Author’s response to reviews

Title: Primary hepatic neuroendocrine carcinoma: report of two cases and literature review

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Author’s response to reviews:

Dear Dr. Said,

We thank you and the reviewers, Drs. Schmidt and Smith, for reflecting on the value of our submission and giving us valuable feedback and constructive advice. In response, we have edited our manuscript significantly to improve its suitability for publication in BMC Clinical Pathology.

We were pleased to see that Dr. Schmidt recommended acceptance of our manuscript. While we agree with Dr. Schmidt that changing from a narrative to systematic review would strengthen our manuscript, we feel such a review is beyond our current scope. We hope to work on such a systematic review in the future. We have revised the current manuscript to ensure that the coverage of previous literature is even-handed and extensive.

We appreciate Dr. Smith’s appreciative comments regarding the writing as well as the recommendation of additional revisions. In response, we have extensively revised the manuscript with the assistance of multiple colleagues to help with proofreading, and we have incorporated these changes into a new version with all changes highlighted in blue.

To address Dr. Smith’s second comment, we have adjusted the histologic images using Photoshop to remove the pink background and increase the contrast. To be consistent, we have added to the figure legends of Figs 4 and 6 “the image was adjusted in Photoshop to remove the pink background and increase the contrast.” However, we are not sure whether we need to include this description in the figure legends and whether we should include the original histologic images before adjustment as Supplementary Figures. We will rely on the recommendation of your editorial team in this matter.
Lastly, Dr. Smith brought up very interesting and important questions such as the possibility of ‘hepatocellular and cholangiocarcinoma with high grade neuroendocrine differentiation’, and ‘multifocality as primary’. While co-occurrence of hepatocellular carcinoma (HCC) or cholangiocarcinoma and PHNEC is extremely rare. However, ‘multifocality as primary’ in PHNEC has been reported, and surprisingly around 20% of PHNEC cases have been found to be bilobar (in both sides of the liver). We provide a more detailed response to Dr. Smith in the section below and have incorporated our response in the Discussion of the main manuscript. Unfortunately, since we did not have autopsy samples for the two cases, we could not completely exclude the possibility of HCC with high grade neuroendocrine differentiation, or the possibility co-occurrence of cholangiocarcinoma in case two. Although resolving this issue is beyond our capability for this project, it will be an aim of our long-term research as we seek to extract genomic data from multi-dissection samples for other, future PHNEC cases.

We hope that you find that we have addressed the reviewers’ comments clearly and comprehensively. We would be happy to address any other questions that may arise. Again, we thank you and Drs. Schmidt and Smith for the constructive and insightful comments that have made it possible to significantly improve our manuscript, and we hope that the revised version meets criteria for publication in BMC Clinical Pathology.

Sincerely,

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Reviewer reports:

Robert Schmidt, MD, PhD, MBA, MS, MMED (Reviewer 1): This is a very well-written manuscript I believe it is acceptable for publication in its current form. The authors might consider the following optional revision to enhance the manuscript:

Reviewer 1 Response 1: We were pleased to receive Dr. Schmidt’s recommendation of acceptance of our manuscript for publication.

The review of the literature appears to be comprehensive but falls short of the standards of a systematic review. Your manuscript would be much stronger if you took the steps to make this a systematic review rather than a narrative review. There are several similar case study and narrative review papers in the literature. Conducting a systematic review would conform to current standards of evidence, distinguish your paper from previous narrative reviews, and provide a stronger contribution to the field. As it stands, your paper is a very nicely written case study and review, but the contribution is unclear.
The problem with narrative reviews is that the reader has no way of knowing whether the review as systematically gathered the evidence. It is possible that one author based their review on one set of studies and another author based their review on a different set of studies. Thus, although it may be unintentional, there is an inherent risk of bias in narrative reviews. For that reason, they are considered low-quality evidence. In contrast, a systematic review enables a reader to evaluate the process that was used to gather evidence and provides assurance that the review was comprehensive. My sense is that your team conducted a very thorough review; however, there is no way for me to evaluate your review because you did not describe the process you used to gather evidence. My guess is that it would not take a lot of work to turn this into a systematic review which would be considered higher-quality evidence than a narrative review.

Reviewer 1 Response 2: While we agree with Dr. Schmidt that changing from a narrative to systematic review would strengthen our manuscript, we feel such a review is beyond our current scope. We hope to work on such a systematic review in the future. We have revised the current manuscript to ensure that the coverage of previous literature is even-handed and extensive. A revised version is provided with changes highlighted in blue.

Steven Christopher Smith, MD, PhD (Reviewer 2): The authors are to be congratulated for preparing an interesting report of two cases.

Reviewer 2 Response 1: We greatly appreciate Dr. Smith’s recognition of the value of our case reports.

Their presentation would be improved as follows:

1) While the quality of written English is rather good, I would recommend one additional read/revision in this regard. There are articles missing, and strange wording (such as the first sentence of discussion; the word "lump" used in description of imaging findings etc).

Reviewer 2 Response 2:

We appreciate Dr. Smith’s appreciative comments regarding the writing as well as the recommendation of additional revisions. In response, we have extensively revised the manuscript with the assistance of multiple colleagues to help with proofreading, including Drs. Ya-ting Chang and Chen Shen, and senior Scientific Writer Dr. Carmen Robinett. We have added their names in the Acknowledgements in appreciation of their time and professional help. In particular, we have revised ‘lump’ to ‘mass’ in the description of imaging findings. All other changes have been incorporated into an updated version with all changes highlighted in blue.

2) The histologic images need to be white background and contrast corrected.
Reviewer 2 Response 3:

We have adjusted the histologic images using Photoshop to remove the pink background and increase the contrast, with the help of our colleagues from the JAX Creative team, Medical Illustrators and Animators Jane Cha and Matt Wimsatt. In appreciation of their professional help, we have added them to the Acknowledgements. To be consistent, we have added to the figure legends of Figs 4 and 6 “The image was adjusted in Photoshop to remove the pink background and increase the contrast, and the original image before adjustment is provided in Supplementary Figure 1/2” However, we are not sure whether we need to include this description in the figure legends and whether we should include the original histologic images before adjustment as Supplementary figures. We will rely on editorial input to guide our decision.

3) The second case has two features that are somewhat troublesome with regards to believing a hepatic primary. Multifocality in this setting is generally construed as evidence of metastasis. Also, the presentation of jaundice is, in and of itself, a feature suggestive of cholangiocarcinoma, a neoplasm that, like hepatocellular carcinoma, may be associated with extensive neuroendocrine differentiation such as may not be detected by the biopsies described. Essentially, on what grounds, for both cases, do the authors 1) exclude hepatocellular and cholangiocarcinoma with high grade neuroendocrine differentiation, and 2) in the scenario of the second case presented, interpret the multifocality as primary? Have prior multifocal primary hepatic neuroendocrine carcinomas been described? Is there any suggestion of syndromal neoplasia, such as might explain multifocality in the context of this rare liver tumor? These considerations are essential to evaluation of such a case, where formal resection was not performed. Are there any data from autopsy?

Reviewer 2 Response 4:

We appreciate Dr. Smith’s thorough thoughts and great questions.

Dr. Smith asked “do the authors 1) exclude hepatocellular and cholangiocarcinoma with high grade neuroendocrine differentiation”.

a) Unfortunately, since we did not have autopsy samples for the two cases, we could not exclude hepatocellular carcinoma (HCC) with high grade neuroendocrine differentiation. However, co-occurrence of HCC and PHNEC is extremely rare, and we only found 12 cases in the English literature [1-4] and one in the Korean literature [5]. Interestingly, all 12 cases in the English literature are male patients in the age distributions of 40 s (one case), 50 s (2 cases), 60 s (4 cases), and 70 s (5 cases), and the Korean literature reported a case of a 68-year-old female. Almost all patients (11 out of 13) had documented liver disease, chronic hepatitis C (6 cases), chronic hepatitis B (4 cases), and cirrhosis of unknown cause (one case). Our two cases were both males around 60 years of age, and case one had hepatitis B and was positive for the HCC marker HepPar-1, suggesting the possibility of co-occurring HCC and PHNEC. Due to the lack of autopsy samples, we cannot absolutely exclude this possibility.
b) As for the possibility of ‘cholangiocarcinoma with high grade neuroendocrine differentiation’, for case one, since we did not see either lesions of the bile duct through multiple imaging approaches or symptoms suggesting obstruction of the bile duct, we excluded the possibility of cholangiocarcinoma. For case two, without autopsy samples, we could not exclude cholangiocarcinoma with high grade neuroendocrine differentiation.

Dr. Smith further asked “2) in the scenario of the second case presented, interpret the multifocality as primary?”.

a) Dr. Smith mentioned that “Multifocality in this setting is generally construed as evidence of metastasis”. It is true that one study of pancreatic NEC detected multifocal liver metastases by PET/CT [6]. Liver metastases of NEC are very common; however, for both cases we presented, gastroscopy, colonoscopy and PET-CT examinations failed to find lesions in any other organ, which led us to exclude the possibility of tumor origin from organs other than the liver. Both cases had large liver lesions, and from biopsy we confirmed both liver lesions were NEC. As we only observed lesions in the liver for case one, we are especially confident of the diagnosis of PHNEC.

b) To address the possibility of ‘multifocality as primary’ in PHNEC, we surveyed the literature extensively and found multiple reports suggestive of multiple tumors in the liver for PHNEC. One review reported that 37.2% (35 out of 94) of PHNEC cases had multiple tumors involved, and 23.4% (22 out of 94) were bilobar [7]; another review reported that 23.7% (28 out of 118 cases) of PHNEC were ‘multicentric’ with a right-lobe bias (48.4%, 60/124), and 18.5% (23/124) were bilobar [8]. Thus, bilobar liver lesions in case two can be ‘multicentric’ or ‘multifocal’ PHNEC.

Lastly, Dr. Smith asked “Is there any suggestion of syndromal neoplasia, such as might explain multifocality in the context of this rare liver tumor?” We did not find a link between multifocality of PHNEC and syndromal neoplasia in the literature. It has been previously reported that PHNEC is normally endocrinologically silent (i.e. the tumors do not present with carcinoid syndrome) due to the rapid degradation of neoplastic-derived hormones via portal circulation, and only 6.8% (6 out of 88 cases) of PHNEC presented with classic carcinoid syndrome [8], although another review reported slightly higher 16.7% (14 out of 84) carcinoid syndrome-presenting cases [7].

Dr. Smith brought up very interesting and important questions, but these are beyond our capability for this project. However, we have incorporated our response in the Discussion of the main manuscript. For studies without multi-dissection of the tumors from surgery or autopsy, it is difficult to completely exclude the co-occurrence of other primary sources. Although we cannot resolve this issue for the cases we are reporting, it will be an aim of our long-term research as we seek to extract genomic data from multi-dissection samples for other, future PHNEC cases.

Reference:


