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Dear Sir or Madam

Please find enclosed the revised manuscript entitled **Intra-ampullary papillary-tubular neoplasm combined with ampullary neuroendocrine carcinoma: A case report** by Zavrtanik, et al.

We would like to thank the reviewers for the comments and suggestions on the manuscript. We have addressed all the comments, as discussed in more detail below.

We believe this manuscript is now suitable for publication in World Journal of Clinical Cases.

Sincerely,

Prof. Aleš Tomažič, MD, PhD
Corresponding author

Response to reviewers:

Reviewer #1:
Scientific Quality: Grade E (Do not publish)
Language Quality: Grade B (Minor language polishing)
Conclusion: Rejection
Specific Comments to Authors: 1. It is a good case and review of rare tumor. 2. But, it does not add to any information in the management or clinical practice. 3. The combinations of various cell lines are possible at ampulla, but still surgery remains the first choice. Endoscopic resection as alternative treatment depending on the clinical circumstances. 4. Adjuvant treatment is always considered at more dominant cell line. 5. So, no further information is added to clinical management by the article.

Comment: *Thank you for your comment. The aim of our manuscript was to present a rare tumor combining intra-ampullary papillary-tubular neoplasm and ampullary neuroendocrine carcinoma describing its clinical and histopathological features in detail. Due to their rarity, such tumors are characterized by diagnostic pitfalls and represent a major challenge for patient management in terms of their biology and clinical behaviour. Although no further information is provided regarding clinical management of ampullary tumors, this tumor is interesting as it is formed of two different entities that are associated with contrasting clinical outcomes and solid evidence on optimal treatment strategy is lacking. All this encourage publication of such reports. We believe our manuscript makes an important contribution to better understanding the natural history of these tumors which is crucial for further research in this field aiming at standardized treatment implementation.*

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The authors report the first case of IAPN associated with NEC. Cases of impulsive complications of mixed neuroendocrine-nonendocrine neoplasia and two different tumors are extremely rare; in addition, the histopathological findings after resection were examined in great detail. I have included several comments below and ask that you respond to them carefully. 1. It is difficult to accept that a tumor that was negative for chromogranin became a neuroendocrine tumor. I request that the objectivity of the pathological diagnosis be ensured by second opinion.

Comment: *Thank you for your remark. Neuroendocrine carcinomas are poorly differentiated epithelial neoplasms with morphological and immunohistochemical features of neuroendocrine differentiation. Chromogranin A and synaptophysin are the recommended general neuroendocrine markers, however, neuroendocrine carcinomas are less likely to express either of the general neuroendocrine markers (Faggiano et al., Sorbye et al., Garcia-Carbonero et al.). Therefore, according to the 2019 World Health Organisation classification, the essential diagnostic criteria for small intestine and ampullary neuroendocrine carcinomas lack the criterion of synaptophysin and chromogranin A expression (as is the case for the*

diagnosis of neuroendocrine tumors). Instead, the diagnosis is based on typical morphological features including small cell carcinoma or large cell carcinoma pattern with poorly differentiated cells growing in sheets or poorly formed trabeculae and demonstrating high mitotic rate and Ki-67 proliferation index (WHO Classification of Tumours). Furthermore, the tumor cells showed positive staining for insulinoma-associated protein 1 (INSM1) which is a sensitive and highly specific marker of neuroendocrine differentiation.

References:

Faggiano A, Sabourin JC, Ducreux M, Lumbroso J, Duvillard P, Leboulleux S, Dromain C, Colao A, Schlumberger M, Baudin E. Pulmonary and extrapulmonary poorly differentiated large cell neuroendocrine carcinomas: diagnostic and prognostic features. *Cancer* 2017;**110**:265–74 [PMID: 17569104 DOI: 10.1002/cncr.22791]

Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer* 2014;**120**:2814–23 [PMID: 24771552 DOI: 10.1002/CNCR.28721]

Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, Sedlackova E, Toumpanakis C, Anlauf M, Cwikla JB, Caplin M, O'Toole D, Perren A. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology* 2016;**103**:186–94 [PMID: 26731334 DOI: 10.1159/000443172]

Perren A, Basturk O, Bellizzi AM, Scoazec JY, Sipos B. Small intestinal and ampullary neuroendocrine neoplasms. In: WHO Classification of Tumours Editorial Board. Digestive System Tumours. WHO Classification of Tumours. 5th ed. Lyon: IARC, 2019: 131–134

2 . Did this patient underwent pathological examination of the liver metastases by liver biopsy?

Comment: *Thank you for pointing that out. The patient did not undergo liver biopsy at the treating oncologist's discretion. In the setting of known malignant disease (in our case being neuroendocrine carcinoma which most frequently (> 70%) metastases to the liver), it was concluded with high certainty that newly formed hypervascular liver lesions in our patient were due to systemic progression of neuroendocrine carcinoma and no time was wasted in initiating systemic therapy.*