

APC-24-20 review comments and author response

Reviewer A

Thank you for the case report on the rare histology cancer patient. The report describes a 47-year-old female initially diagnosed with acute pancreatitis, later found to have metastatic CCCP with rapid disease progression.

Several questions:

1. Is the core biopsy done at the subcutaneous nodule? No liver biopsy or pancreatic biopsy?
 - a. Reply: Yes, it was a core biopsy. There were no liver or pancreatic biopsies.
 - b. Changes in the text: none. This is stated on page 2 line 94.
2. Is that possible this could be uterine clear cell carcinoma with metastasis? What is the reason/path for her hysterectomy?
 - a. Reply: The hysterectomy pathology included chronic cystic cervicitis with squamous metaplasia, proliferative endometrium with benign polyps, and an intramural leiomyoma. There was no evidence of clear cell carcinoma in her uterus.
 - i. Changes in the text: This was added to page 3 line 103-105.
 - b. Reply: She had a hysterectomy for heavy menstrual bleeding.
 - i. Changes in the text: This was added to page 2 line 78.
 - c. The pathology of the subcutaneous nodule had immunohistochemical stains diffusely positive for CK7, focally positive for CK20, CDX2 and GATA3 but negative for TTF1 and PAX8 which in the clinical context is compatible with pancreaticobiliary tract origin.
 - i. Changes in the text: none, details are already included in page 3 line 100-101.
3. How long has the patient been on gemcitabine/abraxane?
 - a. Reply: The patient has been on gemcitabine/Abraxane since January of 2024, adding up to 8 months.
 - b. Changes in the text: page 3 line 121-123.
4. Did she get germline and somatic mutation testing?
 - a. Reply: She did have a referral to genetics who performed germline and somatic testing. She was found to have a single pathogenic variant in the gene FANCL, indicating she was a carrier of Fanconi Anemia, but there was no genetic mutation for pancreatic cancer.
 - b. Changes in the text: page 3 line 112-115.
5. It is a pity that staining for HNF-1 β was not available at the institution. Is that

possible to send it out for testing to confirm the expression of HNF-1 β in this case?

- a. Reply: We do not currently perform HNF-1 β testing at the Cleveland Clinic and will refrain from the added expense of a send out test.
- b. Changes in the text: page 4 line 161-162.

Reviewer B

In this article, the authors report a case of a clear cell carcinoma of the pancreas. The manuscript is poorly written and requires grammar and spell check before submitting for review.

1. Page 3, Case presentation should be briefly described, instead of copying and pasting from clinical history like authors did from line 71-line 118
 - a. Reply: The case presentation was shortened and revised to be more concise. Details of the workup that included lab values and reference ranges were removed.
 - b. Changes in the text: page 2-3, lines 77-125.
2. There are no new findings in this paper.
 - a. Reply: This paper illustrates the need for HNF-1 β staining to be available and utilized at institutions as it can give insight into the prognostic factors of this unique disease and has the potential for use in targeted treatments. Without support and research papers to show the utility of HNF-1 β staining, clinicians may not be aware of this marker's potential.
3. Figure 6; Kaplan-Meier survival curve is from work of another group without reference.
 - a. Reply: Due to concern for copyright violations and given the fact that deletion of this figure does not change the significance of this paper, this figure was removed from the paper.
 - b. Changes in the text: removed from page 4, line 154-155.
4. Authors write about the importance of HNF-1B in diagnosis and prognosis and state that this staining is not available in their institution. Can they send it to reference lab to perform the stain? There is no specific staining indicating pancreatic origin performed. Authors should describe differential diagnosis and prove that this is not metastasis from another source.
 - a. Reply: We do not currently perform HNF-1 β testing at the Cleveland Clinic and will refrain from the added expense of a send out test.
 - b. Reply: The specific staining that indicates pancreaticobiliary origin is included in the immunohistochemical results highlighted on page 3 lines 100-101.

- c. Reply: Differential diagnosis discussion was added and included in the “Discussion” body of the text.
 - i. Changes in the text: page 4 lines 147-152.

APC-24-20-R1 review comments and author response

Reviewer Comment

Comment 1: The manuscript highlighted the importance of HNF-1B in diagnosis and prognosis of clear cell carcinoma however there is no information in this case on HNF-1B, which is a defect. I would not recommend this for publication.

Reply 1: HNF1-B is discussed throughout line 141-148. On line 163-164, we discuss that HNF-1B testing unfortunately was not available at our institution. We did not feel it was ethical to send out the test and incur an additional cost to the patient. I included this in the paper.

Update: “Unfortunately, staining for HNF-1 β was not available at our institution and we did not feel it was ethical to add costs to the patient by seeking a send-out test.”