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Title: Primary malignant melanoma of the biliary tract: case report and review of the literature.

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WORLD JOURNAL OF CLINICAL CASES

Dear Editor

Thank you very much for the opportunity to publish our article entitled “Primary malignant melanoma of the biliary tract: case report and review of the literature.”, in the World Journal of Clinical Cases. We appreciate the valuable feedback from Reviewers. Following your instructions we have undertaken appropriate modifications as follows:

Reviewer #1:

Comments: In this case report and review of the literature, some comments are listed:

1.The English writing is poor, it should be edited by English native speaker.

Answer: As certified in the attached document, the article has been reviewed by an English native speaker. Although another REVIEWER has reported that the article is WELL WRITTEN, we have undertaken a second revision to improve the English of the manuscript. All changes appear in RED in the new version of the article.

Comments: 2.Regarding the treatment, p1, last line, it is wrong about“ resection of the common hepatic conduct” , it will be “duct”. Please confirm whether the patient received bil. hepatojejunostomy or other ? wording“ start immunotherapy with nivolumab.” was suggested. Please check” The patient remains disease-free 36 months after metastatic lung lesion rather than initial diagnosis (surgery for CHD).

Answer: The phrase "resection of the common hepatic conduct" has been corrected and now appears as: "resection of the common hepatic duct" (in RED in the new version of the manuscript).

The phrase “to start treatment with nivolumab” has been corrected and now appears as: “to start immunotherapy with nivolumab”, (in RED in the new version of the manuscript).

The phrase "The patient remains disease-free 36 months after diagnosis.", has been corrected and now appears as: "The patient remains disease-free 36 months after the treatment of metastatic lung lesions", (all changes appear in RED in the new version of the manuscript).

Comments: 3.P2, conclusion, it is confused when you said “primary metastatic biliary melanoma”. It should be” primary biliary melanoma, S/P resection with lung metastasis, treated successfully with immunotherapy”

Answer: The phrase “the first case of primary metastatic biliary melanoma successfully treated with immunotherapy” has been corrected and now appears as: “the first case of primary biliary malignant melanoma with lung metastases successfully treated with immunotherapy”, (all changes appear in RED in the new version of the manuscript).

Comments: 4.Page 2, in case presentation, you performed Cholangio-NMR first, then did abdominal CT scan. Is it useful for diagnosis if you perform CT scan after NMR. Do you perform ERCP before surgical intervention ?

Answer: Cholangio-NMR means: Magnetic resonance cholangiopancreatography. CT is useful to exclude metastasis. The phrase has been corrected and now appears as: “Magnetic resonance cholangiopancreatography (MRC) revealed dilatation of the intrahepatic biliary tract and stenosis of the common hepatic duct. ...Abdominal computed tomography (CT) confirmed the findings of the NMRC and was negative for distant metastasis.” (in RED in the new version of the manuscript).

Comments: 5.Page 3, is it IV or oral for nivolumab?

Answer: The current administration of nivolumab is intravenous. For greater precision the phrase has been modified as follows: “After confirming the diagnosis of pulmonary metastasis of primary malignant melanoma of the biliary tract it was decided to start treatment with intravenous nivolumab at a dose of 3 mg/kg every 2 weeks.” (in RED in the new version of the manuscript).

Comments: 6.Page 4, I did not understand the sentence” This case reveals the excellent response to immunotherapy for all kinds of patients regardless of the primary origin of the melanoma.” It should be rewritten.

Answer: This phrase has been rewritten as follows: "While most immunotherapy clinical trials only include malignant melanomas of the skin, this case exemplifies that the excellent response of malignant melanoma to this therapy is not limited exclusively to primary malignant melanomas of the skin." (in RED in the new version of the manuscript).

Comments: 7. Pag 4, Conclusion, it still mild confused when you described “The case of the patient with metastatic primary biliary melanoma” please verify it.

Answer: The phrase has been rewritten for clarity as follows: “Here, for the first time, we describe a case of primary biliary malignant melanoma with pulmonary metastases, successfully treated with immunotherapy.” (in RED in the new version of the manuscript).

Reviewer #2:

Comments: The manuscript entitled “Primary malignant melanoma of the biliary tract: case report and review of the literature” is well written.

Comments, 1. The abstract part, in the background section “the patient reported here is the first case of primary metastatic biliary melanoma treated....after

diagnosis". The reader would be confused about the primary or metastatic melanoma of biliary tract. The sentence should be rewrite to "pulmonary metastatic biliary melanoma".

Answer: The phrase has been rewritten for clarity as follows: "The patient reported here is the first case of primary malignant melanoma of the biliary tract with pulmonary metastasis treated with immunotherapy." (All changes appear in RED in the new version of the article).

Comments, 2. What is Cholangio-NMR? This abbreviation should be explained.

Answer: Cholangio-NMR means: Magnetic resonance cholangiopancreatography. The phrase has been corrected and now appears as: "Magnetic resonance cholangiopancreatography (MRC) revealed dilatation of the intrahepatic biliary tract and stenosis of the common hepatic duct." (All changes appear in RED in the new version of the article).

Comments, 3. The figure of CT should be demonstrated in this manuscript. CT findings should be described more details.

Answer: Unfortunately we do not have a CT figure with suitable quality for publication. For this reason no CT figure had been sent along with the manuscript.

Comments, 4. There are some benign biliary stricture condition that should be preoperatively excluded including IgG4-related sclerosing cholangitis. How about the serum IgG4 level?

Answer: Due to the high suspicion of neoplasia an IgG4-related sclerosing cholangitis had not been included in the differential diagnosis. For this reason we do not have the IgG4 seric levels either.

Comments, 5. How about the preoperative cytology and biopsy? ERCP was performed?

Answer: Preoperative cytology has been falsely negative for malignancy. Consequently, the following sentence has been included in the new version of the manuscript: "Cytological samples obtained by endoscopic retrograde cholangiopancreatography were negative for malignancy (non-representative samples)." (All changes appear in RED in the new version of the article).

Comments, 6. What is the learning point in this case?

Answer: Primary malignant melanoma of the biliary tract is a very rare entity. While most immunotherapy clinical trials only include malignant melanomas of the skin, this case exemplifies that the excellent response of malignant melanoma to this therapy is not limited exclusively to primary malignant melanomas of the skin. Here, for the first time, we describe a case of primary biliary malignant melanoma with pulmonary metastases, successfully treated with immunotherapy.

Reviewer #3:

Comments: Thank you for the report of a rare case. I have some question.

Comments 1. In page 1, what did "NMR" mean ?

Answer: Cholangio-NMR means: Magnetic resonance cholangiopancreatography. The phrase has been corrected and now appears as: "Magnetic resonance

cholangiopancreatography (MRC) revealed dilatation of the intrahepatic biliary tract and stenosis of the common hepatic duct.” (All changes appear in RED in the new version of the article).

Comments 2. 5 criteria was shown to diagnose primary melanoma in page 3. What items did the case meet?

Answer: In the present case, the histopathological and immunohistochemical (positive for HMB45, vimentin and S100 protein but negative for cytokeratins) studies confirmed the diagnosis of malignant melanoma. In addition, this case has met the 5 criteria proposed for the diagnosis of primary melanoma in the biliary tract proposed by Ricci et al.

Comments 3. I couldn't find figure 2 and 3.

Answer: Figures 2 and 3 have been included in the manuscript. We do not know why you have not been able to find them.

Comments 4. In table 3, what did "CHC" mean ?

Answer: CHC has been a mistake. It has been corrected. CHD means: common hepatic duct. (All changes appear in RED in the new version of the article).

Thank you for your consideration.
Yours sincerely,

Soledad Cameselle-García, MD