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CLINICAL CASE REPORT

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Case Report of Contrast-Enhanced Ultrasound Features of Primary Hepatic Neuroendocrine Tumor

A CARE-Compliant Article

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Abstract: Primary hepatic neuroendocrine tumors (PHNETs) are very rare and their clinical features and treatment outcomes are not well understood. It is difficult to reach a proper diagnosis before biopsy or resection. The aim of this study was to analyze the imaging features of PHNETs on contrast-enhanced ultrasound (CEUS). The clinical characteristics, CEUS findings, pathological features, treatment and prognosis of 6 patients with PHNET treated in our hospital were retrospectively analyzed.

Most PHNETs occurred in middle-aged patients, and the most common clinical manifestation was right upper quadrant palpable mass and abdominal pain. Multiple small anechoic intralesional cavities occurred frequently in PHNET. Multilocular cystic with internal septation or monolocular with wall nodule could also be detected. On contrast-enhanced ultrasonography (CEUS), heterogeneous hyperenhancement in the arterial phase and wash-out hypoenhancement were observed in most patients, while computed tomography scanning yielded similar results. Diagnosis of PHNET was confirmed by immunohistochemical result and follow-up with the absence of extrahepatic primary sites. Five patients received surgical resection and 2 cases exhibited recurrence. Transcatheter arterial chemoembolization was performed in 1 patient with recurrence. Only 1 patient received conservative care. The median overall survival in 5 patients who underwent surgical treatment was 27 months (18–36 months). PHNET is a rare tumor, and its diagnosis is difficult. The CEUS features reported in this series may enrich the knowledge base for characterization of PHNET.

(*Medicine* 95(21):e3450)

Abbreviations: CEUS = contrast-enhanced ultrasound, CR = complete response, CT = computed tomography, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, NETs = neuroendocrine tumors, PD = progressive disease, PHNETs = primary hepatic neuroendocrine tumors, PR = partial response, SD = stable disease, TACE = transcatheter arterial chemoembolization.

INTRODUCTION

Neuroendocrine tumors (NETs) are mainly seen in organs of the bronchopulmonary, gastrointestinal tract, and pancreas, but can also occur in almost any other organs like the bladder and biliary tree. NETs not only behave in a benign fashion but also exhibit the characteristics of invasion and metastasis.[1] More than 80% of the NETs found in the liver are metastatic, primary hepatic NETs (PHNETs) are very rare. Fewer than 150 cases of PHNET have been reported in the literature.[2–6] However, its rarity makes it difficult to reach a proper diagnosis before biopsy or resection, and their clinical features and treatment outcomes are not well understood. In this study, we present our experience with 6 PHNET cases of contrast-enhanced ultrasound (CEUS) features.

METHODS

Patients

During the 10 years from January 2004 to October 2014, 6 patients were pathologically diagnosed as PHNET in our institute. The diagnosis was confirmed by pathological examination, including a positive immunohistochemical staining result. Computed tomography (CT) scanning and gastrointestinal endoscopy were performed to rule out extrahepatic neuroendocrine tumors. No extrahepatic lesion was found radiologically either preoperatively or during the follow-up period in our research except for recurrence in the liver after treatment. The CEUS and CT imaging, laboratory examination, and clinical data of these 6 patients were retrospectively analyzed. Written informed consent was obtained from all patients, and the study was approved by the first affiliated hospital of Sun Yat-Sen University Institutional Review Board.

CEUS Examinations

All US examinations were performed by 2 experienced radiologists with at least 8 years' experience of liver ultrasound using a Aplio SSA-770A or Aplio 500 (Toshiba Medical Systems, Tokyo, Japan) scanner equipped with a 375BT convex transducer (frequency range, 1.9–6.0 MHz). The entire liver was scanned thoroughly, and the target lesions were identified. In the case of multiple lesions, the largest and most clearly displayed lesion was selected for evaluation. The location, size, shape, boundary, and

Editor: Giuseppe Scalisi.
Received: December 13, 2015; revised: March 25, 2016; accepted: March 29, 2016.
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This study is funded by the National Nature Science Foundation of China (No: 81471672 and No: 81301238).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003450

TABLE 1. Ultrasonographic (B-Mode and CEUS) and Histological Stage of the PHNET in 6 Cases

	B-Mode US		CEUS		
Case No.	Tumor Size (cm)	US Pattern	Arterial	Portal Venous	Late Venous
1	18.4	Mix solid cystic	Hyper; hetero	Iso	Hypo
2	13.0	Multilocular cystic	Hypo; hetero	Iso (periphery); non (central)	Iso (periphery); non (central)
3	14.6	Mix solid cystic	Hyper; hetero	Hypo	Hypo
4	12.7	Mix solid cystic	Hyper; hetero	Hypo	Hypo
5	4.8	Iso	Hyper; homo	Hyper (periphery); hypo (central)	Hypo
6	5.1	Monolocular with wall nodule	Hyper; hetero	Hypo	Hypo

echogenicity of the lesion were recorded. After activating the contrast harmonic imaging mode, a bolus injection of 2.4 mL of SonoVue (Bracco, Milan, Italy) was administered intravenously via an antecubital vein, followed immediately by a 5 mL saline flush. The arterial, portal venous, and late phases were defined as 0 to 30 seconds, 31 to 120 seconds, and 121 to 360 seconds after injection, respectively. The enhancement level and pattern were recorded.

Statistical Analysis

The results are given as median values and ranges. Overall survival was estimated by the Kaplan–Meier method. Overall survival was measured from the initial diagnosis of PHNET to the death from any cause or lastest follow-up.[7] Observations were right-censored on September 30, 2015. Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL).

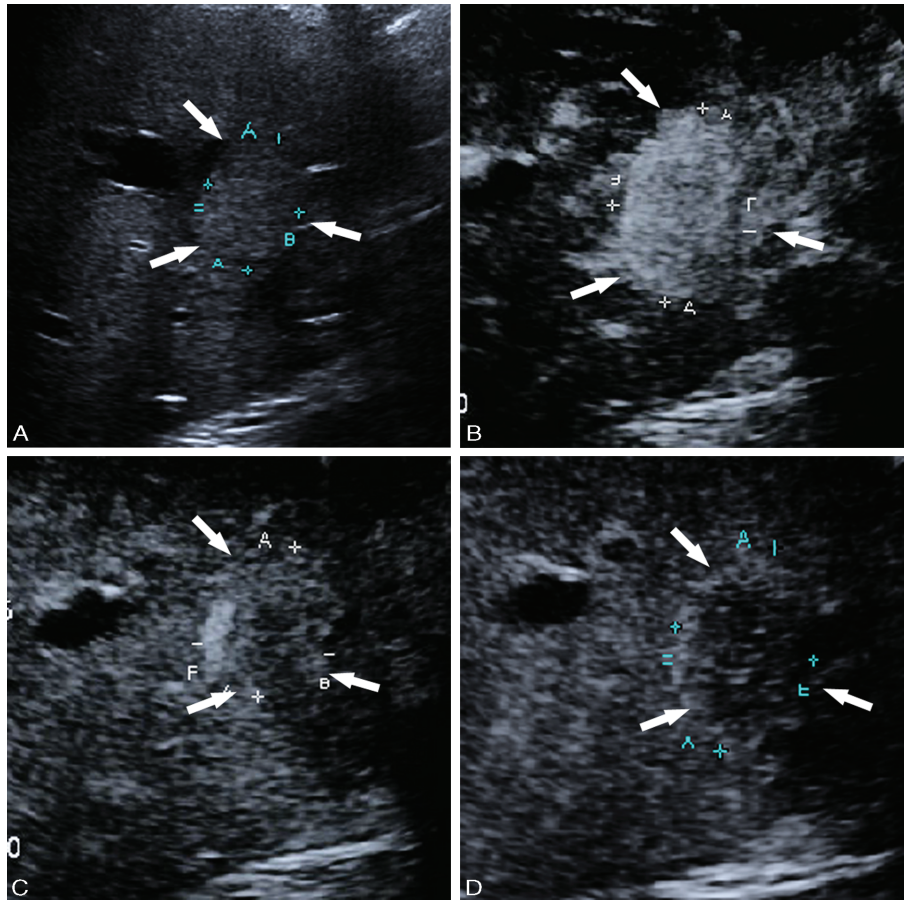

FIGURE 1. Primary hepatic neuroendocrine tumor in a 58-year-old woman (case 5). A, Conventional B-mode ultrasonography revealed an isoechoic lesion (arrow) 4.8 cm in diameter. B–D, Contrast-enhanced ultrasonography obtained at 18 s (B), 43 s (C), and 168 s (D) showed homogeneous hyperenhancement in the arterial phase (B), hyperenhancement in the periphery and hypoenhancement in the central in the portal venous phase (C), and hypoenhancement in the late phase (D).

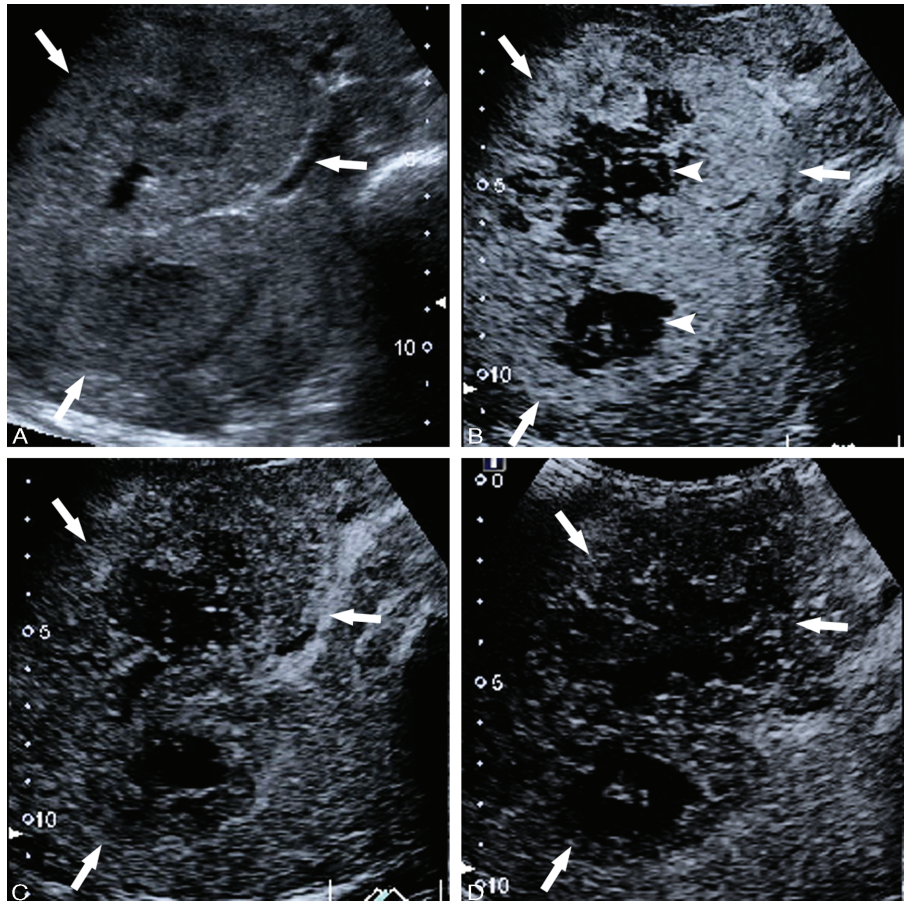

FIGURE 2. Primary hepatic neuroendocrine tumor in a 67-year-old woman (case 4). A, Conventional B-mode ultrasonography revealed a mixed solid cystic lesion (arrow) 12.7 cm in diameter. B–D, Contrast-enhanced ultrasonography obtained at 21 s (B), 73 s (C), and 140 s (D) showed heterogeneous hyperenhancement with a nonenhancement area (arrow head) in the arterial phase (B) and hypoenhancement in the portal venous and late phases.

RESULTS

Patients' Characteristics and Laboratory Results

Of the 6 cases, half were male and half were female, with an average age of 59.2 ± 5.5 years (range, 50–67 years). The most common clinical manifestation was a right upper quadrant palpable mass and abdominal pain, found in 5 patients (83.3%), and the other tumor was found in medical examination by chance. Jaundice was found in 1 case. No case displayed nausea or vomiting. No patient showed carcinoid syndrome.[8,9] Five patients had a history of hepatitis B virus infection (Table 1). The carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) level was elevated in 4 and 2 patients, respectively. The serum α-fetoprotein and serum carbohydrate antigen 125 (CA125) values were within the normal range in all patients.

CEUS Findings

Conventional B-mode ultrasonography revealed a single hepatic lesion in 5 patients (83.3%) and multiple lesions in 1 patient (16.7%). The lesions were found in the left liver lobe in 3 patients (50.0%), and 1 per patient in the right lobe, hilar, and in both lobes in the other 3. The mean size of the tumors was 11.4 cm (range, 4.8–18.4 cm). As shown in Table 1, the lesions were mixed solid cystic in 5 cases (83.3%) and isoechoic in the remaining 1 (16.7%) (Figure 1). Among the 5 mixed solid cystic lesions, 3 lesions (60.0%) were mainly composed of solid tissue with several small anechoic intralesional cavities (Figure 2), a multilocular cystic lesion in 1 case (Figure 3), and monolocular with wall nodule (Figure 4) in 1 case (17%). Intrahepatic biliary duct dilation occurred in 1 case (case 5). Enlarged lymph nodes were found adjacent to the porta, superior, and inferior vena cava in 2 cases.

CEUS showed early hyperenhancement in the arterial phase in 5 cases (83.3%); in the remaining case, the enhancement of the lesions was less than that of the surrounding liver. In 4 of the 5 hyperenhanced lesions (80.0%), enhancement homogeneity during the arterial phase had a heterogeneous pattern. The remaining lesion was homogeneously enhanced in the arterial phase. All lesions had clear enhancement margins, and surrounding vessels were found in 5 lesions (83.3%). During the portal and late venous phase, wash-out to hypoenhancement was observed in 3 patients (50.0%). Two patients (33.3%) who showed hypoenhancement in the arterial phase

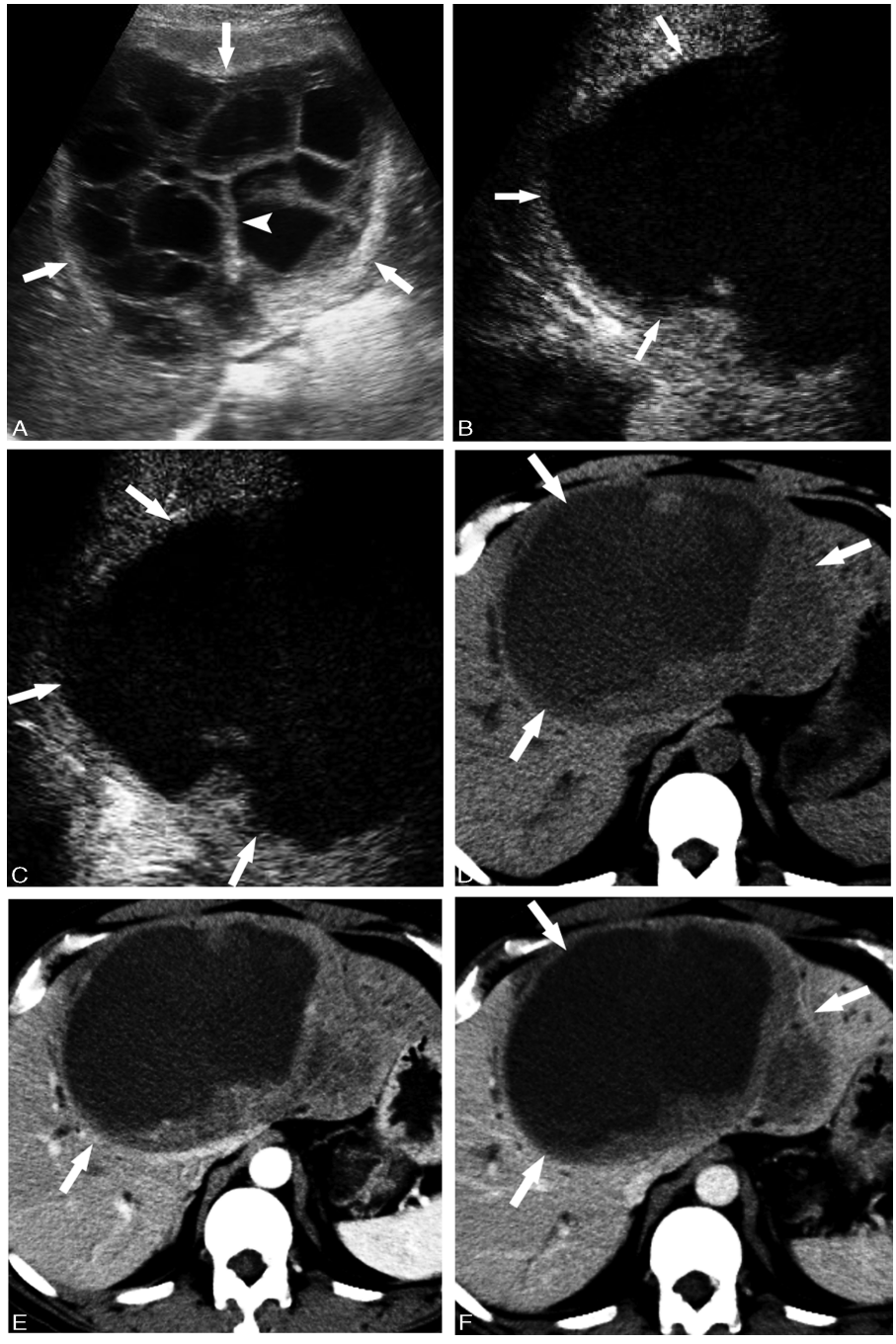

FIGURE 3. Primary hepatic neuroendocrine tumor in a 50-year-old man (case 2). A, Conventional B-mode ultrasonography revealed a multilocular cystic lesion (arrow) with several septa (arrow head) 13.0 cm in diameter. B, C, Contrast-enhanced ultrasonography obtained at 27 s (B) and 88 s (C) showed hypoenhancement in the arterial phase (B) and iso-enhancement in the periphery and nonenhancement in the central in the portal venous phase (C). CT revealed a well-circumscribed, heterogeneous, hypodense lesion in the plain phase (D) and hypoenhancement in both the arterial (E) and portal venous phases (F).

exhibited sustained isoenhanced in the periphery and nonenhanced in the central area. In the remaining patient (who showed hyperenhancement during the arterial phase), sustained hyperechogenicity in the periphery and fade-out to hypoenhancement in the central area was observed (Table 1). Preoperative diagnosis was HCC in 3 patients, hepatobiliary cystadenoma in 2 patient, and cholangiocarcinoma in 1 patient.

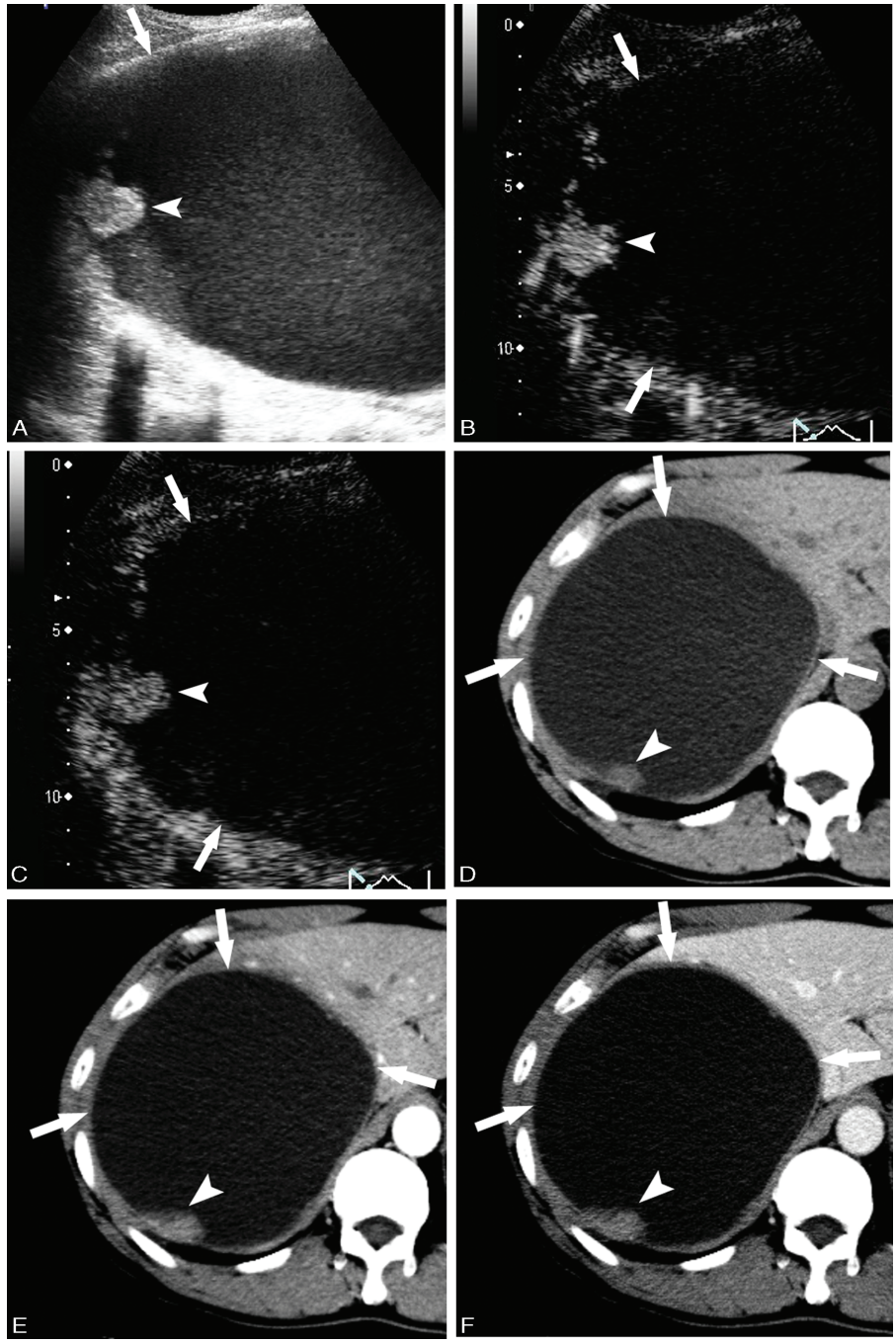

FIGURE 4. Primary hepatic neuroendocrine tumor in a 59-year-old man (case 6). A, Conventional B-mode ultrasonography revealed a monolocular lesion (arrow) with a wall nodule (arrow head) 17.6 cm in diameter. B, C, Contrast-enhanced ultrasonography obtained at 18 s (B) and 45 s (C) showed hyperenhancement in the wall nodule (arrow head) in the arterial phase (B) and hypoenhancement in the portal venous phase (C). CT revealed a cystic lesion (arrow) with a wall nodule (arrow head) in the plain phase (D) and hyperenhancement in the wall nodule (arrow head) in the arterial phase (E) and hypoenhancement in the portal venous phase (F).

Clinical Treatment and Outcomes

Five patients underwent surgical resection, and recurrence was found in 2 cases. Transcatheter arterial chemoembolization (TACE) was performed in 1 patient with recurrence. The other patient received conservative care only because of personal reasons. Follow-up ultrasound examination revealed that the mass had significantly increased, and recurrence was found in the whole liver. None of the patients were treated with a somatostatin analog.

The median overall survival in the 5 patients who underwent surgical treatment was 27 months (range, 18–36 months). The patients who received conservative care survived for 101 months since the first lesion was found. All patients were followed until September 30, 2015. The median follow-up time was 36 months (18–101 months).

DISCUSSION

PHNET was rarely seen and mostly discovered by health examination. It occurred in middle-aged patients and was frequently found in females.[10,11] Some studies had reported that a single tumor was more frequent, and no significant difference was found between the 2 lobes of the liver.[12,13] One tumor was found in the hilar in this report, which was not seen in previous reports. Five of the 6 patients had a history of HBV infection in our cases. However, few PHNET cases reported existing hepatitis virus infection.[14,15] The most common symptoms found in this study were right upper quadrant palpable mass and abdominal pain in both our cases and previous reports.[16] No patient with carcinoid syndrome was found, which agreed with a report that carcinoid syndrome was usually caused by metastatic neuroendocrine tumors.[17]

The laboratory indicators such as α-fetoprotein, carcinoembryonic antigen, and CA19-9 had almost no diagnostic value. Serum analysis of chromogranin A was the most specific marker for NETs as it was secreted by neuroendocrine cells and had a specificity of 84% to 95% and a sensitivity of 87% to 100%.[18] One study reported that serum 5-hydroxyindoleacetic acid (5-HIAA) levels in 24-hour urine might be effective markers, with a sensitivity of 73% and specificity of 90%.[19] Because a diagnosis of NET was not initially considered in our cases, the urine 5-HIAA level and serum chromogranin A level were not measured preoperatively.

It is difficult to differentiate PHNET from other liver tumors, such as hepatocellular carcinoma (HCC) and hepatobiliary cystadenoma, in imaging findings. One hypothesis proposed that hepatic neuroendocrine tumors might originate from a single malignant stem cell precursor of other hepatic malignant tumors. Intrahepatic cholangiocarcinoma (ICC) and HCC have been reported to undergo neuroendocrine differentiation.[20] Ultrasonography, CT, and MRI lack good specificity due to the similarity of PHNET and HCC. Cystic changes frequently occur in PHNET, which is difficult to differentiate from the colliquation necrosis in HCC.[21,22] In our cases, several small anechoic intralesional cavities, possibly related to central necrosis and/or hemorrhaging, were detected in 3 cases (50.0%) that were misdiagnosed as HCC. Two cases demonstrated multilocular cystic with internal septation or monolocular with wall nodule, which is the same as a benign tumor of cystadenoma in radiological findings.[23] On CEUS, enhanced mural nodules can be found on the cyst wall both in PHNET and cystadenoma.[24] The other case was diagnosed as ICC before operation. The lesion was found in the hilar, accompanied with intrahepatic biliary duct dilation and enlarged lymph nodes adjacent to the superior and inferior vena cava. On CEUS, hyperenhancement was observed in the arterial phase and sustained hyperechogenicity in the periphery, and fade-out to hypoenhancement in the central area was observed in the portal venous phase. The whole lesion faded to hypoenhancement in the delay phase.

Hepatectomy was the most effective option for localized PHNET without distant metastasis or lymph node metastasis until now.[5] Some studies reported that the 5-year survival rate was 78% to 80%[5] and the 5-year recurrence rate was 18% to 26%,[6] respectively, while the mean survival time was 148 months. In our study, recurrence was found in 2 cases after surgery, and metastasis to adjacent lymph or vertebra was found in 3 cases. At the end of our study, 3 patients were still alive. Most research suggests that resection of tumors might lead to a higher survival rate in patients with PHNET. The patient who received only conservative care in our study survived for 101 months. The patient had no clinical symptoms, no laboratory abnormalities at diagnosis, and a very good performance status. The lesion was 5.1 cm and turned into multiple lesions in the whole liver with sizes of 1.8 to 17.6 cm. These data suggest that PHNET has a rather benign course compared with other malignant tumors, and the prognosis was affected by performance status.

There are several limitations of our study, including the limited number of patients and the retrospective study design. However, this type of retrospective study can still be helpful in the diagnosis and treatment of future patients with PHNETs. Additionally, we did not have results for plasma chromogranin A, which is used to diagnose and monitor neuroendocrine tumors during treatment. Finally, the treatment modality was limited in this study in that variable treatment modalities were not compared.

In summary, PHNET is a rare liver primary tumor that has a unique specificity during its occurrence and development. When mixed solid cystic change is found in imaging, PHNET should also be considered in addition to HCC and hepatobiliary cystadenoma. Some PHNETs that demonstrate multilocular cystic with internal septation or monolocular with the wall nodule should also be differentiated from cystadenoma. The final diagnosis mainly depends on pathological and immunohistochemical examinations. At present, the most effective therapy for localized PHNET is hepatectomy. For patients with recurrence or without surgical opportunities, TACE, PEIT, and liver transplantation can be alternatives.

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