Primary hepatic neuroendocrine neoplasm presenting as a massive cystic liver tumor mimicking mucinous cystic neoplasm of the liver: A case report and literature review

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Abstract. Neuroendocrine neoplasms (NENs) preferentially arise in the bronchopulmonary tree or the gastrointestinal tract. Notably, primary hepatic NENs are extremely rare. The present study describes a case of hepatic NEN presenting as a giant hepatic cystic lesion. A 42-year-old woman presented with a large liver tumor. Contrast-enhanced abdominal computed tomography revealed a cystic tumor (18 cm) in their left liver. The tumor exhibited liquid components and mural solid nodules with enhanced effects. The lesion was diagnosed as mucinous cystic carcinoma (MCC) preoperatively. The patient underwent a left hepatectomy, and the postoperative course was uneventful. The patient has been alive without recurrence for 36 months postoperatively. The pathological diagnosis was NEN G2. This patient had ectopic pancreatic tissue in the liver and thus the ectopic pancreatic origin of the tumor was suspected. The present study describes a case of resected cystic primary NEN of the liver that was difficult to differentiate from mucinous cystic neoplasms. As primary liver NENs are extremely rare, further studies are needed to establish their diagnosis and treatment.

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Abbreviations: NENs, neuroendocrine neoplasms; MCC, mucinous cystic carcinoma; IPNB, intraductal papillary neoplasms of the bile duct; MCNs, mucinous cystic neoplasms; EOB-MRI, gadoxetic acid-enhanced magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose F18; HPF, high power fields; PGP, protein gene product; CD, cluster differentiation

Key words: primary hepatic neuroendocrine neoplasms, cystic tumor of the liver, mucinous cystic neoplasms, ectopic pancreas, huge liver tumor

Introduction

Neuroendocrine neoplasms (NENs) are a group of heterogeneous tumors that originate from neuroendocrine cells. They arise preferentially in the bronchopulmonary tree (30%) or the gastrointestinal tract (50%) (1). NENs have an average annual incidence of 2 per 100,000 cases of all gastrointestinal tract tumors. Primary hepatic NENs are extremely rare. They were first described by Edmondson et al in 1958 (2). Since then, less than 150 cases of primary hepatic NENs have been described in the literature. Reported cases of hepatic NENs have primarily occurred in adults (age range: 8-83 years; mean: 50 years) and are slightly more common in females (3,4).

Patients with hepatic NENs rarely experience carcinoid syndrome symptoms (5,6). They either present with mass effects of the lesion or with incidentally diagnosed (3) tumors near the hilum, which may cause jaundice.

As a small number of cases has been reported in the literature, and no definitive imaging features have yet been established, few cases have been preoperatively diagnosed as NENs.

Herein, we report our experience of a primary hepatic NEN that was difficult to differentiate from cystic liver tumors such as mucinous cystic carcinoma (MCC), which also contains solid components within a large cystic part.

Case report

A 42-year-old woman was referred to our institution with a large liver tumor identified on abdominal ultrasonography. She presented with mild dysphagia and left hypochondrium pain for two months. Her medical history included previously diagnosed uterine myoma, for which she was undergoing outpatient follow-up. She had a history of smoking, having smoked 20 cigarettes per day from 20 to 37 years of age. She did not have any history of alcohol consumption. On physical examination, her upper abdomen was soft and slightly distended.

She underwent routine laboratory testing. Peripheral blood, blood chemistry, and hemostasis were found to be within

normal limits. Carcinoembryonic antigen was within normal limits [0.5 ng/ml (normal limit 0-5.0)], but carbohydrate antigen 19-9 [42.7 U/ml (normal limit 0-37.0)] was slightly elevated. Testing done for hepatitis virus infection was all negative. The indocyanine green clearance test (retention rate at 15 min) was normal at 9.0%, and the Child-Pugh classification was grade A, so liver function was normal.

Ultrasonography revealed a huge cystic liver tumor in the left lobe. An irregular solid component was observed in the cystic lesion (Fig. 1).

Contrast-enhanced abdominal CT revealed a large cystic tumor (18 cm) in the left liver. The tumor exhibited liquid components as well as solid mural nodules with enhanced effects. No connection between the tumor and the intrahepatic bile duct could be confirmed. In the dynamic study, a heterogeneous contrast effect was observed in the solid component in the arterial phase, followed by a gradual enhancement effect (Fig. 2). The multilocular cystic lesion with a solid structure was suspected to be a malignant neoplasm, such as intraductal papillary neoplasms of the bile duct (IPNB) or mucinous cystic neoplasms (MCNs). No vascular invasions, lymph node metastases, or distant metastases were detected.

Gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) revealed that the liver tumor was a multilocular cystic tumor with a solid component. It exhibited heterogeneous contrast in the early phase and a gradual increase in contrast enhancement. No apparent connection with the bile ducts was observed. Since it was a multilocular cystic lesion with a solid structure, malignant transformation from an MCN was suspected. No significant lymphadenopathy or suspicion of distant metastasis was detected preoperatively (Fig. 3).

Esophagogastroduodenoscopy and colonoscopy were also performed. No primary lesions with a potential to metastasize were observed. Positron emission tomography/computed tomography (PET/CT) revealed a large cystic mass (>18 cm). A strong accumulation of fluorodeoxyglucose F18 (FDG) was observed at the tumor edge, and the site was considered malignant (Fig. 4).

We diagnosed the tumor as hepatic MCC and also considered hepatic hemangiosarcoma, mixed hepatocellular carcinoma, and IPNB as differential diagnoses. We planned radical resection for this tumor.

The patient underwent left hepatectomy. The postoperative course was uneventful, and the patient was discharged 10 days after the surgery. The patient is alive without recurrence for three years after the surgery.

The pathological diagnosis was neuroendocrine neoplasms G2.

Macroscopically, the tumor occupied the left lobe of the liver (Fig. 5A). It was a mixture of solid and liquid components in half proportions. The cut surface of the tumor was grayish-white. On histopathological examination (Fig. 5B), eosinophilic cuboidal tumor cells with intercalated capillary vessels proliferated in the form of alveolar, fused alveolar, rosette, and fused tubular glands. Tumor foci around small blood vessels had degenerated and exhibited a pseudopapillary appearance. The nuclei were round, mildly enlarged, and relatively homogeneous. The border of the tumor was clear, and there was no vascular invasion. The surgical margins were negative for the tumor.

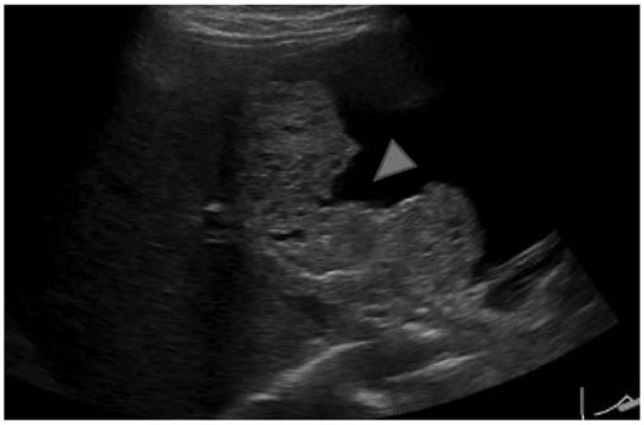

Figure 1. Abdominal ultrasonography. An irregular solid component (arrowhead) is confirmed in the cystic lesion.

Immunohistochemical procedures for CD56, synaptophysin, chromogranin-A, PGP9.5, and Ki-67 were performed by Dako Autostainer Link 48 (Agilent, Santa Clara, CA, USA) according to the manufacturer's instructions. The following primary antibodies: anti-CD56 (prediluted, clone MRQ-42, Nichirei Biosciences, Tokyo, Japan), anti-synaptophysin (prediluted, clone SP11, Diagnostic Biosystems, CA, USA), chromogranin-A (1:200, clone DAK-A3, DAKO, CA, USA), PGP9.5 (1:800, code No. Z 5116, DAKO, CA, USA), and anti-Ki-67 (prediluted, clone MIB1, DAKO, CA, USA) were used. 3,3'-Diaminobenzidine tetrahydrochloride (DAB) was used as a chromogen with counterstain by hematoxylin.

The mitotic index was five cells/10 high power fields (HPF). Immunohistochemical examination revealed protein gene product (PGP) 9.5 (-), cluster differentiation (CD) 56 (+), synaptophysin (+), chromogranin-A (-), and Ki-67 to be 14%. This was equivalent to NEN G2, according to the 2019 World Health Organization Classification of Neuroendocrine Neoplasms (7).

Ectopic pancreatic tissue was observed in the normal liver tissue of the resected specimen. However, there was no continuity between the ectopic pancreatic tissue and the tumor (Fig. 6).

Discussion

Reports of primary hepatic NENs are infrequent in the literature; hepatic NENs account for 0.4% of resected primary liver tumors (8). They usually present at a relatively young age (mean age of 50 years) and demonstrate a slightly higher prevalence in females. They are often asymptomatic and various treatments are available (8), such as hepatic lobectomy, which has demonstrated good long-term survival (9-11), systemic chemotherapy (10), transhepatic arterial chemoembolization (TACE) (12), radiofrequency ablation (13), and liver transplantation (14). The prognosis is often reported to be particularly good after resection (10,11).

Pathologically, in gross appearance, these tumors are solitary, with well-defined margins (4), consistent softness, and little necrosis. Immunostaining is required for the diagnosis (15).

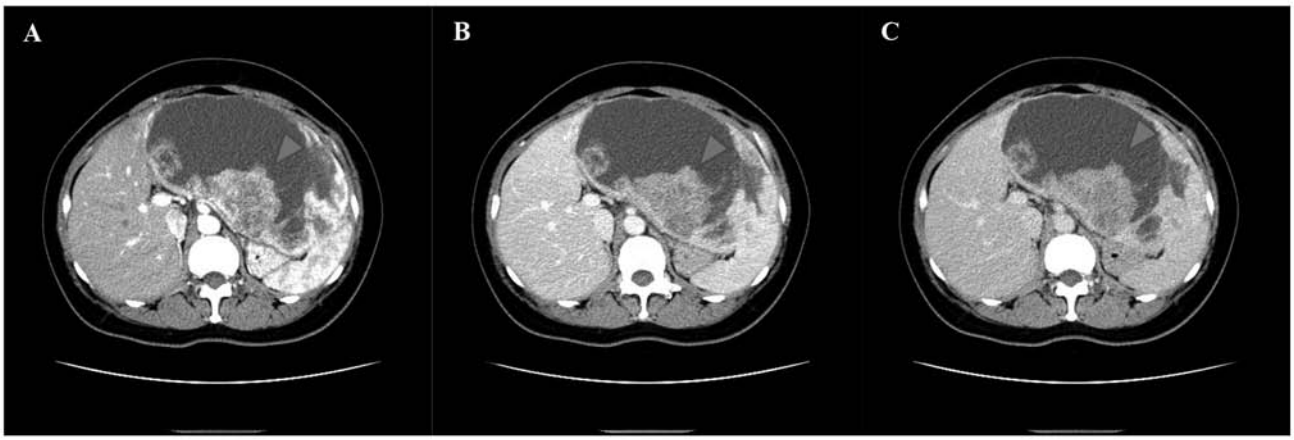

Figure 2. Abdominal dynamic CT. (A) Arterial phase, (B) portal venous phase (C) delayed phase. Arrowheads show a solid component in the tumor. A heterogeneous contrast effect is observed in the solid component of the arterial phase, followed by a gradual enhancement effect. CT, computed tomography.

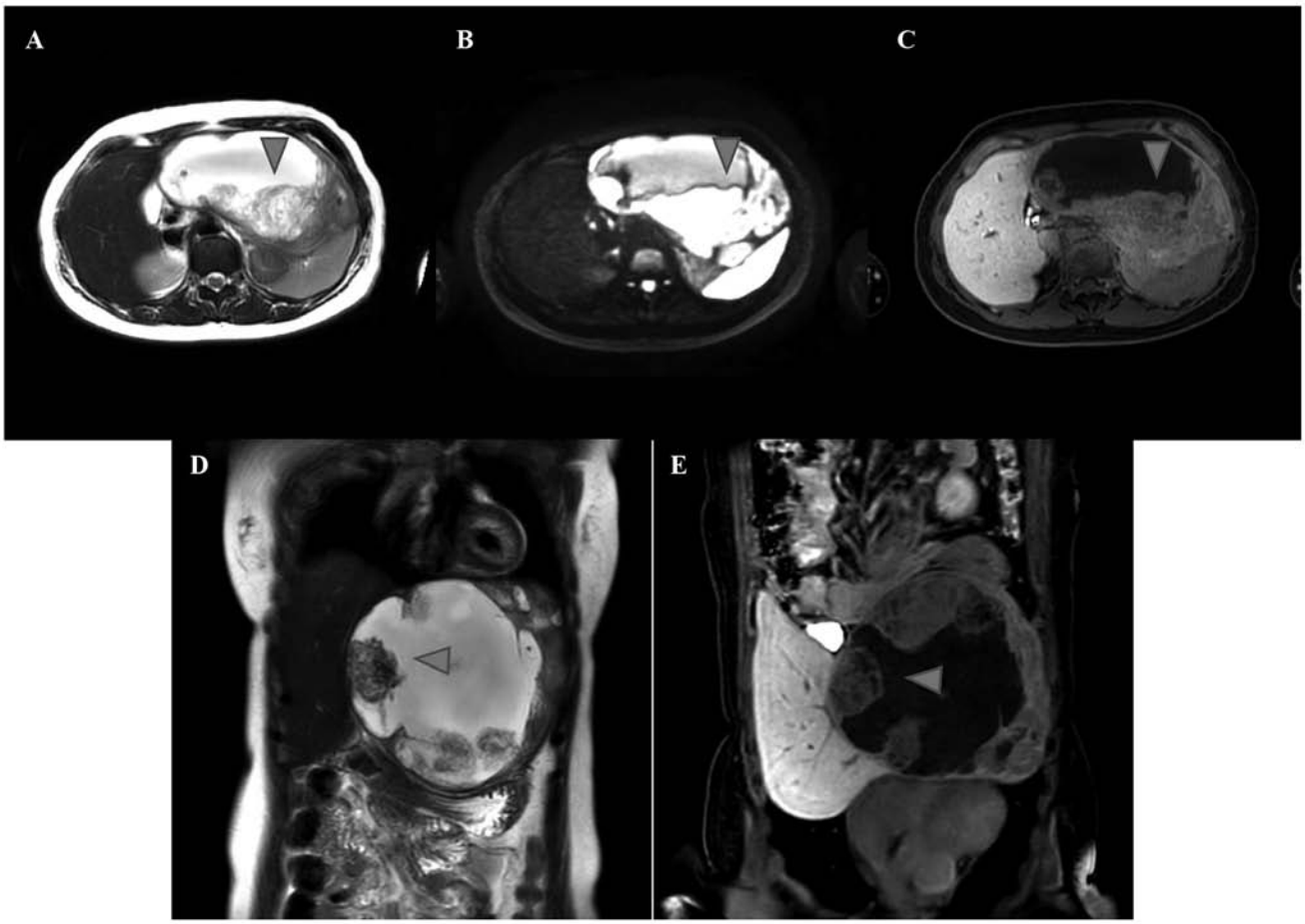

Figure 3. Abdominal MRI. (A) T2-weighted image, (B) diffusion-weighted image, (C) Gd-EOB-DTPA-enhanced MRI, (D) T2-weighted image (coronal), (E) Gd-EOB-DTPA-enhanced MRI (coronal). EOB-MRI shows that the liver tumor is a multilocular cystic tumor with a solid component, with heterogeneous contrast in the early phase and a gradual increase in contrast enhancement. The solid component in the tumor shows high intensity on the T2-weighted image and very high intensity on the diffusion-weighted image. Gd-EOB-DPTA, gadolinium-ethoxybenzyl-diethylene-triamine-pentaacetic acid; EOB-MRI, ethoxybenzyl magnetic resonance imaging.

The reasons for the low incidence of NENs of hepatic origin are being investigated. NENs originate from neuro-ectodermal cells, which migrate from the neural crest to the rest of the body during embryogenesis. However, these cells do not routinely migrate to the liver, and therefore, there are few reported cases of hepatic NENs (16). Hsueh et al pointed out that primary hepatic NENs may arise from ectopic adrenal or pancreatic tissues present in the liver (17). Alternatively, Alpert et al proposed that argentaffin cells within the bile duct epithelium are the cause of these tumors (18). In addition,

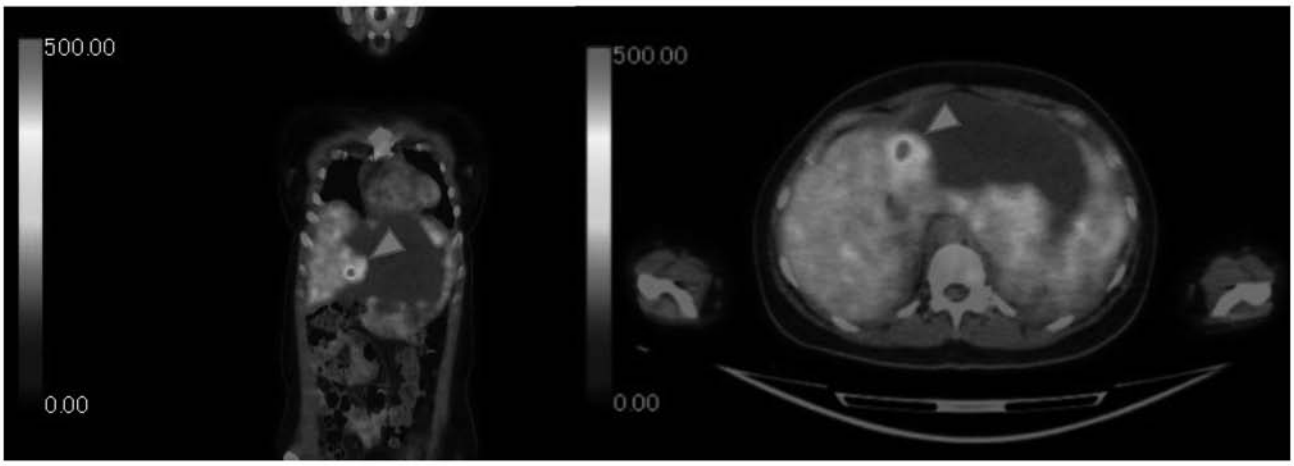

Figure 4. PET. PET shows the mass revealing an intense accumulation of FDG at the edge of the tumor. PET positron emission tomography; FDG, fluorodeoxyglucose F18.

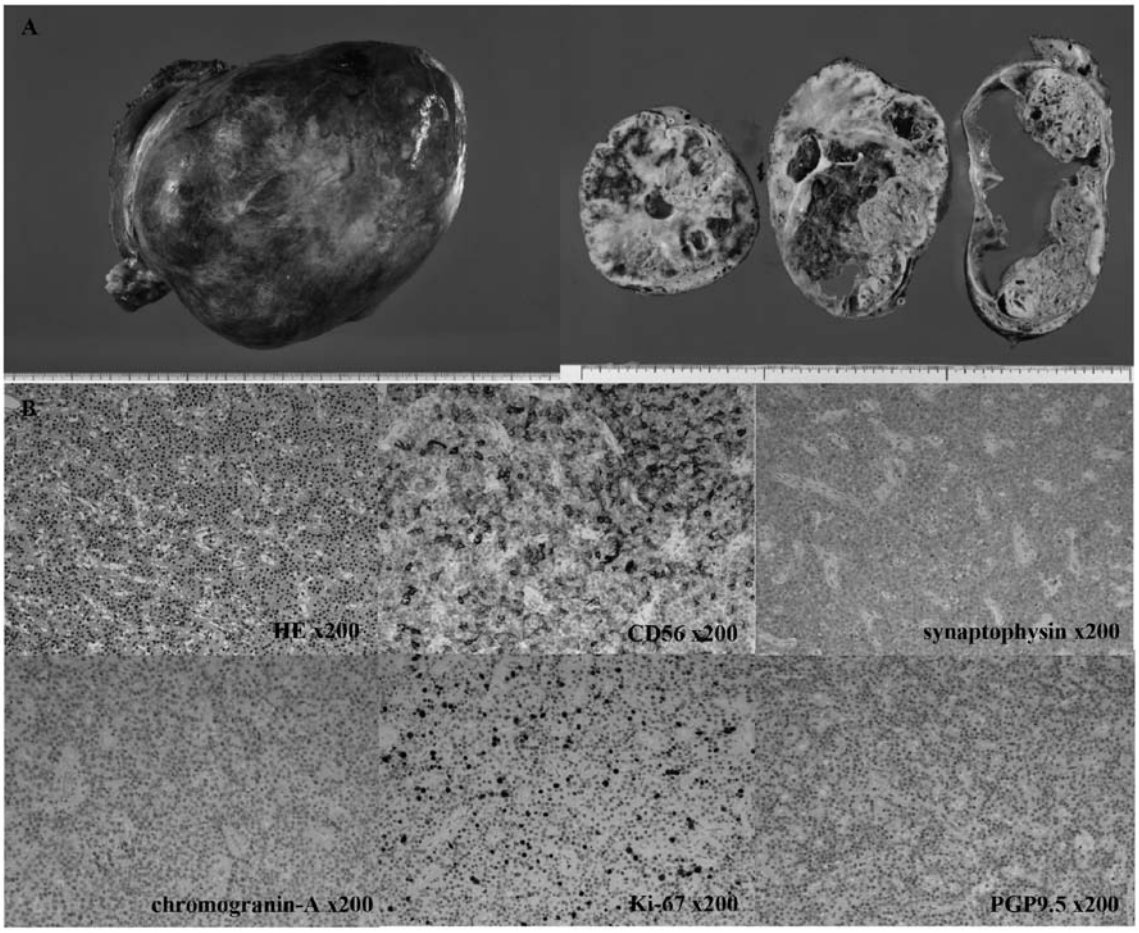

Figure 5. Pathological examination. (A) Macroscopic pathological appearance; Macroscopically, the tumor occupied the left lobe of the liver. The tumor was a mixture of solid and liquid components in half proportions. (B) Histopathological examination, immunohistochemical examination, PGP9.5 (-), CD56 (+), synaptophysin (+), chromogranin-A (-), and Ki-67 were 14%. HE, x200; CD56, x200; synaptophysin, x200; chromogranin, x200; Ki-67, x200; PGP9.5, x200. CD, cluster differentiation; PGP, protein gene product.

the presence of these cells in the bile duct epithelium may be the cause of primary hepatic NENs. In either case, chronic inflammation of the biliary system may lead to intestinal epithelialization, which in turn promotes the development of NENs (3,16).

A third theory proposes that NENs arise through the neuroendocrine differentiation of malignant stem cells (12). Despite the existence of various theories, no study has been published that clearly defines the pathogenesis of primary hepatic NENs.

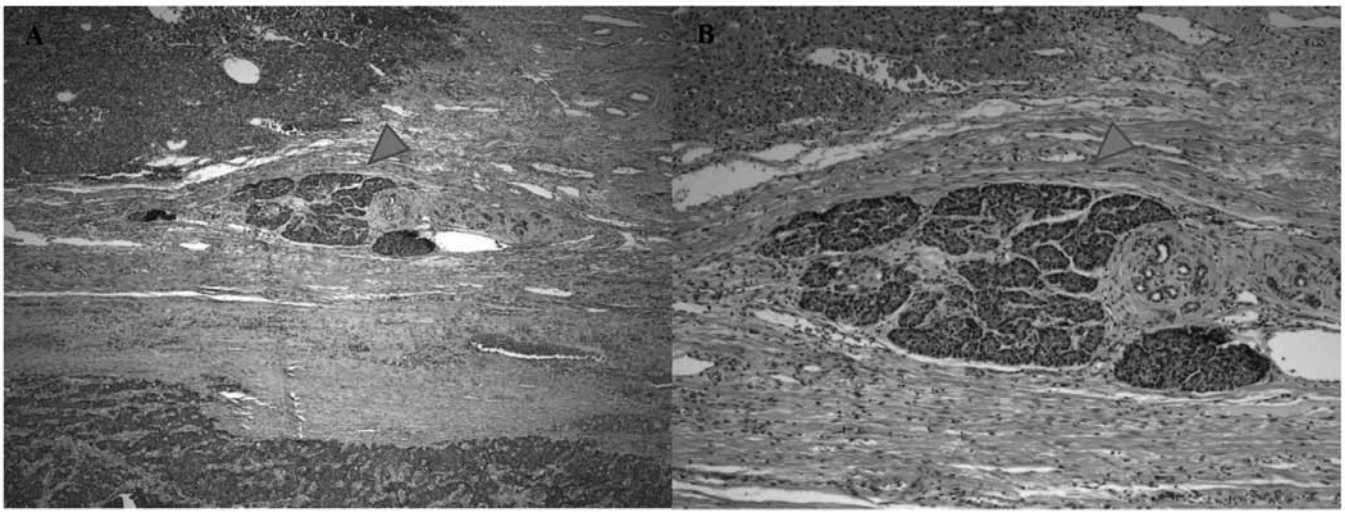

Figure 6. Ectopic pancreas in the liver. Arrowheads show ectopic pancreas. (A) HE, x40; (B) HE, x100.

In this case, the ectopic pancreatic tissues near the tumor were not contiguous with the tumor; however, there were several ectopic pancreatic tissues in the resected liver tissue. Considering previous reports, this is consistent with the assumption that the tumor originated from ectopic pancreatic tissue.

Cystic pancreatic NENs, which are also of parenchymal organs, have been reported to be present in approximately 10% of large pancreatic NENs resections. Though this is relatively rare, there have been reports of the cyst-like portion of hepatic NENs. It has been theorized that the cause of cystic degeneration of pancreatic NEN is related to infarction and cystic degeneration secondary to tumor necrosis or intraregional hemorrhage. Although the presence of cysticercosis has also been noted to correlate with tumor size, Goh *et al* concluded that it is most likely a morphological variant of the same entity as solid-only NEN (19).

In terms of imaging, because of the paucity of reported cases, characteristic imaging findings have not been compiled, and few cases have been accurately diagnosed preoperatively. Preoperative imaging reports have described the solid component as a variable (20-23).

In this case, ultrasonography examination demonstrated hyperechoic of a mixed echoic component in the tumor. Our patient underwent a hepatectomy, and the diagnosis was confirmed by immunostaining, consistent with previous reports; however, it was still difficult to establish the diagnosis preoperatively. The tumor was large on imaging, measuring 18 cm, with a relatively large percentage of cysts; the tumor was present as part of the cyst and had the characteristics of MCC on imaging, with a mildly elevated CA19-9 level.

To date, there have been no reports of NENs of hepatic origin requiring differentiation from huge hepatic cystic tumors, such as MCNs of the liver, as a preoperative diagnosis. MCNs of the liver are also rare, with an incidence of 1 in 2-100,000, and they constitute <5% of liver cysts (24-26) MCNs are unicystic or multicystic with a clear fibrous coating, often with cyst formation within the cyst. Watery, hemorrhagic, or mucinous contents are present. They are most commonly found in the left lobe of the liver and are more common in women. They are typically associated with abdominal pain and satiety and may be accompanied by elevated CA19-9 levels. In malignant cases, there is a multifocal cystic tumor with small cysts within the cyst wall, irregular walls, thickening of the septa, and papillary projections. It is believed that the cystic lesion does not communicate with the bile duct. When malignancy is suspected in MCN, it is difficult to perform a histological examination because of concerns about seeding by biopsy. Therefore, imaging features by multiple modalities are essential. FDG/PET has been reported to have a positivity rate of 13-53% for well-differentiated NENs (27). In this case, the diagnosis was NEN G2 based on the WHO classification (7), suggesting it contains malignant potential. Octreoscan may be useful for differentiating cystic tumors of the liver from primary hepatic NENs.

As for treatment, in this case, we performed a left hepatectomy without lymph node dissection for a case equivalent to G2 and without distant metastasis. Resection of this case was consequently appropriate, as resection is often the curative treatment for primary liver tumors of suspected malignancy if liver function and other tolerable characteristics are not compromised.

In the future, NENs should be considered, although less frequently, as a differential diagnosis for large cystic tumors of the liver. NENs should also be kept in mind, although it is difficult to obtain a definitive diagnosis other than by pathological examination; an Octreoscan may be useful for diagnosis if NENs are present. If PET shows FDG uptake in the liver tumor and there is no distant metastasis, aggressive hepatic resection may be prognostic.

In this study, we experienced a rare case of a cystic primary neuroendocrine tumor of the liver that was difficult to differentiate from sporadic MCN, which had not been reported yet. As this is a single case report, we are unable to determine at this time the details of whether dissection or anatomic resection is necessary. Further case series and careful investigation are needed to establish the diagnosis and treatment.

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Availability of data and materials

The data used and/or analyzed during this published article are available from the corresponding author upon reasonable request.

Authors' contributions

TN and HY collaborated in the conception and design of the study. TN acquired the data. TT, MT, SM, HI, KK, ET, TM, TS, SB, HT, and TO performed data analysis and interpretation. TN and HY confirm the authenticity of all the raw data. All authors were involved in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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