

Re: Manuscript ID 78999

Title: Treatment of Monomorphic Epitheliotropic Intestinal T-cell lymphoma with surgical resection followed by CHOP regimen and stem-cell transplant: A case report

Name of Journal: World Journal of Gastrointestinal Oncology

### **Cover and Rebuttal letter**

Dear Editor,

On behalf of all co-authors, I express my sincerest gratitude for your time and response as well as the reviewers' insightful and suggestive comments on our manuscript. We would like to thank the reviewers for their positive assessment and we sincerely appreciate the time they have invested to improve our manuscript, and we have carefully read and considered all comments. We did not see any point we disagree with and will therefore largely follow the suggestions of the reviewers.

We have modified our manuscript in response to the extensive and suggestive reviewers' comments. A few points required some additional explanation to address the reviewers' comments, which is provided below. We sincerely hope that our revised manuscript will be considered for publication by World Journal of Gastrointestinal Oncology. Below, we will respond to each reviewers' comments point by point (the reviewers' comments are in italics)

Sincerely, on behalf of all authors

Linbo Wang

#### ***Reviewer #1:***

This is a nicely written case report, and the authors are to be congratulated on apparently achieving a good result despite an initial error in diagnosis that apparently delayed care and could have led to a disastrous complication.

- 1. Can the authors in retrospect offer any insights into how the diagnosis could / should have been made more expeditiously so that this delay could have been avoided? For instance (although the lymph node enlargement here seems to have been due to hyperplasia), is it not unusual to see lymph node enlargement in GIST? Should this have steered the treating clinicians away from a GIST diagnosis. What other insights can they offer?*

**Response:** Thanks for your very insightful comments and remarks. A biopsy could have prevented the delay of the diagnosis of such a poor prognosis disease entity; however, as GIST proved to be the most favorable diagnosis preoperatively based on the CT imaging

features (clear margin over 13cm in size), biopsy was avoided as applying biopsy in GISTs has been significantly associated with tumor bleeding and seeding. Therefore, further studies need to be warranted to differentiate GISTs from other Gastrointestinal malignancies.

Moreover, lymphadenopathy could have hinted towards a different diagnosis other than GIST, as the presence of lymphadenopathy is an important feature differentiating lymphoma from GIST. However, since all tumor markers including CEA were within normal range, GIST was considered as the most favorable diagnosis.

Other insights that can be considered is the geographical distribution of MEITL as well as the presenting symptoms; an Asian patient presenting with a rapidly growing tumor, abdominal pain, distension and rapid weight loss should alert physicians towards this alarming disease. As observed in our case, the tumor significantly enlarged in between 2 weeks

2. *It may not be necessary to show all of the images. For instance, since the PET scan was normal, do we really need to see all of it?*

**Response:** Thanks for your suggestion. As recommended, the PET scan (Figure 2) carried out in the previous year revealing no abnormalities was removed. The post-operative PET scan has been significantly cropped to demonstrate only the relevant outcome.

### ***Reviewer #2:***

Dear Authors, you have delivered a nice-written manuscript describing a rare type of T-cell intestinal Lymphoma. Please pay attention to the following points and provide your correspondence:

1. *Line 75: please correct us such: we report a case of MEITL (use an article, not a number).*

**Response:** Thank you for correcting the typo. As suggested, the following sentence was modified “**Case summary:** We report a case of MEITL...”

2. *Line 76: you may use the brand name GLEEVEC® after providing the medication name Imatinib.*

**Response:** Thank you for bringing it up. The brand name GLEEVEC® was replaced by the medication name Imatinib

3. *Line 157: please provide the reason for a PET/CT scan in the previous year. Did your patient have symptoms a longer time ago?*

**Response:** Thanks for your concerning remark. The PET/CT scan carried in the previous year was part of a routine health check-up. The patient only started experiencing symptoms 2 months prior to administration at our hospital.

4. *Table 2: CEA is the most common Marker if gastrointestinal malignancy is suspected. Did you measure CEA in your patient?*

**Response:** CEA was measured preoperatively in our patient and was within normal range. The value of CEA was added in the tumor markers' table (Table 2) in our manuscript. In addition, the value of CA19-9 was also added. Given that all tumor markers including CEA were within normal range, GIST was considered as the initial preoperative diagnosis.

5. *Line 214-219: the tumor has infiltrated several abdominal structures. I suppose that a multivisceral resection was obligatory in order to reject the tumor. Please provide a more detailed description of the surgery you conducted.*

**Response:** Thank you for pointing it out. Laparotomy was performed with an abdominal midline incision starting 5cm below the xiphoid process, extending until 8cm below the umbilicus, with a total length of about 20cm. Inflammatory adhesions were observed between the tumor and the mesentery of the small intestine and descending colon. Lysis of intestinal adhesions between the tumor and transverse mesentery, descending mesentery and intestinal wall were carried out carefully revealing the upper and outer edge of the tumor. Due to a large tumor scope and local inflammatory reaction caused by intestinal wall perforation, a step by step tumor resection was devised intraoperatively so as to guarantee a tumor-free operation. After sharp separation from the rear of the tumor, the tumor and the involved intestinal tube were turned inward. The relationship between the tumor, small intestine and involved mesentery were clear and the location of the superior mesenteric artery, superior mesenteric vein and inferior mesenteric artery were exposed. At approximately 10cm from the end of the ileum, the invaded mesentery was resected. The invaded and perforated intestinal tube, about 5cm in length, was resected along with the tumor. Intestinal anastomosis was performed to establish connection **between two formerly distant portions of the intestine**, thus restoring intestinal continuity. The length of the retrieved sample of small intestine was 53.5 cm and the size of the tumor was 15 x 14 x 10cm. The jejunum was surrounded by the tumor until the ileum. The total operative time was 335 minutes with an estimated blood loss of 100ml.

6. *Line 254-255: the enlarged lymph nodes were due to lymphoid hyperplasia rather than metastasis. The CT scan of abdomen cannot distinguish between the two entities. What were the pathology findings of the resected lymph nodes?*

**Response:** Thanks for the concerning remark. Numerous lymphoid follicles with germinal centers were observed in lamina propria.

7. *Line 332: if an immediate laparotomy is indicated please explain why you despite that*

*started a neoadjuvant treatment with Imatinib. Did you expect a tumor size reduction which would enable a more organ-protective operation?*

**Response:** Thanks for your very insightful comments. As GIST was considered as the preliminary diagnosis preoperatively, Imatinib was administered as it has been proven effective in the neoadjuvant treatment of GIST such as reduction in the size of the tumor, thus enabling a tumor free surgery and improving long term survival. The neoadjuvant use of Imatinib is recommended to facilitate resection and avoid mutilating surgery by decreasing tumor size

***Reviewer #3:***

*1. Can you say more about the surgery?*

**Response:** Thank you for bringing it up. Laparotomy was performed with an abdominal midline incision starting 5cm below the xiphoid process, extending until 8cm below the umbilicus, with a total length of about 20cm. Inflammatory adhesions were observed between the tumor and the mesentery of the small intestine and descending colon. Lysis of intestinal adhesions between the tumor and transverse mesentery, descending mesentery and intestinal wall were carried out carefully revealing the upper and outer edge of the tumor. Due to a large tumor scope and local inflammatory reaction caused by intestinal wall perforation, a step by step tumor resection was devised intraoperatively so as to guarantee a tumor-free operation. After sharp separation from the rear of the tumor, the tumor and the involved intestinal tube were turned inward. The relationship between the tumor, small intestine and involved mesentery were clear and the location of the superior mesenteric artery, superior mesenteric vein and inferior mesenteric artery were exposed. At approximately 10cm from the end of the ileum, the invaded mesentery was resected. The invaded and perforated intestinal tube, about 5cm in length, was resected along with the tumor. Intestinal anastomosis was performed to establish connection **between two formerly distant portions of the intestine**, thus restoring intestinal continuity. The length of the retrieved sample of small intestine was 53.5 cm and the size of the tumor was 15 x 14 x 10cm. The jejunum was surrounded by the tumor until the ileum. The total operative time was 335 minutes with an estimated blood loss of 100ml.

*2. I suggest selecting some PET-CT images and not show them all in reduced size.*

**Response:** Thank you for your remarkable suggestions. As suggested, the PET scan (Figure 2) carried out in the previous year revealing no abnormalities was removed. The post-operative PET scan has been cropped significantly to demonstrate only the relevant outcome.

*3. How did you exclude adenocarcinoma? Why treatment for GIST was the started if adenocarcinoma still a differential diagnosis? It seems difficult to differentiate by the image presented*

**Response:** Thank you for pointing it out. Adenocarcinoma was still considered as a differential diagnosis but GIST was favored over other malignancies based on the imaging features; CT revealed a significantly large tumor size with a clear margin over 13 cm in size without causing bowel obstruction. Given the location, size and appearance of the tumor on imaging features, GIST was initially considered. Moreover, given that all tumor markers including CEA were within normal range, GIST was favorably considered as the initial preoperative diagnosis. Thus, Imatinib was administered as it has been proven effective in the neoadjuvant treatment of GIST such as reduction in the size of the tumor, thus enabling a tumor free surgery and improving long term survival. The neoadjuvant use of Imatinib is recommended to facilitate resection and avoid mutilating surgery by decreasing tumor size

Based on the literature review we conducted, an interesting insight that could have hinted towards a different preliminary diagnosis other than GIST is lymphadenopathy.

A significant limitation in this study would be the use of endoscopic assisted biopsy; as GIST proved to be the most favorable diagnosis preoperatively based on the CT imaging features (clear margin over 13cm in size), biopsy was avoided as applying biopsy in GISTs has been significantly associated with tumor bleeding and seeding. Therefore, further studies need to be warranted to differentiate GISTs from other Gastrointestinal malignancies.