Author's response to reviews

Title: Leiomyosarcoma of sigmoid colon with multiple liver metastases and gastric cancer: case report

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Author's response to reviews: see over
We submit the revised version of the MS: 1024868892694604 entitled “Leiomyosarcoma of the sigmoid colon with multiple liver metastases and gastric cancer: A case report” by Hamai Y et al.

We performed additional immunohistochemical analyses for the gastric lesion and LMS (Figure 7), and added the description about the results in this manuscript. Furthermore, we have made point-by-point responses to the reviewer’s comments.

This manuscript was edited by the professional editing service “Edanz” according to editorial recommendation. Therefore, English in this manuscript was partially corrected by the native English editor. However, there is no change regarding the content of this manuscript.

Our responses are described in the attached sheets. We hope that this revised version will be satisfactorily suitable for publication in BMC Gastroenterology.

Sincerely,
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Responses to reviewer’s comments

Reviewer 1

1. As suggested by reviewer 1, we added the following sentences about the reason for the resection of liver metastasis after the diagnosis of colon LMS with liver metastases. (page 5, line 10 – page 5, lines 12);
   “This was because we considered that there might be only a limited chance of a good response to chemotherapy in the case of the LMS, and all of the liver metastases were also completely resectable.”

2. As suggested by reviewer 1, we added the following section about the possibility of a LMS-metastasis in the large bowel and liver from an LMS of the soft tissue. (page 6, lines 10 – page 6, lines 16);
   “Moreover, in the diagnosis of the present case, LMSs in both the liver and colon were possibly metastatic tumors that originated from primary LMS in another organ. Actually, LMS of the left thigh that metastasized to the liver, large bowel and lymph nodes has been reported [12]. However, in the present study, soft tissue tumor was not detected using periodically-performed CT and PET-CT scans in the course of treatment.”

Responses to reviewer’s comments

Reviewer 2

1. The reviewer 2 pointed out that the style of manuscript. We rewrote this manuscript in accordance with the overview of manuscript sections for case reports in your instructions for authors.

2. As suggested by the reviewer 2, we changed the sentence about pathological evaluation of chemotherapy response in gastric cancer. (page 2, line 11 – page 2, line 12) and (page 4, line 7 – page 4, line 9)
   “Pathological examination revealed that no viable tumor cells remained in the stomach and chemotherapy resulted in complete remission of the gastric cancer.”

3. As suggested by the reviewer 2, we reduced the key words to 5 words. (Abstract page);
   “Key words: leiomyosarcoma, gastric cancer, liver metastasis, surgery, chemotherapy”

4. As indicated by the reviewer 2, we changed the background and added the sentences to clearly state on why this report is being published.
Abstract page;

**Background:** Leiomyosarcoma of the gastrointestinal tract is an extremely rare high-grade neoplasm with poor prognosis. For advanced leiomyosarcoma with distant metastasis, the decision as to the choice of the most appropriate therapeutic strategy, including chemotherapy and surgery, is difficult. Here, we present an unusual case of leiomyosarcoma of the sigmoid colon with liver metastases and gastric cancer. The survival of this patient was prolonged by a combined modality therapy involving chemotherapy and surgery.

Unlike gastrointestinal stromal tumors (GIST) effective molecular therapy is not available for LMS. Thus, the decision regarding the selection of an optimal therapeutic strategy for advanced LMS with metastasis is difficult [1, 3].

5. As indicated by the reviewer 2, we added the patient's clinical features and relevant investigation in case presentation.

She was not a carrier of the hepatitis virus, or an alcoholic with previous hepatic disease. Furthermore, she did not have a family history of malignant neoplasia.

6. As indicated by the reviewer 2, we added the following sentence about the discovery of the sigmoid colon mass in case presentation.

Furthermore, a tumor-like mass in the sigmoid colon was incidentally discovered on CT scan and positron emission tomography/computed tomography (PET-CT) during this therapeutic process;

7. As indicated by the reviewer 2, we added the following words in case presentation.

“2 years and 5 months after the commencement of first-line chemotherapy”

8. As indicated by the reviewer 2, we added the following sentences about the effect of same chemotherapy for LMS and gastric cancer.

Only first line chemotherapy with docetaxel and S-1 was found to be effective against both the gastric cancer and LMS in our patient. The overall response rate of this regimen is reported to be 56.3% for gastric cancer [5]. It was considered that docetaxel, which is so frequently used and effective against both LMS and gastric cancer, could simultaneously reduce the size of these tumors.”
9. As indicated by the reviewer 2, we added the following sentences about the immunohistochemical analysis on tissues from the gastric lesion.

   (page 6, line 23 – page 7, line 3)
   “Furthermore, we recently performed additional immunohistochemical analyses for gastric lesions to distinguish them from LMS. The biopsy tissue of the gastric lesion was immunohistochemically negative for desmin, SMA and h-caldesmon, and positive for cytokeratin (AE1/AE3 and CAM5.2) (Figure 7B-F). The LMS and gastric lesions represented a completely different histological picture and immunohistochemical profiles. Thus, we could conclude that this case represents a combination of colonic LMS that metastasized to the liver and gastric cancer.”

10. As indicated by the reviewer 2, we added the following sentences about possible explanations on the simultaneous occurrence of 2 separate primary malignancies.

   (page 8, line 3 – page 8, line 11)
   “The tumorigenesis of gastric cancer and LMS has been reported to involve various factors [19-22]. Common factors, such as infection with the Epstein-Barr virus and molecular alterations in RASSF1A, were also indicated in the occurrence of these tumors [23, 24]. Furthermore, in an experimental model, simultaneous exposure to both nitrosoguanidine and acetylsalicylic acid caused synchronous development of both gastric cancer and LMS [25]. Intragastric application of N-methylnitrosourea also revealed increased susceptibility to chemical tumorigenesis of gastric cancer and sarcoma in p53 knockout mice [26]. In the present case, it is not clear if the association is a simple coincidental coexistence or if the two types of lesion are connected by a causal relationship that might involve a common aetiology and tumorigenic mechanisms.”

Responses to reviewer’s comments
Reviewer 3

1. As suggested by the reviewer 3, we used the abbreviation of LMS for leiomyosarcoma in abstract and text.

   (page 2, line 2 – page 2, line 3)

   **Background:** Leiomyosarcoma (LMS) of the gastrointestinal tract is an extremely rare high-grade neoplasm with poor prognosis.

   (page 3, line 2 – page 3, line 3)
   “Leiomyosarcoma (LMS) of the gastrointestinal (GI) tract is extremely rare, and only a few reports have been published in reviews of GI mesenchymal tumors [1, 2].”
2. As suggested by the reviewer 3, we added the following sentences about the number of mitoses in LMS specimens.

(page 4, line 10 – page 4, line 11)
“Furthermore, an average of 20 mitoses per 10 high power fields was observed in the liver tumors, which were diagnosed as being LMS with high mitotic activity.”

3. As suggested by the reviewer 3, we changed the indicated sentences in case presentation.

(page 4, line 12 – page 4, line 16)
“Until that point, we considered that the liver tumors were metastases that had developed from the gastric cancer. However, the histological type of the liver tumors was LMS and not adenocarcinoma. Thus, we had to assume that the liver LMSs were primary tumors that developed from liver or metastatic tumors from an unknown primary LMS.”

4. As suggested by the reviewer 3, we changed the indicated sentences in conclusions.

(page 6, line 1 – page 6, line 3)
“The barium enema and CT scan did not detect LMS of the sigmoid colon in our patient at the first admission. This was because the intramural tumor was probably very small and hidden in the colonic wall.”

5. As suggested by the reviewer 3, we performed additional immunohistochemical analyses of LMS by vimentin (Figure 7), and added the following sentences about immunohistochemical analysis for a definitive diagnosis of LMS.

(page 6, line 5 – page 5, line 9)
“Furthermore, the specimens were also positive for vimentin in additional immunohistochemical analysis (Figure 7A). This combination of highly-specific immunohistochemical findings provided a definitive diagnosis of colon LMS and multiple liver metastases.”

6. As suggested by the reviewer 3, we added the following sentences about the rationale regarding indication for surgical resection.

(page 7, line 26 – page 8, line 1)
“This was because of the fact that these factors would have pointed to a decreased probability of complete resection being achievable.”

7. As suggested about language in this manuscript by the reviewer 3 and editorial office, this manuscript was edited by the professional editing service “Edanz” recommended by editorial office.