who underwent surgery with curative intent (conservative or radical). From those cases the number that recurred is expressed as a percentage of the total number of cases in each subgroup. This was done separately for the subgroups of, conservative and radical surgery and for both PIPTB and SIPTB.

Changes in the text:
Lines 384-389 - "An estimate of failure or disease recurrence after initial surgical treatment considering only those cases undergoing curative intent surgery (conservative or radical) and with reported outcomes was calculated. For PIPTB this is 50% for conservative surgery and 22.2% for radical surgery. Utilising the same criteria but for SIPTB, then the chance of failure for conservative surgery comes to 40%, while 43.8% for radical surgery, however both groups contained small numbers."

- *Part 3*

Timing of recurrence is difficult to accurately report due to limited follow-up information. An estimate is now included for PIPTB and for SIPTB.

Changes in the text:
Lines 243-244 - "The timing of recurrence after surgery for PIPTB was inconsistently reported but most recurrences were within 2 years."
Lines 268-269 - "Recurrence after surgery for SIPTB was inconsistently reported but most recurrences were seen within 1 year."

- *Part 4*

The authors are unaware of a staging system for IPTB.

Changes in the text: Nil

Minor comments

Comment 4:
Results section - The authors should make it clear that PIPTB + SIPTB = 57 cases in total. Although this is eventually mentioned, it should be made clearer for the readers given the different acronyms being used

Reply 4:
This has been updated.

Changes in the text:
Line 213 - "The cases of IPTB include both PIPTB and SIPTB."

Comment 5:
Line 192 n=10 but % is 43.5% - please clarify

Reply 5:
This has been clarified.

Changes in the text:
Lines 219-220 - "There were 23 cases tested for HPV or p16 status and 43.5% (n=10) of those tested for HPV were positive."

Comment 6:
Line 198 n=3 but % is 27.2% - please clarify

Reply6:
This has been clarified.

Changes in the text:
Line 226: - "Of the 11 cases tested for HPV or p16, 27.2% (n=3) were positive."

Comment 7:
Line 218 n-7 but % is 58.3% - please clarify

Reply 7:
This has been clarified.

Changes in the text:
Lines 249-250 - "There were 12 cases tested for HPV or p16 and 58.3% (n=7) of cases tested were positive."

Comment 8:

Line 222 - suggest “three cases did not have surgery”, rather than “underwent no surgery”

Reply 8:
This has been changed.

Changes in the text:
Line 253 - “three cases did not have surgery”