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Title: Gastrointestinal stromal tumor of the stomach with axillary lymph node metastasis: a case report

Author Name: Kubo Naoki

Gastrointestinal stromal tumor of the stomach with axillary lymph node metastasis: a case report

Naoki Kubo, Nobumichi Takeuchi

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Dr. Lian-Sheng Ma

Editor World Journal of Gastroenterology

Dear Dr. Lian-Sheng

We are very grateful to you and the reviewers for your helpful comments on the original version of our manuscript and useful suggestions that have helped us to improve our paper considerably. As indicated in the responses that follow, we have addressed all the comments made by reviewers, and have taken their suggestions into account in the revised version.

Comments reviewed by 03025589

Major comment (1-5)

1. You concluded that imatinib was not effective in consecutive controlling the primary gastric lesion and resection should be considered in similar cases. However, I don't think that the case report leads to this conclusion because it is only one case report and the appropriate therapy for GIST with lymph node metastasis remains controversial. Please reconsider the conclusion more suitably.

Response

In accordance with the reviewer suggestions, we changed the following new sentence in Conclusion.

Revised; p 8 line 4-9

In conclusion, the axillary lymph nodes can be a site of GIST metastasis, and imatinib chemotherapy may be useful for controlling distant lymph node metastasis from GIST. Although we performed a resection for the original lesion because the distant metastasis had been controlled by imatinib, the appropriate therapy for GIST with distant metastasis remains controversial. Further studies are needed to clarify the duration of chemotherapy and an appropriate surgical intervention that will be effective for treating distant lymph node metastasis.

2. It is important to estimate the re-appraisal of risk classifications for GIST. Please describe the histopathological examination of primary biopsy and surgical resection of GIST and risk classification such as mitotic index and modified Fletcher classification. 5 line 8. How did you follow up the patient? Please add more clear information.

Response

In accordance with the reviewers suggestions, we added the following new sentence .

Revised; p 4 line 13

The mitotic index was 5/50 in high-power field and the MIB-1 labeling index was 10%.

Revised; p 4 line 19-20

the mitotic index was 15/50 in high-power field and the MIB-1 labeling index was 10%.

Revised; p 5 line 8-9

; the mitotic index was 20/50 in high-power field and the MIB-1 labeling index was 30%.

3. In this case report, the patient was treated by adjuvant chemotherapy; imatinib, regorafenib, and sunitinib in the order. However, it seems to be an unconventional method. Please discuss in more detail.

Response

It reported that GIST responsiveness to sunitinib varies by KIT genotype; exon 9-mutant or wild-type GISTs are more sensitive than exon 11-mutant in imatinib –resistant or –intolerant GIST(Heinrich et. J Clin Oncol 2008;26:5352-5359). Gene sequence analysis of our patient showed KIT exon 11 mutation. So we attempted to treat using regorafenib over sunitinib after therapy of imatinib. But the liver metastasis increased 2 months later, and we started treatment using sunitinib because we had no choice.

We changed the following new sentence.

Revised; p5 line10-12

However, liver metastases appeared after 13 months of treatment using imatinib, which we attempted to treat using regorafenib because gene sequence analysis of the tumor showed a KIT exon 11 mutation.

4. You mentioned that "the 6-month follow-up revealed rapid response in the primary lesion" in page 5 line 8. How did you follow up the patient? Please add more clear information.

Response

For a year since we started imatinib ,we followed up by every three month CT and every six month PET. We added the following new sentence .

Revised; p 4 line20 -p5 line 3

Based on these findings, we started treatment using oral imatinib (400mg/day) and in the next year, after starting imatinib, we followed up the patient every 3 months by using CT and every 6 months by

using PET. The 6-month follow-up revealed rapid response in the primary lesion and complete remission in the mediastinal lymph nodes.

5. You mentioned that " gastroscopy revealed a large tumor with ulceration in the upper stomach body" in page 4 line17. To understand more clearly, please add the endoscopic pictures of the lesion.

Response

We added the endoscopic pictures of the lesion as Figure 1.

Minor comment (1-2)

1. There seems to be some references in the wrong position. Please check again carefully.

Response

We added some reference and corrected the position of some references additionally.

2. English editing should be sought.

Response

We performed English editing again.

Comments reviewed by 03505493

Major comment (1-4)

1. Please give the pathological data complete of the metastatic lymph node: size, diameter of the metastasis, presence or absence of extranodal extension, mitosis in the metastasis in relationship with the primary (more, less, whatever?)

Response

In accordance with the reviewer suggestions, we added the following new sentence.

Revised; p 4 line 13

The mitotic index was 5/50 in high-power field and the MIB-1 labeling index was 10%.

Revised; p 4 line 17-20

The specimen was 1.4 cm in diameter, and there was no extranodal extension, it exhibited monotonous spindle cells (Figure 3A) and was diagnosed as a metastasis of the GIST, because it exhibited positive immunohistochemical staining for c-kit(Figure 3E) and DOG1 (Figure 3F), the mitotic index was 15/50 in high-power field and the MIB-1 labeling index was 10%.

Revised; p 5 line 8-9

; the mitotic index was 20/50 in high-power field and the MIB-1 labeling index was 30%.

2. In the figure please remove CD34: it is not specific for GIST, you can replace it with other marker more specific as DOG1.

Response

In accordance with the reviewer suggestions, in the figure 3 we removed CD34 and replaced it with DOG1

3. In the same figure, please show that it is a lymph node...I see only tumor, no lymph node, please give also a photograph with lower magnification

Response

In accordance with the reviewer suggestions, we added photograph in the figure 3 and changed the following new sentence

Figure3. Pathological findings of the biopsied left axilla lymph node. Analysis of the tumor revealed tunicate formation and the survival of lymphoid tissue ((A) hematoxylin and eosin staining, (B) silver impregnation, and (C) Leukocyte common antigen (LCA) (magnification: ×40)). (D) The tumor exhibited monotonous spindle cells (hematoxylin and eosin staining), and the cells were positive for (E) c-kit and (F) DOG1 (magnification: ×100).

4. please discuss more in depth the staging for metastatic GIST: a metastasis in a regional lymph node (gastric) is so different from an axillary metastatic lymph node, different in the prognosis, different in the staging? please discuss this point.

Response

In accordance with the reviewer suggestions, , we added the following new sentence.

Revised; p 6 line 17- p7 line 4

Tumor size, location, mitotic rate, and C-KIT and PDGFRA genotype are the major determinants of the malignant potential of the tumor, and have significant impact on prognosis [11].In the TNM (tumor-node-metastasis) system for GISTs, the presences of lymph node metastasis is classified as stage IV, which generally portends a poor prognosis, but cases with long-term survival have also been reported [5.12]. Valadao reported that lymph node metastasis is not related to poor prognosis; however, the study included a small number of patients [13]. Furthermore, it is unclear whether there is a difference of prognosis according to the site of lymph node metastasis, because reports of distant lymph node metastasis are very rare.

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

Sincerely yours,

Naoki Kubo M.D

Department of Surgery, Department of surgery, Ina central hospital, 1313-1, koshiroukubo, Inashi, Nagano 396-8555, Japan.

Phone number: +81 265 72 3121

Fax number: +81 265 78 2248

E-mail: nkazumihp@yahoo.co.jp