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Title: Intrahepatic cholangiocarcinoma in patients with primary sclerosing cholangitis and ulcerative colitis: 2 case reports

Point-by-Point Response

We are very grateful to the reviewers for their comments on this study and the related manuscript. The responses to the reviewers' questions and comments are provided below. Notably, the changes made do not influence the content, conclusions, or framework of the paper. We have not listed below all the minor changes made; however, these are highlighted in red text in the revised manuscript for your convenience.

Reviewer #1:
Dear editors and authors of the manuscript! The topic of the manuscript is extremely interesting, because there are no large randomized studies that would give an unambiguous opinion about high-risk background diseases for intrahepatic cholangiocarcinoma. However, there is no doubt that chronic autoimmune inflammation in the digestive tract is an absolute risk of developing cancer. The authors have shown confirmation of this thesis by the described clinical cases. But the concept is not new.

Response: Thank you for your insightful comment. It is well known that CCC can arise from PSC in long-term follow-up cases. However, in this case report, one patient had almost no symptoms; yet the tumor had grown considerably by the time of diagnosis and surgery and adjuvant chemotherapy was ineffective, resulting in death. Another patient had a relatively small lesion that could have been surgically removed but died due to liver dysfunction. We learned from these cases that when CCC arises in PSC patients with UC, the prognosis may be significantly worse. We believe it is necessary to disseminate this lesson widely to clinicians, and thus we have decided to seek publication of this case report.

Comments:
1. is it possible to provide data on immunohistochemical examination of tumors?

Response: In Case 1, immunohistochemical testing of tumor cells was performed. The tumor cells showed CK7(+), Ck19(+), MUC1(partly+), CD10(-), HepPar-1(-), AFP(-), Arginase-1(-), Glypican-

3(-), CD117(-), and CD56(-). This information has been added to the text. (Page 9, Lines 187–189)

2. Figures 1 and 3 are a double.

Response: Thank you for pointing out our mistake. We have corrected Figure 3 as needed.

3. The discussion does not contain significant scientific results achieved by the authors, which affects the perception of the manuscript.

Response: Thank you for your accurate comment. To address this, in the final portion of the discussion, we have added that the two cases we experienced can serve as lessons for future medical practice. A more thorough description of these lessons has also been provided within the related text. (Page 11, Lines 248–251)

4. I would recommend the authors to change the design concept of their manuscript, what is the uniqueness of the cases? After all patients with ulcerative colitis and primary sclerosing cholangitis should still be under constant diagnostic and therapeutic control in view of the chronic course of the disease with periods of exacerbation. It was strange in this case to miss the formation of 10 cm in diameter.

Response: Thank you for your comments. It may seem strange to overlook a tumor with a diameter of 10 cm. However, the patient was largely asymptomatic until they started complaining of lower right abdominal pain. This suggests that the tumor grew relatively rapidly with few symptoms. To address your comment, we have also added a relevant description of this aspect to the discussion section. (Page 11, Lines 252–254)

Reviewer #2:
Specific Comments to Authors: Dear Author, thank you for sharing your research. Unfortunately, after a careful revision, I think that a double case report doesn't fit this Journal. In particular, your manuscript doesn't add any novel consideration or treatment in the field of gastrointestinal surgery or gastroenterology. Regards

Response: Thank you for your comment. While it is not uncommon for CCC to arise from PSC in long-term follow-up cases, this case report highlights two particular cases. One patient had minimal symptoms; yet the tumor had significantly grown by the time of discovery, resulting in death despite unsuccessful surgery and chemotherapy. The other patient had a relatively small lesion that could have

been surgically removed; however, the patient died due to a liver dysfunction that developed afterward. These cases serve as a lesson – when CCC arises in PSC patients with UC, the prognosis may be considerably worse. We believe it is important to disseminate this lesson widely to clinicians and thus have decided to seek publication of this case report.