

Peer Review File

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**Reviewer A**

The authors present a case report of EHE in a young woman that was sadly undiagnosed for a period of two years, during which the EHE grew in the liver and metastasized to the lung and bones. Their case report is well written and highlights the challenges of establishing the diagnosis of this rare tumor. I specifically agree with the need to involve a multidisciplinary team of liver experts when dealing with uncommon clinical presentations. Furthermore, it is paramount to seek the assistance of expert hepatic pathologists, as there are pathologic features to suggest EHE both on plain staining, as well on IHC. The authors eloquently stress these points in the manuscript. I have three minor revision requests:

**Comment 1:** The introduction reads: "Epithelioid hemangioendothelioma (EHE) is a rare sarcoma with a varied presentation, from indolent nodules to aggressive angiosarcomas." Angiosarcoma is totally different pathologic entity, so I recommend that the authors revise this sentence to make it clear that EHE and angiosarcomas are different tumor entities.

**Reply 1:** Thank you for making us aware about this mistake. We corrected the manuscript as recommended.

**Changes in the text:** We have modified our text as advised (please see it on page 2, line 10).

**Comment 2:** Could the authors comment on liver transplantation for EHE even in the setting of metastatic disease? There is data to suggest that liver transplantation for EHE offers a significant survival benefit even in patients with pulmonary metastases.

**Reply 2:** Thank you for this essential suggestion. Liver transplantation for patients with metastatic EHE is a very interesting topic that certainly deserves a comment in our manuscript.

**Changes in the text:** We added a new paragraph in the case report to discuss this possibility and to explain why the patient did not receive surgical treatment (please see it on page 3, lines 27-28 and on page 4, lines 1-2. We also added a new reference that can be seen on page 8, lines 3-5).

**Comment 3:** I recommend that the authors include the following recent reference in the bibliography:

Tumor Biology Impacts Survival in Surgically Managed Primary Hepatic Vascular Malignancies.

Dogea E, Mokdad AA, Bhattatiry M, Porembka MR, Polanco PM, Mansour JC, Choti MA,

Augustine MM.

J Surg Res. 2021 Aug;264:481-489. doi: 10.1016/j.jss.2021.02.043. Epub 2021 Apr 12.

This recent paper highlights that the grade of EHE is associated with survival and that therefore not all EHE tumors are slow growing and indolent.

**Reply 2:** Thank you for sharing this recent article with important information about the disease. We made a comment on this work and included it in the references.

**Changes in the text:** We added a comment on the histologic grade and its role in the disease management, according to the findings of this new reference (please see it on page 6, lines 3-4 and the new reference on page 9, lines 3-4).

### **Reviewer B**

Dr. Costa de Oliveira Ribeiro and colleagues from Universidade Estadual Paulista Júlio de Mesquita Filho report a case of hepatic epithelioid hemangioendothelioma with evidence of rapid progression. The authors utilized volumetry to highlight the growth of the tumor, showing that our understanding of HEHE may not be complete as it has been thought to be indolent.

Major Comments:

**Comment 1:** It would be helpful to include literature, or lack of, that discusses the presumed indolent nature, this would contrast and highlight the case report

**Reply 1:** Thank you for helping us to improve our work. We included some additional references that have discussed the indolent nature of HEHE. We also included a reference about a prior HEHE in which the largest nodule had its growing rate measured. The dissimilar reports of these references will certainly contribute to show the controversies about HEHE growing rate.

**Changes in the text:** We added some new references (5, 6, 7 and 18) and new comments on them. Please see the first comment on page 2, lines 18-20, where the references 5, 6 and 7 were cited due to their reports about the HEHE indolent nature. In addition, please see a second comment on page 6, lines 13-15, where the reference 18 is cited because the authors measured one lesion and estimated its growing rate.

**Comment 2:** Are there any additional staining or testing that could be done to differentiate this as a variant of HEHE?

**Reply 2:** Thank you for this important observation that improved the case description. We made an additional immunohistochemistry analysis showing that the tumor cells are positive for TFE3, thus suggesting the presence of the YAP1-TFE3 fusion.

**Changes in the text:** Please see the new figure (Figure 8) and the additional comments on

page 4, lines 18-19. The figure legend was included on page 11, line 12.

Minor Comments:

**Comment 3:** Abbreviations: EHE should be epithelioid hemangioendothelioma, not hepatic epithelioid hemangioendothelioma

**Reply 3:** We totally agree with Reviewer B. The abbreviation was changed to HEHE.

**Changes in the text:** The abbreviation was changed throughout the manuscript. Please see it on page 1, line 30, and page 2, lines 5, 9 and 19, and so on.

**Comment 4:** Consider clarifying “achieve” on line 5 page 6

**Reply 4:** We agree that the word “achieve” was not properly used in this sentence and should be replaced.

**Changes in the text:** We changed the sentence (please see it on page 6, line 21).

**Comment 5:** Figure 1: please label panels

**Reply 5:** The label panel of Figure 1 was placed at the end of the manuscript, after the references.

**Changes in the text:** Please see the Figure 1 label on page 10, lines 3-6.

**Comment 6:** Figure 2: please label panels

**Reply 6:** The label panel of Figure 2 was placed at the end of the manuscript, after the references.

**Changes in the text:** Please see the Figure 2 label on page 10, lines 8-13.

**Comment 7:** Figure 3: please label panels

**Reply 7:** The label panel of Figure 3 was placed at the end of the manuscript, after the references.

**Changes in the text:** Please see the Figure 3 label on page 10, lines 15-20.

**Comment 8:** Figure 4: please label panels

**Reply 8:** The label panel of Figure 4 was placed at the end of the manuscript, after the references.

**Changes in the text:** Please see the Figure 4 label on page 10, lines 22-23.

**Comment 9:** Figure 5: please label panels

**Reply 9:** The label panel of Figure 5 was placed at the end of the manuscript, after the references.

**Changes in the text:** Please see the Figure 5 label on page 10, line 25, and on page 11, lines

1-4.

**Comment 10:** Figure 6: please label panels, and note what the different colors mean

**Reply 10:** The label panel of Figure 6 was placed at the end of the manuscript, after the references.

**Changes in the text:** We added an explanation to the reader, clarifying that the normal liver parenchyma is shown in green and the tumors are presented in other colors. Please see the Figure 6 label on page 11, lines 6-7.

**Comment 11:** Figure 7: please label panels, and note what the different colors mean

**Reply 11:** The label panel of Figure 7 was placed at the end of the manuscript, after the references.

**Changes in the text:** We added an explanation to the reader, clarifying that the normal liver parenchyma is shown in green and the tumors are presented in other colors. Please see the Figure 7 label on page 11, lines 9-10.

**Comment 12:** Table 1: what does committed volume mean?

**Reply 12:** We agree that the word “committed” was not properly used in this part of the manuscript and should be replaced.

**Changes in the text:** We changed the word (please see it on the corrected version of Table 1).

### **Reviewer C**

In general, a very interesting and clinically relevant cases report. However, I have several questions especially concerning the pathology part:

**Comment 1:** please clarify: the histological pictures shown in the manuscript were diagnosed as normal liver? For me as a liver pathologist this is hard to believe. I strongly encourage the authors to include at least H&E stains of ALL liver biopsies taken from the patient to demonstrate also the pitfall for pathologists. From the clinical course I expect the EHE presented here to be Tfe3-Yap translocated. The authors must include stainings of TFE3 and Camta1 to show the EHE subtype.

**Reply 1:** We totally agree with Reviewer C. Despite the findings in the biopsy specimen, it is hard to believe that the disease was not recognized. The doctor who assessed the liver samples is a general pathologist, who could have shared the images with an experienced pathologist. The exact words of the first histological analyzes were “No signs of malignancy. The histologic specimen is formed by granulation tissue with marked fibrosis and

hyalinization, embracing and compressing biliary ducts and hepatocytes. Some of these cells contain vacuolated cytoplasm and are disposed in cords”. Unfortunately, diagnostic mistakes are not rare in EHE, and this case shows how the lack of an experienced pathologist can be deleterious, especially assessing liver nodules. The initial histological analysis simply overlooked the tumor cell cords, mistakenly assuming that they were hepatocytes. As a result, no further staining or immunohistochemistry assay was carried out, and the presence of a malignant disease was wrongly denied. After two laparoscopic-guided biopsies suggesting no malignancy, the pediatricians withheld the diagnostic investigation. Certainly, a consultation with a more experienced pathologist could have avoided this terrible mistake.

We do not have additional H&E material to add, but we performed the TFE3 staining. The result was included as a new figure, and the results suggest that the tumor is caused by the YAP1-TFE3 fusion, as you mentioned. Thank you for this important comment.

**Changes in the text:** We included the first histological description on page 3, lines 5-7, and additional explanations on page 5, lines 15-21. A TFE3 staining was included as well, showing that your comments about the Tfe3-Yap translocation were right. Thank you for leading us to improve our manuscript.

**Comment 2:** Please correct the mistake in the introduction part: EHE do NOT present as angiosarcomas. This is just wrong. They are two different entities with very different prognosis.

**Reply 2:** Thank you for making us aware about this mistake. We corrected the manuscript as recommended.

**Changes in the text:** We have modified our text as advised (please see it on page 2, line 10).