ANSWERING REVIEWERS

September 08, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Mannuscipt No:13267.doc).

Title: Lymphoepithelioma-like Cholangiocarcinoma: A Mimic of Hepatocellular Carcinoma on Imaging Features

Author: Tsan-Chieh Liao, Chien-An Liu*, Nai-Chi Chiu, Yi-Chen Yeh, &Yi-You Chiou.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13267

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

#Reviewer 1

1. Although the study is of potential interest and relevance, there is space for improvement.

➔ **Response:** Thank you for your comment. We revised and added more detail descriptions in this article. All changes were marked in red.

Reviewer 2

1. INTRODUCTION. Lymphoepitelioma like cholangiocarcinoma (LELC) is a rare tumor (around 15 cases, all from Far East, have been reported so far). For this reason, a more detailed description of the biomolecular and clinical features of this tumor should be of interest for an audience of clinical hepatologists: The Authors should refer to a recent paper, which addresses

these issues. (Chan AW Histopathology 2014).

➔ **Response:** Thank you for your comment. We added a more description of the biomolecular in the introduction section, the change was made at page 1 in line 7-11 as "*These case reports focused on histological and immunohistochemical analyses. Apart from histological and imminohischemical, a recent study which reported 7 female cases of EBV-associated LELC demonstrated mocular genetic pathology, such as frequent DNA hypermethylation [9]. However, few radiological features have been described"*. The change was marked in red.

2. b) CASE PRESENTATION. The Authors state that the lesion did not meet the criteria for diagnosing HCC according to AASLD Practice Guidelines. It should be clarified why these criteria are not met. The CT portal and late phases are not described.

➔ **Response:** Thank you for your comment. We added a description to clarified why these criteria were not met, the change was made at page 2 in line 1-4 as " *According to AASLD Practice Guidelines [10] and the CT scan was not a dynamic contrast enhanced study as well as the acquisition time of the arterial phase was too early to be differentiated as a small hepatocellular carcinoma (HCC) or other hepatic tumors,……*". The change was marked in red.

3-1 c) CASE PRESENTATION. Why does the description of the sonographic examination come after the CT and MRI findings?

➔ **Response:** Thank you for your comment. We revised the description which describe the sonographic examination was prior to the MRI findings at page 2 in line 6-8 and line 10-12 as "*The repeated sonographic examination and dynamic abdominal MRI were scheduled to investigate the possibility of other hepatic neoplasms as well……..Sonographic examination revealed a small well-defined and homogeneous hypoechoic nodule measuring 1.7 x 1.2 cm in size with protruding into the liver surface (Figure 3) at lateral segment*. The change was marked in red.

3-2 c) By the way, (although it is not an AASLD criterium) did the patient have a CEUS examination?

➔ **Response:** The patient did not have a CEUS examination because the contrast-enhanced exam cannot be performed due to unavailable ultrasound contrast agents in our country. The change was marked in red.

4 CASE PRESENTATION: "……. The tumor cells were diffusely positive for CK……" Which CKs?

➔ **Response:** Thank you for your comment. We added (AE1/AE3) following CK to describe which kind of it. The chang was made at page 3 in line 5 as "*The tumor cells were diffusely positive for **CK (AE1/AE3)** and Epstein-Barr-virus-encoded RNA (EBER) in situ hybridization (Figure 4D)*". The term "CK (AE1/AE3)" was marked in red.

5 CASE PRESENTATION: Which was the histological diagnosis of the surrounding tissue?

➔ **Response:** Thank you for your comment. We added a more description for the histological diagnosis of the surrounding tissue. The change was made at page 3 in line 7-8 as "*The adjacent non-tumorous liver tissue did not reveal significant histopathological abnormality.*" The change was marked in red.

6 d) DISCUSSION: The enhancement of the CT arterial phase is weaker than that observed in the corresponding MRI phase. Can you comment on this finding?

➔ **Response:** Thank you for your comment. In our case, the reason of the enchased of CT arterial phase weaker than that observed in the corresponding MRI phase is that the CT scan may be not a dynamic contrast enhanced study as well as the acquisition time of the arterial phase was too early. We added the description in Case presentation section at page 2 in line 1-2 as "*...the CT scan may be not a dynamic contrast enhanced study as well as the acquisition time of the arterial phase was too early...*". The change was marked in red

7 Given the discrepancies between the arterial phases of CT and MRI (no further comparison is offered), which are the clinical implications of this report? (should a fine needle biopsy be advised before surgery?

➔ **Response:** Thank you for your suggestion. According to AASLD Practice Guidelines, the dynamic contrast enchased MRI showed typical imaging patterns of HCC so that biopsy was not performed before surgery in our case. In addition, we totally agreed with you and we added descriptions at page 5 in line 14-18 as "*Because of some intrahepatic tumors contain both elements of cholangiocarcinoma and HCC in the same nodule in result the imaging*

characteristics may overlap [20]. HCC and metastatic tumors should be considered when typical characteristics of mass-forming cholangiocarcinoma are not observed. ***Therefore biopsy may be needed for confirmation of the diagnosis before surgery.***" The change was marked in red.

8 Is a FDG-PET scan of help in this context?).

➔ **Response:** Thank you for your comment. We added the description for ^{18}FDG-PET at page 5 in line 18-22 as "*In addition, ^{18}FDG-PET was of value for the diagnosis, staging of cholangiocarcinoma, and high accuracy in detecting unsuspected distant metastases [21]. However, to best of our knowledge, ^{18}FDG-PET applied to discriminate from LELC and other histological type cholangiocarcinoma has not been studied.*" The change was marked in red.

#reviewer 3

The clinical case reported is Well described but according my opinion The lelc is not Well described in general: more dettails about The rare disease result appreciable.

➔ **Response:** Thank you for your comment. We revised and added more detail descriptions in this article. All changes were marked in red.

#reviewer 4

1) The manuscript should be reformatted according the style requirement of WJG.

➔ **Response:** Thank you for your comment. We reformed the manuscript according the style requirement of Would Journal of Gastroenteralogy.

2) The manuscript is well written, the clinical characteristics are carefully observed and interpreted, however, images from a single case were presented in the paper, the authors have made an important suggestions of imaging pattern of lymphoepithelioma-like cholagiocarcinoma mimics that of hepatocellular carcinoma (HCC). Again, because it's a single case, the conclusion should be carefully drawn.

➔ **Response:** Thank you for your comment. We revised the conclusion at page 6 in line 1-7 as *"In conclusion, these previous studies indicated that LELC is a rare variant of cholangiocarcinoma which affects more middle-age female. This case report and review article*

is the first study to describe the findings from ultrasound, CT, and MRI. Various atypical patterns of mass-forming cholangiocarcinoma are based on tumor components. Even though the imaging findings of the liver tumor seem like a typical pattern of HCC, the LELC still need to be considered in the differential list, especially in female with EBV infection. Diagnosing LELCs remains a challenge for clinic physicians, surgeons, and radiologists.". The change was marked in red.

3 References and typesetting were corrected

➔ **Response:** We reformatted the manuscript and reference according the style requirement of World Journal of Gastroenterology.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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