71161-Answering Reviewers

Dear Editor,

We sincerely thank the efforts from the editor board members and reviewers. The comments from reviewers are excellent and we have revised our manuscript accordingly.

We responded to each comment point-by-point and believe that the revision of this manuscript improved the quality of our study. All changes to the manuscript are highlighted in the revised manuscript.

Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: Well written article and discussion is well presented

Thanks for your comments.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Authors reported a rare case of a 42-year-old female who had nonspecific upper abdominal pain for 4 years, with radiological abnormalities of pancreas that mimicked AIP. Finally, pancreatic biopsy was performed through EUS-guided fine needle aspiration biopsy (EUS-FNA/FNB) and non-functional PNETs was finally diagnosed. STATUS: ACCETTABLE FOR PUBBLICATION PENDING MINOR REVISIONS General considerations: This is a CASE REPORT article. The work is interesting and the paper is very well-written. It is certainly not the first on this topic, but it is very useful “to stress” the difficult differential diagnosis between pancreatic cancer and chronic pancreatitis. Abstract: the abstract appropriately summarize the manuscript without discrepancies between the abstract and the remainder of the manuscript. Keywords: adequate. Reference: inadequate. Please, follow my suggestions.

Paper On some aspects, the authors should address: 1)About the case presentation, was a fist-line ultrasound (US) examination performed? You have not reported the US images. If there are, add them.
Our response: Thanks for your reminder. The patient has been in a long-term outpatient follow-up in another department of our hospital, and MRI has been performed every year since 2015. In order to have a better comparison, we considered

MRI review. Therefore, The patient did not perfome basal US examination.

2)Why did you not consider to integrate imaging evaluation with basal US examination or contrast-enhanced ultrasound (CEUS)? Please, discuss it.

Our response: Thanks for your reminder. We discussed for that as follow, and also added in main text.

"In fact, ultrasound (US) is a first-line examination for abdominal discomfort. However, the operator-sensitive modality is highly subjective, leading to wide variation regarding sensitivity and specificity. Only a mean of 39% (range 17–79%) of PNETs were detected[34]. The recent new technology of contrast-enhanced ultrasonography (CEUS), which can allow continuous evaluation of tumour enhancement patterns in the arterial, venous, and late phases, has led to improvement in the diagnostic capabilities, especially in the detection of liver metastases[34, 35]. EUS can obtain the histological characteristics of gastrointestinal hierarchical structure and ultrasound images of the surrounding organs and is recognized as one of the most important preoperative procedures in the evaluation and management of PNETs[36, 37]. First, EUS can detect lesions smaller than 2–3 cm in diameter, which are not often detected by CT[38]. In many systematic reviews, EUS identified PNETs in over 90% of cases[34, 39]. More importantly, tissue specimens can be obtained by fine-needle aspiration through EUS. For this case, the patient was in a long-term outpatient follow-up in another department of our hospital, and MRI was performed every year since 2015. To have a better comparison, we considered MRI review. Therefore, the patient did not undergo a basal US examination first."

3)In the discussion, it would be appropriate to describe the cross-sectional findings of the NETs. Specifically, I would like you to deep-in the possibility that NETs can manifest without mass effect, that is a diffuse enlargement of the organ without any evidence of focal lesions. Are similar cases described in the literature?

Our response: Thanks for your commends. It is difficult to find small diffuse pancreatic enlargement without symptoms unless the patient requires abdominal imaging. When the pancreas is enlarged to a certain extent, compression symptoms such as jaundice and gastrointestinal discomfort such as abdominal pain may occur. We also expolre on pubmed and found that most pancreatic endocrine tumors are shown as isolated, well-defined, enhanced solid masses rather than diffuse enlargement. And we found a similar case reports as follow: a history of diabetes presented with skin rash and weight loss and have a diffuse enlargement of pancreas

by CT, final diagnosis functional PNETs - glucagonoma. (Qin Y, et al. Glucagonoma with diffuse enlargement of pancreas mimicking autoimmune pancreatitis diagnosed by EUS-guided FNA. Gastrointest Endosc. 2021. PMID: 34058215).

4) I suggest to open a small discussion about the possibility of misdiagnosing a NET in presence of other alterations in the bilio-pancreatic district. In a paper of my research group, which I advise you to discuss and cite, we describe the case of a patient with non-functioning well-differentiated neuroendocrine carcinoma of the head of the pancreas associated with extra-hepatic cholangiocarcinoma. This would also be an opportunity to mention the MPMs (multiple primary malignancies), that is the occurrence of two or more primary malignant tumors arising in the same patient. The article is the following: -Maurea S, Corvino A, Imbriaco M, Avitabile G, Mainenti P, Camera L, Galizia G, Salvatore M. Simultaneous non-functioning neuroendocrine carcinoma of the pancreas and extra-hepatic cholangiocarcinoma. A case of early diagnosis and favorable post-surgical outcome. JOP. 2011 May 6;12(3):255-8. PMID: 21546703.

Our response: Agreed and thanks for your commends. We have a short discussion on this issue, as follows, and also added in main text：

"For lesions in the biliopancreatic region suggested by imaging, multidirectional and comprehensive analysis combined with an evaluation of clinical symptoms is needed. We should not ignore the suggestive role of imaging. Without any clinical symptoms, pancreatic mass is often found by imaging physical examination, such as intraductal papillary mucinous neoplasm (IPMN)[40]. One study showed the case of a patient with nonfunctioning well-differentiated neuroendocrine carcinoma of the head of the pancreas associated with extrahepatic cholangiocarcinoma by MRI and confirmed by surgery[41]. In this case, EUS was ultimately selected according to the imaging changes of MRI over the years."

Figures 1) I have not found figures of US imaging. If there are, add them.

Our response: Thanks for your reminder. The paitent did not perfome the US imaging.

2)In Figure 1, the triangle does not indicate the main pancreatic duct. Please, correct it.

Our response: Thanks for your kindly reminder. We have corrected the Figure 1 and also the Figure 2a.