

October 28, 2018

RE: Manuscript NO 40850

Dear Dr. Fang-Fang Ji and Reviewers:

We sincerely thank you for your kind remarks and helpful feedback in review of our submitted manuscript entitled "Radiation-Associated Epithelial-Myoepithelial Carcinoma Among Five Secondary Malignancies After Hodgkin Lymphoma: A single case report and literature review" (Manuscript # 40850).

We have attempted, to the best of our ability, to respond to your excellent feedback in all regards. Please find a point-by-point response to each reviewer's comments below.

Review 1 Comments:

Minor English revision is necessary. -What is the authors proposal for the occurrence of such kind of malignant tumors in the patient? -The authors should explain the important information that the case provided clearly.

Response to Reviewer 1:

Thank you for your feedback regarding our submission and we have applied your requests to the best of our ability. We have applied edits to the manuscript and reviewed the submission for proper English grammar. Our proposal is that historically used mantle-field radiation increased the risk for secondary malignancies, and we highlight this in our patient with five such secondary malignancies that are all within the field of radiation that is covered in this "mantle-field." Additionally, we focus on radiation-associated epithelial-myoepithelial carcinoma as this is an exceedingly rare entity, only once previously described in the literature. Finally, we have added an "Article Highlights" section which provides a summary of the important information and the unique presentation and lessons illustrated.

Reviewer 2 Comments:

In the current case report, the authors described a case of a 56-year-old male patient who presented with a neck mass diagnosed as epithelial-myoepithelial carcinoma of the left submandibular gland approximately 30 years after mantle field radiation and chemotherapy for Hodgkin's lymphoma. Overall, the case report is well presented. Only small flaws should be modified. 1. Pay attention to the spelling

and grammar and avoid errors, such as " lymphomaand underwentmantle" should be " lymphoma and underwent mantle". Too much similar errors exist.

Response to Reviewer 2:

We sincerely appreciate your interest in the case we have submitted and are excited that you find it to be well presented. We did review the spelling and grammar and I have searched for the errors you mention above. Specifically, you noted some combined words "lymphomaand underwentmantle," though we are not able to find these errors. We believe this may have been due to a formatting issue in the publishing viewer, as in our Microsoft Word document, these errors are not present. We thank you for pointing this out, as it has encouraged us to double check for any other possible formatting errors.

Reviewer 3 Comments:

Authors describe a very interesting and rare case of EMC associated with prior RT for HL. Case is well written with relevant radiology and histology images. Appropriate description of management and follow-up. I have few comments for the authors. Suggestions: - Cahan's criteria were proposed in 1948 for post-RT sarcoma. It has a relatively broad inclusion criteria to call a neoplasm, 'radiation-induced malignancy'. This patient had chemotherapy for HL and DLBCL before diagnosis of EMC. Establishing a casual relationship between RT and ECM is difficult given rarity of diagnosis. Should a title "Radiation- associated ECM" instead of "Radiation-induced ECM" be better? How would author respond to this? - Page 6- Please use doxorubicin and vincristine which are common terms for hydroxydaunorubicin and oncovin. - Was the brain lesion biopsied? Why WBRT + IT AraC was used instead of high-dose methotrexate for secondary CNS DLBCL? - follicular lesion of undetermined significance (FLUS) composed predominantly of Hurthle cells is technically not a malignancy. What was the final diagnosis on thyroidectomy? - Hodgkin's lymphoma is now called just "Hodgkin lymphoma" (WHO classification of lymphoid malignancies 2016)

Response to Reviewer 3:

-We thank you for your excellent feedback and for pointing out the importance of Cahan's criteria. While we suspect that these are radiation-induced secondary malignancies as they did arise within radiation field used commonly in mantle field radiation therapy, we do acknowledge that the patient was also susceptible to a host of systemic therapies. As such, we agree that the term "radiation-associated" is more appropriate than "radiation-induced" and we have modified the title and manuscript to reflect this.

-On page 6, we have used the more common terms doxorubicin and vincristine, as you have requested. Thank you for noting this important modification.

-The patient's brain lesions were not biopsied as the patient was known to have multiple underlying malignancies, so a non-malignant etiology was less likely. WBRT and IT AraC was used per discretion of the medical oncology team due to CNS penetration and toxicity profile.

-While FNA revealed the follicular lesion with Hurthle cells was initially of undetermined significance, the final diagnosis of the thyroid nodule following hemithyroidectomy was Hurthle cell adenoma as noted in the report.

-We agree with your important comment regarding adaptation of more modern terminology and referring to the patient's first malignancy as "Hodgkin lymphoma" and not "Hodgkin's."

Again, thank you for your time and consideration of our manuscript. We hope that our unique case presentation is now acceptable for publication in *World Journal of Clinical Oncology*. Please do let us know should there be any additional modifications you would like.

Sincerely,

Mohamed Khattab, MD