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CASE REPORT

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Cystic Primary Hepatic Neuroendocrine Tumor

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Neuroendocrine tumors (NETs) can arise throughout the body. Most NETs in the liver are metastatic tumors; primary hepatic NET (PHNET) is extremely rare. A diagnosis of PHNET is very difficult. No single modality can diagnose PHNET by itself, and it often resembles other hypervascular masses of the liver. This paper reports the case of a 51-year old female with a large hepatic mass. Unlike most of PHNETs reported previously, it was composed of a solid mass with mainly multiple cystic lesions, which led to an erroneous diagnosis of hepatic mucinous cystadenoma or cystadenocarcinoma. PHNET with cystic lesions is extremely rare, and the features are not well studied. This case may help physicians suspect PHNET in a differential diagnosis of an atypical hepatic mass. **(Korean J Gastroenterol 2021;78:300-304)**

Key Words: Liver neoplasms; Neurodendocrine tumors; Cystadenocarcinoma; Mucinous; Neuroendocrine tumors

INTRODUCTION

Neuroendocrine tumors (NET) are derived from neuroendocrine cells, which are distributed throughout the body. The gastrointestinal tract and respiratory tract are the most common primary organs of these tumors. Most NETs found in the liver result from metastases that arise from the primary organs. Primary hepatic NETs (PHNETs) account for only 0.3% of all NET cases.[1]

In addition to its scarcity, a diagnosis of PHNET is very difficult. No serologic marker is known to be specific to PHNET,[2] and it is difficult to differentiate PHNET from other hypervascular hepatic malignancies, such as hepatocellular carcinoma or intrahepatic cholangiocarcinoma, by the image findings. Most PHNETs are solid masses, so a cystic portion of the mass makes a diagnosis even more difficult. Moreover, many patients are asymptomatic. If symptoms are present, they complain of non-specific symptoms, such as abdominal discomfort. All of these features can lead to a delay in diagnosis, which can deteriorate the prognosis of a patient.

This paper reports the case of a 51-year old female without any underlying chronic liver disease. She was initially suspected of having a hepatic mucinous cystadenoma or cystadenocarcinoma because of the cystic portion. Only by a pathology examination after surgical resection was she re-diagnosed with a neuroendocrine tumor. The diagnosis of PHNET was confirmed because all the preoperative examinations, including PET-CT, endoscopy excluded other primary ori-

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gins of NET.

CASE REPORT

A 51-year old female was referred to the Dankook University Hospital for a cystic mass in segment III of the liver found by abdominal ultrasound and enhanced abdominopelvic CT. She had suffered from abdominal discomfort and mild dyspnea for more than 2 months before she visited the primary clinic, where she underwent ultrasound and CT examinations. On the enhanced CT scan, a huge, encapsulated, multilocular cystic mass (14.7×10.0×11.0 cm in size) with an enhancing peripheral solid portion and internal septum was found in segment III of the liver (Fig. 1). Her liver parenchyma was homogenous without evidence of liver cirrhosis.

She denied alcohol consumption and smoking. The blood test revealed negative results for the hepatitis B antigen and anti-hepatitis C antibody. The blood tests were normal for tumor markers, such as AFP, prothrombin-induced by vitamin K absence or antagonist-II, CEA, and CA 19-9. Liver function test including AST, ALT, albumin, total bilirubin was normal while the prothrombin time was prolonged mildly to 14.4 sec (normal range 10.3-13.1 sec).

Liver MRI was performed to obtain more information. Liver MRI also revealed a cystic non-smooth margined multiseptated mass lesion occupying hepatic segments II and III, with an exophytic nature and indentation of the surrounding stomach and abutment to the pancreatic body. Septal enhancement was noted from the early arterial phase, and the fluid-fluid level was noted on the T2 weighted image in the cystic portion (Fig. 2).

PET-CT revealed an approximately 14 cm-sized multiseptated cystic mass with metabolic defect and mild rim hypermetabolism with a maximum standardized uptake value

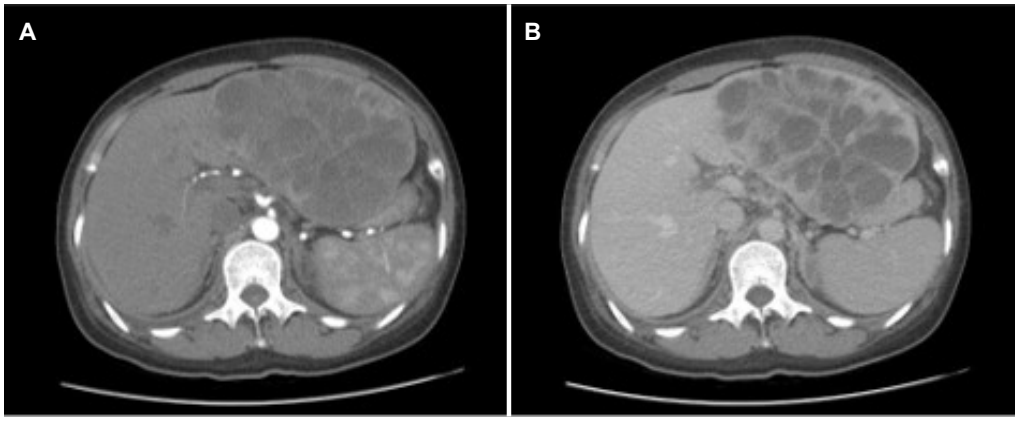

Fig. 1. Dynamic liver computed tomography scan. (A) Arterial phase. 14.7×12.7 cm sized non-enhancing multicystic lesion with thick internal septum is found in the left lobe. (B) Delayed phase. Lower density multicystic lesion compared to liver parenchyma is found.

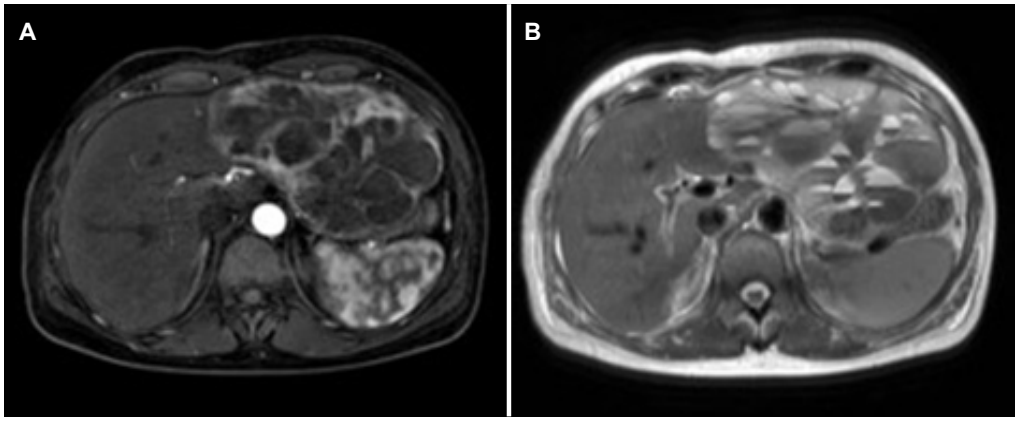

Fig. 2. Liver magnetic resonance imaging findings. (A) Early (15 seconds) arterial phase. Non-smooth margined multiseptated mass with septal enhancement is found in hepatic segment II, III. (B) T2WI phase. Fluid level without evidence of blood is found in the cystic portion.

(SUV_{max}) of 2.4. No other hypermetabolic lesions indicating a distant metastasis were found except for hypermetabolic uterine myoma. Esophagogastroduodenoscopy and colonoscopy revealed non-specific findings except for extrinsic compression at the lesser curvature, posterior wall of the high body by outer mass, and 3 mm-sized colon polyp at sigmoid colon, respectively. A huge mass (14 cm) and exophytic border indicated its malignant potential, while the mildly elevated standard uptake value suggested the possibility of low-grade malignancy. Therefore, a mucinous cystadenocarcinoma was suggested as the most probable diagnosis.

Based on her image findings, a left hepatectomy with lymph node dissection was planned under the impression of mucinous cystadenocarcinoma. A preoperative liver biopsy was not performed due to the risk of seeding or rupture of the cystic mass. The 15 minutes indocyanine green test was 16.1%. She underwent a left hepatectomy with a lymph node dissection.

The hepatectomy specimen revealed a huge exophytic tumor measuring 14×12 cm (Fig. 3A). The sectioned surface of the tumor was a well-circumscribed pale brown soft solid mass with various sized multiple cystic cavities containing hemorrhagic serous fluid (Fig. 3B). Microscopically, the tumor revealed trabecular or cribriform growth patterns. Multifocal cystic degeneration was associated with the tumor. The tumor cells had abundant eosinophilic cytoplasm and uniform round nuclei with minimal nuclear atypia (Fig. 4A). There were five mitotic figures per 10 high-power fields. Immunohistochemically, the tumor cells were diffusely positive for neuroendocrine markers, such as chromogranin A, neuron-specific enolase, synaptophysin (Fig. 4B), and CD56 and were weakly positive for CDX-2. The tumor cells were negative for CK19, CK20, Hepar-1, and

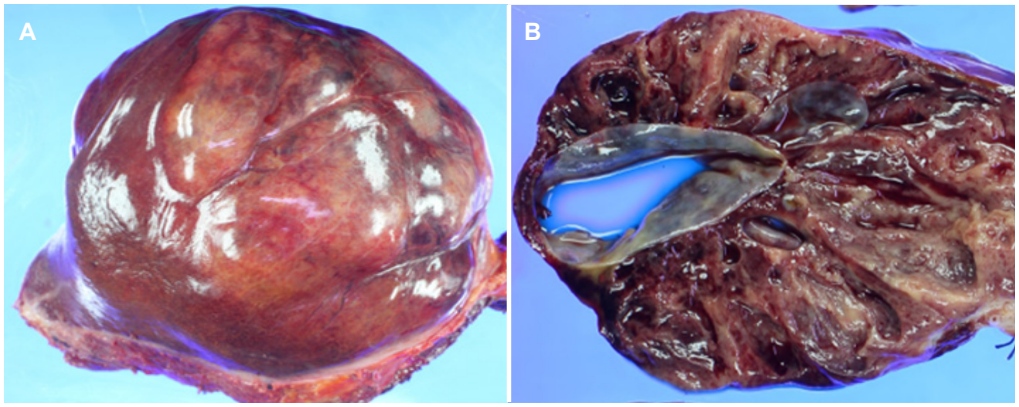

Fig. 3. Gross findings. (A) Hepatectomy specimen shows a huge exophytic tumor with a smooth surface. (B) The sectioned surface of the tumor is a well-circumscribed pale brown soft solid with various sized multiple cysts.

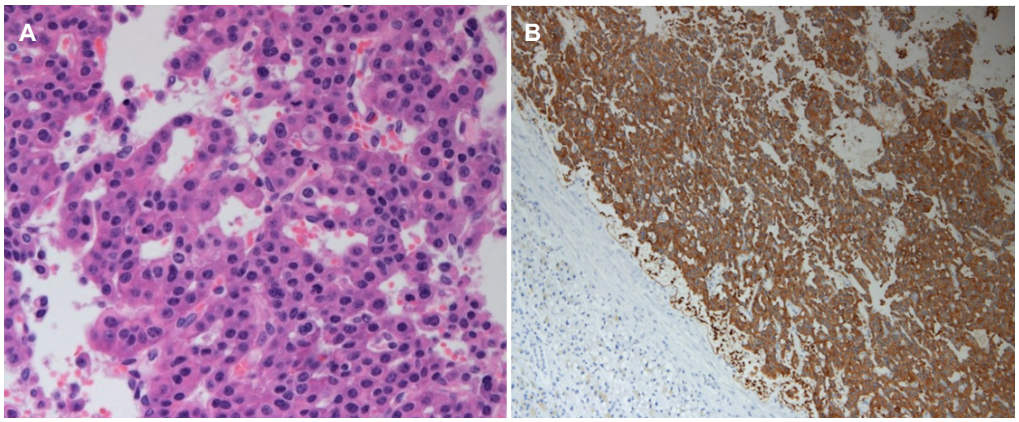

Fig. 4. Microscopic findings. (A) The tumor cells display abundant eosinophilic cytoplasm and uniform round nuclei with fine chromatin (hematoxylin and eosin stain, ×400). (B) Immunohistochemically, tumor cells are diffusely positive for synaptophysin (immunohistochemistry, ×200).

arginase-1. The Ki-67-labeling index was approximately 2%.

The final diagnosis was a neuroendocrine tumor, grade 2. The tumor was diagnosed as a PHNET because her preoperative PET-CT showed no evidence of other primary neuroendocrine tumors. As a margin-negative resection was achieved, the patient will be followed up closely every 3 months with liver CT without adjunctive therapy.

DISCUSSION

Since the first case report of PHNET by Edmondson in 1958, less than 200 cases have been reported. Little is known regarding its etiology, disease course, and clinical features owing to its rarity. PHNET is often found during health check-up without any alarm signs because of its silent nature.[3] In the present case, the mild, vague abdominal pain was not sufficient for her to visit the hospital, which led to a delayed diagnosis. Moreover, in the case of NETs without carcinoid syndrome, as in the present case, it is often diagnosed after the mass is enlarged. In retrospect, the patient did not present any symptoms that could indicate carcinoid syndrome. The patients showed no symptoms, such as flushing or diarrhea, and complained of ambiguous abdominal pain. The pain reported was attributed to a large liver mass rather than abdominal pain due to intestinal hypermotility, which is usually accompanied during carcinoid syndrome. This study did not examine the serologic markers, such as serum serotonin or 5-hydroxyindoleacetic acid, because PHNET was not the preliminary diagnosis.

According to reports thus far, most PHNETs appeared in the form of a solid nodular lesion, and only a few cystic cases have been reported.[4-6] In the present case, however, it was a large multilocular cystic mass with septation, which led to the erroneous impression of hepatic mucinous cystadenoma or cystadenocarcinoma. A biopsy with an immunohistochemical examination can be helpful in diagnosis, but the cystic features of the mass made the authors hesitate to perform a biopsy. Moreover, there is controversy regarding the efficacy of a preoperative biopsy. According to Hwang et al.[7], diagnostic accuracy was only 57.1%, with an additional risk of bleeding and tumor seeding, which led to the decision not to perform a preoperative biopsy. A needle biopsy should be done only in inoperable cases or in differentiating metastatic liver masses from the double primary hepatic mass in the presence of extrahepatic mass.[7]

An abdominal ultrasound scan, abdominal CT, and liver MRI are essential diagnostic tools for evaluating hepatic masses, including the size, component, and invasion of the adjacent anatomic structures. PET-CT cannot give a definitive diagnosis of PHNET, but the diagnosis of PHNET was confirmed by excluding other primary NETs by a PET-CT scan. The somatostatin receptor imaging modality, such as octreotide scan, is an upgraded modality for detecting NETs with improved sensitivity.

Despite the lack of global treatment guidelines, surgical resection is the mainstay of treatment. According to Knox et al.[8], the resectability is 70%, and the 5-year survival rate after hepatectomy was 78%. A partial hepatectomy, as well as portal vein ligation for a staged hepatectomy, is done depending on the postoperative residual hepatic function.[9] On the other hand, recurrence after hepatectomy is not uncommon. According to Jung et al.[10], seven out of 13 patients who underwent a liver resection had a confirmed recurrence. Three patients with a recurrence had initial microscopically margin-positive resection (R1 resection), while four out of 10 patients with a margin-negative resection (R0 resection) had a confirmed recurrence.[10] Somatostatin analogs, which is helpful in GI NETs with carcinoid syndrome, can be additional options because some studies argue that it can prevent recurrence from large PHNET after R1 resection.[3]

Because a microscopically margin-negative resection was achieved, the patient will undergo close monitoring to check for recurrence with CT scans without somatostatin analogs. Further studies on the effect of somatostatin analogs on recurrence after R0 resection are warranted.

The serum chromogranin A level is another excellent method for the early detection of tumor recurrence. Although the serum chromogranin A level has a limitation in that they cannot differentiate PHNET from other primary NETs, it has high sensitivity and specificity for detecting neuroendocrine tumors. Therefore, this non-invasive tool will be used to check for recurrence after hepatectomy.

In unresectable cases, transarterial chemoembolization or adjuvant chemotherapy, mostly 5-fluorouracil based regimens, can be considered to decrease the tumor burden and for symptom control, despite the limited evidence.

In conclusion, a precise preoperative diagnosis of PHNET is challenging owing to its rarity and non-specific image findings. As PHNET can present in cystic form, PHNETs should

be suspected, particularly when the patient has no underlying liver disease or risk factors for hepatic malignancies. Surgical resection is the mainstay of treatment, and close observation for recurrence is crucial. Further studies concerning the identification of this tumor and effective treatment will be needed.

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