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June 28, 2016

Shui Qiu
Scientific editor
Xue-Mei Gong
Science editor

World Journal of Clinical Oncology

RE: Manuscript No.:26628

Dear Shui Qiu and Xue-Mei Gong

Thank you very much for your kind letter of 12 June, 2016 with regard to our manuscript entitled " Granulocyte colony-stimulating factor-producing hepatocellular carcinoma with abrupt changes ” (No.:26628) together with the comments from the reviewers. The comments of the reviewers have been helpful in allowing us to revise our manuscript. We have studied these comments carefully and have made the corrections requested.

Our incorporation of the reviewers’ suggestions is as follows:

Comments from Reviewer 00068723:
Comment 1:
How did the author speculate that G-CSF was produced by HCC?

Reply:
We just got the idea that G-CSF was produced by HCC by investigating the histological findings. According to the histological findings, huge amount of neutrophils infiltrated to the tumor tissue. It’s the reason to have the hypothesis.

Comment 2:
How was the authors prompted to analyze G-CSF with the patient's blood sample?

Reply:
After looking up the histological findings, we decided to analyze G-CSF. Once we checked G-CSF using pre-operative blood samples, we found that the G-CSF level was higher than that of normal range. So we decided to follow up the blood G-CSF level

Comment 3:
White blood cells infiltrated to the HCC tissue. Was there any possibility that bacterial infection was complicated?
The authors concluded that G-CSF was produced by HCC. Was there any possibility that bacterial infection complicated with HCC, and G-CSF elevated?

Reply:
We thank the reviewer for this very important comment.
In accordance with the reviewer commented, we had to consider bacterial infection. In our case, we first consider this case as HCC with bacterial infection. But we ruled out bacterial infection from the aspect of same result below.
1, although we used wide spectrum antibiotics therapy when the patient got high fever before operation, it was not effective at all.
2, just after resected the specimen, we sent fluid inside the tumor to a laboratory for culture. But the result was completely negative.

Comment 4:
How do the authors recommend that clinicians suspect of HCC producing G-CSF? This point would add more value to this article at the last part of Discussion.

Reply:
We appreciate reviewer's comment. We think clinicians had better to perform further examination like CT scan, MRI and PET-CT to the patient who have treatment-resistant high fever with hyperleukocytosis.

If the imaging test for the patient shows liver tumor with atypical features, clinicians suspect of G-CSF producing HCC.

Comment 5:
It would be better to present blood test variables in tables with normal ranges. For example, G-CSF was above normal levels. If normal range of G-CSF was available, the readers could compare the patient's G-SCF with normal range.

Reply:
We added the normal ranges to the tables.

Comment 6:
Figure 3. Scale bars are missing.

Reply:
We added the scale bars in the Figure 3.

Comments from Reviewer 03253495:
Comment 1:
I strongly suggest to add in Introduction a brief description of HCC carcinogenesis (in order to provide the reader with a proper molecular background of the topic). In this regard, please cite the following three recent papers: 1) Facciorusso A, Antonino M, Del Prete V, Neve V, Scavo MP, Barone M. Are hematopoietic stem cells involved in hepatocarcinogenesis? Hepatobiliary Surg Nutr. 2014 Aug;3(4):199-206. 2) Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. J Hepatol. 2016 Apr;64(1 Suppl):S84-S101. doi: 10.1016/j.jhep.2016.02.021. Review. 3) Facciorusso A, Villani R, Bellanti F, Mitarotonda D, Vendemiale G, Serviddio G. Mitochondrial Signaling And Hepatocellular Carcinoma: Molecular Mechanisms And Therapeutic Implications. Curr Pharm Des. 2016 Feb 9. [Epub ahead of print]

Reply:
Thank you for the detailed comment.
We add a brief description of HCC carcinogenesis in the introduction citing

recommended papers.

Comments from Reviewer 03488616:
Comment 1:
The authors detailed many aspects of this case in his report, however, the causative factor for this type of HCC was not mentioned

Reply:
As the reviewer commented, the causative factor for G-CSF producing HCC has remained unclear. Further basic studies are required in order to shed light on the carcinogenesis of G-CSF producing HCC.

Comment 2:
The authors demonstrated WBCs, neutrophils count and CRP levels in figure 2 b, however, there is no figure demonstrating serum levels of G-CSF at admission, pre and postoperatively.

Reply:
We added a table demonstrating serum levels of G-CSF as figure 2C.

Comments from Reviewer 00722050:
Comment 1:
I would suggest to stress more on the FUO. This is key, i.e. more physicians should include this kind of tumors in the differential diagnosis of FUO. FUO: Fever of Unknown Origin.

Reply:
We strongly appreciate the reviewer's comment on this point. We added the description about FUO in the discussion part of the manuscript.

The detailed review of this manuscript is appreciated and I believe the manuscript has been improved satisfactorily. I hope it will now be accepted as a Regular Article for publication in *World Journal of Clinical Oncology*.