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Title: Esophageal carcinoma originating in the surface epithelium and showing esophageal gland duct differentiation as determined by immunohistochemical analysis: A case report

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Esophageal carcinoma originating in the surface epithelium and showing esophageal gland duct differentiation as determined by immunohistochemical analysis: A case report

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Dr. Ya-Juan Ma,
Science Editor World Journal of Gastroenterology

Dear Dr. Ya-Juan Ma,

We are very grateful to you and the reviewers for your helpful comments on our manuscript. The useful suggestions have allowed us to improve our paper considerably.

As indicated in the following responses, we addressed all of the comments made by the reviewers, and have taken all of their suggestions into account in the revised version of the manuscript.

Comments reviewed by 00052396

This manuscript by Tamura et al reports a very interesting case of esophageal carcinoma. This reviewer suggests two issues:

1. A population of esophageal stem cells may be located in the glandular neck region of the esophageal submucosal gland ducts. If cancer derives from these cells, cancer may appear with features of both the squamous epithelial cells and gland cells. The authors may discuss potential cellular origin of the carcinoma in this case, and potential strategies of identifying cellular origin. For example, next-generation sequencing may provide some help. Further characterization of differentiation markers may also help.

Response: Thank you for the suggestion. Accordingly, we have added the following sentences to the Discussion section (pg. 11, lines 2-9):

Therefore, it follows that the tumor of the present case exhibited bidirectional differentiation of a unique esophageal gland duct and conventional squamous epithelium. Recent studies have shown that uncommitted stem cells are located in the papillae of the basal layer of the esophageal epithelium. Although some reports consider that bilayered adenocarcinomas must arise in the original gland ducts because of the morphological similarities between the ducts and the tumors, we believe that tumor

origin and tumor differentiation should not be confused. Molecular techniques such as next-generation sequencing will contribute to elucidating the origin of this unique carcinoma.

2.Discussion section may be shortened.

Response: Thank you for the suggestion. We have eliminated many sentences and shortened the Discussion section from 971 words to 833 words.

Comments reviewed by 03473712

Please note that adenocarcinoma of esophagus is no longer a rare tumor; In some countries, it is overtaking squamous cell cancer in incidence.

Response: Thank you for the comment. In accordance with your suggestion, we have added the following sentences to the Introduction and Discussion sections:

Revised Introduction; pg. 6 lines 1–2:

Although the frequency of esophageal adenocarcinoma has dramatically increased in recent years in the United States, squamous cell carcinoma remains predominant and adenocarcinomas are relatively rare in Asian countries.

Revised Discussion; pg. 8 lines 17–18:

The frequency of esophageal adenocarcinoma has increased in the United States, although squamous cell carcinoma remains predominant in Asian countries.

We hope that the revised version of our manuscript is now suitable for publication in *World Journal of Gastroenterology*, and we look forward to hearing from you at your earliest convenience.

Yours Sincerely,

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