Peer Review File

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Reviewer A

This is an excellent and well written and systematic review of an extremely rare condition, tonsillar schwannoma. There are only 13 case reports in the literature, and this manuscript elegantly collates and describes the overall presentation, diagnosis and management of the condition. It significantly adds to our knowledge base.

Reviewer B

This systematic review of 13 cases of palatine tonsil Schwannoma. It discusses presentation of these cases and how they were managed. The methods of the systematic review are sound. The paper concludes with an algorithm of presentation, history, and examination and then suggested management of these lesions based on how the 13 case studies in the literature were managed. Overall reading how these lesions have presented and been managed is interesting.

COMMENT 1: I would have preferred this paper to discuss this more within the context of a unilateral tonsil enlargement or mass as this is how the lesions present and it is not until biopsy or complete excision that the diagnosis of schwannoma is retrospectively made. Thus, anyone looking for information on how to manage tonsillar schwannoma is far more likely to do this after the tonsil has been excised (ie the case has already been essentially managed) rather than prior and so the discussion and conclusion of the paper should be targetted more to allow colleagues to identify if their management of a tonsillar schwannoma is within expected parameters. A paragraph on differential unilateral tonsil enlargement in the introduction should be included.

REPLY 1: I think the majority of clinicians would manage unilateral tonsillar enlargement as a malignancy until proven otherwise. As per this paper there are some distinguishing features on CT and MRI, however I agree that in the majority of cases the tonsil would be removed and then histopathology would confirm the diagnosis.

CHANGES IN THE TEXT:
Differential diagnoses for unilateral tonsillar hypertrophy include infectious (tonsillitis, peritonsillar abscess), inflammatory (Kawasaki Disease, Kimura's disease) and neoplastic lesions, both benign (polyp, squamous papilloma, haemangioma) and malignant (squamous cell carcinoma, lymphoma) [10-12].

COMMENT 2: The paper describes the management of all 13 cases well, however, what is not done well is the justification of the proposed management algorithm.

REPLY 2: Agreed – I have added the justification for our proposed management algorithm.

CHANGES IN THE TEXT:

Based on the management of the thirteen cases of tonsillar schwannoma worldwide we propose a management algorithm as outlined below (Figure 2.). Presentation of a unilateral tonsillar mass is usually considered malignant until proven otherwise, thus a thorough history and examination will determine the level of clinical suspicion. Both imaging modalities – CT and MRI – provides useful information and helps to differentiate between invasive, malignant, and benign lesions, however neither are diagnostic for schwannomas. The imaging of choice is dependent on the resources available at the institution. Biopsy of lesions yields unreliable results and therefore is not a necessary step in the workup of these patients. Ultimately, unilateral tonsillectomy is both a diagnostic and therapeutic procedure in this condition. There is no consensus on the post-operative follow-up interval in the cases, however there should be standard post-operative care and further follow-up at appropriate intervals to monitor for recurrence.

COMMENT 3: There is some confusion in the section on biopsy. It suggests that FNA has low accuracy and incisional biopsy has significant disadvantages yet in the algorithm suggests intra oral biopsy. This needs clarification and some justification of why an intral oral biopsy is recommended

REPLY 3: Agree with the comment. Intra-oral biopsy is not required based on the low rate of accuracy. The treatment algorithm has been changed to reflect this and I have addressed it in my justification for the treatment algorithm.

CHANGES IN THE TEXT:

Treatment algorithm: removed intra-oral biopsy

COMMENT 4: Imaging - both CT and MRI are suggested, however, no discussion regarding the advantages/disadvantages of each modality is undertaken and simply the expected findings are presented.

REPLY 4: There is no clear consensus in the literature for which imaging modality is superior in the imaging of schwannomas and neither imaging technique is diagnostic. Furthermore, it would be highly dependent on the resources at the institution that the patient presents. Both imaging techniques can provide valuable information, but ultimately the patient needs resection of the tumour and histopathological diagnosis.

CHANGES IN THE TEXT:

Both imaging modalities – CT and MRI – provides useful information and helps to differentiate between invasive, malignant, and benign lesions, however neither are diagnostic for schwannomas. The imaging of choice is dependent on the resources available at the institution.

COMMENT 5: Management: Discussion of how schwannomas are managed elsewhere surgically in terms of complete resection would be useful to be included as a justification of the surgical resection of tonsillar lesions.

REPLY 5: Agree with comments. Changes made as below.

CHANGES IN TEXT: The surgical management of extracranial head and neck schwannomas in other locations is based on weighing the risks and benefits of surgery, preoperative symptoms and the anticipated severity of postoperative neurological deficits. Complete resection of the tumour results in palsy of the associated nerve, however with intracapsular enucleation only 31% of patient have a postoperative nerve palsy at six month follow up – there is no difference in the recurrence rates (0% at two years) between the two methods [22]. The risk of nerve palsy post tonsillectomy is exceedingly rare, but may affect the glossopharyngeal nerve resulting in referred otalgia and transient dysgeusia [23]. Tonsillectomy is the treatment of choice for other benign conditions, such as recurrent tonsillitis, sleep disordered breathing and obstructive sleep apnoea and therefore would be reasonable surgical approach for the treatment of tonsillar schwannoma.

COMMENT 6: In addition, post operative follow-up suggested in the algorithm is completely different from the follow-up reported in the case series with no justification for this.

REPLY 6: There is no consensus between the cases on the follow-up interval post-operatively. This is also the case with other head and neck schwannomas. Therefore, a standard post-operative follow is necessary, with another follow-up at an appropriate interval to monitor for recurrence. We recommend 6- 12 months as this is the average follow-up period in the cases presented.

CHANGES IN TEXT:
There is no consensus on the post-operative follow-up interval in the cases, however there should be standard post-operative care and further follow-up at appropriate intervals to monitor for recurrence.

Overall, the methods of reviewing the case reports are sound, however, the justification for each section of management (biopsy, imaging, surgery, follow-up) is not sufficiently explained.

COMMENT 7: Grammatical issues
Figure 1 - "not related to schwannoma of the ..." Suspect this is missing the word tonsil
Surgical options - should be performed not "preformed"

REPLY 7: Changes have been made

Editorial Comments

Abstract

COMMENT 1. Please state the time period of the literature search.

REPLY 1: I had added the date of my literature search in the methods section.

CHANGES IN TEXT:

A search of PubMed, Medline and Embase databases was conducted on 5th May 2023 to identify all published cases.

COMMENT 2. The Results section appears to contain more methodological details than specific findings. For instance, the description of imaging techniques (e.g., CT and MRI) and surgical approaches (e.g., tonsillectomy and bilateral) should be presented more distinctly.
REPLY 2: Agreed. This section has been revised, please see below.
CHANGES IN TEXT 2:
A total of thirteen patients from thirteen cases studies were included in this systematic review. We found that this condition was present within a broad age range (eight to seventy-four years of age) and affected females (nine cases) more than males (four cases). There were two main reasons patients presented for review – (1) progressive dysphagia and (2) noticing an enlarging mass on intra-oral self-examination. Clinical examination findings were consistent among the case reports, with no evidence to suggest a malignant lesion. In all cases, patients underwent at least one form of imaging, which showed the lesion had features consistent with a schwannoma. Three patients also had a fine needle aspiration of the lesion, which produced a non-diagnostic result, suggesting that biopsy is not required prior to definitive management. Definitive management was unilateral tonsillectomy and there was no documented recurrence, although the follow-up period was highly variable.

COMMENT 3. The term 'simple quantitative and qualitative review' lacks academic precision. Furthermore, regarding the statement “Due to the nature and number of cases, a meta-analysis of the data was not possible”, the study seems to primarily provide qualitative results.
REPLY 3: Changes made as suggested
CHANGES IN TEXT 3:
‘Statistical Analysis’ section: Due to the small number of cases, a meta-analysis of the data was not possible. A descriptive statistical analysis and qualitative review of the data collected was conducted using Microsoft Excel.

COMMENT 4. “a guideline for the management of palatine tonsillar schwannoma was developed”, consider using the term 'Management Algorithm' instead of 'guideline' for greater clarity.
REPLY 4: Agreed.
CHANGES IN TEXT 4:
Based on the above findings a management algorithm for palatine tonsillar schwannoma was developed for the clinical management of this rare disease.

COMMENT 5. The conclusion currently conveys no information. We recommend that the authors make the valuable insights clearer and provide comments on the clinical implications of the findings.
REPLY 5: Agreed.
CHANGES IN TEXT 5:
In clinical practice, all unilateral palatine tonsillar masses are treated as malignancy until proven otherwise, and thorough history and examination will determine the level of clinical suspicion. Although in all cases tonsillectomy was the definitive management for this benign condition, there is high variability in investigations and follow-up. Our management algorithm proposes one form

of imaging is sufficient and biopsy is not required. We also aim to standardise follow-up at six to eight weeks post procedure and then again in six to twelve months to rule out recurrence.

COMMENT 6. Including "systematic review" as one of the Keywords.
REPLY 6: Agreed.
CHANGES IN TEXT 6:
KEY WORDS: Palatine tonsil schwannoma; tonsil neurilemmomas; schwannoma; systematic review

Methods
COMMENT 7. Please specify the specific dates when each database was last searched or consulted.
REPLY 7: Data base was searched on 5th May 2023
CHANGES IN TEXT 7:
A review of the published literature was performed on 5th May 2023 in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

COMMENT 8. "and was reviewed by CM, senior author and fellowship trained Otolaryngologist", should include the name of the senior author for proper attribution. And also need to acknowledge him in the Acknowledge section.
REPLY 8: I have added HER full name to that particular line and added her to the Acknowledge section.
CHANGES IN TEXT 8:
The final list of articles included thirteen case reports and was reviewed by Catherine Meller, senior author and fellowship trained Otolaryngologist
Acknowledgements section: The author would like to thank Associate Professor Catherine Meller from Faculty of Medicine, Health and Human Sciences, Macquarie University, for the guidance and support she provided throughout the entire systematic review process.

Results
COMMENT 9. The authors need to report the final included studies with reference number for ease of reading and double-checking in the first beginning. In addition, add the corresponding reference number to the paper included for each results section. For example, "Schwannoma was found in the right tonsil in seven cases and in the left tonsil in four cases".
RELPY 9: I didn't completely understand the first part of this comment "The authors need to report the final included studies with reference number for ease of reading and double-checking in the first beginning.". I have included a nice summary table (Table 1.), which summarised the results for each reference (i.e case report). In my opinion this makes the body of text easier to read as it doesn't get crowded with references, however, as per the comments I have included the relevant references for each finding as asked by the reviewer.
CHANGES IN TEXT 9:
There were only three paediatric cases and it appears to affect females (nine cases) [6, 14-20] more than males (four cases) [8, 9, 21, 22].
Most patients with tonsillar schwannoma present with either progressive dysphagia due to mass effect of the lesion [6, 8, 17, 18] or notice an enlarging unilateral mass on intraoral self-

examination [7, 14-16, 20, 22]. Other presenting symptoms include throat pain [19, 21] and sensation of a foreign body [9].
Ten out of the thirteen cases reported were treated with tonsillectomy of the abnormal tonsil only [6-9, 14, 16, 17, 19-21]. Three cases performed a wide local excision of the tumour only and did not remove the entire affected tonsil [15, 18, 22].
Seven cases discussed follow up at a particular post-operative interval, ranging between two weeks and twelve months [8, 14-16, 18, 21, 22]. Three cases did not specify a particular interval for post-operative follow up [7, 17, 19] and three cases did not discuss follow up at all [6, 9, 20].

COMMENT 10. There need some revisions about the flow diagram. Please delete "reports not retrieved (n=0)"; revise "foreign language" to "non-English"; "Reports included from manual search of references (n=2)" should be added along the "Records identified from Databases (n=56)". Then the following numbers should be revised accordingly. We recommend the authors to use the templated flow diagram in PRISMA 2020 as it has already encompassed such sources.
REPLY 10: Flow diagram updated
CHANGES IN TEXT 10: Flow diagram updated

COMMENT 11. Similarly, the results section seems to contain discussion-like content. The authors should report specific findings related to presenting symptoms, clinical appearance, biopsy, etc., without offering commentary. For example, the statement "The accuracy of fine needle aspiration cytology in diagnosing other head and neck schwannomas is low… and the experience of the Cytopathologist [2]", is the authors' opinion and not results. Opinions or interpretations should be reserved for the Discussion section. Please check thoroughly to avoid this concern.
REPLY 11: Agreed. I have made the appropriate changes and moved the discussion-like content to the discussion section.

COMMENT 12. The authors have stated their use of JBI for quality appraisal. But there is no description about this in the Results section. It is advisable to include a comprehensive presentation of risk-of-bias assessments for each of the included studies, adhering to the JBI guidelines.
REPLY 12: Each study included in the review was assessed against the JBI Critical Appraisal Checklist For Case Reports. The outcome of this assessment has been included in a supplementary appendix.
CHANGES IN TEXT:
'Quality/risk of bias' Section: Risk of bias was assessed using the Joanna Briggs Institute checklist standardised tool developed for case reports, which includes eight questions (13) - the detailed assessment can be found in the supplementary appendix online.

COMMENT 13. The authors should enclose the study limitation section, such as the weaknesses or confounders of the included articles, the drawback of the methodology of this systematic review etc.
REPLY: Addressed in 'Limitations" section.
CHANGES IN TEXT 13:

The rarity of this disease is reflected in the small number of cases reported in the literature since 1975. Furthermore, the evidence in this systematic review is comprised solely of case reports and hence the quality of evidence must be considered. The bias of the included case reports was low when assess with JBI checklist (see Appendix 1) as the data required to complete this review was all available in the published literature. Publication bias cannot be determined as meta-analysis or effect estimate could not be completed. Selection bias was avoided as all the available published cases of palatine tonsillar schwannoma was included in this review.

Possible limitations of this review arose from the varying duration or lack of information about post-operative follow-up. The variability in follow-up ranged from two weeks to eighteen months. There was no follow-up beyond eighteen months, which can potentially underestimate disease recurrence. There was variability in demographic data reported for each patient, such as ethnicity, smoking status, personal or family history of tumours etc., which can limit the generalisability of the results from this review.

This study is the first systematic review on palatine tonsillar schwannomas and can provide Otolaryngologists with valuable insights on how to investigate and manage this rare disease.