Peer Review File

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Reviewer A

In this case report, Dr. Zhang and his/her colleagues reported a case report of primary mucoepidermoid carcinoma (MEC) of the breast. The manuscript is nicely written and ample clinical data have been provided. Although this tumor entity is rare and may attract the audiences, but some major concerns still exist:
1. Salivary MEC is well known to harbor MAML2 fusion. Extra-salivary MEC cases have also been reported to carry this fusion (e.g. MEC of the lung, thyroid). It is crucial to perform additional testing (FISH, NGS) for this case to know if the reported case has MAML2 fusion. In addition, this patient has a history of BRCA1-positive breast cancer, so it is important to know if the tumor is positive for BRCA1 mutation.
2. Please write a separate paragraph in the Discussion to discuss current knowledge and understanding of the pathogenesis of MEC in salivary versus extra-salivary origins. Primary MEC in salivary gland, lung, and breast are associated with MAML2 fusion (PMID 26796488, 26575266, 30380176) but the pathogenesis of primary thyroid MEC seems to be MAML2-independent (PMID 36394696).

Response to Reviewer A: Thank you for the comments.

1. We acknowledge that salivary and extra-salivary MEC tumors are known to harbor MAML2 fusion. Kindly note, diagnosis of mucoepidermoid carcinoma is a morphologic histopathology diagnosis and MAML2 rearrangement is not considered among the essential diagnostic criteria for the diagnosis of MEC. During Clinicopathologic discussions, MAML2 workup was considered, however, due to lack of resources and lack of impact on diagnosis, prognosis, and management, the decision was made to NOT send tumor block for the test.

   To clarify, this patient does not have a history of BRCA1-positive breast cancer. Her daughter, a BRCA-1 carrier, was diagnosed with breast cancer at age 38; however, the patient's genetic testing for BRCA-1 was negative.

2. Thank you for the suggestion. We agree the molecular pathogenesis of MEC is an area to be explored. This paragraph has been added to the discussion.

Changes in the text:
We have added a paragraph in the Discussion to discuss the current knowledge of molecular pathogenesis of MEC in salivary and extra-salivary origins (Page 10, line 227-240).

Reviewer B

Mucoepidermoid Carcinoma; A Rare Salivary Gland-type Tumor of the Breast is a well written case report and review of Literature. There are few comments.
1. As this lesion is very rare and since ER positivity is 51-60% in this case, was this case tested for MAML2 rearrangement? If not done, then its better to confirm the diagnosis with either FISH or molecular studies.
2. Also if authors provide better quality of images especially the areas with mucinous cells then it will be great.

Response to Reviewer B: Thank you for the comments.

1. Few mammary MEC have been described to have hormone receptor expression. The discussion and table describe ER-positive MEC cases. Please note, the presence of ER further supports the

diagnosis of mammary MEC. While the diagnosis of MEC is purely based on morphologic features, MAML2 rearrangement is NOT an essential criterion for diagnosis in Mammary MEC. Due to lack of resources, the test is not performed.

2. Please review both Figures 2 and 3 with cystic mucin areas which are delineated well with positive CK7 and mucicarmine. The right picture in Figure 2 shows cysts with pale mucins in the lumen. Figure 3 shows dual population of cells. P63 marks the epidermoid cells while CK7 and mucicarmine stains mucous cells.

Changes in the text: We have provided the highest quality images to the best of our ability on Pages 20-21, Lines 403-429, Figures 1-4

Reviewer C

Include all references before finishing a sentence. Example " Mucoepidermoid carcinoma (MEC) is an invasive tumor of the breast that histologically
75 resembles its salivary gland counterpart (1). Instead of ". (1)"
Line 116: replace PMHX by past medical history (PMHx).
Line 122: be specific for BRCA -1, germline or somatic?
If possible and to avoid identification of patient's identity, try to change details on age. For example: in line 128, replace at age 38 by late 30s.
Line 130: was discharged instead of sent home.
Line 146: 47 cases have been reported.
Line 147: delete "at present" .
Line 147: delete Our patient was a 67-year-old woman presenting nearly one standard deviation 150 (15.0) above the mean age. This info is not relevant.
Line 161. Delete extra . after patients.
Line 200: replace " required highlighting" with " are needed to explore..."
Line 204: clarify small sample size. If this is a review, the few numbers of patients are explained by MEC being rare. I would not mention this as a limitation.

Make all the conclusions based on the review of existing cases.
It is known that the patient's daughter has a BRCA mutation, what about the patient?

Figure 5: change axis name "cases" to " number of cases"

Response to Reviewer C: Thank you for the comments. Please see the clarifications to select comments below.

Line 122: We do not have specifications on germline or somatic mutation of BRCA-1 for the patient's daughter
Line 204: Given some studies in the past have reported multiple cases at one institution, we felt it was applicable to mention we have only encountered one case.
BRCA mutation: We have mentioned on Page 8 line 134 that the patient's BRCA-1 genetic results are negative.

Changes in the text:
Reference formatting: All references have been edited.
Line 116: Text modified to "past medical history" as advised (Page 7, line 128)

Line 122: As we are unable to specify germline or somatic mutation of BRCA-1, no change has been made. Age has been changed to “late thirties” as advised (Page 8, line 135)
Line 130: Text modified to “discharged” as advised (Page 8, line 143).
Line 146: Text modified as advised (Page 9, line 181)
Line 147: Text deleted as advised (Page 9, line 182)
Line 147: Text deleted as advised (Page 9, line 183)
Line 161: Text deleted as advised (Page 9, line 194)
Line 200: Text modified to “are needed to explore” (Page 11, Line 258)
Line 204: “Small sample size” has been deleted as advised (Page 11, Line 262)
Figure 5: Text modified as advised (Page 22, Figure 5)

Reviewer D

In this case report, the authors reported a case of mucoepidermoid carcinoma of the breast and discussed the diagnostic work-up, surgical, and adjunctive treatments for breast MEC.
This kind of case seemed very rare, and worthy of publication.

Minor points
To use an abbreviation, write the full name in the first use (PMHx).

At the end of the case presentation section, add a comment about the patient’s final status and follow-up period.

Insert the scale bar into the Figure 1-4.
[END]

Response to Reviewer D: Thank you for the comments.
Upon review of several case reports, it was not customary to include a scale bar on pathology figures.
Please see other changes addressed below

Changes in the text:
Text modified to “past medical history” as advised (Page 7, line 128)
Summary of the patient’s final status and follow-up period has been added at the end of the case presentation section. (Page 9, Line 150; Page 10 Line 176)

Reviewer E

It is a very interesting case and worth reporting. However, I was unable to find the meaning of the abbreviation "PMHx".
On the other hand, in the literature review there is no mention of the molecular profile of this rare breast tumor, particularly in the article:
Venetis K, Sajjadi E, Ivanova M, Andaloro S, Pessina S, Zanetti C, Ranghiero A, Citelli G, Rossi C, Lucioni M, Malapelle U, Pagni F, Barberis M, Guerini-Rocco E, Viale G, Fusco N. The molecular landscape of breast mucoepidermoid carcinoma. Cancer Med. 2023 May;12(9):10725-10737. doi: 10.1002/cam4.5754. Epub 2023 Mar 14. PMID: 36916425; PMCID: PMC10225218.

Response to Reviewer E: Thank you for the comments. We agree the molecular pathogenesis of MEC is an area to be explored. This paragraph has been added to the discussion.

Changes in the text:
Text “PMHx” modified to “past medical history” as advised (Page 7, line 128)
We have added a paragraph in the Discussion to discuss the current knowledge of molecular pathogenesis of MEC in salivary and extra-salivary origins (Page 10, line 227-240).