Format for ANSWERING REVIEWERS

8th of July 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3614-Review.doc).

Title: A rare case of primary choriocarcinoma in the sigmoid colon

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Name of Journal: *World Journal of Gastroenterology*

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We reviewed recent published case report and found a new one. We also included this latest case in this manuscript.
The revised parts were underlined in the manuscript.
The manuscript has been improved according to the suggestions of reviewers:

Major

1. Generally, the effect of chemotherapy for choriocarcinoma from placenta is reported to be high. Why is the prognosis of colorectal choriocarcinoma poor even if chemotherapy was performed? The authors should discuss this point.

(Answer) Choriocarcinoma is the most common malignant form of gestational trophoblastic neoplasia (GTN). The standard chemotherapeutic regimen for GTN is EMA/CO (a combination of etoposide, methotrexate, and dactinomycin, alternating with cyclophosphamide and vincristine). EMA/CO is reported to have a 60–90.6% complete remission rate and an 86.2% 5-year overall survival (OS) (Lancet Oncol 2007; 8: 715–24). However, the prognosis of choriocarcinoma from clorerectal origin is extremely poor as shown in this case report (median survival period without systemic chemotherapy: 1.0 months vs. with systemic chemotherapy: 9 months). The response of colorectal choriocarcinoma to chemotherapy is much worse than that of choriocarcinoma derived from germ cells. The cause of this difference in chemosensitivities is still unknown. It is known that the colorectal choriocarcinoma cells undergo a syncytiotrophoblastic differentiation through retrodifferentiation or metaplasia of the adenocarcinoma component, rather than originating directly from ectopic germ cells. Therefore, it is possible that the differences in chemosensitivities may be associated with the origin of carcinoma cells. We discussed these points in the Discussion (Page7, line4-17).

2. The standard chemotherapy of choriocarcinoma is EMA/CO therapy. The authors should explain why they did not check the in vitro sensitivity of etoposide, methotrexate, and actinomycin-D.

(Answer) The standard chemotherapeutic regimen for GTN is EMA/CO (a combination of etoposide, methotrexate, and dactinomycin, alternating with cyclophosphamide and vincristine) (Lancet Oncol 2007; 8: 715–24). The preoperative diagnosis was poorly differentiated adenocarcinoma in sigmoid colon cancer; therefore the anti-tumor drugs were examined routinely. Unfortunately, the cell culture was not maintained long enough for additional examination of anti-tumor drugs for the EMA/CO regimen after results of immunohistochemical staining was obtained. We have also regretted this point. We added these points in the Discussion (Page8, line24-Page9, line2).

3. The therapeutic effect for this patient seems to be disappointing compared with a result of CD-DST. The authors should compare colorectal choriocarcinoma with common colorectal adenocarcinoma about effects of chemotherapy based on CD-DST.

(Answer) Our study demonstrates that patients with synchronous stage IV colorectal cancer who were treated with tumor-sensitive chemotherapeutics as evidenced by CD-DST testing had higher response rates (85.71%) than those in patients with drugs that CD-DST testing did not identify as tumor-sensitive (41.67%). Moreover, progression-free

survival (PFS) and OS were superior in patients treated with in vitro sensitive drugs by CD-DST (median PFS, 696.5 days vs. 297.5 days; median OS, 1023.4 days vs. 518.5 days) (Cancer Chemother Pharmacol. 2013 in press; PMID: 23728705). Although the best regimen according to the results of CD-DST suppressed rapid progression of choriocarcinoma in this case, the therapeutic effect for this patient is not remarkable compared with our previous findings of CD-DST in common colorectal adenocarcinoma. We could not evaluate hepatic metastatic lesions with CD-DST in this case. It is possible that the chemosensitivity of the hepatic metastasis may be different from that of the primary lesion. Therefore, we mentioned about these points in our revised manuscript (Page8, line18-Page9, line7). Moreover, we revised our conclusion regarding CD-DST. Since the best regimen according to results of CD-DST suppressed rapid progression of choriocarcinoma in this case, CD-DST may provide at least in part therapeutic insight for the selection of appropriate antitumor agents that may be effective for treating patients with colonic choriocarcinoma on an individual basis.

Minor

1. In discussion, the description of quoted references is too long (Tokisue et al ….., Harada et al…….., Verbeek et al…….). The authors should make more concise about these sentences.

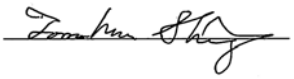
(Answer) We revised and shorten our Discussion according to comments of major point.

2. Is macroscopic appearance of colorectal choriocarcinoma different from conventional colorectal adenocarcinoma? The author should show the pictures of colonoscopy and barium enema.

(Answer) Thank you for your suggestion. We added the pictures of colonoscopy and barium enema as Figure 1.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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