Response to the Reviewers' comments.

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| Reviewer Name: | Anonymous |
| Review Time: | 2017-06-21 00:26 |
| Comments To Authors: | Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic disease of the liver. Some cases of PBC complicated by HCC have been previously reported. In this report, the authors present a case of PBC metachronously complicated by cHCC-CCC and HCC. The authors concludes that in patients with PBC, it is necessary to check up not only liver function but also carcinogenesis including HCC, CCC and cHCC-CCC.<br><br>1. This case report is well organized and clearly describes the clinical information. But the discussion section needs to be strengthened. Disease diagnosis, differential diagnosis, treatment, and experiences need to be thoroughly discussed.<br><br>The authors appreciate the reviewer's comment. We described more deeply with regard to the disease and the differential diagnoses in Discussion. (Please see page 8, line 13.)<br><br>2. The multi-centric tumorigenesis resulted from PBC is rarely reported and would be of interest to the specialists in the field. It is advisable to further perform biomolecular studies based on different tumor specimens.<br><br>Immunohistochemistry using the biomolecular markers (CK7, CK18, CK19 and Hepatocyte) has been already performed for the first cHCC-CCC in Figure 2. It was additionally performed for the second HCC, resulted in the multi-centric carcinogenesis. We described in Case Presentation without a figure. (Please see page 7, line 6.) |
| Classification: | Grade C (Good) |
| Language Evaluation: | Grade B: minor language polishing |
| Conclusion: | Accept |
| Comments To Authors(File): | |

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| Reviewer Name: | Anonymous |
| Review Time: | 2017-06-24 18:55 |
| Comments To Authors: | The authors present a very rare and interesting case of combination of HCC and ICC in cirrhosis and a metacronous case of HCC. The appearence of cHCC-ICC in cirrhosis is rare even in large cohorts and generally it appears in viral (HBV and/or HCV) infected patients. Some changes should be made.<br>1) First of all, the term primary biliary cirrhosis should be changed in the recent EASL/AASLD proposed term "PRIMARY BILIARY COLANGITIS".<br><br>We changed the title and the introduction regarding the abbreviation of PBC. (Please see page 3, line 2.)<br><br>2) Was Ca125 detected in both the cases?<br><br>We are very sorry to have not checked CA125 due to the limitation covered by the health insurance.<br><br>3) Was CEUS performed in the patient? If not explain. If yes report the CEUS findings? Did authors use Sonovue or Sonoazoid?<br><br>We absolutely respect the reviewer's comment. Although CEUS using sonazoid is available in our hospital, it is not included in the preoperative routine imaging studies.<br><br>4) Authors should better explain why they chose surgery in their patient. Their explanation appears too simplistic: the first nodule was clearly visible on US and, considering the specific patterns of enhanced CT and MRI for HCC in cirrhosis, percutaneous RF ablation in a 74 |

years old patient should be the best approach. On the other hand, was percutaneous US guided biopsy considered prior to surgery? The same thing for the second nodule.

The operative indication for each time is described in Case Presentation. The first one was that the tumor was involved in MHV. If RFA performed, the cooling effect around MHV would be occurred, leading to the insufficient ablation. The second one was that the tumor was not detected using ultrasonography preoperatively. Moreover, the tumor was not detected even with intraoperative CEUS. Therefore, we performed partial resection based on the anatomical structure including the Glissonean sheath and the hepatic vein.

5) The 2 tables with laboratory data are unnecessary.

The authors really respect this comment. However, the authors think that preoperative laboratory data including liver function test and tumor markers are informative to understand the condition of PBC and the tumors. We omitted some data and simplified 2 tables.

6) Figures are good

We thank for the reviewer's comment.

7) References should be updated: consider and discuss in the discussion section: Incidental Intra-Hepatic Cholangiocarcinoma and Hepatocholangiocarcinoma in Liver Transplantation: A Single-Center Experience. Serra V, Tarantino G, Guidetti C, Aldrovandi S, Cuoghi M, Olivieri T, Assirati G, De Ruvo N, Magistri P, Ballarin R, Di Benedetto F. Transplant Proc. 2016 Mar;48(2):366-9. doi: 10.1016/j.transproceed.2015.12.044. and Combined hepatocellular carcinoma and cholangiocarcinoma (biphenotypic) tumors: clinical characteristics, imaging features of contrast-enhanced ultrasound and computed tomography. Li R, Yang D, Tang CL, Cai P, Ma KS, Ding SY, Zhang XH, Guo DY, Yan XC. BMC Cancer. 2016 Feb 25;16:158. doi: 10.1186/s12885-016-2156-x.

According to this comment, we added the second reference. (Please see page 8, line 23.) The author could not regard the first reference as an appropriate one for this case report.

Classification: Grade C (Good)

Language Evaluation: Grade A: priority publishing

Conclusion: Minor revision

Comments To Authors(File):

Reviewer Name: Anonymous

Review Time: 2017-07-02 00:16

Comments To Authors:

This is an original and interesting paper describing a liver tumor on liver cirrhosis that has never been previously reported. However, several changes and corrections should be carried out before publication

1 The name Primary biliary cirrhosis should be replaced by Primary biliary cholangitis in title and text since in the new nomenclature the word ¨cirrhosis ¨ was changed to ¨cholangitis ¨(Beuers U. et al. Changing Nomenclature for PBC: From 'Cirrhosis' to 'Cholangitis. Am J Gastroenterol 2015; 110:1536–1538)

We absolutely respect this comment and modified the title and the introduction with the reference of Beuers et al. (Please see page 5, line 2.)

2 Dynamic characteristics and contrast behavior of cHCC-CCC in the arterial and venous phase of TC and RMI should be more deeply described by authors within the ¨Case report section ¨: A better description at this point could help the reader to understand more why a resection of small tumor associated with normal serum level of tumor markers was carried out.

We appreciate the reviewer's comment and described in detail in Case Presentation. (Please see page 8, line 14) The operative indication for each tumor has already been described.

3 A potential metabolic syndrome as a risk factor for carcinogenesis was raised by authors within ¨discussion section¨. However, a diagnosis of metabolic syndrome in absence of both serum insulin level and HOMA score determination in patients with normal BMI is very difficult to understand. This paragraph should be modified or removed from the text.

The authors completely agree with the reviewer's comment. As we had not regarded the carcinogenesis as metabolic syndrome derived one, both serum insulin level and HOMA score were not checked. Finally, we decided to remove this paragraph.

4 Where authors say in the discussion section ¨In the present case, as Theise et al. indicated, the result of EpCAM immunohistochemistry (a stem cell marker), might be consistent with that of mixed type cHCC-CCC¨, a bibliographic reference is lacking.

We moved the citation to let the readers understand better. (Please see page 9, line 18)

5 Normal range of liver function tests are lacking within table 1.

The authors believe that the normal range of liver function tests do not differ very much in the world and leave it as before.

6 Data are not clearly showed in Table 1. Two tables with separate data should be carried out.

We omit some data and simplified both Table 1 and 2.

Classification: Grade C (Good)

Language Evaluation: Grade B: minor language polishing

Conclusion: Minor revision

Reviewer Name: Abu Bakar Hafeez Bhatti

Review Time: 2017-07-02 01:13

Comments To Authors: Authors have reported a single case of a PBC female patient with development ver related tumors over a 24 year period. Please clarify the following.

1) Was this patient under surveillance or screening since the first liver mass she developed was found incidentally? Are there any screening recommendations in PBC patients?

The authors respect this comment and add the recommended surveillance with a reference. As the patient with PBC is to be screened routinely, the hepatologist has followed-up this case every 6 to 12 months since the first diagnosis of PBC. (Please see page 6, line 3.)

2) The first tumor was resected along with part of MHV. Was the vein involved on histopathology? If it was, was a partial resection considered appropriate treatment?

We appreciate the reviewer's comment. The pathological study revealed that MHV was involved in the first tumor. If anatomical resection was planned, central bisectionectomy would be appropriate. However, we decided to perform partial resection due to insufficient liver function reserve of PBC. (Please see page 6, line 14.)

3) Later, partial resection of another liver segment was performed. Do you think this patient would benefit from more radical procedures like liver transplant for example. I understand that she is not cirrhotic and has no decompensations but she has had multiple tumors with one possibly involving MHV.

The authors completely agreed with the reviewer's comment. We think that the best treatment for this patient is liver transplantation as the reviewer mentioned. However, there is the limitation of not only the deceased donor pool and but also the living donor.

4) What is her follow up routine post resection?

The author believe that imaging studies with CT and/or MRI and tumor markers including AFP, PIVKA-II, CEA, CA19-9 are necessary.

5) Was any adjuvant chemo given to her? Thank you

The authors believe that there is no evidence of adjuvant chemo therapy for cHCC-CCC and HCC.

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| Classification: | Grade C (Good) |
| Language Evaluation: | Grade B: minor language polishing |
| Conclusion: | Minor revision |