Author’s response to reviews

Title: Calcified mucinous adenocarcinoma of stomach metastatic to the iris: An autopsy case

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Dear Editor-in-Chief and Referee:

Please find enclosed the edited manuscript in Word format [file name: JMCR-D-18-00730 R-1]

Title: Calcified mucinous adenocarcinoma of stomach metastatic to the iris: An autopsy case
Author: Miki Kaneko; Tadashi Namisaki; Hiroaki Takaya; Hitoshi Mori; Mitsuteru Kitade; Yasushi Okura; Kenichiro Seki; Shinya Sato; Keisuke Nakanishi; Koh Kitagawa; Takahiro Ozutsumi; Naotaka Shimozato; Kosuke Kaji; Tomoyuki Otani; Tokiko Nakai; Chiho Obayashi; Akira Mitoro; Junichi Yamao; Hitoshi Yoshiji

Name of Journal: Journal of Medical Case Reports
Manuscript NO: JMCR-D-18-00730 R-1

We are very grateful to you and the reviewer for the comments and thoughtful suggestions regarding our manuscript. We have thoroughly addressed all concerns and issues raised and have revised our manuscript accordingly. All changes in the revised version are highlighted in yellow. We believe that the manuscript has greatly improved with your inputs and hope that it meets the standards of Journal of Medical Case Reports. We have provided point-by-point responses to the reviewers’ comments below.

Reviewer #1:
1. Do you believe the case report is authentic? Yes

2. Do you have any ethical concerns? NO

Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Response: In accordance with the reviewer’s comment, we have attached a copy of the written consent and included a description of the findings on page 11 lines 193–195.

3. Does the Introduction explain the relevance of the case to the medical literature? Yes

4. Does the article report the following information? Where information is missing, please specify.
   a. The relevant patient information, including:
      - De-identified demographic information (age, gender, ethnicity)
      - Main symptoms of the patient
      - Medical, family and psychosocial history
      - Relevant past interventions and their outcomes.

   b. The relevant physical examination findings
c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month.

d. Diagnostic assessments, including:
   - Diagnostic methods
   - Challenges (e.g., financial, language/cultural)
   - Reasoning and prognostic characteristics (e.g., staging), where applicable

e. Types and mechanism of intervention

f. A summary of the clinical course of all follow-up visits

Comments: All relevant information is included

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments: My main concern with this report is the actual diagnosis of mucinous adenocarcinoma. Based on the images provided, this looks more like a "Signet ring cell carcinoma" - a diagnosis that is made when at least 50% of the tumor cells have a signet ring cell morphology. Per some sources, "mucinous gastric cancer" is histologically characterized by extracellular mucinous pools that constitute at least 50% of tumor volume. Mucinous cancer can have cells with signet ring cell morphology but that should be <50%. Although the distinction between the two can be blurry sometimes, the diagnosis is based on the predominant component. The figures provided in this report favor a "Signet ring cell Carcinoma" except for the figure with calcifications floating in mucin pools. It would certainly help if the authors can provide images that truly show a tumor that has abundant mucin with scattered tumor cells to clinch this diagnosis.

Response: We thank the reviewer for these valuable comments. According to the reviewer’s comment, we have added a new figure (Figure 3d) and revised the manuscript accordingly. The biopsy of a gastric tissue specimen revealed poorly differentiated carcinoma with signet-ring cell features (Figure 1b). The patient was diagnosed with poorly differentiated gastric adenocarcinoma metastatic to the iris, peritoneum, and lymph nodes. We have included a description of these findings on page 6 lines 96–97 and line 99-101.

Histologic examination revealed poorly differentiated adenocarcinoma containing signet-ring cells beneath a preserved surface epithelium (Figure 3b) and calcifications among the mucous lakes in the deep layers (Figure 3c). Other areas showed abundant scattered signet-ring cells floating in the abundant mucin (Figure 3d). The final diagnosis was mucinous gastric adenocarcinoma metastatic to the iris, peritoneum, and lymph nodes.

Histologic examination of a gastric tissue specimen obtained through endoscopic biopsy revealed poorly differentiated carcinoma with signet-ring cell features. Computed tomography revealed a tumor with multiple punctate calcifications in the thickened gastric wall with diffuse low attenuation and multiple lymph node metastases, including the para-aortic lymph nodes, and peritoneal dissemination. The final diagnosis was mucinous gastric adenocarcinoma because mucinous adenocarcinoma is diagnosed when more than half of the tumor area contains extracellular mucin pools. We have included a description of these findings on page 2 lines 36–40, page 3 lines 45–47, and page 7 lines 117–121.

2. The findings in this report are by no means new as calcifications are more common in mucinous adenocarcinomas than any other subtype of gastric cancer. Also there have been autopsy reports of
calcifications seen in gastric mucinous adenocarcinomas as far back as 1967 ([https://pubs.rsna.org/doi/abs/10.1148/88.5.1002?journalCode=radiology](https://pubs.rsna.org/doi/abs/10.1148/88.5.1002?journalCode=radiology)). Metastasis to the iris has been noted in gastric signet ring cell carcinoma but in my literature search I did not come across iris metastasis in gastric mucinous adenocarcinoma. So, if this is truly a gastric mucinous adenocarcinoma, it would be the first report of such a case.

3. There are some grammatical errors in the manuscript. For instance, in line 161, the word "preceeding" should read "preceeded" to make the sentence grammatically correct. There are a few other instances like these in the report that need correcting.

Response: The revised manuscript has now been edited and corrected by a native English speaker. We have made careful modifications to the original manuscript and have proof-read it to minimize typographical and grammatical errors.

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

   Yes

7. Is the Abstract representative of the case presented?

   Comments: Mostly representative. However, the diagnosis of a Mucinous adenocarcinoma (vs. Signet ring cell carcinoma) needs clarification.

Response: Mucinous adenocarcinoma is diagnosed when more than half of the tumor area contains extracellular mucin pools, and signet-ring cell carcinoma is diagnosed when adenocarcinoma is seen with a predominant component (>50%) of isolated tumor cells that contain mucin [Bu Z et al, Chin J Cancer Res 2013, new reference No. 13]. We have included a description of these findings on page 7 lines 115–121.

8. Does the case represent a useful contribution to the medical literature?

   Comments: Somewhat. There are a few case reports already in the literature with calcifications seen in gastric mucinous adenocarcinomas. Nonetheless, fewer cases have iris metastasis.

9. Additional comments for the author(s)? There are some grammatical errors in the manuscript. For instance, in line 161, the word "preceeding" should read "preceeded" to make the sentence grammatically correct. There are a few other instances like these in the report. Please correct the same.

Response: We apologize for the error. As mentioned earlier, the revised manuscript has now been edited and corrected by a native English speaker. Furthermore, we have made careful modifications to the original manuscript and carefully proof-read it to minimize typographical and grammatical errors.

Reference