Peer Review File

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Response to reviewer A:

1. **Comment 1:** Introduction is adequate, although some sentences in the discussion could be included in the introduction and retired from the discussion.

   Reply 1: Thanks so much for the reviewer's comment. We made some revisions to the introduction and discussion. The sentence "**Paraganglioma (PGL) is defined as neuroendocrine tumor (NET) that can or can't produce catecholamine**" was deleted in the part of the introduction. "**Paraganglioma is a rare vascular, neuroendocrine tumor of paraganglia cell cluster originated from the neural crest that has co-migrated with the autonomic nervous system. The majority of the tumor are benign as only 10% of them are malignant and patients often have no obvious clinical symptoms.**" was moved to the part of the introduction. In the discussion, the sentence "**The occurrence of PGL is usually associated with some genetic mutations: succinate dehydrogenase (SDH) subunits (SDHx), Von Hippel–Lin (VHL), endothelial PAS domain protein 1 (EPAS1)/ hypoxia-inducible factor 2α (HIF2A) and prolyl hydroxylase 1/2 (PHD1/2)**" was moved from the first paragraph to the fourth for introducing the PGL more clearly.

   Changes in the text: We have modified the text as advised (see Page 4, line 72-79; see Page 9, line 186-189; in "manuscript without track changes").

2. **Comment 2:** The explanation of the case is a little short. Which tumor makers did you perform?

   Reply 2: Thank you for your advice and we added more information about the patient in the part of the case presentation. The tumor marker for alpha-fetoprotein (AFP,1.3ng/mL), carcinoembryonic antigen (CEA,2.7ng/mL), carbohydrate

antigen199(CA199, <2U/mL), carbohydrate antigen125(CA125,22.5U/mL), serum ferritin(40.1ng/mL), carbohydrate antigen153(CA153,10.8U/mL) were all in the normal range.

Changes in the text: We have modified the text as advised (see Page 5, lines 98-113; in "manuscript without track changes").

3. **Comment 3:** Reviewing images of MRI and CT mass is in the neck of the pancreas nor in the head, at least that is the impression of these images.

   Reply 3: Thank you very much for your comment. Jong Eun Lee has reported that the pancreatic head lies to the right of the superior mesenteric vein (SMV) and the pancreatic neck is lying anterior to the SMV. (1) We have a discussion with radiologists on this problem. They thought the tumor is located in the junction of the pancreatic head and neck, and it is closer to the neck. Therefore, we also believe that it may be more suitable to think the tumor is located in the neck of the pancreas. We decide to adopt your suggestion and revise relevant parts of the article.

   Changes in the text: We have modified the text as advised (see Page 1, line 3; see Page 2, line 28,31,37,42; see Page 4, line 76,80; see Page 5, line 105,109; see Page 7, line 142; see Page 9, line 195; see Page 16, line 376,381; in "manuscript without track changes")

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4. **Comment 4:** Another question is why didn't you think that this mass could be a neuroendocrine tumor of the pancreas, a primary tumor because is difficult identify that this tumor no depend of the pancreas gland.

   Reply 4: We appreciate your comments very much and it is indeed difficult to distinguish this mass from pancreatic neuroendocrine tumor and primary pancreatic tumor. The tumor markers are all in the normal range in blood. It may be a paraganglioma, Castleman's disease, pancreatic neuroendocrine tumor(pNET), or a primary tumor of the pancreas.

1) Pancreatic neuroendocrine tumor(pNET) is classified as functional pNET and non-functional pNET, and the tumor markers for Cg A, Syn, PPP and NSE could be high in the blood. Functional pNET usually has classical symptoms like carcinoid syndrome, Whipple's triplet syndrome, Zollinger-Ellison syndrome, glucagonoma syndrome, Vemer-Morrison syndrome and so on. Usually, their sizes are smaller than 2cm in diameter in CT images. About non-functional pNET, it presents asymptomatic or symptoms of local compression. In the images of enhanced CT, non-functional pNET presents heterogeneous enhancement, necrosis and cystic degeneration.
2) Patients with pancreatic cancer have symptoms of obstructive jaundice and tumor markers for CA199 and CEA are elevated in the blood. On CT, tumor often appears as a heterogeneous hypoattenuating mass and upstream pancreatic duct dilation or the double-duct sign caused by pancreatic and common bile duct obstruction. It typically infiltrates the peripancreatic structures and results in the encasement of adjacent vasculature and adjacent organs.
3) The cystic tumor of the pancreas presents as a cystic low-density mass without enhancement in the arterial phase, which is also different from the mass in the case.

In this case, this mass doesn’t have these classical characteristics of pNET, pancreatic cancer and cystic tumor of the pancreas so it is really difficult to differentially diagnose them. We decided to resect the tumor and made a definitive diagnosis based on pathology. Intraoperative frozen-section examination: The tumor is rich in blood, waiting for the definite diagnosis of routine pathology and immunohistochemistry. Postoperative pathology: the tumor cells are polygonal, the chromatin of cells is fine, the cytoplasm of cells is abundant and tumor cells are arranged in clusters or nests. The results of immunohistochemistry show: CK (pan) (-), Ki-67(+, <1%,), Melan A (-), chromogranin (Cg A) (+), synaptophysin (Syn) (+), supporting cells (S-100) (+) and supporting cells (S-100). All of these prove that the tumor is a paraganglioma.

Changes in the text: We have modified the text as advised (see Page 5, line98-113; see Page 9-10, line203-216; Table 2; in "manuscript without track changes").

5. **Comment 5:** Why didn't you perform a preoperative biopsy?

   Reply 5: Your suggestion is very valuable and we are sorry that we don't explain it clearly in the original text. The tumor's size (3.1×3.8 cm) was large and the patient had obvious abdominal pain, which was indication of surgery. Puncture has certain risks like pancreatic fistula, bleeding, intestinal perforation and so on. It can only obtain a small amount of cytopathological tissue, which could cause false positive or false negative results. Additionally, waiting for the results of puncture may delay treatment and cause tumor progression. The technique of laparoscopic surgery is safe and mature with little harm to patients and it can obtain more tumor tissue for pathological diagnosis. Therefore, after discussing with the patient, we decided to perform laparoscopic exploratory surgery first, and sent the tumor to perform intraoperative frozen section pathological diagnosis after resection. The operation way was determined according to the pathological results of intraoperative freezing.

   Changes in the text: We have modified the text as advised (see Page5-6, line114-119; in "manuscript without track changes").

6. **Comment 6:** Is adequate although probably you should include a differential diagnosis between this two diseases and neuroendocrine tumor of pancreatic gland that could be similar to the description of the CT and MRI.

   Reply 6: We appreciate your comments very much and it's really necessary for clinicians to make a differential diagnosis between the two diseases and pancreatic neuroendocrine tumor(pNET). pNET often has the mutation of ATRX/DAXX, ARID1A, MEN-1, MUTYH and mTOR. (2) The tumor is malignant and located in the pancreas. It is classified as non-functional pNET and functional pNET. The non-functional pNET is asymptomatic or has a symptom of local compression, but

the functional pNET is presented as carcinoid syndrome, Whipple's triplet syndrome, Zollinger-Ellison syndrome, glucagonoma syndrome and Vemer-Morrison syndrome. The tumor markers for Cg A, Syn, PPP and NSE can be high in the blood. (3) In the MRI images, the tumor presents hypointense for T1WI. On T2WI, it mostly shows hyperintense but a few of them are in isointense or hypointense. As for the non-functional pNET in the enhanced CT images, the diameter of the tumor mostly exceeds 5cm and the tumor shows heterogeneous enhancement, necrosis and cystic degeneration. Functional pNET often has a smaller diameter (<2cm), clear boundary and rich blood supply in CT images. Radical resection is the main treatment measure and it can be combined with radiotherapy, chemotherapy and targeted therapy.

Changes in the text: We have modified the text as advised (see Page9-10, line203-216; Table2; in "manuscript without track changes").

7. **Comment 7:** Figure 5 could be suppressed, probably it not provide more information.

   Reply 7: Thank you very much for your comment about Figure 5. We are so sorry that the magazine of "Gland surgery" demands that the article should follow the attached guidelines/checklist for reporting standards. The timeline for the case (Figure 5) is a necessary part of the attached guidelines/checklist for reporting standards so it would be more appropriate to keep Figure 5 in the original text.

Response to reviewer B:

1. **Comment 1:** Could the authors provide more details on the CT and MRI description of the tumor?

   Reply 1: Thanks so much for the reviewer's comment. Your suggestion is very useful, so we add more details on the CT and MRI description of the tumor. An enhanced abdominal computed tomography scan (CT, Figure 1) showed a 3.1×3.8 cm mass with abundant blood in the neck of the pancreas, significantly enhanced during the arterial phase and had a smooth and well-defined boundary. There were

no significant enlarged retroperitoneal lymph nodes. No obvious abnormalities were observed in the liver, gallbladder, spleen, kidney and gastrointestinal tract. The mass could be Castleman's disease. Magnetic resonance imaging (MRI, Figure2) revealed an abdominal mass in the pancreatic neck. It presented hypointense or isointense on T1WI and hyperintense on T2WI. The mass had a clear outline, with a fine boundary to the pancreas. It was obviously enhanced after the enhanced scan, and vascular shadow was visible at the edge. It could be Castleman's disease and please exclude paraganglioma based on clinical practice.

Changes in the text: We have modified the text as advised (see Page5, line104-113; in "manuscript without track changes").

2. **Comment 2:** Could the authors provide more details on the germline or somatic mutations for the patient and the tumor? If possible. As mentioned in Table2, paraganglioma has some signature genetic mutations distinguished from Castleman's disease. "relevant genetic information was not special" is too general.

   Reply 2: It is our careless that we don't express the meaning of "relevant genetic information was not special" clearly. For the sentence, we just want to express that this patient has no family history of paraganglioma and we have already revised this sentence in the original text. When discussing genetic testing with patients and their families before surgery, they refused it. Therefore, we don't gain the information of the germline or somatic mutations for the case. Thank you very much for your comment.

   Changes in the text: We have modified the text as advised (see Page5, line97; in "manuscript without track changes").

3. **Comment 3:** Could the authors provide the catecholamine in blood and urine for this case? "The laboratory findings and physical examination were normal and the tumor marker was no special" is too general.

   Reply 3: Thank you for your valuable advice and we are so sorry that we don't describe the case detailly. It is in the normal range for the catecholamine in the

blood (Norepinephrine: 1.0 nmol/L, Epinephrine: 180 pmol/L) and urine (Norepinephrine: 221.5 nmol/24h, Epinephrine: 183.6 nmol/24h) and the patient don't have paroxysmal hypertension or tachycardia.

Changes in the text: We have modified the text as advised (see Page5, line101-104; in "manuscript without track changes").

4. **Comment 4:** What are the unique characters of this patient comparing with all the cases listed in Table 1?

   Reply 4: We are very sorry for our negligence of describing on unique characters of this patient comparing with all the other cases. The mass in the case is simply resected by laparoscopic technique without excessive surgical treatment and the prognosis for simple excision of the tumor is equally good to radical surgery such as pancreaticoduodenectomy. In addition, the laparoscopic technique alleviated the patient's injuries and shortened the postoperative in-hospital day.

   Changes in the text: We have modified the text as advised (see Page8, line178-185; in "manuscript without track changes").

Reference

1. Lee JE, Shin SS, Kim SJ, Heo SH, Lim HS, Kim JW, et al. A pictorial review of diagnostic pitfalls of developmental anomalies and variants in pancreatic imaging. Clin Imaging. 2018;48:32-9.

2. Han X, Lou W. Advances in Research on Genotyping and the Molecular Mechanism of Pancreatic Neuroendocrine Neoplasias. Medical Journal of Peking Union Medical College Hospital. 2020;11(4):377-82.

3. Li X, Cui Y. The clinical characteristics and comprehensive treatment progress of pancreatic neuroendocrine neoplasm. Abdominal surgery. 2020;33(05):391-5.