**Author Response Letter to Reviewer Comments:**

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**Column:** Case Report

**Title:** Primary hepatic neuroendocrine tumor: a case report and literature review

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**Reviewer code:** 03545422, 01204294 and 00722438

**First decision:** 2016-03-30 11:46

**Scientific editor:** Yuan Qi

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Dear Editor:

Enclosed, please find our revised manuscript entitled ***“***Primary hepatic neuroendocrine tumor: a case report and literature review***”***. This manuscript is being submitted for consideration as a case report in *World Journal of Clinical Case.*

You will find a final manuscript with all revisions highlighted corresponding to this revised manuscript. In this letter you will find a point-by-point response to each of the reviewer’s concerns.

We have carefully revised the manuscript. We appreciate the thoughtful and positive reviews from the reviewers. We hope that the revised manuscript will now be suitable for publication, and thank you to the reviewers for their effort and time.

Sincerely yours,

Jeong Eun Song, MD

**Authors’ Rebuttal to Reviewers’ Comments:**

In the following we discuss the points raised by the reviewers and the changes in the manuscript to address these points. We appreciate these thoughtful comments, and hope that our responses and in particular our revisions have allowed this paper to achieve priority sufficient for publication in *World Journal of* *Clinical Case*.

**Reviewer Code: 03545422**

**Reviewer’s Comments:** The paper is well written. You might describe better the case, including why you didn't perform blood analysis to discover a neuroendocrine tumour or a spect. This patient underwent to liver resection without a proper diagnosis. Moreover you need a long-term follow up to be sure that this tumor is not a secondarism. Pathological analisis need to include CD 56 reactivity and role of endothelial cells in the pathogenesis of the tumor. Also describe better the surgical approach(typical resection, wedge resection or transpalnt) in the discussion. Primary case of neuroendocrine liver tumour are very rare you have to revise your references including more cases.

**Authors’ Response**: Thank you for your comments.

1. Why you didn't perform blood analysis to discover a neuroendocrine tumour or a spect? This patient underwent to liver resection without a proper diagnosis.

Answer : The patient did not have any risk of hepatocellular carcinoma, but the characteristic finding from dynamic liver magnetic resonance imaging led to a diagnosis of HCC. We recommended liver biopsy to the patient for finding other causes of hepatic mass. However, the patient refused liver biopsy and wanted to undergo hepatic resection. Before surgery, we didn’t think that the hepatic mass was PHNET. So, we couldn’t perform blood analysis to discover a neuroendocrine tumor.

1. Pathological analisis need to include CD 56 reactivity.

Answer: Revised Case report section (with revision highlighted)

**CASE REPORT**

Immunohistochemical staining revealed that tumor cells were diffusely positive for synaptophysin, chromogranin A and CD56, with a Ki67 index of 10%, indicating nuclear reactivity.

1. Also describe better the surgical approach(typical resection, wedge resection or transpalnt) in the discussion.

Answer: Revised Discussion section (with revision highlighted)

**DISCUSSION**

No treatment guideline for PHNET has been recently established, but surgical resection(e.g., wedge resection or formal lobectomy) is the treatment of choice that can provide a complete cure[[15](#_ENREF_15), [26](#_ENREF_26)]. PHNETs are associated with a resectability rate of 70% and a 5-year survival rate after hepatectomy of 78%[[5](#_ENREF_5)]. Recent study shows that the extent of the disease and type of surgery dose not affect the survival rate[[25](#_ENREF_25)]. In patients with unresectable disease, various palliative options exist, such as systemic 5 fluorouracil[[27](#_ENREF_27)], hepatic artery embolization[[28](#_ENREF_28)], and octreotide therapy[[29](#_ENREF_29)]. However, data on these are limited. Currently, liver transplantation has been suggested to be a treatment option in selected patients with multiple lesions or impaired liver function[[30](#_ENREF_30)].

1. Primary case of neuroendocrine liver tumour are very rare you have to revise your references including more cases.

Anwer : Thank you for your comments. We revised discussion section adding more references.

**Reviewer Code: 01204294**

**Reviewer’s Comments:** Dear authors, This case report is well-written and interesting. Major comments 1) In general, the diagnosis of primary hepatic neuroendocrine tumors (PHNET) is done after a long (5-10 years) period of negative postoperative follow-up meaning the absence of any evidence of a primary extrahepatic neuroendocrine tumor. As known, the neuroendocrine tumors might be very small (< 1 cm). Thus, a long period of follow-up is required to be sure that the liver lesion is a PHNET. The follow-up data are missing in the paper. 2) The literature review, which is stated in the title, is missing. It would be better to have a table showing the literature review. Minor comment: - in the abstract please change the definition "right hepatic resection" into "right hepatectomy".

**Authors’ Response:** Thank you for your comments.

1. The follow-up data are missing in the paper.

Answer: Revised Case report section (with revision highlighted)

**CASE REPORT**

The tumor was considered as a metastatic NET, so further evaluation was undertaken to search for the primary tumor. Chest CT, and upper and lower gastrointestinal endoscopies were performed, and the results were negative for any tumor. The patient underwent an indium-111-DTPA-octreotide scan, which revealed no lesions positive for somatostatin receptor (Figure 3). The final diagnosis was PHNET based on the pathological and imaging results. At 2-years follow-up the patients shows no signs of liver recurrence or appearance of another primary neuroendocrine tumor.

1. The literature review, which is stated in the title, is missing. It would be better to have a table showing the literature review.

Answer: Thank you for your comments. We revised discussion section adding more references.

1. Minor comment: - in the abstract please change the definition "right hepatic resection" into "right hepatectomy".

Answer: Revised Case report section (with revision highlighted)

**Abstract**

Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare and difficult to distinguish from other liver tumors, such as hepatocellular carcinoma (HCC) and cholangiocarcinoma, based on medical imaging findings. A 70-year-old man was referred for evaluation of liver mass incidentally discovered on abdominal computed tomography. The characteristic finding from dynamic liver magnetic resonance imaging led to a diagnosis of HCC. The patient underwent right hepatectomy. Histopathological and immunohistochemical examination revealed

**Reviewer Code: 00722438**

**Reviewer’s Comments:** This is a well written case report of a rare pathology. It lacks long term follow-up in order to support the immunohistological diagnosis of PHNET. The literature review should reflect Authors observations of the published articles in order to point out the anamnestic, clinical, diagnostic and histological characteristics of this rare tumor. The discussion would be enriched if follow-up best strategy is mentioned.

**Authors’ Response:** Thank you for your comments. We tried to revise Discussion section in order to point out the anamnestic, clinical, diagnostic and histological characteristics adding more references. Please check our revised manuscript highlighted. Also, we mentioned that long-term follow-up is best strategy.