

List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Paraneoplastic Leukemoid reaction in a Patient with Sarcomatoid Hepatocellular Carcinoma: A Case Report." (ID:45502). Those comments of you are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our case report. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewers' comments are as following:

1. Responses to reviewer#1

(1). Comment: Your references need work and should be standardized. Some are appropriately abbreviated. Others not. References 1, 17–20, 24, 26, and 27 include the issue (month). The rest do not. References 5 and 7 have misspellings. Reference 16 is incomplete.

Response: We are very sorry for our negligence of the format and spelling of the references, the errors listed above has been corrected. In addition, we have added Pubmed citation numbers and DOI citation to reference list as required. All authors have been listed too.

(2). Comment: Your images could be improved. Specifically Figures 1D and 4 should be submitted with higher magnification to support your description.

Response: Figures 1D and 4 has been modified as require.

- (3). Comment: There are multiple grammar issues that should be addressed by a native English speaker to include the appropriate verb tense in a sentence. Other examples include: 1) Poisoned = toxic granules, p.5; 2) characterized by lower levels of bilirubin, p.9.

Response: We are very sorry for our grammar issues in this paper and we have sent the article to the designated institution for language modification and retouching as required by the magazine. In addition, we have asked several colleagues who are skilled authors of English language papers to check the English. We hope that the language is now acceptable for the next review process. Specially, "poisoned granules" has been modified to "toxic granules".

- (4). Comment: What was the course of patient death?

Response: We are very sorry that the family members of the patient did not cooperate with the follow-up work after discharge, so we are unable to know the specific circumstances of the patient's death. We tried to communicate with the patient's family many times, but still did not get the ideal response. We have made a brief description of this situation in the follow-up column.

- (5). Comment: Please discuss Reference #1.

Response: Considering the reviewer's suggestion, we have briefly discussed Reference #1, see page 8 for details.

2. Responses to reviewer #3

- (1). Comment: "Sarcomatoid hepatocellular carcinoma (SHC) is a rare histological subtype of hepatocellular carcinoma (HCC), with largely unclear clinical manifestations and outcomes". "Largely unclear" is not a good characterization of clinical manifestations and outcomes. These observations may be "variable", "nonspecific", "incompletely described", and a number of other things, but they should be clear to the physician, otherwise the physician's report would be unreliable. Please rephrase your text to make the reader know whether the difficulty is due to the peculiarities of these observations, to the small number of cases reported, or to limitations in diagnostic resources (equipment, tests, and so on).

Response: It is really true as reviewer #3 suggested that "largely unclear" should be replaced with "variable", "nonspecific" or "incompletely described", and after careful consideration we decided to change it to "incompletely described" in order to reflect the small sample size of this type of liver cancer and its clinical manifestations have not been fully known to clinicians.

- (2). Comment: "Generally, the less pronounced paraneoplastic leukemoid reaction (PLR) is much more frequent and is not accompanied by the

increased serum levels of other inflammatory markers and shows no response to antibiotic therapy". I suggest to rewrite it as follows, to make it easier to understand: "The most common presentation of the paraneoplastic leukemoid reaction is less severe and lacks increases in levels of inflammatory markers. It shows no response to antibiotic therapy".

Response: We strongly agree with the reviewer's revision of this part and we have re-written this part according to the reviewer's suggestion, see page 3 for details.

- (3). Comment: "Typically, the hepatocellular markers were negative in the malignant spindle cell component, whereas CK and vimentin were positive in most SCC patients[8,9]. SHC is distinct from nonsarcomatoid liver cancer; however, the former is still likely to be misdiagnosed as intrahepatic cholangiocarcinoma (IHCC)". CK should be defined at the first mention. Also, I suggest to rephrase the second sentence as: SHC is distinct from nonsarcomatoid liver cancer. However, it can be confused with as intrahepatic cholangiocarcinoma (IHCC), making differential diagnosis necessary"

Response: We are very sorry for our negligence of this and the word "CK" has been defined as "creatin kinase" in page 4 line 1. In addition, the second sentence has been rephrased as the reviewer's require.

(4). Comment: "Laboratory examination suggested a white blood cell (WBC) count of 43,790/ μ L, with 87.1% neutrophils, hemoglobin of 12.7 g/dL, platelet of 36,200/mm³, total bilirubin of 0.12 mg/dL, direct bilirubin of 0.05 mg/dL, albumin of 3.7 g/dL, aspartate aminotransferase of 18U/L, and alanine aminotransferase of 22U/L. Subsequently, the patient developed fever of 38.6 °C, which did not subside after antibiotic infusion, and her blood WBC levels were not significantly declined". Laboratory examinations do not "suggest" numeric values. The correct term is "determined", or "showed". Also, WBC are not "declined", but can be diminished, reduced, or lowered.

Response: We are very sorry for the wrong application of the word "suggested " and it has been changed to "showed". Meanwhile , the word "declined" has been changed to "lowed".

(5). Comment: "The results of the bone marrow examination showed that the proportion of granulocyte-neutrophil nucleated cells was increased by 40%, and poisoned granules could be observed (Fig. 1)". Granules cannot be "poisoned", but they can result from exposure of the organism to poisons as well as other toxicants. I suggest to use the term "toxic granulations", which is used in pathology.

Response: We agree the reviewer's good advice. The word "poisoned" has been corrected to "toxic".

(6). Comment: "Computed tomography (CT) revealed a 9.3-cm focal hepatic mass in the left lobe of the liver, along with dilatation of the intrahepatic bile duct (Fig. 2)". The proper term is computerized tomography.

Response: It is really true as the reviewer suggested that the term "Computed tomography" should be changed to "computerized tomography". Thus, we have made corrections according to the reviewer's good instructions.

(7). Comment: "Postoperative pathology examination had revealed that the poorly differentiated malignant cells were positive for CD34, Vimentin, EMA and CK7, while negative for CK19 (Fig. 4), which was suggestive of SHC". EMA, CK7 and CK19 should be defined at first mention.

Response: We are very sorry for our negligence of these. We have changed "EMA" to "human epithelial membrane antigen", "CK7" to "cytokeratin 7", and "CK19" to "cytokeratin 19".

(8). Comment: "Caption to Figure 1. Bone marrow smears(A, B, C) showed that hyperplasia was extremely active, the proportion of granulocyte-neutrophil nucleus cells increased, and most of the granulocytes were coarse and numerous". A granulocyte may contain coarse granules and these may be numerous. These attributes are those of the granules, not the cells.

Response: Considering the reviewer's good instruction, we have changed the subject to "granules".

- (9). Comment: "Computed tomography showed a 9.3-cm focal hepatic mass in the left lobe of the liver and dilatation of intrahepatic bile duct, as indicated by the arrow. The collection shows different segments displaying different densities". The proper term is computerized tomography. The second sentence is difficult to understand. Please clarify what is meant.

Response: Considering the reviewer's good suggestion, we have changed the term "Computed tomography" to "computerized tomography". Meanwhile, the second sentence has been removed to avoid confusions for readers,.

- (10). Comment: "However, some of the literature reports that the WBC count can be normal or reduced in a few cases[13]". The definition of a leukemoid reaction is that WBC counts are increased. Hence this part of the text confuses the reader.

Response: We agree the reviewer's advice and this part does cause confusion for readers. So we removed this sentence to ensure consistency in our description of the leukemoid reaction definition.

- (11). Comment: "Some scholars believe that PLR is more likely to occur in malignant tumor patients with a greater age, especially for those at middle-

age.” Cancer is strongly associated with ageing, with the remarkable exceptions of childhood hematological malignancies (leukemia, lymphoma) and of tumors arising from defects in organogenesis (Wilm’s Tumor, teratocarcinomas). Typically a malignant tumor patient is at least middle age and older. Hence, this part of the text confuses the reader. Please clarify.

Response: We agree the reviewer's good advice. The purpose of this sentence is to highlight that some scholars believe that malignant tumor patients with PLR are mostly middle-aged, but because of our inappropriate wording, this meaning is not fully revealed. Considering the reviewer’s suggestion, we have modified this sentence to “some scholars believe that PLR is more likely to occur in malignant tumor patients at middle-age”.

(12). Comment: “All these laboratory profiles are the favorable prognostic factors of HCC”. The text confuses the reader, because it deals with the unfavorable prognostic factors of SHC, but expresses it as the lack of the favorable prognostic factors of HCC, which is not the subject of the report.

Response: According to the reviewer's good instruction, we have deleted this sentence to avoid misunderstanding.

(13). Comment: “This case showed that SHC was a poorly differentiated liver tumor with a high malignant grade, and PLR might serve as an indicator of

its poor prognosis. In our case, SHC combined with a PLR was fatal, reflecting that such condition was aggressive". I disagree. This is the report of one case and no evidence is provided that SHC in this case had a poor prognosis because PLR was present. The value of the report is not linked to this claim, since it adds a useful reference about a rare combination of findings.

Response: Thanks to the reviewer for pointing out the inadequacies of this sentence. The purpose of this article is to give clinicians a reference by introducing a rare clinical case. So we have revised this sentence to just highlight the dangers of this clinical state, which may let our paper be more rigorous.

Special thanks to you for your good comments.

Reviewer #1: please discuss Reference #1.

Reviewer #3: "This case showed that... such condition was aggressive".

Comment: I disagree. This is the report of one case and no evidence is provided that SHC in this case had a poor prognosis because PLR was present. The value of the report is not linked to this claim, since it adds a useful reference about a rare combination of findings.

Other changes:

1. The manuscript was prepared with word-processing software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins;
2. The part of "Supported by..." was deleted;
3. The telephone and fax was added;
4. Completed the acknowledgement section;
5. Reference #7 was changed to a more recent paper without affecting the meaning of the original text;
6. Reference #9 was deleted because it was published too long ago. This operation did not affect the original text;
7. Pubmed citation numbers and DOI citation was added to reference list;
8. All authors of all references was listed.

We appreciate for Editors' and Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Sincerely yours ,

Bo Hu