

Replies to reviewer 1's (Reviewer's code: 01557283) comments:

We appreciate for your kind recommendation and criticism. Specific to your opinion, we have made modification of the manuscript and a point-by-point response, as follows:

1. Case Report. Case 2. Figure legends should be shown, and immunohistochemical findings should be shown in this case 2. Was the diagnosis of the Case 2 patient the HEAML or metastases of the renal angiomyolipoma? Did the Case 2 patient undergo liver tumor biopsy or not?

➤ Reply 1: Detailed figure legends and immunohistochemical findings for case 2 have been added in the revised manuscript. In case 2, the patient was diagnosed as epithelioid angiomyolipoma at left kidney for the first time, which was completely removed. Thereafter, the liver mass was the main complain and focus of treatment, as well as the leading cause of death. A CT-guided liver tumor puncture biopsy was performed and confirmed the pathological diagnosis of epithelioid angiomyolipoma. Therefore, the appropriate diagnosis for the patient was secondary hepatic epithelioid angiomyolipoma of renal origin.

2. Literature review. General data. Was CA19-9 elevation significantly associated with HEAML? Was TSC significantly associated with HEAML?

➤ Reply 2: Among the 409 cases in our review, only 4 patients were reported with CA19-9 elevation. And there was no other studies revealing the association between CA19-9 and HEAML. As for TSC, it was reported that there was an association with TSC in more than 50% of the AML in the kidney, but this association had been estimated to be only 5%-15% of the patients presenting with solitary liver tumors.<sup>[1]</sup> In our review, TSC was found in 7 patients (1.7%), which might be underestimated due to unmentioned information. However, TSC was probably a risk factor for malignant behavior of epithelioid angiomyolipoma.<sup>[2,3]</sup>

3. Discussion. The authors described that the median time of postoperative relapse was 42.5 months in case of malignancy. Therefore, was periodic re-examination during 5-years necessary after surgery similarly to the gastrointestinal cancers?

➤ Reply 3: The median time of postoperative relapse was 42.5 months. Therefore, periodic reexamination was necessary to timely detection of recurrence, especially within 5 years after surgery, just like gastrointestinal cancers. We have added these information in the revised manuscript.

4. Discussion. The authors showed that 15 cases of malignancy were identified because of intrahepatic recurrence or distant metastasis, while the pathological examination did not demonstrate malignancy distinctly on the first operation. Did this evidence show that synchronous metastasis to other organs was very rare in the HEAML?

➤ Reply 4: Synchronous metastasis to other organs was very rare when HEAML was diagnosed for the first time. However, multiple organs might be involved when intrahepatic recurrence or distant metastasis occurred.

5. Figures and Tables should be separately presented after the text. In addition, figure legends should be presented in the Figure Legends Section.

➤ Reply 5: In the revised manuscript, figures and tables have been presented separately after the text, and figure legends have been presented in the Figure Legends Section.

Thanks again for your professional review and criticism. Hope for your further recommendation.

## Reference

1. Kamimura K, Nomoto M, Aoyagi Y. Hepatic angiomyolipoma: diagnostic findings and management. Int J Hepatol 2012;2012:410781. [PMID: 23320180 DOI:10.1155/2012/410781]

2. Klompenhouwer AJ, Verver D, Janki S, Bramer WM, Doukas M, Dwarkasing RS, de Man RA, IJzermans JN. Management of hepatic angiomyolipoma: A systematic review. *Liver Int* 2017;37:1272-1280. [PMID:28177188 DOI:10.1111/liv.13381]
3. Nese N, Martignoni G, Fletcher CD, et al. Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: a clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. *Am J Surg Pathol*. 2011;35:161-176. [PMID:21263237 DOI:10.1097/PAS.0b013e318206f2a9]

Replies to reviewer 2's (Reviewer's code: 01555255) comments:

We appreciate for your kind recommendation and criticism. Specific to your opinion, we have made modification of the manuscript and a point-by-point response, as follows:

1. Introduction section: literature report that most patients with hepatic angiomyolipoma, are asymptomatic and this condition may be discovered incidentally during regular health check - ups or follow - up examinations for other diseases. The main symptom is abdominal discomfort. The pathogenesis of hepatic angiomyolipoma has not yet been clarified. There is an association with tuberous sclerosis complex in more than 50% of the angiomyolipomas in the kidney, but this association has been estimated to be present in only 5% - 15% of the patients presenting with solitary liver tumors. It usually occur in non - cirrhotic livers and are not accompanied by serological abnormalities, and occurs more frequently in women. Please include this information in the section.
  - Reply 1: The information you mentioned is very constructive for overall understanding of hepatic AML, and has been added into the revised manuscript. Besides, HEAML is a special type of AML in liver. Compared with typical AML, HEAML was histologically dominated by epithelioid cells and contained much less adipose cells.
2. Discussion section: recently, a systematic review on this topic has been published (Liver Int. 2017 Sep;37(9):1272-1280). Please include it in the References section. I suggest also to report the novelty of the present observation. These two clinical case have a particular presentation, or is in line with previous data? Is possible the association with changes in lipid metabolism?
  - Reply 2: The systematic review you mentioned above<sup>[1]</sup> provided a good summary, especially on the management of hepatic AML. We have cited several key opinions of this article and included it in the reference section. Compared

with the above article, our cases report and literature review had some novelties. Firstly, the two cases represented primary and secondary HEAML respectively, which differed much in the prognosis. Secondly, our literature review mainly focused on the diagnosis of HEAML, especially the presentation of imaging examinations, while the above systematic review put more emphasis on the management of hepatic AML. Recently, the role of lipid metabolism on cancer has drawn great attention,<sup>[2,3]</sup> however, there has no direct evidence on the association of HEAML and abnormal lipid metabolism till now.

3. To help the reader, please use the complete words, when you report acronyms in the text.
- Reply 3: We have modified the paper and added complete words when the acronyms appeared for the first time.

Thanks again for your professional review and criticism. Hope for your further recommendation.

## Reference

- 1 Klompenhouwer AJ, Verver D, Janki S, Bramer WM, Doukas M, Dwarkasing RS, de Man RA, IJzermans JN. Management of hepatic angiomyolipoma: A systematic review. *Liver Int* 2017;37:1272-1280. [PMID:28177188 DOI:10.1111/liv.13381]
- 2 Hotamisligil, G?Khan S . Inflammation, metaflammation and immunometabolic disorders[J]. *Nature* 2017;542(7640):177-185. [PMID:28179656 DOI:10.1038/nature21363]
- 3 . Sung H, Siegel RL, Torre LA, Pearson-Stuttard J, Islami F, Fedewa SA, et al. Global patterns in excess body weight and the associated cancer burden[J]. *CA Cancer J Clin* 2018. [DOI: 10.3322/caac.21499]

Replies to reviewer 3's (Reviewer's code: 02440884) comments:

We appreciate for your kind recommendation and criticism. Specific to your opinion, we have made modification of the manuscript and a point-by-point response, as follows:

1. Histological and immunohistological figures should be given in more quality.

There are several artefacts and injuries.

➤ Reply 1: High-resolution (600dpi) histological and immunohistological figures have been re-uploaded.

2. Ckpan should be given as Keratin-pan or Kpan.

➤ Reply 2: Ckpan has been modified as Keratin-pan (Kpan) in the revised manuscript.

Thanks again for your professional review and criticism. Hope for your further recommendation.

Replies to editor's comment:

We appreciate for your kind recommendation. Specific to your opinion, we have made modification of the manuscript and a point-by-point response, as follows:

1. Please stamp the official seal of the hospital and upload the informed consent form again.

➤ Reply 1: We have re-uploaded the informed consents sealed by Changzheng Hospital.

2. Please provide and upload the approved grant application form(s).

➤ Reply 2: Certification materials of relevant grants have been uploaded.

3. Please provide the telephone and fax number of the author's office.

➤ Reply 3: The telephone and fax number is +86 021 63276788 and has been added in the revised manuscript.

4. Please update this section according to the guideline for case report.

➤ Reply 4: We have subdivided case report sections according to the guideline for case report.

Thanks again for your professional recommendation. Hope for your further recommendation.