



PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology

Manuscript NO: 61338

Title: Hepatocellular carcinoma with Biliary and Neuroendocrine Differentiation: A Case Report and Review of the Literature

Reviewer's code: 00006009

Position: Associate Editor

Academic degree: MD, PhD

Professional title: Head, Professor

Reviewer's Country/Territory: France

Author's Country/Territory: United States

Manuscript submission date: 2020-12-03

Reviewer chosen by: Lian-Sheng Ma

Reviewer accepted review: 2020-12-04 09:15

Reviewer performed review: 2020-12-04 10:22

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

SPECIFIC COMMENTS TO AUTHORS

Interesting case report. Some clarifications are however needed: 1) did the patient underwent octreoscan before or after surgery? If no explain why. If yes indicate the findings. 2) was HCV eradicated? 3) How rectal neuroendocrine tumor was classified and managed? Did the patient receive adjuvant therapeutics after endoscopic resection?

The case report is poorly written. The titles of paragraphs are useless and confusing. CT scan results are never detailed. MRI result are incomplete: whether tumor washout was observed at the portal phase is not indicated. Management is intriguing: authors indicate that 'pathologic findings raised the possibility of metastatic disease at the time' but hepatic surgery was however decided and only staging laparoscopy was performed. What about extraabdominal metastases? FDG and Gallium-68 PET-scan are inadequate for that purpose. Finally the discussion is somewhat poor. Hypothesis regarding common molecular mechanisms involved in the 3 observed tumor differentiations, for instance, would have been interesting. A complete discussion regarding imaging would also have been interesting by explaining why the diagnosis of HCC, NET or cholangiocarcinoma monodifferentiated tumors could have been challenged.



PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology

Manuscript NO: 61338

Title: Hepatocellular carcinoma with Biliary and Neuroendocrine Differentiation: A Case Report and Review of the Literature

Reviewer's code: 02544565

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Attending Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2020-12-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-12-06 07:51

Reviewer performed review: 2020-12-13 08:09

Review time: 7 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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https://www.wjgnet.com

SPECIFIC COMMENTS TO AUTHORS

This is a case report of a very rare liver tumor presenting with differentiation to HCC/CCC/NEC. As the authors described in the discussion, only few similar cases have been reported so far, and this is a very rare case report. It's very well written, but it's necessary to add a few more points. Please refer to the following points for correction and resubmit. Major point 1) The final histopathological diagnosis in this case was a mixed tumor in which the lesion in segment 4 was differentiated into hepatocellular carcinoma (HCC), cholangiocellular carcinoma (CCC), and neuroendocrine carcinoma (NEC). And, the lesion of Segment 7 was mANEC which mixed cholangiocellular carcinoma and neuroendocrine carcinoma. Although this is a very rare and interesting case, imaging is not well described. In these 2 lesions, details on contrast-enhanced dynamic CT and imaging on MRI (T1-weighted, T2-weighted, DWI, etc.) should be described in detail. Please explain the CT/MRI findings while comparing with the lesion distribution in the postoperative specimen as well. 2) The patient underwent endoscopic resection for rectal carcinoids in 2012 and 2017. It cannot be denied that the origin of the present hepatic lesion is metastasis from rectal carcinoid. Therefore, the size of the endoscopically resected lesion and the presence or absence of vascular/lymphatic invasion should be described. 3) The authors describe this case is intra-hepatic metastatic case. Please discuss in more detail about the mechanism of tumor and explain why the final diagnosis was metastasis rather than simultaneous occurrence or collision tumor. 4) The authors describe that NEC has a worse prognosis than HCC, CCC, or mixed HCC-CCC. Why did they choose to treat CCC rather than NEC in postoperative chemotherapy? Since the histological diagnosis of lymph node metastasis that recurred after surgery was based on the CCC component, did they select GEM/CDDP therapy as adjuvant chemotherapy? Please mention which disease (HCC,



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CCC, NEC) was dominant in the resected specimen. Postoperative chemotherapy for NEC may have been the choice in terms of prognostic factors. Therefore, selection of chemo regimen for postoperative chemotherapy should be discussed in more detail. 4) Please create a table that summarizes the case reports so far after adding the following case. Clin J Gastroenterol 2014 Oct;7(5):449-54. doi: 10.1007/s12328-014-0521-3. Epub 2014 Aug 13. Primary hepatic neuroendocrine carcinoma with a cholangiocellular carcinoma component in one nodule Yoshihito Kano 1, Sei Kakinuma, Fumio Goto, Seishin Azuma, Yuki Nishimura-Sakurai, Yasuhiro Itsui, Mina Nakagawa, Atsushi Kudo, Minoru Tanabe, Susumu Kirimura, Tomonori Amano, Takashi Ito, Takumi Akashi, Yasuhiro Asahina, Mamoru Watanabe



PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology

Manuscript NO: 61338

Title: Hepatocellular carcinoma with Biliary and Neuroendocrine Differentiation: A Case Report and Review of the Literature

Reviewer's code: 02541391

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2020-12-03

Reviewer chosen by: Lian-Sheng Ma

Reviewer accepted review: 2020-12-07 05:33

Reviewer performed review: 2020-12-17 22:08

Review time: 10 Days and 16 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

Although the manuscript presents an interesting and rare case (hepatocellular carcinoma with biliary and neuroendocrine differentiation), many parts of the article require revision. 1. The content of the manuscript does not fully reflect the title as the authors did not include a "Review Literature" section. I recommend that the authors summarize in a table similar cases published so far, even if their number was small. 2. History of past illness (neuroendocrine tumors in the rectum, detected on routine colonoscopies and removed endoscopically in 2012 and 2017), requires more explanations and clarifications. 3. The link between previous history of hepatitis C and history of low grade well differentiated neuroendocrine tumor, on the one hand, and current tumors detected, requires a detailed approach.