

April 7, 2020

Dr.Subrata Ghosh

Editor-in-Chief

*World Journal of Gastroenterology*

Dear Editors:

Thank you for your letter dated April 3, 2020. We appreciate the reviewers' comments regarding our manuscript entitled, "Multiple carcinosarcomas of the esophagus with adeno-carcinomatous components: A case report." Please find enclosed the edited manuscript in Word format (file name: maindocument.doc), which has been improved according to the suggestions of the reviewers. Point-by-point responses to the reviewers' comments are given below.

**Title:** Multiple carcinosarcomas of the esophagus with adeno-carcinomatous components:  
A case report

**Author:** Hiroshi Okamoto, Hiroshi Kikuchi, Hiroshi Naganuma, Takashi Kamei

**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 55091

The revised parts were underlined in the manuscripts.

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1:

This case report a rare case of mixed esophageal carcinosarcoma with adenocarcinoma in multiple lesions and sarcomatous lymph node metastases. This is a very interesting case report, and a lot of meaningful work has been done.

**Reply:** Thank you very much for your review and helpful comments. We appreciate that you found our paper interesting.

Reviewer 2:

Multiple carcinosarcomas of the esophagus with adeno-carcinomatous components is a rare case. I think it's valuable to publish. However, based on what you found; you didn't have direct evidence to indicate the relationship with EMT. Due to just one case, compared with discussion with molecular mechanism of the disease onset, I would like to recommend you to clarify the characters of this rare case and differential diagnosis, This is more effective to clinic work.

**Reply: Thank you very much for your review and helpful comments and we think your indication is very important. Regard to differential diagnosis, collision cancer can be considered as a differential diagnosis. However, we do not consider the condition to be collision cancer owing to its morphological findings. We added the issue in the discussion section (Page 10, line 4-6). Regard to mechanism of the disease onset, elements of the fibrotic and tumor-related microenvironment, including hypoxia and inflammation, can activate EMT-promoting transcription factors by via induction of transforming growth factor  $\beta$  (TGF- $\beta$ ) and hypoxia inducible factor. In this case, the laboratory data at the time of diagnosis revealed an elevated inflammatory response. We think that such inflammation may serve to activate EMT. However, the issue requires further study. We added this issue in the discussion section (Page 11, line 18-20).**

We do hope that the manuscript is now acceptable for publication in *World Journal of Gastroenterology*.

Thank you for your consideration.

Sincerely,

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