Responses to the Associate Editor's and Reviewers' Comments

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Dear reviewers and editorial staffs in *World Journal of Clinical Cases*

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Title: Successful treatment of retroperitoneal choriocarcinoma with widespread metastases using EMA-CO: Case report

Authors: Jina Yun, Sangwook Lee, Sung Hee Lim, Se Hyung Kim, Chan Kyu Kim and Seong Kyu Park

We would like to thank you for the thoughtful guidance from you and the reviewers. We are really grateful for the detailed comments and excellent suggestions we have received and these made a much better paper. According to reviewers' comments, we have revised our manuscript entitled "Successful treatment of retroperitoneal choriocarcinoma with widespread metastases using EMA-CO: Case report". Below we provide a point-to-point response to each of the comments. The changes within the revised manuscript were highlighted (underlined and in blue). Point-by-point responses to the reviewers' comments are provided below.

Reviewer #1 :

<MAJOR COMMENTS>

1) Reviewer's comment: Nonseminomatous germ cell tumor of the testis (NSGCT) including those with a burnt-out primary and mixed choriocarcinoma has a high cure rate. In many respect, a chemo-sensitive tumor being cured with an effective but not commonly used regimen, such as EMA-CO, is not unexpected. Personally, this manuscript merits acceptance for publication with major revisions based on the finding that a seldomly used regimen is

curative in a high-risk NSGCT.

Final diagnosis, primary RP choriocarcinoma, p6: Need to correct all reiterated erroneous statements that this reported case is a retroperitoneal choriocarcinoma in the title, abstract, and text. According to Abell et al (1965), the criteria for a diagnosis of primary extragonadal GCT include “the lesion is located high in the retroperitoneum with adjacent lymph node involvement but without involvement of the lower aortic, iliac, or pelvic lymph nodes.” This patient has his retroperitoneal mass below the renal hilum on the left side corresponding to the landing zone of his left primary burnt-out GCT. Therefore, by definition, this case is not an extragonadal primary retroperitoneal choriocarcinoma. Abell MR, fayos JV, Lampe I. Retroperitoneal germinomas (seminomas) without evidence of testicular involvement. Cancer 1965;18273-90.

Author’s response: As you recommended, we changed “retroperitoneal choriocarcinoma with widespread metastases” to “a high-risk nonseminomatous germ cell tumor” in the title.

We changed “primary retroperitoneal choriocarcinoma with liver and lung metastases” to “a burnt-out primary germ cell tumors (GCT) with retroperitoneum, liver and lung metastases” in the abstract. (Abstract, Case summary, line 1, p3)

We changed “retroperitoneal male choriocarcinoma” to “a high-risk NSGCT in male” and “retroperitoneal choriocarcinoma” to “a high-risk NSGCT” in the abstract. (Abstract, Conclusion, line 1 and 3, p3)

We changed “retroperitoneal choriocarcinoma with widespread metastases” to “high-risk NSGCT” in the core tip. (Core tip. Line 5, p4)

We changed “primary retroperitoneal” to “burnt-out” and added “retroperitoneum” in the Final diagnosis. (Case presentation, Final diagnosis, p6).

2) Reviewer’s comment: First 3 references relate to poor prognosis of extragonadal GCTs. They do not apply to a burnt-out primary GCT. Again, the sensitivity of an extragonadal choriocarcinoma may be dependent on the chemosensitivity of the primary malignancy. For example, urothelial cancer is relatively chemosensitive. Hence, urothelial carcinoma with choriocarcinomatous differentiation is potentially curable with chemotherapy. Msaouel P,

Zhang M, Tu SM. Prolonged remission of upper urinary tract urothelial carcinoma with prominent choriocarcinomatous differentiation: a case report. Clin Genitourin Cancer 2017;15:e73-77.

Author's response: We appreciate the reviewer's comment. As you recommended, we deleted first 3 references and added two sentences; "However, pure choriocarcinoma of the testis with serum β-HCG > 50,000mIU/mL and with nonpulmonary visceral metastases accounts for the relatively poor prognosis. These patients require early aggressive treatment to improve their chance of survival." (Introduction, line 6, p5)

Changed 3 references below:

1. International Germ Cell Cancer Collaborative Group, International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol, 1997. 15(2): p. 594-603.

2. Reilley, M.J. and L.C. Pagliaro, Testicular choriocarcinoma: a rare variant that requires a unique treatment approach. Curr Oncol Rep, 2015. 17(2): p. 2.

3. Einhorn, L.H., et al., High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med, 2007. 357(4): p. 340-8.

3) Reviewer's comment: Abstract, Background, line 2: Statement that choriocarcinoma has "inherent" resistance is erroneous. According to Tu et al (2016), all 4 patients with burnt-out primary NSGCT were cured, but all 3 patients with pure primary choriocarcinoma died. Importantly, a majority of patients with high-risk clinical stage IIIC mixed choriocarcinoma did not have pure choriocarcinoma and their cure rate was >70%. Tu SM, Bilen MA, Hess KR, et al. Intratumoral heterogeneity: Role of differentiation in a potentially lethal phenotype of testicular cancer. Cancer 2016; 122:1836-43

Author's response: We appreciate the reviewer's comment. As you recommended, we changed "inherent resistance to anticancer drugs" to "rapid disease progression" in the Abstract. (Abstract, Background, line 2)

4) Reviewer's comment: One should mention that the 3-yr OS was 75% for poor-prognosis group using a regimen comprising cyclical POMB/ACE is similar and expected to be comparable to EMA-CO with respect to efficacy. Bower M, Newlands ES, Holden L, et al. Treatment of men with metastatic non-seminomatous germ cell tumours with cyclical POMB/ACE chemotherapy. Ann Oncol 1997;8:477-83.

Author's response: As you recommended, we mentioned "Bower et al[17] showed that cyclical POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide) regimen appears to be better than conventional BEP chemotherapy in poor prognosis NSGCT patients. The 3-yr OS was 75% for the poor-prognosis group using POMB/ACE regimen. Because EMA-CO and POMB/ACE regimens are similar, we expected EMA-CO to have comparable efficacy to POMB/ACE." in the Discussion. (Discussion, last paragraph, p9)

5) Reviewer's comment: An important observation about this patient that deserves a discussion is the fact that his HCG never become normal after EMA-CO and he received 8 cycles of treatment. One question that should have been asked: might he have been cured with BEP x4 as he would have been with the standard of care for high risk NSGCT (S3 disease)? After all, his HCG was already down to 3,000s after BEP x2, before the treatment was switched to EMA-CO. In other words, did he really need EMA-CO x8 to be cured? His HCG started to taper after EMA-CO x2-3. The lingering HCG suggests sequestration or entrapment of HCG in necrotic tumor, which the pathology from surgery confirmed. Mohler JL, Siami PF, Flanigan RC. False positive beta-human chorionic gonadotropin in testicular cancer. Urology. 1987;30(3):252-254.

Author's response: I totally agree with what you pointed out. As you recommended, we added the phrase;

"After two cycles of BEP, the anticancer drug of this patient was changed to EMA-CO regimen, and of course, there is an issue on whether it was adequtate to change the anticancer drug because β-HCG decreased from 317,449 mIU/mL to 3,354 mIU/mL. However, the size of the nonpulmonary visceral metastatic sites, liver metastatic masses increased and new

lesions were found, so anticancer drugs were forced to be changed. It still remains to be seen whether the response would have been different with the continued treatment of BEP regimen.

Another question that kept arising while treating this patient was the consideration of the appropriate duration of EMA-CO chemotherapy treatment. After 6 cycles of EMA-CO, pulmonary metastasis was not seen in CT and was subsequently determined to be resectable. However, β-HCG was still high at 164 mIU/mL. When two more cycles of EMA-CO chemotherapy were added and the residual masses were completely removed, the β-HCG fell to 8.1 mIU/mL. Then, a month later, it reached normal level. Mohler et al[15] suggested that phagocytosis of necrotic tumor apparently released entrapped β-HCG resulting in a false positive tumor marker. The pathological examination of mass removed in this case also confirmed all necrotic lesions. When we additionally stained the necrotic tissue, the β-HCG was strongly stained. The lingering HCG is thought to have been sequestration or entrapment in the necrotic tumor." In the Discussion. (Discussion, p8-9)

6) Reviewer's comment: Page 7, paragrapg 2, Last two sentences: Need to correct erroneous statement, "retroperitoneal mass is too huge to say that this is metastasis." It is common to have a burnt-out primary GCT and a humangous RP mass, especially for seminomas. Because choriocarcinoma tends to be fulminant and systemic, having a large RP mass actually suggests that this case is more compatible with a primary mixed choriocarcinoma rather than a primary retrioperitoneal choriocarcinoma, which former of which entails a better prognosis as mentioned in #3 above.

Author's response: As you recommended, we added the phrase "According to Abell *et al* (1965)[10], the criteria for a diagnosis of primary extragonadal GCT include that the lesion is located high in the retroperitoneum with adjacent lymph node involvement but without involvement of the lower aortic, iliac, or pelvic lymph nodes. In this case, the patient has his retroperitoneal mass below the renal hilum on the left side corresponding to the landing zone of his left primary burnt-out GCT. Therefore, by definition, we diagnosed the burned-out testicular choriocarcinoma with retroperitoneum, liver and lung metastases, and not as an extragonadal primary retroperitoneal choriocarcinoma." which you quoted to the Discussion, p8.

AND we deleted the phrase “In this case, we also cannot clearly distinguish the primary retroperitoneal choriocarcinoma of the lung and liver metastasis from burned-out testicular choriocarcinoma with metastasis. Nevertheless, retroperitoneal tumor mass is too huge to say that this is metastasis.” In the Discussion. (Discussion, line 23, p7)

<MINOR COMMENTS>

7) Reviewer’s comment: Abstract, Case summary, line 4, p3: progressive disease suggests that after BEP x2 HCG should continue to increase (in fact it sharply decreased indicating favorable response) and the RP mass should increase in size (which was not the case). A more accurate and appropriate statement would be a mixed response.

Author’s response: As you recommended, we changed the “progressive disease” to “mixed response”. (Abstract, Case summary, line 4, p3)

8) Reviewer’s comment: History of past illness, page 5: change “free previous” medical history to “unremarkable past” medical history.

Author’s response: As you recommended, we changed the “free previous” medical history to “unremarkable past” medical history. (History of past illness, page 5)

We really appreciate your comments about our study, and wish our manuscript could be accepted for publication.

Sincerely,

Seong Kyu Park, MD, Professor, Division of Hematology-Oncology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University School of Medicine, 170 Jomaru-ro, Bucheon 14584, Korea

E-mail: skpark@schmc.ac.kr

Telephone: 82-32-621-5185

Fax: 82-32-322-1773