

29 March 2021

Editor in Chief

World Journal of Hepatology

Dear Sir,

We are pleased to have been given the chance to revise our manuscript No. 64415, entitled “Distant metastasis of Hepatocellular carcinoma to the cavernous sinus, Meckel’s cave, the petrous bone and cranial nerves: A case report and review of literature” for publication in World Journal of Hepatology.

We also appreciate the constructive comments from the reviewers.

We addressed the reviewers’ comments and revised the manuscript, accordingly, based on the recommendations and suggestions. The modifications are in red and highlighted text.

A response to the reviewers’ comments is provided below.

We hope that the revised version, which includes modified tables and figures, will meet the requirements for publication.

Sincerely yours,

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Reviewer #1:

1. The overall structure of the manuscript is complete and contains a title, abstract, keywords, introduction, case presentation, discussion, and references.
2. In this manuscript, a rare case of HCV-related multiple hepatocellular carcinomas (HCC) metastasizing to the cavernous sinus and the petrous bone involving multiple cranial nerves in an 82-year-old woman is described.

This is presented in the introduction section, along with the relevant background, rationale, aim, significant findings and potential significance of the case.

Therefore, this section is suitable to attract readers' attention.

3. The source of the data presented is reliable and indicated by the information presented in the Results section.
4. The manuscript cites all critical, relevant, and timely references.
5. There is not an indication of academic misconduct in the study.
6. The manuscript contributes to understanding the pathogenesis of the disease and treatment.
7. The manuscript describes an essential direction of research.
8. The title of the manuscript does not contain a grammatical error.
9. The language of the paper reaches the standard of publishing Peer-reviewer's

Conclusion:

1. The new vision that the manuscript offers to readers is that HCC can metastasize to CNS, leading to particular symptoms.
2. The manuscript falls within the scope of gastroenterology.
3. The experiences and lessons presented in the manuscript improve the readers' practice.
4. The content of the manuscript has value for publication. However, necessitate revisions according to the comments listed below.

The weaknesses of the manuscript are:

1. The authors should avoid repetitions during the text.
2. More detailed information about laboratory values, including pretreatment values of AFP. Besides, the follow-up information should be presented more precisely.
3. The clinicopathological findings of the similar previous cases should be presented as a table.

Thank the reviewer for the valuable advice.

According to your advice, I have revised our manuscript as follows:

1. The authors should avoid repetitions during the text.

We deleted the sentence "the lung being the most fragility (about 50%) and the regional lymph nodes often being the locations of metastases. Also, bone metastases are frequent, and patients may show a bone metastasis as first signs of occult HCC. Adrenal metastases are found in up to 15% of autopsies, and some cases of pedunculated HCC have been considered as actual metastasis to the right adrenal gland from a nearby HCC" in Discussion according to your advice regarding avoidance of repetition, because almost the same phrase was described in Introduction " HCC often involves metastasis in the liver, but metastasis out of the liver to the lung, bone, and adrenal glands is less frequent, whereas cranial nerves are commonly not involved".

2. More detailed information about laboratory values, including pretreatment values of AFP. Besides, the follow-up information should be presented more precisely.

We described more detail information about laboratory values including pre and monthly post treatment values of AFP with molecular targeted therapy and follow-up information including  $\gamma$  knife treatment.

3. The clinicopathological findings of the similar previous cases should be presented as a table.

The clinicopathological findings of the similar previous cases from literature were presented in Table 2.

Reviewer #2: The authors describe an uncommon clinical presentation of hepatocellular carcinoma with metastasis to the central nervous system, accompanied by high quality images. It would be interesting to include pretreatment values of alpha fetoprotein, more information on the patient outcome after diagnosis of the metastasis to Merckel's cave and whether different treatment options were pursued.

Thank the reviewer for this important comment.

We described pre and monthly post treatment values of AFP, and more information on the patient's outcome after diagnosis of the metastasis to Merckel's cave.

Reviewer #3: The subject of the paper is interesting because of the infrequency of the pathology described. Few comments:

1. The case report is too concise.
2. Cases from literature should be summarized in a table.

Thank the reviewer for this thoughtful suggestion.

Regarding your suggestion, I have revised our manuscript as follows:

1. We describe the report more precisely including the treatment regimen and the patient's outcome such as  $\gamma$  knife treatment, and the change of AFP value.
2. We summarized cases from literature in the table.