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 intraluminal 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)

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. 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. 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 an 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
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. Observations were right-censored on September 30, 2015. Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL).

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

| Case No. | Tumor Size (cm) | US Pattern | B-Mode US | CEUS                          |
|----------|-----------------|------------|-----------|-------------------------------|
|          |                 |            | 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 |

### 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).
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. Jaundice was found in 1 case. No case displayed nausea or vomiting. No patient showed carcinoid syndrome.5,6 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 intrallesional 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 hypoenhanced 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
exhibited sustained isoenhanced in the periphery and none-
anced in the central area. In the remaining patient (who
showed hyperenhancement during the arterial phase), sus-
tained hyperechogenicity in the periphery and fade-out to
hypo-enhancement in the central area was observed
(Table 1). Preoperative diagnosis was HCC in 3 patients,
hepatobiliary cystadenoma in 2 patient, and cholangiocarci-
noma in 1 patient.

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 hypo-enhancement 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
hypo-enhancement in both the arterial (E) and portal venous phases (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. Some studies had reported that a single tumor was more frequent, and no significant difference was found between the 2 lobes of the liver. 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. The most common symptoms found in this study were right upper quadrant palpable mass and abdominal pain. The mean size of 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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