

Thanks for the reviewers for their positive and constructive comments. In response to reviewers' suggestions, we have modified the manuscript by addressing the suggestions from the reviewers that were considered necessary for this manuscript by the reviewers, and also highlighted the changes in the manuscript for review.

Reviewer#1: This paper showed a case of MSNN of the pancreas. This case is rare and interesting. However it will require some revisions before publication.

1, Please impact new findings in this report compared with previous case reports.

Reply: We thank the reviewer for his/her positive comments. As for the new findings of this manuscript, we first reclassified the PanNET components in the MSNNs reported previously by using the latest 2017 WHO classification of pancreatic neuroendocrine neoplasms, and further compared the clinicopathological characteristics between VHL-associated and non-VHL-associated MSNNs. In addition, to the best of our knowledge, we are the first to report a MSNN with a diffuse PSCN component involving the entire pancreas in a Chinese woman, which was shown in Table 1 for details.

Reviewer#2: In this paper, the authors presented a rare variant of pancreatic tumor, which is difficult to be diagnosed and treated. the paper is valuable but some points need to be addressed:

1. Typing of manuscript, including references list, should respect the Basihideng criteria.

Reply: We thank the reviewer for his/her positive comments. We have revised the format of our manuscript according to the Basihideng criteria.

2. Case presentation - the authors mentioned that the serum parameters were in normal limits. It is necessary mentioning the exact values and the normal ranges used for data interpretation.

Reply: We apologize for this oversight. We already added the normal ranges of the serum parameters in the laboratory examinations section.

3. Case presentation- physical exam - in two consecutive phrases the authors mentioned "CT scan revealed"...please rephrase.

Reply: Thank you for pointing this out. We have rephrased the sentence in the manuscript.

4. Case presentation - as the neuroendocrine component was recently to associate HER-2 positivity in cystic lesions of pancreas, especially in malignant cases (use papers such *Pathol Res Pract.* 2019 ;215(1):82-89. doi: 10.1016/j.prp.2018.10.019), to increase the scientific value of the paper, I suggest to add to the immunoprofile HER-2 antibody.

Reply: We further detected HER-2 antibody in our present case, however, both the diffuse serous cystadenoma and the well-differentiated PanNET were negative for HER-2 antibody (shown in the supplement materials). As for the reviewer mentioned, Gurzu et al. (*Pathol Res Pract.*2019;215(1):82-89. doi:10.1016/j.prp.2018.10.019) examined HER-2 in four pancreatic mucinous cystic neoplasms (MCN), in which three cases showed HER-2 positivity in both dysplastic and invasive component indicating a possibility of trastuzumab therapy^[1]. However, the neuroendocrine component in their study was MCN with neuroendocrine differentiation or with neuroendocrine

immunophenotype rather than a real neuroendocrine tumor. The photos of the tumor cells positive for neuroendocrine immunochemical markers (such as CD56, Chromogranin A) showed in their paper with a tubular/glandular structure, it's a feature of ductal origin tumor (MCN with high-grade dysplasia or with invasive adenocarcinoma). In addition, HER-2 positive area and neuroendocrine markers positive region was different in the figures, photographs of different antibodies expressed in the same area would be more convincing. Adenocarcinoma with a neuroendocrine differentiation or with focal neuroendocrine immunophenotype was reported previously in pancreas^[2], stomach^[3], etc.

In our present case, we reported a diffused serous cystic neoplasm (SCN) with a concomitant well-differentiated PanNET. Pancreatic SCNs are different type of neoplasm from MCNs, in the light of its rarity, the significance and prognostic value of HER-2 expression in Pancreatic SCN are remain unclear, and no literature has been reported. For the well-differentiated PanNETs, in an IHC-based analysis of 140 PanNETs, HER-2 was positive in 2% (3/140) cases. Of the 130 PanNET further evaluated as a tissue microarray by FISH, only 1.5% (2/130) cases had HER-2 gene amplification^[4]. The same result of minority expression of HER-2 in PanNETs were consisted with the retrospective studies from Proca et al (0/27)^[5]. and Goebel et al (0/10)^[6]. In the present case report of a mixed serous-neuroendocrine neoplasm (MSNN), both components negative for HER-2.

We cautiously believe that because of the limited cases of MSNNs accumulated in the literature, it is impossible to draw any conclusion of the relationship between HER-2 and the biological behavior and prognosis of MSNN. Thus, we decided just to list the HER-2 expression result in the pathological findings section without discussion its relationship with MSNN. However, we sincerely thanks for the reviewers for his/her constructive comments. We will continue collect relevant cases, in the light to further clarify the correlation between HER-2 and MSNNs.

Reference:

1. Gurzu S et al. *Pathol Res Pract*. 2019 Jan;215(1):82-89.
2. Lee SH et al. *Pancreas*. 2019 May/Jun;48(5):662-669.
3. Zou Y et al. *J Gastric Cancer*. 2019 Mar;19(1):121-131.
4. Corbo V et al. *Ann Oncol*. 2012 Jan;23(1):127-34.
5. Proca DM et al. *Appl Immunohistochem Mol Morphol*. 2008 Jan;16(1):44-7.
6. Goebel SU, et al. *Cancer Res*. 2002 Jul 1;62(13):3702-10.