

Primary hepatic neuroendocrine carcinoma: clinical analysis of 11 cases

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BACKGROUND: Primary hepatic neuroendocrine carcinoma (PHNEC) is extremely rare, and fewer than 300 cases have been reported in the English/Chinese-language literature, therefore it is difficult to make a proper diagnosis and determine a therapeutic approach.

METHODS: Eleven PHNEC patients were admitted to our hospital between January 1996 and May 2008. Laboratory examination, digestive endoscopy, B-ultrasonography, CT, MRI, or PET-CT were performed on the patients for preoperative diagnosis. All patients received liver resection. Some patients received transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection treatment (PEIT), or octreotide injection when a recurrence was found. The patients' clinical data were recorded and all patients were followed up.

RESULTS: The patients were confirmed pathologically as having PHNEC. Their median follow-up time was 33 months (12-107 months). All patients survived, and the longest post-operative survival time was 107 months, the longest disease-free survival time was 98 months, the 1-year survival rate was 100%, and the 1-year recurrence rate was 45.5% (5/11).

CONCLUSIONS: Since PHNEC is easy to confuse with hepatocellular carcinoma, careful screening of symptoms is needed to avoid misdiagnosis. Resection is the first choice of treatment for PHNEC and provides the most favorable outcomes including long-term survival. Other treatment such as TACE and PEIT can be considered as well, especially when a tumor recurs.

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KEY WORDS: carcinoma, neuroendocrine; carcinoid tumor; liver neoplasms; liver resection

Introduction

Neuroendocrine carcinoma (NEC) is rarely originated from neuroendocrine cells but is mostly seen in the gastrointestinal tract and pancreas. Oberndorfer first defined it as karzinoid (carcinoid) in 1907; it is described as a tumor that resembles an adenocarcinoma, yet behaves in a more benign fashion.^[1] However, further clinical reports showed that some carcinoids still have the characteristics of invasion and metastasis. The liver is more often involved by metastatic NEC. Primary hepatic neuroendocrine carcinoma (PHNEC) is more rare than NEC; therefore it is difficult to reach a proper diagnosis and determine a therapeutic approach. We present 11 cases in this paper.

Methods

The 11 PHNEC patients whose average age was 49.5±8.2 years (34-58 years) were admitted to our hospital between January 1996 and May 2008. B-ultrasonography, CT, MRI scan and digestive endoscopy were performed for diagnosis. All except one patient with the possibility of carcinoid were confirmed to have primary liver cancer. All patients were AFP(-) and CEA(-) except one with CA19-9(+) (patient 5). Digestive endoscopy was performed for all patients and no NEC was found in the stomach, duodenum, colon, or rectum. Of these, only 4 patients tested positive for hepatitis B infection.

Hepatectomy was taken in all patients who had been detected during operation to preclude tumors of the stomach, intestine, colon, and pancreas. Patients with a single tumor received radical excisions; others with multiple tumors underwent excision of all tumors including those found outside the liver. Only 2 patients received adjuvant transcatheter arterial chemoemboli-

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zation (TACE) after liver resection. The others did not receive any treatment until recurrence was found. TACE, percutaneous ethanol injection treatment (PEIT), or octreotide injection was performed in patients with recurrence.

Results

All patients were confirmed pathologically to have PHNEC. They were followed up until June 30, 2009. Because serum 5-HT, chromogranin A (CgA), and urinary 5-hydroxyindoleacetic acid (5-HIAA) examinations cannot be conducted at our hospital, B-ultrasonography, CT or/and MRI were used for postoperative examination. The median follow-up time was 33 months (12-107 months). The patients survived, and the longest postoperative survival time was 107 months. The longest disease-free survival time was 98 months, the 1-year survival rate was 100%, and the 1-year recurrence rate was 45.5% (5/11). The Table shows the clinical data of all PHNEC patients.

Discussion

Due to confusion around the terms carcinoid and NEC, the World Health Organization^[2] named these species of tumors as NEC in 2000, and classified them into 3 categories: 1) well-differentiated NEC, i.e., typical carcinoid or carcinoid; 2) moderately-differentiated NEC, i.e., atypical carcinoid; 3) poorly-differentiated NEC, i.e., small cell carcinoma. Based on the combination of typical clinical symptoms, NEC can be determined as functioning or non-functioning. A functioning NEC shares the same symptoms as carcinoid syndrome.^[3]

Gastrointestinal tract NEC is often metastasized to the liver, but PHNEC is rarely seen. Generally speaking, PHNEC occurs at various ages, especially in young and middle-aged patients. PHNEC is not gender specific. A

single tumor is more frequent and there is no significant difference between the two lobes of the liver.^[4, 5] Most patients are discovered by health examination with a solid liver mass.^[6] Within our series, only 4 patients had abdominal pain and diarrhea.

It is difficult to differentiate PHNEC from other solid tumors, especially hepatocellular carcinoma (HCC), before operation; meanwhile, arguments still occur on the value and risk of liver biopsy; therefore, postoperative pathologic examination is the main method for a final diagnosis.

Laboratory examination

HCC detection indices, such as AFP, CEA, and CA19-9 have almost no diagnostic value.^[4, 6] Serum 5-HT or 5-HIAA levels in 24-hour urine may be effective diagnostic indices, with a sensitivity of 73% and a specificity of over 90%.^[7] Research revealed that patients with continuing low urinary 5-HIAA show a higher survival rate than those with high urinary 5-HIAA.^[8] Serum CgA^[3, 9, 10] is a sensitive index in diagnosing NEC, with a sensitivity of 87%-100% and a specificity of 92%. Moreover, CgA can be used to monitor tumor recurrence.

Imaging detection

Ultrasonography, CT, and MRI lack good specificity due to the similarity of PHNEC to hemangioma and HCC.^[11] However, we found almost 50% (5/11) of our patients with solid tumor with cystic changes on ultrasonography, CT, and MRI (Figs. 1, 2). It differs from the colliquation necrosis in HCC and is helpful for differential diagnosis. Some reports express the same idea.^[11, 12] PHNEC often demonstrates high 18F-FDG uptake in PET-CT. It was reported that PET-CT specificity and sensitivity are increased with some specific metabolic substrates, even discovering a tumor as small as 2 mm in diameter.^[13, 14] Octreoscan is also an ideal imaging procedure, with a specificity near 83%, and can discover concealed foci.^[15]



Fig. 1. CT scan images of a PHNEC patient. **A:** Plain CT scan showing a hypodense liver mass with cystic changes and fluid level; **B:** In the arterial phase, the tumor was enhanced except for the cystic area; **C:** In the late phase, the density of the tumor was lower than the normal liver.

Table. Clinical data of PHNEC patients

Patient	Gender, Age (yr)	Presentation	B-ultrasonography findings	CT findings	MRI findings	Tumor number	Surgical treatment	HE staining	Masson staining	Immunohistochemistry		Postoperative treatment	Disease-free survival (months)	Overall survival (months)	Status
										NSE	CgA				
1	Male, 51	Abdominal pain	Hypochoic solid hepatic mass	Low density hepatic mass, enhanced in periphery		Multiple	Tumor excision in left and right lobes	Moderately differentiated, with PVE				None	48	107	Alive, recurrence (no extra-liver metastasis)
2	Male, 34	Medical exam	Hypochoic solid hepatic mass			Multiple	Right hepatectomy and right caudate lobe excision	Small cell	+	+		TACE 1 month after liver resection	98	98	Alive, no recurrence
3	Female, 52	Diarrhea	Hypochoic cystic and solid liver mass	Low density cystic and solid liver mass, enhanced in periphery, abdominal cavity lymph node metastasis, PVE		Multiple	Right hepatectomy, PVE and lymph node excision	Moderately differentiated, with PVE	+	+	+	TACE (twice) with recurrence	5	47	Alive, recurrence (no extra-liver metastasis)
4	Male, 59	Medical exam	Hypochoic solid liver mass			Single	Left hepatectomy	Well-differentiated	+	-		None	34	34	Alive, no recurrence
5	Male, 54	Medical exam	Hyperchoic cystic and solid liver mass	Cystic and solid hepatic mass, enhanced in periphery		Single	Left hepatectomy	Well-differentiated	+	+		None	24	24	Alive, no recurrence
6	Male, 43	Abdominal pain	Hyperchoic solid hepatic mass	Cystic and solid hepatic mass, enhanced in periphery		Multiple	Right hepatectomy	Well-differentiated	+	+	+	None	15	15	Alive, no recurrence
7	Female, 50	Medical exam	Hyperchoic solid hepatic mass	Low density hepatic mass, enhanced in periphery		Multiple	Tumor excision in left and right liver lobes	Well-differentiated	+	+	-	None	5	14	Alive, recurrence (no extra-liver metastasis)
8	Male, 37	Diarrhea	Hyperchoic solid hepatic mass	High density cystic and solid hepatic mass, enhanced in periphery		Multiple	Tumor excision in left and right liver lobes	Well-differentiated	+	+	-	PEIT with recurrence	1	13	Alive, recurrence (no extra-liver metastasis)
9	Female, 58	Medical exam	Cystic and hyperchoic solid hepatic mass	Cystic and solid hepatic mass, enhanced in periphery		Single	Left hepatectomy	Well-differentiated	+	+	-	None	39	148*	Alive, no recurrence
10	Female, 56	Medical exam	Hyperchoic solid hepatic mass	Low density cystic and solid hepatic mass, enhanced in periphery		Multiple	Tumor excision in left and right liver lobes	Well-differentiated	+	+	-	TACE 1 month after liver resection and recurrence	5	33	Alive, recurrence (no extra-liver metastasis)
11	Male, 50	Medical exam	Hyperchoic solid hepatic mass	High density hepatic mass, enhanced in periphery		Multiple	Tumor excision in left and right liver lobes	Well-differentiated	+	+	-	TACE and octreotide injection with recurrence	3	12	Alive, recurrence (no extra-liver metastasis)

*: This patient was followed up for 109 months for the tumor before operation. PVE: portal vein embolus.

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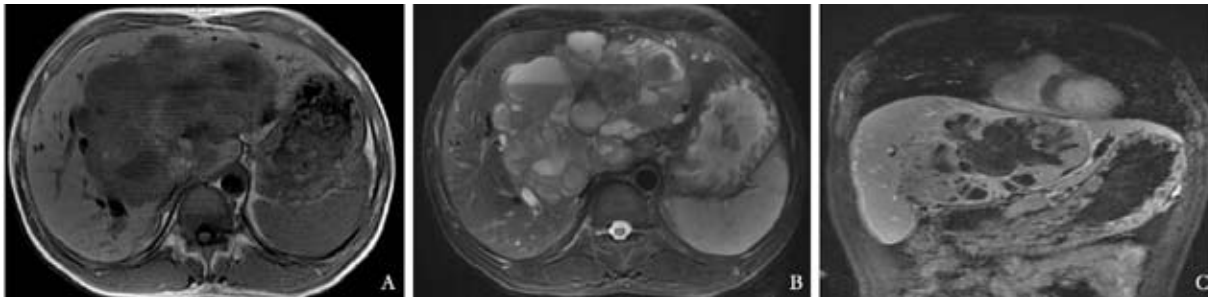


Fig. 2. MRI scan images of a PHNEC patient. **A:** T1-weighted MRI showing a large low density liver mass with a lower density cystic area in the middle lobe; **B:** T2-weighted MRI showing a high density liver mass, especially in the cystic area with a fluid level; **C:** Coronal view image showing a large cystic-solid mass in the middle lobe.

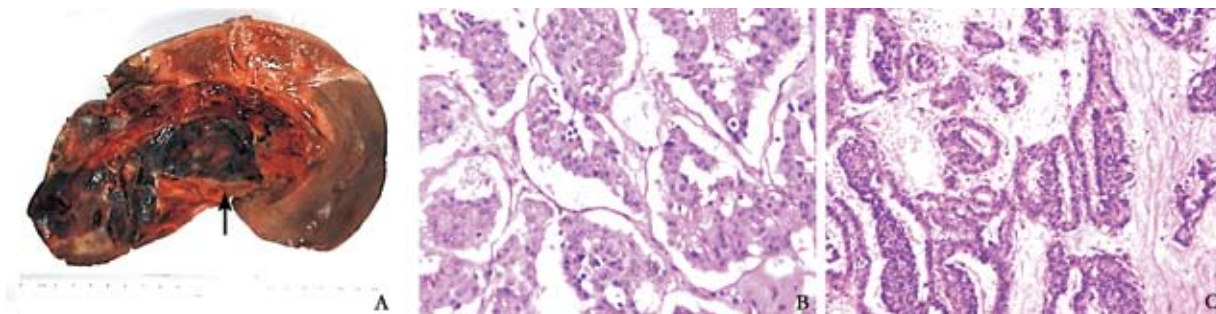


Fig. 3. Pathologic examination of PHNEC. **A:** The tumor was 16×10 cm, dark red, without pepsos, with a capsular space at the center (max diameter 1.9 cm), with hemorrhage at the middle (arrow); **B:** HE staining showing tumor cells lined up in a nest structure, surrounded by cuboidal cells; cancer nests were encased by blood sinusoids; lumen extended and had hemorrhage; cancer boundary was clear (original magnification ×400); **C:** immunohistochemistry: NSE(+) (original magnification ×200).

Pathologic diagnosis

Pathologic diagnosis is the most accurate diagnostic method (Fig. 3). Routine HE staining is not specific for diagnosis, but it is helpful in classifying the tumor grade. Some special stains, such as Masson's and Grimelius, can raise the diagnosis rate to 80% or above^[12] and our result was 100% (9/9). Immunohistochemical analysis also raises the positive rate and accuracy through detecting PHNEC correlative markers, such as neuron-specific enolase (NSE), CgA and neurilemma cell S-100 protein, and synaptic membranes protein (SYP). Among these, the sensitivity of NSE is 80%-90%^[16] and our result was 90% (9/10).

Treatment of PHNEC

Until now the most effective therapy for PHNEC is hepatectomy. Massive research reported that the survival rate is satisfactory in spite of recurrence,^[12, 17] especially for carcinoid, the 5-year recurrence rate is 18% and the 5-year survival rate is 74%-78%.^[18, 19] Until the end of our study, 54.5% of the patients (6/11) had recurrence, but all patients are still alive, including 4 patients with

moderately-differentiated or poorly-differentiated tumors. The longest disease-free survival time was 98 months and the patient had a poorly-differentiated tumor (patient 2). One patient (patient 9) in our series has survived for more than 148 months since the discovery of the tumor and 39 months since hepatectomy, without tumor recurrence. This result suggests that resection of all tumors leads to a higher survival rate in patients with PHNEC.

There is still no report of effective systemic chemotherapy for PHNEC and typical treatment for recurrence. TACE (transcatheter arterial chemoembolization), as the common treatment protocol for liver cancer, has an ideal effect for metastatic hepatic NEC according to a report,^[20] but for PHNEC, there is no certain result with a large sample set. The effectiveness of other local treatments such as radiofrequency therapy and PEIT have not been reported yet. These methods may be considered for small tumors with diameters ≤3 cm because of direct damaging effect on the tumors. One patient (patient 8) in our series had 3 recurring tumors one month after hepatectomy. He received PEIT three times within 2 weeks and the tumors decreased significantly without any

new recurrence during a 13-month follow-up.

The value of liver transplantation for PHNEC is still a problem. Some research suggests that transplantation can be taken into consideration for patients with multiple liver tumors or bad liver function due to its effectiveness and higher survival rate rather than liver excision.^[21]

In summary, a rare liver primary tumor, PHNEC has a unique specificity during its occurrence and development. Final diagnosis mainly depends on pathological and immunohistochemical examinations. We need to develop more convenient and effective features in imaging and laboratory detection to differentiate PHNEC from HCC, hemangioma, and other solid liver masses. For patients without a history of chronic liver disease, but with normal serum AFP level and cystic changes in the tumor, combined with diarrhea and abdominal pain, PHNEC should be considered. Serum 5-HT, CgA, or urinary 5-HIAA levels should be assessed for these patients. At present the main therapy for PHNEC is hepatectomy, especially for carcinoid cases. To patients without surgical opportunities, TACE, PEIT, and liver transplantation can be alternatives after evaluation of their effectiveness.

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