

## PEER-REVIEW REPORT

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

**Reviewer's code:** 01746337

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

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. Major comments: 1. 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. 2. 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. 3. 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 4. 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. 5. 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. 6. Page 7, paragraph 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



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of which entails a better prognosis as mentioned in #3 above. Minor comments: 7. 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. 8. History of past illness, page 5: change “free previous” medical history to “unremarkable past” medical history.