Peer Review File

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Reviewer A

Comment 1: Did the patient undergo germline mutation analysis and was the diagnosis MEN1 confirmed?

Reply 1: Thank you for your kind comments. Germline mutation analysis was performed, and MEN1 germline mutation was confirmed. Therefore, the diagnosis of MEN1 was confirmed.

Changes in the text: We have added the results of MEN1 germline mutation analysis in our text as "MEN1 germline mutation analysis was performed and confirmed") (see Page 3, Line 62-63).

Comment 2: The diagnosis of ZES is fairly certain with a FSG >10 times ULN and a gastrin positive (I presume IHC, but this is not clearly mentioned in the manuscript) liver tumor. The author conclude that this is a hepatic primary gastrinoma, however they also state to have performed a pancreatico-duodenectomy but do not report the duodenal pathology. Liver primary gastrinoma is extremely rare and still controversial as to its existence. It is more likely that there are small duodenal primaries of which the liver lesions is a metastases. As can for example be seen in the study by Hackeng et al. Metastatic Patterns of Duodenopancreatic Neuroendocrine Tumors in Patients With Multiple Endocrine Neoplasia Type 1 Am J Surg Pathol 2021 were in 6 patients with MEN1 and hypergastrinemia, periduodenopancreatic lymph node metastases expressed gastrin, and clustered with minute duodenal gastrinomas, not with larger PanNETs. It is therefore more likely in this case that the liver lesion is a metastatic duodenal gastrinoma. At least throughout slides through the entire duodenum should be made before the current conclusion is justified. Additionally I wonder what the WHO grade and classification of the liver tumor was, this should be mentioned.

Reply 2: Thank you for your kind comments. The duodenum of the

pancreaticoduodenectomy specimens has been repeatedly sectioned and examined, but no primary gastrinoma lesions were found. In addition, the solitary liver gastrinoma and absence of lymph node metastasis in the 20 examined lymph nodes (0/20) support the possibility of primary liver gastrinoma. Hence, we considered that the diagnosis of primary liver gastrinoma is possible. The WHO grade of the liver tumor was G2 (see Page 4, Line 74).

Changes in the text: We have modified the text (see Page 3, Line 60-61).

Comment 3: The conclusion that the pancreatic head lesion is an insulinoma may be correct although some information is missing. Only a c-peptide was presented and this was below 2 nmol/L so this does not make a definitive diagnosis of insulinoma. (see Endocrine society guideline). No insulin value was presented. Was exogeneous insulin or SU use excluded? Also symptoms are described as "recurrent weakness", were symptoms compatible with insulinoma? The fact that the tumor stains for insulin is insufficient argument.

Reply 3: Thank you for your kind comments. We added the information about the insulin level in the text (The insulin level was 7.54 μU/mL (normal: 1.9-23.0 uU/mL)). When this patient had attack of weakness, the serum glucose was as low as 2 mmol/L, and C-peptide was 1.92 nmol/L. She had no history of using exogeneous insulin or SU. According to the Endocrine Society Guideline (glucose < 3 mmol/L, insulin ≥3 μU/mL, C-peptide ≥ 0.2 nmol/L), the diagnosis of insulinoma could be established. Admittedly, recurrent weakness was not typical clinical manifestation for insulinoma, it might be the reason that the patient had coexistence of glucagonoma, which could release glucagon to antagonize the effects of hyperinsulinemia by insulinoma and lead to absence of typical hyperglycemic symptoms.

Changes in the text: We have added the insulin level in our text ("the insulin (7.54 μU/mL; normal: 1.9-23.0 μU/mL)) (see Page 3, Line 43-44).

Comment 4: The conclusion that the tail tumor is a glucagonoma is not warranted. No glucagon value is presented and there seems to be no clinical glucagonoma

syndrome. Therefore, mere staining for glucagon does not make the tumor a glucagonoma. See Hofland et al. European Neuroendocrine Tumor Society (ENETS) 2023 Guidance Paper for Functioning Pancreatic Neuroendocrine Tumour Syndromes.

Reply 4: Thank you for your kind comments. Since the measurement of serum glucagon was unavailable in most hospitals, including ours, the patient had no value of serum glucagon. The fact that the patient had no clinical glucagonoma syndrome was probably related to the co-existence of insulinoma, since the hyperinsulinemia by insulinoma might antagonize the effects of hyperglucagonemia, and lead to absence of typical hyperglucagonemic symptoms. Conversely, glucagon might antagonize the effects of hyperinsulinemia by insulinoma, it might be the reason that the patient had only recurrent weakness but no typical hypoglycemic symptoms. Hence, the diagnosis of glucagonoma was made according to the immunohistochemical staining.

Changes in the text: None.

Comment 5: Both pancreatic tumors are negative on the somatostatin receptor imaging. What was the final classification and grade of these tumors?

Reply 5: Thank you for your kind comments. The tumor at pancreatic head was G2, whereas the tumor at pancreatic tail was G1.

Changes in the text: The result was mentioned in the text (see Page 4, Line 73-74).