CASE REPORT

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Primary Hepatic Neuroendocrine Tumor Arising at a Young Age: Rare Case Report and Literature Review

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Neuroendocrine tumors (NETs) are low-grade malignancies arising from neuroendocrine cells. Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare and difficult to differentiate from other liver tumors, such as hepatocellular carcinoma (HCC) or cholangiocarcinoma. A 22-year-old male presented with intermittent abdominal pain. A preoperative imaging study revealed a 5.1cm-sized heterogeneously enhancing mass in S6 of the liver, suggesting HCC. Laparoscopic right hepatectomy was performed, and a well-demarcated brown solid mass was found. The pathology report revealed a neuroendocrine tumor of the liver. 18F-fluorodeoxyglucose-positron emission tomography/computed tomography was performed postoperatively to exclude extrahepatic lesions, and no lesions were found. This is a rare case of PHNET that developed at a young age and was misdiagnosed as HCC preoperatively. This suggests that PHNET should be considered one of the differential diagnoses when a non-specific enhanced hepatic tumor is found, even when the patient is young. (*Korean J Gastroenterol* 2022;79:35-40)

Key Words: Neuroendocrine tumors; Operative

INTRODUCTION

Neuroendocrine tumors (NETs) are low-grade malignancies arising from neuroendocrine cells. NET rarely occurs primarily in the gastrointestinal tract (54.5%) and bronchus (30.1%).¹ Primary hepatic NETs (PHNETs) are extremely rare, but the liver is the most common organ affected by metastatic NET. The most frequently reported symptom of PHNET is non-specific abdominal pain (33%).^{2,3} PHNET is difficult to differentiate from other liver tumors, such as hepatocellular carcinoma (HCC) or cholangiocarcinoma, based on radiological

findings. Hence, it is diagnosed based on immunohistochemical analysis after surgery.

This paper reports a case of PHNET, in which the preoperative radiologic diagnosis was HCC, but the tumor was confirmed postoperatively as PHNET by immunohistochemistry. The present case is meaningful because it was the youngest diagnosed thus far.

CASE REPORT

A 22-year-old male presented with intermittent abdominal

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pain lasting three months. The patient showed normal vital signs. A physical examination showed that the abdomen was generally soft, but no palpable mass was noted. The blood tests showed normal values for AFP and PIVKA II (protein induced by vitamin K absence or antagonists-II) as tumor markers and negative hepatitis B and C serology. An esophagogastroduodenoscopy revealed an ulcer in the duodenal bulb, but otherwise normal findings. The duodenal lesion was pathologically confirmed as a chronic ulcer. Ultrasonography (US) revealed a 5×4 cm-sized mixed echogenic mass with an anechoic area in the right hepatic lobe was observed, which was considered to be hemangioma or other liver tumor (Fig. 1). Arterial phase abdominal CT showed a 5.0 cm-sized heterogeneously enhancing mass in the S6 of the liver with a partial enhancing pattern in the portal phase (Fig. 2). In contrast, MRI revealed a 5.0 cm-sized well-defined solid mass with a cystic component. The solid mass showed arterial hyper-enhancement and a delayed washout pattern in the portal phase, strongly indicating HCC (Fig. 3).

Laparoscopic right hepatectomy was performed based on a preoperative diagnosis of HCC of the right liver lobe. A whit-

ish mass was observed on the liver surface in the surgical field. Pathologically, a 6.6×4.2 cm-sized yellow-to-brown solid mass was found in the S6 parenchyma. No tumor cells were present at the surgical margins (Fig. 4). Microscopy of the mass showed tumor cells with abundant eosinophilic cytoplasm and uniform round nuclei. Immunohistochemically, the tumor cells were positive for epithelial markers, such as cytokeratin, and neuroendocrine markers, including CD56, synaptophysin, chromogranin A (CgA), and neuron-specific enolase, with a Ki-67 labeling index of 1-2%, and a mitotic rate of 1/10 high power field (HPF). A final diagnosis of NET, G1 was rendered (Fig. 5). ¹⁸F-fluorodeoxyglucose (FDG)-PET/CT was performed postoperatively to identify the extrahepatic lesions. No lesions outside the liver were found. The patient recovered uneventfully.

DISCUSSION

According to the 2019 World Health Organization (WHO) neuroendocrine neoplasms classification, well differentiated are classified as NET and poorly differentiated as neuro-

Fig. 1. (A-C) Abdominal ultrasonography and color Doppler image showed 5.0×4.0 cm mixed echoic mass in right hepatic lobe (arrows of A, B).

Fig. 2. (A-C) Abdominal computed tomography showed a 5.1 cm enhancing mass in S6 of the liver in the arterial phase, partial enhancing in the portal phase, and a washout pattern in the delayed phase (arrow in A, arterial phase; B, portal phase; C, delayed phase).

endocrine carcinoma. Among them, NETs are classified into grades one-three according to the mitotic rate. Grades 1, 2, and 3 are classified as low, intermediate, and high, respectively. NET rarely occurs primarily in the gastrointestinal tract (up to 50%) and bronchus (up to 30%).¹ Although PHNET is extremely rare (up to 0.3%), the liver is the most common organ affected by metastatic NET (32-75%).³ Therefore, the possi-

bility of metastatic NET should be considered in cases where NET is found in the liver. An octreotide scan has a high sensitivity of 85-90% for metastatic NET to the liver but relatively low sensitivity for PHNET.⁴ On the other hand, an octreotide scan was not conducted in the present case because the radiologic findings strongly suggested HCC. Furthermore, both esophagogastroduodenoscopy and colonoscopy might be con-

Fig. 3. (A) Abdominal magnetic resonance imaging showed the lesion demonstrating peripheral enhancement on the arterial phase (arrow), (B) contrast washout with peripheral rim enhancement on the portal (arrow), (C) 20-min delayed phase (arrow), and (D) cystic component (T2WI; arrow).

Fig. 4. (A, B) Surgical specimen of the liver revealed a 6.6×4.2 cm yellow-to-brown solid mass in S6 (arrows).

ducted to locate a GI tract lesion.² A preoperative CT scan showed arterial enhancement and portal phase partial enhancement followed by washout in the delayed phase, which is similar to HCC.⁵ Preoperative MRI showed a solid mass with early enhancement and a delayed washout pattern and presented a cystic portion of hypo-enhancement in T1-weighted enhancement in the T2-weighted image in the solid mass. In up to 40% of HCC patients, some hypervascular lesions with rapid growth may show cystic or hemorrhagic changes on the MRI findings.^{6,7} Therefore, it is difficult to diagnose PHNET preoperatively using a radiographic examination alone. Although preoperative blood tests and tumor marker tests show normal results, different levels of CgA and 5-hydroxyindole acetic acid (5-HIAA) can help diagnose NET. While 5-HIAA has a low sensitivity for PHNET,⁸ CgA has a sensitivity of 85-100% and a specificity of 85-95% for the tumor. Therefore, CgA can be a useful marker for diagnosing PHNET.⁹

There are no recommendations for the treatment of PHNET.^{2,8,10} According to previous reviews of hepatectomy for PHNET, the 5-year survival rate after surgery was 75-80% with a recurrence rate of 18%.¹¹ Other therapeutic options include

liver transplantation, trans-arterial chemoembolization (TACE), and radiofrequency ablation (RFA). TACE is effective in PHNET with intrahepatic metastasis, and RFA can be useful for unresectable PHNET.^{12,13} The prognosis of PHNET varies according to the NET grade based on the WHO classification. In 2016, Park et al.² reported that grade 3 NETs have poor prognoses. The lower cellular proliferation grades (G1/G2) were demonstrated as a favorable prognostic factor for PHNET.^{9,14} In addition, previous reports showed a tendency that the older patients presented with a higher tumor grade. This case was diagnosed at a young age and had a low tumor grade which followed the tendency. A literature review revealed 19 domestic cases where surgical approaches were performed, including the present case, from January 1997 to February 2021 (Table 1).¹⁵⁻²⁰ All were diagnosed in their thirties or older. The radiologic findings of these cases showed an arterial phase enhanced solid mass with or without cystic portion. Similar to the present case, another two cases were initially diagnosed with HCC, and TACE was then performed before liver resection.¹⁵ Ki-67 proliferative index was the only significant risk factors for tumor recurrence.¹⁵ Recurrent cas-

Fig. 5. Microscopy findings of the liver mass showed (A) a well-demarcated tumor (hematoxylin and eosin stain [H&E], $\times 20$), and (B) diffuse and cord-like growth pattern of tumor cells (H&E, $\times 40$), and (C) uniform round to ovoid tumor cells (H&E, $\times 100$), and (D) in immunohistochemical staining, the tumor cells were positive for chromogranin ($\times 20$).

es were positive surgical tumor margin (R1 resection) grade 3.¹⁵ No recurrence occurred in G1.¹⁵ The present case was diagnosed with HCC from the radiology findings, but PHNET was diagnosed after a surgical resection. This patient is the youngest case. The Ki-67 proliferative index was 2%, and the mitotic rate was 1/10 HPF, which indicated NET, G1. In addition, the probability of recurrence in the future is expected

to be low because an R0 resection was performed.

There were some limitations in the present case. The liver is the most common organ affected by metastatic NET, so the first step is to find the other primary lesion when NET is diagnosed in the liver. GI tract NETs should have been excluded by esophagogastroduodenoscopy and colonoscopy. In addition, FDG-PET/CT was performed to check for metastases

Table 1. Clinical and Tumor Characteristics of the Primary Hepatic Neuroendocrine Tumor in the Patient Group Who Underwent Surgical Approach in Korea (from January 1997 to February 2021)

No.	Sex	Age	Clinical features	Tumor No.	Image finding	Tumor size (cm)	Operation	Resection type	Tumor grade	Timing of recurrence (month)
1 (Jung et al. ¹⁵ [2019])	M	48	Abdominal pain	1	N/D	12.0	RH	R0	G1	-
2	F	45	Abdominal pain	1	Heterogenous arterial enhancement and washout mass	4.3	LMS	R0	G1	-
3	F	37	Abdominal pain	1	N/D	4.0	LH+BDR+PVT	R1	G3	13
4	M	55	Incidental	1	N/D	4.2	RH	R0	G2	-
5	F	42	Incidental	1	N/D	3.2	LMS+S1+BDR	R0	G1	-
6	F	64	Abdominal pain	1	N/D	15.0	RH	R0	G3	47
7	M	62	Abdominal pain	1	Heterogenous arterial enhancement and washout mass	8.0	CBS	R0	G3	1
8	M	50	Abdominal pain	1	N/D	18.0	LTS	R1	G3	2
9	F	48	Incidental	1	N/D	3.0	RPS	R0	G2	23
10	M	26	Abdominal pain	1	Hypervascular mass and central necrosis	29.0	LH	R0	G2	5
11	M	69	Chest discomfort	1	N/D	4.2	RPS	R0	N/D	-
12	M	48	Abdominal discomfort	1	Well demarcated mass at the arterial phase	4.6	LTS	R0	G1	-
13	M	70	Abdominal discomfort	1	N/D	15.0	CBS	R1	G3	1
Oh et al. ¹⁶ (1998)	M	48	Epigastric pain	1	Arterial phase enhanced solid mass and cystic lesion	13.0	RH	R0	N/D	N/D
Kim et al. ¹⁸ (2021)	F	51	Abdominal discomfort	1	Multi-locular cystic mass	14.0	LH	R0	G2	N/D
Lee et al. ²⁰ (2015)	M	67	Lt. hemiparesis	1+brain metastasis	Rim- enhancing mass with central necrosis	10.0	RH	R0	G3	N/D
Kim et al. ¹⁷ (2013)	F	67	Nausea	1	Heterogenous arterial enhancement and washout mass	10.0	CH	R0	G3	N/D
Lee et al. ¹⁹ (2006)	F	75	Fever RUQ pain	1	Multi-locular cystic mass	20.0	Aspiration No resection	-	N/D	N/D
Our case	M	22	Epigastric pain	1	Solid mass and cystic component	6.0	RH	R0	G1	-

M, male; F, female; N/D, no data; RH, right hepatectomy; LMS, left medial sectionectomy; LH, left hepatectomy; BDR, bile duct resection; PVT, portal vein thrombectomy; S1, caudate lobe resection; CBS, central bisectionectomy; LTS, left trisectionectomy; RPS, right posterior sectionectomy; CH, central hepatectomy; RUQ, right upper quadrant.

after surgery. An octreotide scan would be preferable for finding the primary lesion of NET than FDG-PET/CT.

This study experienced a case of PHNET that occurred at a young age. The case was misdiagnosed preoperatively as HCC because of the enhancing pattern radiologically. In case of a young age and no risk factor of HCC, it is important to consider PHNET as a possible diagnosis of hypervascular tumors.

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