Author’s response to reviews

Title: Lymphoepithelial carcinoma: a case report of a rare tumor of the larynx

Authors:

NAWAL HAMMAS (nawalhammas@gmail.com)
Najib Benmansour (benmansour.dr@gmail.com)
Mohamed Nour-dine EL Alami El Amine (alami.mn@Gmail.com)
Laila Chbani (chbanil@yahoo.fr)
Hind El Fatemi (elfatemihinde@gmail.com)

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Author’s response to reviews:

Cover letter

Dear editor and reviewers,

In this letter, I present a point-by-point response to your comments. All changes to the manuscript are indicated in the text by highlighting. Thank you

Henrik Hellquist (Reviewer 1):

1) Typos;
   - Abstract in Conclusion; aggressive: correction made
   - Line 52 delete the dot before tonsillar: correction made
   - line 30 aggressive: correction made
   - line 33 contrepart: correction made
   - References: # 8 lymphoepitheliomal, #9 lymphoelias: correction made

2) Suggestions
Abstract, 2nd and 3rd sentence to merge It is extremely rare in the larynx and should be distinguished from squamous cell: change made.

Case presentation, first sentence; An 81-year-old Moroccan man, smoker for 40 years, presented with a one year history of dysphonia, dyspnea and dysphagia: change made.

Discussion, line 36 change within bracket to (male/female ratio 3:1): change made.

Conclusion Delete sentence 3 and change the last sentence to e.g. A correct diagnosis and a close collaboration between the pathologist and clinicians is mandatory for an optimal treatment strategy: change made.

Changes: Introduction line 28 delete ref # 2 and 3 and keep # 5 but change in reference list # 5 to the 2017 WHO classification, not the old 2005 that currently is in the reference list: change made.

3) Important:

- More information needed: As lymphoepithelial carcinoma is an undifferentiated malignancy, there are several potential differential diagnoses not discussed at all in the manuscript: these differential diagnosis were added in the manuscript.

- Firstly what keratin antibody was used: we used cytokeratin 5/6. I mentioned it in the manuscript.

- the authors need to exclude other malignancies and primarily neuroendocrine markers have to be applied, as well as myogenic marker(s), melanoma markers, LCA and possibly also CD99/NKX2.2. Several non-carcinoma malignancies can show positivity for keratin and therefore the possibility of other undifferentiated tumours has to be excluded, particularly as this tumour is a rarity in the larynx: suggested markers were tested and were negative excluding proposed diagnosis. I added these results in the manuscript.

- the authors state Discussion, line 43: There was also a cervical lymphadenopathy. Please give evidence - imaging or microscopic?: I am sorry, lymphadenectomy was not done and radiologic images are not available

4) References.

- Inconsistency: ref # 6 there are 6 authors et al, whilst ref # 9 only has 3 authors et al: change made.
Isabel Fonseca (Reviewer 2):

- The manuscript "lymphoepithelial carcinoma: a case report of a rare tumor of the larynx" is a long, descriptive study. It would benefit from some editing to shorten its length: change made.

Major issues:

1. Since this is in fact a very rare tumour, the authors should be more descriptive of methods that were used, namely how they determined the EBV status and what kind of immunohistochemistry was performed. Just "keratin positive" is quite short: more details were added.

2. Although the images are not of good quality, they do not illustrate a typical LEC. Comedo necrosis is not a common finding in LEC and a few differential diagnoses should be excluded, namely tumours with basaloid features such as adenoids cystic carcinoma and basaloid squamous carcinoma: Indeed, necrosis is unusual but possible. In a study by MACMILLAN (reference 3) including eight cases of LEC of the larynx and hypopharynx, necrosis was occasionally prominent. Concerning basaloid squamous carcinoma, it contains smaller cells moderately polymorphic without nucleolus, with peripheral palisades of the tumor cells around the sheets, whereas in our case, tumor cells was larger with proeminent nucleus and lymphoid stroma without palisades. Adenoid cystic carcinoma is also a differential diagnosis but it presents frequent perineural invasion and positive immunostaining for CD117. In the present case, tumor cells were different from adenoid cystic carcinoma cells; there was no perineural invasion and we tested CD117 and it was negative. I think that syntitial aspect, cellular morphology, lymphoid stroma and immunohistochemistry are in accordance with the diagnosis of lymphoepithelial carcinoma. Other differential diagnosis are discussed in the manuscript. Images were changed and remplaced by others of better quality.

3. Also in figure 3 there are remarkable epithelial alterations (acanthosis and keratosis). Was the overlying epithelium thoroughly evaluated?: Indeed, there was hyperplasia and a minimal keratosis but without dysplasia. I added it in the manuscript.

Minor comments:

- As mentioned, illustrations must be improved: change made.

- There is a new edition of the WHO blue book (ref. 5): change made.