Peer Review File

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Reviewer A:

The authors describe a case of "medullary carcinoma" in the duodenum treated with pembrolizumab. The use of immune checkpoint inhibiting drugs in GI cancer and tumour response to such treatment is a relatively new and important area of study. Most current data relates to colon cancer, therefore examples of treatment of other GI cancers are of interest. Unfortunately there are a number of weaknesses to this case report which makes meaningful conclusions difficult:

Diagnosis of medullary carcinoma is made on the basis of biopsy histology (supplemented by immunohistochemical profile). It is doubtful whether histological classification of medullary carcinoma can be made on biopsy alone rather than a resection.

There is a previous history of poorly differentiated microsatellite unstable colon cancer with similar but not identical immunohistochemical profile. It is difficult in this case to be sure whether the duodenal tumour is a primary cancer or metastasis.

It seems the patient was lost to follow-up soon after treatment, although his symptoms did improve and a PET-CT is described. In my opinion however, response to immunotherapy cannot reliably be evaluated from this report.

Reply: This case was reviewed with our pathologist, who stated that core biopsy alone was sufficient for histological diagnosis based on the distinct microscopic and immunohistochemical characteristics of the sample. However, we certainly agree that the gold standard for the classification/diagnosis of medullary carcinoma is through resection of the tumor and have acknowledged this as a limitation within the text.

We agree that it was difficult to ascertain whether the patient's duodenal tumor represented a primary cancer or metastatic recurrence of his previous colorectal cancer and have addressed this within our discussion (page 7, lines 168-174).

We agree that it is difficult to evaluate this patient's continued response to immunotherapy given the limited information available in this situation and have acknowledged this as a limitation within the text. Thank you for your thorough review and comments.

Changes in the text: We have acknowledged your comments as limitations in the last paragraph of our discussion section on page 8-9 lines 199-205.

Reviewer B:

The authors presented a rare case of medullary carcinoma of small intestine, which is also the first case located in duodenum. And it showed the first attempt of the immune checkpoint inhibitor-pembrolizumab on medullary carcinoma in the first line setting. We are glad to see authors' exploration of treatment in rare diseases. Now, some issues need to be addressed below.

1. It would be preferable to add the information on treatment of MC in the Background of Abstract, not

only its rarity.

Reply: We have edited the background of our abstract to include the primary treatment of medullary carcinoma based on available data from previous cases.
Changes in the text: We have edited the background of our abstract to include treatment of medullary carcinoma (see Page 2, Lines 49-50)

2. Similar to last point, the Introduction seems a little informative. Please summarize the treatment of MC, so as to stress the first use of pembrolizumab.
Reply: We have included the treatment of medullary carcinoma within our introduction section. Thank you for this suggestion.
Changes in the text: We have added “Given the rarity of the tumor and limited data available, the best treatment for this patient group remains unclear. For localized tumors, surgical resection appears to be the mainstay of treatment based on previous reports” on page 4, lines 92-93.

3. The images of CT of the abdomen and pelvis, EGD, and PET, enabling the visual presentation, need to be presented.
Reply: We have provided the CT abd/pelvis, EGD, and PET images as Figures 1, 2, and 4, respectively.
Changes in the text: We have provided the CT abd/pelvis, EGD, and PET images as Figures 1, 2, and 4, respectively.

4. A more detailed medical history would have been desirable. Did the patient have any other discomfort except abdominal pain, such as nausea, vomiting, diarrhea, weight loss or decreased appetite? And how about his smoking and alcohol status?
Reply: Thank you for the suggestion. We have included additional medical history to our case presentation.
Changes in the text: We have added “He had a 10 pack-year smoking history, but no history of alcohol or drug use” to page 4 line 106-107 and “and distension for two weeks. He also reported nausea, vomiting, decreased appetite, and constipation with black stools” to page 4 lines 105-106.

5. Was there any radiological evidence for improvement of the patient after pembrolizumab treatment? Please provide them if available or explain in text.
Reply: PET/CT was done at an outside facility; we unfortunately do not have access to the PET/CT CD at this time.
Changes in the text: The findings from PET/CT are already included in the text on page 5, lines 132-133.

Minor concerns:
6. The “Discussion” section in the Abstract should be modified as the “Conclusions”. And please highlight the main take-away lesson, clinical impact and potential implications in it.
Reply: We have modified “Discussion” to read “Conclusions” in the abstract as well as included additional text to highlight the main take-away lesson, clinical impact, and potential implications in it.
Changes in the text: We have changed the “Discussion” section to “Conclusions” in the abstract as well as included "In order to corroborate the use of immune checkpoint inhibitors as a treatment option for MC of the colon or small intestine, the aggregation of existing and future case data in this unique patient

group is certainly warranted." on page 3, lines 75-77.

7. A statement like "We present the following case in accordance with the CARE reporting checklist" should be included at the end of the "Introduction".
Reply: We have included the statement at the end of our introduction.
Changes in the text: We have included the statement at the end of our introduction (see page 4, line 100)

8. Other than detailed legends, we recommend the authors to provide a brief caption for Figure 1.
Reply: We have included a brief caption for the figure (now Figure 3).
Changes in the text: We have included a brief caption for the figure (now Figure 3): "Hematoxylin and eosin (H&E) stained slide of one biopsy site of duodenal mass" for Figure 3A and "H&E stained slide of second biopsy site of duodenal mass" for Figure 3B.

9. Please define ALL abbreviations mentioned at the first time in the Abstract and the main text, respectively, such as CT, EGD.
Reply: We have included the definitions of the abbreviations MSI-H, CT, EGD, PET.
Changes in the text: We have included the definitions of the abbreviations MSI-H, CT, EGD, PET within the abstract and main text.