

Peer Review File

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Reviewer A

Comment 1:

Major comment: This is a very interesting and rare case, however, there should be additional substantiation to the claim that the hepatic tumors represent metastatic HAS. At present, the data available does not disprove the notion that the patient has two synchronous primaries (another rare entity). The discussion on HER-2 heterogeneity was very interesting and while it somewhat supports the notion of discordant biopsy results, it does not disprove the possible presence of HCC and concomitant HAS given that prior studies only found 7% discordance in HER-2 testing of HAS malignancies and metastases.

Reply 1: Thank you for the revision and comments. We presume that this were not synchronous lesions as both histopathological analyses had some identical H&E findings in some areas. Moreover, the patient did not have any risk factor for HCC that could make us cogitate the hypothesis of primary tumor of the liver.

Changes in the text: Lines 120-122

Comment 2:

Grammar/writing suggestions:

Reply 2:

- Line 32 omit “the” - **Accepted. Changes in the text: Lines 32**
- Line 33 omit “constant” - **Accepted. Changes in the text: Lines 34**
- The sentence from lines 34-37 should be changed to “Next generation sequencing technology has made it possible to identify and describe the genes and molecular alterations common to gastric cancer thereby contributing to the advancement of targeted therapies.” – **Accepted. Changes in the text: Lines 34-53**
- The final sentence (lines 37-40) should read “Herein, we describe a case of metastatic, HER2 positive esophagogastric junction hepatoid adenocarcinoma and review the management strategies for this rare subgroup of gastric cancer.” - **Accepted. Changes in the text: Lines 34-53**

Comment 3:

Introduction:

Reply 3:

- AFP secreting GI malignancies were actually first described in 1975 by McIntire et al via “Serum alpha-fetoprotein in patients with neoplasms of the gastrointestinal tract”. Ishikura identified HAS. **Changes in the text: Paragraph 1. Lines 68 - 73**
- Paragraph 2, lines 61 to 65 is somewhat inaccurate as HAS is infrequently AFP negative (see Wichelmann, et al’s “A Unique Case of Alpha-Fetoprotein-Negative Hepatoid Adenocarcinoma of the Stomach With Associated Signet Ring Cell Histological Features and Linitis Plastica”. Rather, the diagnosis is made based on histopathological findings resembling HCC. **Reply 2: we added the phrase “in the majority of cases”. Changes in the text: Paragraph 2. Line 78.**
- Additionally in paragraph 2, Hep-Par 1 staining is less frequently positive in HAS and is a highly specific marker for HCC. See: Su JS, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY. Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. *World J Gastroenterol.* 2013;19(3):321-327. doi:10.3748/wjg.v19.i3.321 **Reply 3: we added the sentence less frequently before Hep-Par 1 Changes in the text: Paragraph 3. Line 81**

- The sentence within lines 71-73 should be re-written. It is unclear what point is trying to be made. **Reply 4: We tried to introduce about the spatial heterogeneity of biomarkers like PDL1 and HER-2, as they can be discordant in different sites of disease. Changes in the text: Paragraph 4, lines 89-90**
- The sentence within lines 74-76 should be re-written and further clarified. **Changes in the text: Paragraph 5. Lines 94 - 95**

Comment 4:

Introduction:

Grammar/writing suggestions:

Reply 4:

- Line 56 change “through the observation” to “with the description” – **Accepted. Lines 68-70**
- Line 59 change “commonly” to “frequently” – **Accepted. Change in Line 75**
- Line 66 remove “constant” – **Accepted. Line 82**
- Line 67 change “prognostic” to prognosis – **Accepted. Line 83**
- Line 68 should have period after “poor” and “Expressed...” should be a new sentence reading “Median overall survival (mOS) is approximately 1 year.” – **Accepted. Line 84**

Comment 5:

Case Report:

Reply 5:

There are several items missing or that need clarification which are important to the topic at hand.

- 1. Was there any history of alcohol use, known liver disease, or viral hepatitis? These risk factors are an important consideration for risk stratification for the diagnosis of HCC. **The patient did not present any of this risk factors. Changes in the text: Paragraph 1, line 104-106**
- 2. What exactly did the pathology report show from the liver biopsy? The wording from this is confusing. Also, the reference to Figure 1 does not include staining for PDL-1. This should be included if able. **We complemented the liver biopsy description. Changes in the text: Paragraph 1, line 109**
- 3. The lesion’s location should be described in detail in the upper GI endoscopy. **We better described the lesion’s location. Changes in the text: Paragraph 2, line 117 – 118**
- 4. How was CTCAE v 4.0 used to grade hepatitis? CTCAE describes viral hepatitis. Should this read “hepatic failure”? **The patient presented with AST, ALT, bilirubin and INR elevation. We changed the description of the adverse effect. Changes in the text: Paragraph 3, line 128-131**

- 5. Was AFP rechecked prior to FOLFOX + Trastuzumab therapy? Line 97 indicated a serum AFP of 20 ng/mL. **Yes. It was described the alfa fetoprotein decreased from 19.568 to 48 after the start of this treatment (Line 134)**

At present, the information contained within the case report does not fully discredit the notion of synchronous HCC and HAS, especially given that there was dyssynchrony of HER2 and PD-L2 testing between the biopsy sites (i.e. liver biopsy and GEJ mass biopsy). Was any additional staining done to confirm? **Both biopsies had some areas with identical histological findings, and the patient had no HCC risk factors. Changes in the text: Paragraph 2, line 122-123**

Grammar/writing suggestions:

- Line 80: change “The” to “A” and “years” to “year”. Omit “history of” – **Accepted. Line 99**
- Line 81: omit “6 pounds or”. Can include pounds in parentheses if wanted. – **Accepted Line 100**
- Line 81: omit “personal”. – **Accepted. Line 101**
- Line 82: add period after mellitus. This is a run-on sentence. Start the next sentence with “Family oncologic history was significant for...”- **Accepted. Line 102**
- Line 85 is confusingly placed. The Emergency Department clarification should be made in the first sentence (Line 80). – **Accepted. Changes in line 99 and 105-106.**

Lines 85-86: what is a radiologic image screening? Clarify what types of images were taken. **first radiologic screening was made in other hospital, but patient was admitted at our center few days after C1 and then, we performed our baseline images here.**

Line 94: change “evidenced” to “demonstrated” – **Accepted. Line 117**

Sentence within lines 94 to 97 is a run on sentence. – **Accepted. Line 118-120**

Line 98: Who is “us”? This should be omitted – **Accepted. Line 125**

Line 100: CTCAE abbreviation should be defined – **Accepted. Line 127**

Line 106: trastuzumab misspelled – **Accepted. Line 137**

Comment 6:

Discussion:

The discussion is very thorough and covers the treatment choices well. It cites a multitude of recent studies in the field of oncology and reviews the treatment decisions made in the case utilizing data from these recent studies. However, the discussion lacks important clarification regarding the determination of the primary malignancy. I.e. why it was determined that the liver tumors represented metastatic HAS over distinct HCC. There are several reports of synchronous HCC and primary gastric cancer in the literature. Reference:Chen CN, Lee PH, Lee WJ, Chang KJ, Chen KM. Synchronous hepatocellular carcinoma or metastatic hepatic tumor with primary gastric cancer. *Hepatogastroenterology*. 1998 Mar-Apr;45(20):492-5. PMID: 9638434.

Reply 6:

We assume that this were not synchronous lesions because both histopathological analyses had some identical H&E findings in some areas. Moreover, the patient did not have any risk factor for HCC that could make us cogitate the hypothesis of primary tumor of the liver.

Changes in the text: line 122 - 123

Comment 7:

Discussion:

While prior research has shown discordance among HER2 positivity between primary and metastatic tumors, this is somewhat of a rarity. Peng et al conducted a meta-analysis focused on HER2 discordance between primary gastric cancer and metastasis and found only 7% of cases (95% CI: 5-10%) had HER2 discordance. They additionally reported that this number could be lower than reported in the literature. Peng Z, Zou J, Zhang X, et al. HER2 discordance between paired primary gastric cancer and metastasis: a meta-analysis. *Chin J Cancer Res*. 2015;27(2):163-171. doi:10.3978/j.issn.1000-9604.2014.12.09

Reply 7:

We added a paragraph about this study. Lines 200 - 203

Comment 8:

Discussion:

With the information provided in the case report and without additional IHC stains it is difficult to differentiate the true identity of the liver tumors (i.e. did they represent HCC or metastatic HAS) given that the biopsy staining provided was discordant between the specimens. While this case may represent a case of metastatic HAS with high heterogeneity of HER-2 expression, there should be additional supporting information to disprove the notion of two separate primary malignancies. Was Hep-Par1, PLUNC, or CK19 staining completed? These are all IHC stainings that would help to differentiate the tumors. Reference:

Su JS, Chen YT, Wang RC, Wu CY, Lee SW, Lee TY. Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. *World J Gastroenterol*. 2013;19(3):321-327. doi:10.3748/wjg.v19.i3.321

Reply 8:

Based on current literature, we could not differentiate a metastatic HAS from an HCC based only on IHC or images tests, since and hepatoid adenocarcinoma will display same IHC compared to HCC. In our case this diagnosis came from the fact that both have identical H&E areas (tubular and hepatoid area in esophageal lesion identical to liver lesion), no risk factors for HCC and multiple liver lesions.

Changes in the text: line 122 - 123

Comment 9:

Discussion:

Lastly, there are conflicting reports in the literature at present regarding triple phase washout with HAS metastases and thus represents an area that could be added to the discussion. Consider reviewing Lin et al's case series on 8 cases of HAS w/ Liver mets. References: Lin YY, Chen CM, Huang YH, et al. Liver metastasis from hepatoid adenocarcinoma of the stomach mimicking hepatocellular carcinoma: Dynamic computed tomography findings. *World J Gastroenterol*.

2015;21(48):13524-13531. doi:10.3748/wjg.v21.i48.13524

Kashani A, Ellis JC, Kahn M, Jamil LH. Liver metastasis from hepatoid adenocarcinoma of the esophagus mimicking hepatocellular carcinoma. *Gastroenterol Rep (Oxf)*. 2017;5(1):67-71. doi:10.1093/gastro/gov021

Reply 9:

Despite this the rapid wash out being suggestive of HCC, this could note exclude hepatoid adenocarcinoma, so we decided not to discuss this subject at the moment but added this information in the case report. Change in line 115-116

Comment 10:

Discussion:

Reply 10

- Lines 131-132 are unclear in the description of copy number variant and should be re-written. – **Accepted. Lines 166**
- Line 136: CNG should be defined. – **Accepted. Line 171**
- Line 141: this was not the first line therapy used for this patient. **Patient was admitted at our center few days after C1 due to toxicity while was waiting for HER2 status result and Trastuzumab was started in C2. That is why we considered all this as first line.**
- Line 169: need to define IHC – **Accepted. Line 211-212**

Comment 11:

Discussion:**Grammar/writing suggestions:****Reply 11**

- Line 128: remove “in each histology” – **Accepted. Line 163**
- Line 129-130: change “a high-frequency mutations in” to “a higher frequency of mutations in” – **Accepted. Line 164**
- Lines 135-137: run-on sentence should be re-written. – **Accepted. Line 170 – 172.**
- Lines 157-161: run-on sentence should be re-written. Confusing statement and unclear point. – **Accepted. Lines 193 – 199**
- Line 167: would use a different word besides “heavily”. – **Accepted. Line 209 – 210**
- Lines 193-194: sentence is unclear and should be re-written – **Accepted.**
- Line 203: remove “, differently from CHECKMATE 649,”. And remove “, although they were both tested... CPS of 1 or greater” – **Accepted. Line 236 – 238.**

Comment 12:**Conclusion:**

The statement regarding Trastuzumab as the first line is inaccurate - pt was started on FLOT.

Reply 12:

Patient was admitted at our center few days after C1 due to toxicity while was waiting for HER2 status result and Trastuzumab was started in C2. That is why we considered all this as first line.

Comment 13:**Conclusion:**

Concise conclusion that wrapped up the main point of the case report and highlighted the need for additional research along with areas for improvement.

Reply 12:

Thank you

Comment 14:**Grammar/writing suggestions:****Reply 14:**

- Line 222: remove “herein” – **Accepted. Line 266**
- Line 228: change “presented with some good responses in the past months” to “had a good response to treatment.” **Accepted. Line 272.**

Comment 15:**References:**

Thorough review of the literature. Additional sources for consideration provided above.

Reply 15:

Thank you. Very much appreciated.

Comment 16:**Scientific Quality:**

Rare case worthy of publication. Excellent and very thorough discussion though it needs clarification and further support of HAS metastases to the liver as described in detail above.

Reply 16:

Thank you.

Comment 17:**Language Quality:**

Needs significant improvement as indicated and outlined above.

Reply 17:

Thank you. All handled as suggested and recommended.

Reviewer B**Comment 1:**

We can congratulate Authors for a substantive discussion where all choices of treatment has been justified with literature data it is really unfortunate authors don't analyse genomic alteration in the primitive biopsy of stomach. Indeed, genomic analysis concern in these biopsy that HACs was confirmed in histology. Compare genomic alteration between gastric biopsy and liver would be so much pertinent. Perform this analysis could be improve this contents. Could authors please correct or modify this sentence: "Clinical response and decrease in AFP (from 19,568ng/mL to 48ng/mL)" to "19568 ng/ml to 48" (line 103) Line 83: could you delete the useless repetition (6 pounds).

Reply 1:

Thank you for your comments. Unfortunately, genomic analysis from the stomach lesion was not obtained due to cost concerns. We accepted all other suggestions.

