

Dear Editor,

We thank you for your comments concerning our manuscript entitled “**Solitary hepatic lymphangioma mimicking liver malignancy: a case report and literature review**” (manuscript NO: 56082). Those comments were helpful when revising and improving our manuscript, as well being of guiding significance to our work. We have studied the comments and have made the required corrections which we hope meet with your approval. Revised portions are marked using the tracking system in the manuscript. The main corrections in the paper and the responses to the reviewer’s and Editorial Office’s comments are as follows:

Responses to the reviewer’s comments:

Reviewer #1: The manuscript presents the case of an unusual hepatic tumor. The clinical course is well described. This case may help other clinicians to consider lymphangioma as a possible differential diagnosis of hepatic lesions. Before the manuscript can be published several typing errors or inaccuracies must be corrected. E.g. *Schistosome japonicum*, detecting infectious antibodies including...

Response to comment: Before the manuscript can be published several typing errors or inaccuracies must be corrected. E.g. *Schistosome japonicum*, detecting infectious antibodies including...

Response: Thanks, we have corrected the typing errors or inaccuracies in our revised manuscript, including " lymphangomas, *Schistosome japonicum*, detecting infectious antibodies including... "

Reviewer #2: This is a generally well-written case report and I do appreciate the effort made by the authors in terms of literature search. However, it does not add anything to data already available in literature neither it represents a case report of particular interest. Furthermore, the introduction section is poor and there are no data regarding possible ethiopathogenic mechanisms underlying the disease. Is there any genetic background? The discussion is quite poor as well: for instance the authors never discuss data retrieved from literature.

Point-to point response

1. Response to comment: It does not add anything to data already available in literature neither it represents a case report of particular interest.

Response: Thanks, we report a case of solitary hepatic lymphangioma with a typical imaging performance of HCC, thus misdiagnosed as liver cancer and treated with TACE for three rounds, and then complete resection. The unique of our case is that it mimics HCC in imaging, which makes preoperative diagnosis difficult. On the one hand, the management of our case can add useful data of this rare disease to the available literature. On the other hand, our case may help clinicians to consider lymphangioma as a possible differential diagnosis of hepatic lesions.

2. Response to comment: The introduction section is poor and there are no data regarding possible ethiopathogenic mechanisms underlying the disease. Is there any genetic background?

Response: Thanks, we have added data about possible ethiopathogenic mechanisms

and genetic background underlying the disease to the introduction part and as follows: The lymphatic system and venous system lack communication, which leads to the malformation of lymphatics. Lymphangioma is significantly associated with chromosome abnormalities including chromosome X abnormalities (Turner syndrome), trisomy 21 (Down syndrome), trisomy 18, trisomy 13, and triploidy, copy number variants, and genetic mutations such as *alpha serine-threonine protein kinase 1 (AKT1)*, *phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)*, *vascular endothelial growth factor receptor 3 (VEGFR3)*, and *RAS p21 protein activator 1 (RASAI)*. (Giuseppe Noia, et al., PMID: 30475086, DOI:10.1089/lrb.2017.0084; Gabriele Saccone, et al., PMID: 30909010 DOI:10.1016/j.ejogrb.2019.03.014; Naina Bagrodia, et al., PMID: 25888145, DOI:10.1097/MOP.0000000000000209; Soyoung Park, et al. PMID: 30579634, DOI:10.1016/j.pediatrneurol.2018.10.017).

3. Response to comment: The discussion is quite poor as well: for instance the authors never discuss data retrieved from literature.

Response: Thanks, we have strengthened the discussion part as you suggests in the revised manuscript.

Reviewer #3: The case is well written, however, it is clear that the error that underlies everything is to trust only imaging. The authors should better clarify the clinical history of jaundice and *Schistosoma japonicum* infection. They should clarify whether guidelines recommending the use of imaging without biopsy in well-defined cases such as chronic liver disease have not been applied. If this has not been done it is necessary that the authors underline in the discussion the need to perform a biopsy and to follow the guidelines. Authors are suggested to describe the lesion according to the LI-RADs categories. In line 2 of the abstract there is a typo "lymphangomas".

Point-to point response

1. Response to comment: The authors should better clarify the clinical history of jaundice and *Schistosoma japonicum* infection.

Response: Thanks, history of jaundice hepatitis during childhood and *Schistosoma japonicum* infection was reported by the patient and she did not provide any medical evidence. We speculated that yellowing of skin or sclera during childhood, which was mistaken for jaundice hepatitis by the patient, was probably caused by β -thalassemias. The patient came from *Schistosoma japonicum*-endemic area of Hubei province, China, and had water contact history. She once was found positive in fecal examination (Kato-Katz or miracidium hatching test) or serology test and diagnosed as *schistosomiasis japonicum* during annual *Schistosoma japonicum*-infection census. However, serology test of the patients was negative for this admission. We have added more information to this part in revised manuscript.

2. Response to comment: They should clarify whether guidelines recommending the use of imaging without biopsy in well-defined cases such as chronic liver disease have not been applied. If this has not been done it is necessary that the authors underline in the discussion

the need to perform a biopsy and to follow the guidelines.

Response: European Association for the Study of the Liver (EASL) clinical guidelines 2018 of HCC management recommends biopsy of the lesion for cirrhotic liver when the imaging-based diagnosis is inconclusive, especially for lesions < 2 cm in diameter. For non-cirrhotic liver and liver with uncertain cirrhosis, biopsy of liver lesion is also recommended even imaging diagnosis is conclusive. For our case, the lesion is classified as LR-5, diagnosed as HCC with 100% certainty. However, although the patient presented as splenomegaly, diagnosis of liver cirrhosis was still difficult. Thus, according to the guidelines, a biopsy should be performed. Considering the patient was willing to undergo operation finally, biopsy of the lesion was not carried out at that time. Therefore, we summarize the treating experience of our case and underline the need to perform a biopsy and to follow the guidelines in discussion part in revised manuscript.

3. Response to comment: Authors are suggested to describe the lesion according to the LI-RADs categories.

Response: Thanks, we have amended it as you suggested and as follows: Then, the patient accepted further imaging test, enhanced computed tomography (CT) scan, which showed a regular mass with diameter around 3.5cm in size, located in the segment 4b close to falciform ligament, manifested as nonrim-like enhancement in the arterial phase (Figure 1A), and nonperipheral washout appearance in portal venous phase and in delayed scan (Figure 1B and C). The lesion was classified as LR-5 according to Liver Imaging Reporting and Data System (LI-RADS) version 2018.

4. Response to comment: In line 2 of the abstract there is a typo "lymphangomas".

Response: Thanks, amended accordingly in revised manuscript.

Reviewer #4: General comments This case report present a rare case of hepatic lymphangioma which was misdiagnosed as hepatoma, and patient actually recived the treatment as if she had HCC. As we rely heavily on imaging diagnosis for HCC, this case is relevant for clinician. Although it is rare, this case has been reported on multiple case report. However, what unique about this case was mis-diagnosed as a HCC and I believe this would benefit readers and clinicians. Specific comments Abstract line 4, there is a mis-spelling of the word "lymphangioma". Please correct. For clinical presentation, OPTN category or LI-RADs category would be helpful as these are very commonly used in the U.S. for a diagnosis of HCC. For HPI, "the patient had the psychology of anxiety and fears for the surgery and refused to undergo the operation." This sentence need to be re-written. Past medical history: Clarification of "jaundice hepatitis during childhood" should be provided, if details are known. I may recommend clarifying abbreviation on the first appearance. E.g.: HBV, etc. Treatment: 4cm * 3cm, may be better to write 4 cm x 3 cm. Same for the following sentences. "The operation went smoothly." This sentence sounds too casual for the manuscript. Consider re-writing. Lab value, how would you explain the elevation of CA19-9? Figure: Consider using larger figure as it is small.

Point-to point response

1. Response to comment: Abstract line 4, there is a mis-spelling of the word

"lymphangioma". Please correct.

Response: Thanks, amended accordingly in revised manuscript.

2. Response to comment: For clinical presentation, OPTN category or LI-RADs category would be helpful as these are very commonly used in the U.S. for a diagnosis of HCC.

Response: Thanks, amended accordingly in revised manuscript.

3. Response to comment: For HPI, "the patient had the psychology of anxiety and fears for the surgery and refused to undergo the operation." This sentence need to be re-written.

Response: Thanks, we have re-written the sentence and as follows: the patient had fears of surgery and concerns of its complications, and was unwilling to receive operation at first.

4. Response to comment: Past medical history: Clarification of "jaundice hepatitis during childhood" should be provided, if details are known.

Response: Thanks, history of jaundice hepatitis during childhood was reported by the patient and she did not provide any medical evidence. We speculated that yellowing of skin or sclera, which was mistaken for jaundice hepatitis by the patient, was probably caused by β -thalassemias. We have described in detail in revised manuscript.

5. Response to comment: I may recommend clarifying abbreviation on the first appearance. E.g.: HBV, etc.

Response: Thanks, we have amended it as you suggested in the revised manuscript, including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and computed tomography (CT).

6. Response to comment: Treatment: 4cm * 3cm, may be better to write 4 cm x 3 cm.

Response: Thanks, amended accordingly in revised manuscript.

7. Response to comment: Same for the following sentences. "The operation went smoothly." This sentence sounds too casual for the manuscript. Consider re-writing.

Response: Thanks, we have re-written the sentence and as follows: The operation was successfully accomplished.

8. Response to comment: Lab value, how would you explain the elevation of CA19-9?

Response: Thanks, elevation of serum CA19-9 level is highly associated with digestive malignancies, especially pancreatic cancer, gallbladder cancer, bile duct cancer, gastric cancer as well as colorectal cancer, and also results from digestive benign diseases, including cholestatic cholangitis, cholelithiasis, acute pancreatitis, acute hepatitis and hepatic cirrhosis. For our case, the patient had chronic cholecystolithiasis, elevated total bilirubin (57.6 $\mu\text{mol/L}$) and indirect bilirubin (52.9 $\mu\text{mol/L}$) probably caused by β -thalassemias. However, serum level of CA19-9 of our case is 24.4 U/ml, which is in normal range (0~27 U/ml).

9. Response to comment: Figure: Consider using larger figure as it is small.

Response: Thanks, we have prepared and arranged the original and large figures using PowerPoint according to the requirements of the World Journal of Clinical Cases.

Editorial Office's comments

(1) Science Editor: 1 Scientific quality: The manuscript describes a case report of the solitary hepatic lymphangioma with surgery. The topic is within the scope of the WJCC. (1) Classification: Grade C, Grade C, Grade C and Grade E; (2) Summary of the Peer-Review Report: The manuscript presents the case of an unusual hepatic tumor. The clinical course is well described. This case may help other clinicians to consider lymphangioma as a possible differential diagnosis of hepatic lesions. The introduction section is poor and there are no data regarding possible etiopathogenic mechanisms underlying the disease. The discussion is quite poor as well. The questions raised by the reviewers should be answered; and (3) Format: There are 4 tables and 3 figures. A total of 32 references are cited, without references published in the last 3 years. The authors need to update the references. There are no self-citations. 2 Language evaluation: Classification: Grade B, Grade B, Grade B and Grade B. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and the informed consent. The authors need to provide the Copyright License Agreement signed by all authors and fill out the CARE checklist form with page numbers. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by National Natural Science Foundation of China; Foundation for the Development of Science and Technology of Hubei Province; and Foundation of Tongji hospital, Tongji medical Tongji Medical College, Huazhong University of Science and Technology, China. The topic has not previously been published in the WJCC. The corresponding author has not published articles in the BPG. 5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); and (2) Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

Point-to point response

1. Response to comment: Summary of the Peer-Review Report: The introduction section is poor and there are no data regarding possible etiopathogenic mechanisms underlying the disease. The discussion is quite poor as well. The questions raised by the reviewers should be answered

Response: Thanks, we have answered all the questions raised by reviewers and strengthened the introduction and discussion sections.

2. Response to comment: Format: There are 4 tables and 3 figures. A total of 32 references are cited, without references published in the last 3 years. The authors need to update the references.

Response: Thanks, we have updated references in our revised manuscript.

3. Response to comment: Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and the informed consent. The authors need to provide the Copyright License Agreement signed by all authors and fill out the CARE checklist form with page numbers.

Response: Thanks, we have uploaded Copyright License Agreement signed by all authors and the CARE checklist form filled out with page numbers.

4. Response to comment: Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); and (2) Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor..

Response: Thanks, we have uploaded approval documents of The National Natural Science Foundation of China, No. 81803175, and Chen Xiao-ping Foundation for the Development of Science and Technology of Hubei Province, China, No.CXPJJH11900001-2019345. As Foundation of Tongji hospital, Tongji medical Tongji Medical College, Huazhong University of Science and Technology, China, No.2017B001, belongs to internal grant of our hospital, without approval document, and can only be search internal website, screenshot of which has also been uploaded.

We have prepared and arranged the original and large figures using PowerPoint according to the requirements of the World Journal of Clinical Cases.

(2) Editorial Office Director: I have checked the comments written by the science editor.

Response: Thank you very much!

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thank you very much!

We hope these amendments have improved the manuscript without overly influencing the content and framework of the reported work. The changes are marked-up in the revised manuscript.

We thank you for your work on our behalf and trust that the revised manuscript will meet with your approval.

Yours sincerely,

Xiaoping Chen

Corresponding author:

Xiaoping Chen

Email address: chenxpchenxp@163.com

Tel.: +86 02783663400; fax: +86 02783663400.

Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, China