Manuscript NO: 77231

Title: Misdiagnosis of an elevated lesion in the esophagus: A case report of esophageal carcinosarcoma and literature review

Response to Reviewers

Dear Reviewers,

Thank you very much for your time involved in reviewing the manuscript. We have carefully considered the comments and tried our best to address every one of them. We have incorporated all of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments and concerns. All page numbers refer to the revised manuscript file with tracked changes.

We hope the revised manuscript can meet your standards. The authors welcome further constructive comments if any.

Sincerely,

The Authors

Response to Reviewer #1

[general Comment] The author presented a rare case of esophageal

sarcoma treated by endoscopic resection. The authors review previous reports of esophageal sarcoma and contrast them with their own cases.

Response: Thank you very much.

However, it seems to be required some revisions.

[Comment 1]: It is recommended that the authors revise the main text and conclusions to make it easier to see what they want to emphasize most in this paper.

Response:

We agree with the reviewer's assessment. We have rewritten the background, conclusion as well as some wordy parts of the manuscript, to make it easier to get and understand what we really want to express (**The revised manuscript: page 2, Line 3-10; page 2, Line 28-30; page 7, Line 1-7**). The value of beta-catenin in the discussion and conclusion part was deleted since it is not closely related to the subject (**The original manuscript: page 5, Line 19-21**).

[Comment 2]: It would be better to show in a table the examples of past reports and to clearly indicate the characteristics and differences of the self-examined case.

Response:

Thank you for the suggestion. We fully agree that a table in the

article will make it easier to read and get information from studies in the past. Meanwhile, we noticed that it should not be neglected that most of the literature in the past mainly focused on the prognosis of ECS after surgical treatment, other than endoscopic findings, which are not closely related to the subject. At the same time, data has been summarized in their work. Therefore, we modified the manuscript to refer to their work in a more obvious way (references 7 and 8) and did not display them further (**The revised manuscript: page 6, Line 13)**.

[Comment 3]: Did the author discuss esophageal sarcoma as a differential disease in the endoscopic biopsy specimen, including immunostaining, with the pathologist prior to surgery?

Response:

Thank you very much for this wise question. This is just what we were thinking about before the ESD treatment. Before the ESD procedure, we have performed a multidisciplinary consultation including radiologists, pathologists, endoscopists, and surgeons.

After careful revision of the biopsy slides, only the infiltration of inflammatory cells was found, without any sign indicating suspected malignancy. Therefore, immunohistochemistry was not performed (**The revised manuscript: page 4, Line 27)**. We should notice that

this is the characteristic of ESC. A targeted biopsy may help improve biopsy accuracy before further treatment, which was discussed in the manuscript (**The revised manuscript: page 6, Line 1-3)**.

Response to Reviewer #2

[Comment 1] Interesting case report with excellent representative images on a disorder many do not encounter nor know how to manage.

Response: Thank you very much.

Minor typographical errors.

[Comment 2]: Please eliminate any contraction (instead of "can't", please use "cannot).

Response:

Thank you very much for your advice. We have modified the contractions in the revised manuscript (**The revised manuscript: page 2, Line 29; page 3, Line 10-12; page 4, Line 4-5)**.

[Comment 3]: Please change "dysphasia" to "dysphagia" in the case presentation.

Response:

We feel very sorry for our spelling mistakes. In our resubmitted manuscript, these mistakes are revised (**The revised manuscript: page 2, Line 5; page 2, Line 13; page 3, Line 16; page 3, Line 30)**.

[Comment 4]: Please change "founded" to "found".

Response:

We have carefully checked the manuscript and corrected the errors accordingly. Thank you again for your careful revision (**The revised manuscript: page 4, Line 20)**.

Response to Reviewer #3

[general Comment] It is an interesting case that discusses a rare entity.

Response: Thank you very much.

[Comment 1]: The manuscript is difficult to read; please try to simplify the sentences.

Response:

Thank you for your advice. We have rewritten the abstract and conclusion according to the reviewers' suggestions (**The revised manuscript: page 2, Line 3-10; page 2, Line 28-30)**. A language service is also requested after the revision.

[Comment 2]: In the conclusion section, you mentioned that a biopsy from the root or the pedicle is better for the diagnosis. Can we conclude this result from only one case study?

Response:

Thank you for the comment. We fully agree it is not firm to conclude that biopsy from the root is better based on only one case. Meanwhile, it is noticed that biopsy on the root of sarcoma is better to raise biopsy accuracy, due to its behavior (reference 6). Since ECS partly imitates sarcoma, we think it is better to perform the biopsy on the root of the lesion. However, further data is required to prove it.

[Comment 3]: Please add annotations, scale bar, magnification, and type of stain or dye regarding the figures.

Response:

Thank you very much for your advice. For figure 2A, we are sorry to say that this picture was captured from a stereomicroscope, which does not support a digital connection to the computer. Therefore, the scale bar and magnification are not available. Scale bars of other pictures were presented in the lower right corner of each picture.

Magnification, staining and dyes were described in the legendary (**The revised manuscript: page 10, Line 10-14; page 11, Line 1-6)**.

[Comment 4]: As regards the endoscopic figures, what do you mean by lichen. Also, the lesion looks suspicious; I mean, not benign.

Response:

We feel sorry for the misused word of lichen. What we really want to express is the pseudomembranous inflammation on the surface of the lesion, characterized by the formation on a mucosal surface of a false membrane composed of precipitated fibrin, necrotic epithelium, and inflammatory leukocytes. We have corrected the word in the revised manuscript (**The revised manuscript: page 2, Line 15; page 4, Line 20; page 10, Line 4)**.

We thought the lesion was benign based on the following consideration. First, the intra-papillary capillary loops (IPCLs) of the lesion exposed showed no signs of malignancy. Second, the lesion was pedunculated, which is mostly benign. Third, a multidisciplinary consultation was performed to carefully review the biopsy slides, showing no evidence of malignancy. Therefore, the pre-ESD misdiagnosis was made.

[Comment 5]: Regarding the EUS pictures, what is your

explanation for the hypoechoic area and the increased vascularity.

Response:

Thank you for your comment. The hypoechoic area of the lesion (Figure 1E and 1F) is just the cysts of the post-surgery specimen (Figure 2A). based on our literature research, the mechanism of this phenomenon is not well explained currently. It may attribute to the secretion of glands. Further data is required.

The color of Figure 1G showed the elastography of the lesion, other than Doppler imaging. Therefore, the mixture of the color showed heterogeneity of density, other than vascularity (**The revised manuscript: page 10, Line 1-9)**.

[Comment 6]: Some corrections are highlighted with red color in the uploaded file.

Response:

Thank you so much for your valuable work. We have modified the sentence according to your suggestion. Responses are listed separately.

(1) OUTCOME AND FOLLOW-UP: ESD or open surgery? You mentioned that this is a residual tumor in the index ESD, so what is your explanation after the second ESD and the absence of any cancer residual?

Response: We are sorry for the unclear expression. In this part, additional resection means open surgery (**The revised manuscript: page 2, Line 22; page 5, Line 18)**. And there is no cancer residual, indicating the invasion of ECS is within T1b stage.

(2) By contrast, the patient refused to receive additional surgery, and recurrence was found during an endoscope examination 21 months later (these words belong to your case or the Korean study).

Response: Thank you for your advice. This sentence makes our study stand out and emphasizes the value of post-ESD evaluation, compared with the Korean study (**The revised manuscript: page 6, Line 24-25)**.

(3) Targeted biopsies of the root or peduncle after observing with narrow-band imaging or iodine staining are recommended, did you use these techniques before the second ESD?

Response:

We are sorry again for the misunderstanding of the manuscript. As described in the above comment, an open surgery was followed after the ESD treatment (**The revised manuscript: page 2, Line 22)**. The patient's post-ESD pathology showed that there was a possibility of tumor residue. According to the literature review, the patient decided to have additional surgery. We did not perform an endoscopic examination before the open surgery. However, we cherish the idea of targeted biopsy. When looking back again, a second endoscopy of targeted biopsy may be helpful to make a correct diagnosis before

the ESD treatment. This is also an important message of the case.

Response to Reviewer #4

[general Comment] Overall it is an interesting case and an important topic on a rare tumor. I thank the authors for presenting this case.

Response: Thank you very much.

[Comment 1]: In the case presentation both in the abstract and the full text, the authors have stated that the patient presented with dysphasia, I believe that this is a typographical error instead of dysphagia?

Response:

We feel sorry for the spelling mistake and thank you for your careful revision. These mistakes have been corrected in the revised manuscript (**The revised manuscript: page 2, Line 5; page 2, Line 13; page 3, Line 16; page 3, Line 30).**

[Comment 2]: Recommend that the introduction be re-written. I would advise the author to re-write the first line "Patients routinely undergo endoscopic evaluation for dysphagia during which

protruding or elevated lesions..." -"Part of those present as pedunculated characteristics" please re-write this sentence in a grammatically correct way.

Response:

Thanks for your valuable advice. We have re-written the introduction part based on your suggestions (**The revised manuscript: page 3, Line 16-21)**.

[Comment 3]: Please ensure the manuscript is proof read. There are several grammatical mistakes.

Response:

Thank you again for your patience in reading this manuscript. We feel sorry for the grammatical mistakes. Since we are not native English speakers, language service is requested after the revision. Thank you again.

[Comment 4]: Case presentation: Can the authors be a little more elaborate with the patient's complaints? such as duration, progression, associated symptoms, etc?

Response:

Thank you for your advice. We have added more patient's

complaints (**The revised manuscript: page 3, Line 29-30; page 4, Line 1-13)**.

[Comment 5]: Instead of imaging examination I would suggest that the subtitle be replaced with endoscopic examination as that is what the authors have described here in detail.

Response:

Thank you for pointing this out. The reviewer is correct, and we have replaced it (**The revised manuscript: page 4, Line 18)**.

[Comment 6]: Discussion: Several grammatical errors. Recommend the authors to rectify it and proof read it.

Response:

Sorry again for the poor language problem. After revising the manuscript, it will be referred to a language service for proofreading.

Once again, we cherish the time and patience you put in this manuscript and look forward to meeting your expectations.

Yours sincerely,

The authors

June 26, 2022