Experience in primary hepatic neuroendocrine tumor

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Background/aims: We aimed to analyze the clinical characteristics, pathologic features, treatment approaches, and prognostic factors of primary hepatic neuroendocrine tumor. Materials and Methods: We retrospectively analyzed the clinical characteristics, pathologic features, treatment approaches, and prognostic factors of 9 patients with primary hepatic neuroendocrine tumor treated in our hospital from January 2003 to January 2010. Results: The clinical manifestations were nonspecific and variable. The most common clinical manifestation was distention or right upper quadrant pain. Radiological findings are not specific and cannot distinguish primary hepatic neuroendocrine tumor from hepatocellular carcinoma. Diagnosis of primary hepatic neuroendocrine tumor was confirmed immunohistochemically and by the absence of extrahepatic primary sites. No extrahepatic primary lesions were found by ultrasonography, computed tomography, magnetic resonance imaging or positron emission tomography scan either preoperatively or during the follow-up period in our research. Immunohistologically, synaptophysin, chromogranin A and CD56 should be used as markers to precisely diagnose primary hepatic neuroendocrine tumor. The outcome of primary hepatic neuroendocrine tumor is mostly related to its resectability. Total resection of the neoplasm is most commonly proposed. A multimodality of treatments, including chemotherapy, transarterial chemoembolization and radiofrequency ablation, should be used pre- or postoperatively to improve the survival. Conclusions: Primary hepatic neuroendocrine tumor is a rare entity, and its diagnosis is difficult. Preoperative fine needle biopsy is strongly recommended, and primary surgery integrated with chemotherapy, transarterial chemembolization or radiotherapy is considered to be an effective modality for primary hepatic neuroendocrine tumor.

Key words: Liver, endocrine tumors, treatment

Primer hepatik nöroendokrin tümör deneyimi


Anahtar kelimeler: Karaciğer, endokrin tümör, tedavi
INTRODUCTION

Hepatic neuroendocrine tumor (HNET) is a very rare neoplasm, which is often a metastatic tumor that mainly occurs in the gastrointestinal system (1, 2). The first case was reported by Edmondson in 1958 (3). Its rarity makes it difficult to diagnose this special tumor precisely before biopsy or resection of the tumor (4). Further, the diagnosis of primary HNET (PHNET) must achieve two criteria: the liver tumor must have the neuroendocrine characteristic and extrahepatic primary sites must be strictly excluded. As PHNET has no specific clinical manifestations, and intrahepatic or lymph node metastasis occurs in the early stage, early diagnosis and treatment are helpful to improve the general survival rate.

In this study, we retrospectively analyzed the clinical characteristics, pathologic features, treatment approaches, and prognostic factors of nine patients with PHNET treated in our hospital from January 2003 to January 2010. As of April 2011, follow-up time for all patients was at least 24 months in this study.

MATERIALS AND METHODS

During the seven years from January 2003 to January 2010, we selected patients who underwent liver resection or fine needle biopsy in our center to conduct this study. Of these, nine patients were pathologically diagnosed as PHNET. The clinical data of these nine patients were analyzed retrospectively.

Of the 9 cases reported herein, 5 were male (55.6%) and 4 were female (44.4%), with a mean age of 54.4 years (range, 39-64 years). Only 1 patient had a history of hepatitis B virus (HBV) infection, and laboratory examination showed a positive result for HBsAg, HBeAb and HBcAb (Case 5). Liver cirrhosis developed in 1 patient (Case 7). Abnormal liver function was found in 66.7% of patients (6/9). They displayed an elevation of one or more liver function parameters, such as alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). Serum bilirubin was within the normal range in all patients. Serum α-fetoprotein (AFP) level was only elevated in 1 patient in this group, and the carcinoembryonic antigen (CEA) was elevated in 2. Serum carbohydrate antigen 125 (CA-125) and carbohydrate antigen 19-9 (CA-19-9) levels were elevated in 3 of 9 patients (33.3%) and 2 of 9 patients (22.2%), respectively. The masses were found in the left liver lobe in 2 patients, in the right lobe in 5 patients (55.6%), and in both lobes in 2 patients. The diameter of tumors ranged from 1.8 cm to 14.1 cm, with a mean size of 5.54 cm (Table 1).

RESULTS

Clinical Profiles

The clinical manifestations were nonspecific and variable. The most common clinical manifestation was distention or right upper quadrant pain, found in 7 of 9 patients (77.8%). Four patients had a history of weight loss (44.4%). Less common symptoms at initial presentation were general fatigue in 3 patients, fever in 3 patients, and abdominal mass in 1. None of them displayed nausea, vomiting or jaundice. None of these 9 patients showed facial flushing, diarrhea, wheezing, or right heart failure, a carcinoid syndrome due to tumor excretion of serotonin, histamine, prostaglandin and bradykinin (5, 6).

Imaging Findings

All these 9 patients underwent abdominal ultrasound (US) and enhanced computed tomography

<table>
<thead>
<tr>
<th>Patients no.</th>
<th>Localization</th>
<th>Tumor number</th>
<th>Tumor size (cm)</th>
<th>Syn</th>
<th>CgA</th>
<th>CD56</th>
<th>CK-19</th>
<th>TTF-1</th>
<th>Hepatocyte</th>
<th>CDX2</th>
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<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>1</td>
<td>3.7</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>2</td>
<td>Bilateral</td>
<td>2</td>
<td>14.1</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>3</td>
<td>Right</td>
<td>1</td>
<td>4.1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>1</td>
<td>3.0</td>
<td>+</td>
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<tr>
<td>5</td>
<td>Right</td>
<td>1</td>
<td>4.1</td>
<td>+</td>
<td>+</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>6</td>
<td>Right</td>
<td>Multiple</td>
<td>2.7</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
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<td>3.4</td>
<td>+</td>
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<td>-</td>
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</tr>
<tr>
<td>8</td>
<td>Bilateral</td>
<td>2</td>
<td>1.8</td>
<td>+</td>
<td>+</td>
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<tr>
<td>9</td>
<td>Right</td>
<td>1</td>
<td>13.0</td>
<td>+</td>
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</table>

(CT) scanning tests. It appeared that most PHNET masses were not specific in the US examination. A single mass lesion was found in the liver of 5 patients, and larger lesions could be formed by the fusion of two or more smaller ones. US usually revealed a well-demarcated, hypoechoic, hyperechoic, or inhomogeneous echo mass, with a borderline area of annulation around it. CT scans revealed heterogeneous hypodense lesions in the hepatic parenchyma at noncontrast plain phase in all 9 patients. Dynamic liver CT scans revealed enhancement of the occupation in the arterial phase and early fade in the portal phase (Figure 1). A primary extrahepatic site was excluded by a series of tests including US, CT, magnetic resonance imaging (MRI), radiography of the gastrointestinal tract, or positron emission tomography (PET). Five patients underwent a US-guided percutaneous fine needle biopsy, and PHNET was identified by immunohistochemistry. The other 4 patients were diagnosed by postoperative pathology.

Clinical Treatment and Outcome

Six of these patients received surgical intervention, including radical tumor segmentectomy, left or right hemihepatectomy, extended right hemihepatectomy, or laparotomy and biopsy. Abdominal exploration at the time of resection revealed no extrahepatic lesions. One (Case 6) received right hemihepatectomy and cholecystectomy after four consecutive cycles of transarterial chemoembolization (TACE) with oxaliplatin (200 mg) + epirubicin hydrochloride (20 mg) + gemcitabine hydrochloride (1000 mg) + lipiodol (6 ml) and another two cycles of TACE postoperatively. Five patients survived in the operative group, with one recurrence in the right lobe of the liver 16 months after postoperative radiotherapy in a patient who received exploratory laparotomy and biopsy because of recurrently resectable tumor (Case 3), and one patient was lost (Case 9). One patient received chemotherapy (Case 2) with etoposide (100 mg, Day 1-3) + cisplatin (30 mg, Day 1-3); unfortunately, she died of hepatic failure and biliary obstruction after six cycles of chemotherapy. Radiotherapy was performed in 2 patients (Cases 3, 5), one of which was performed postoperatively (Case 3). One patient (Case 8) received radiofrequency ablation (RFA) and also died of hepatic failure 11 days after he gave up advanced treatment. All five surgically treated patients with finished follow-up survived more than two years in this group. The treatments and outcome are summarized in Table 2.

Pathologic Features

The pathology revealed poorly, moderately or mixed differentiated cells. The tumor cells were arranged in glandular tube, trabeculae, irregular nests, or as a single piece. Nuclear atypia was obvious and karyokinesis was found. Some tumor cells showed an infiltrate growth pattern, and the hemal tube was encroached (Figure 2A). Immunohistochemical analysis showed positive stainings for synaptophysin, chromogranin A and CD56, which were unique for neuroendocrine car-

![Figure 1. Computed tomographic findings of a 47-year-old man with PHNET (Case 3). A: In the arterial phase, a 4.1x3.1 cm hypervascular mass was identified in segment-V of the liver. B: Tumor hypervascularity was faded in the portal phase. These imaging features are compatible with those of hepatocellular carcinoma.](image-url)
cinoma (Figure 2 B, C). All 9 tumors tested for synaptophysin, all 7 tumors tested for chromogranin A and all 6 tumors tested for CD56 were positive (100%). Cytokeratin 19 (CK-19) and thyroid transcription factor-1 (TTF-1) were also tested in this research. In CK-19 tested tumors, 7 of 9 (77.8%) were positive, and in TTF-1 tested tumors, 4 of 9 (44.4%) were positive. Caudal type homeobox 2 (CDX2) was tested in 9 specimens and all of them were negative. All hepatocyte stains done in this research were negative (Figure 2D). The clinicopathologic features of this group are summarized in Table 1.

DISCUSSION

Neuroendocrine tumor (NET) is rare neoplasm that usually occurs in the gastrointestinal system, and the liver is a common site for metastases (1). PHNET is very rare, but has been an increase in the incidence of these tumors over time (7). Some reported that most PHNETs are found in female adults more than in males, with the ratio being about 58.5% vs 41.5%, and those with a mean age of over 40 years are most commonly involved (8,9). However, the results of this study differed from the literature reported previously in that only 4 of 9 patients (44.4%) were female. This may be due to the small number of our cases. It appears that the right liver lobe is more easily affected than the left lobe, and bilateral localization has also been observed, as reported (10-13). This epidemiologic feature is concordant with our results. In this study, the masses were found in the left liver lobe in 2 patients, in the right lobe in 5 patients (55.6%), and in both lobes in 2 patients. The relationship between PHNET and hepatitis virus and cirrhosis is not obvious yet. Only 1 patient had a history of HBV infection and another had liver cirrhosis. It seems that PHNETs are not associated with underlying liver disease.

The most common symptoms found in this study were distention or right upper quadrant pain, weight loss and fatigue. It was reported that carcinoid syndrome is the specific clinical manifestation of PHNET, including asthma, flushing, and diarrhea. Histamine, prostaglandin or serotonin secretion by the tumor was related with these manifestations in some reports (5,6). However, others reported that PHNET rarely causes carcinoid syndrome, which is usually caused by metastatic NET (14,15). In our study, no patient with carcinoid syndrome was found. The physical examination was atypical as well. Only hepatomegaly could be found in those with advanced stage of disease.

Diagnosis of PHNET must strictly meet two criteria: histopathological confirmation of the neuroendocrine characteristic and the absence of extrahepatic primary sites. US usually shows hypoechoic, hyperechoic or mixed echogenic lesions with rings around them. In advanced stages, dynamic CT imaging usually revealed hypodense nodules with necrotic changes and containing calcification. In the arterial phase, a hypervascular mass was usually identified, and the hypervascularity faded in the portal phase. These imaging features are compatible with those of hepatocellular carcinoma. Classical PET with fluorodeoxyglucose was proven to be non-advantageous in the diagnosis of NET (16). In our experience, US-guided percutaneous fine needle biopsy can yield more information and provide the final diagnosis of PHNET. In this study, 5 patients underwent fine needle aspiration preoperatively and all of them were confirmed as PHNET postoperatively. Synaptophysin, chro-
The tumor cells were strongly immunoreactive for synaptophysin (immunohistochemistry, original magnification x200). C: The tumor cells were strongly immunoreactive for chromogranin A (immunohistochemistry, original magnification x200). D: The tumor cells were not immunoreactive for hepatocyte marker, whereas normal hepatocytes showed strong immunoreaction (immunohistochemistry, original magnification x200). Ambient hepatocytes are seen located in right side of the field of vision.

mogranin A and CD56 were specific immunohistochemical parameters for neuroendocrine carcinoma. In our research, all tumors tested for synaptophysin, chromogranin A and CD56 were positive (100%). In addition, using monoclonal mouse anti-human hepatocyte, we immunohistochemically examined the expression of hepatocyte antigen, which is present in normal human hepatocytes and is conserved in a majority of hepatocellular carcinomas. This antibody does not label other tumors except for some tumors of gastrointestinal origin. PHNET should be a hepatocyte-negative tumor. Thus, hepatocyte should be used as comarker in diagnosing PHNET. However, the association of these tumors with non-NET markers such as AFP, CA-125 and CA-19-9 is not relevant. Finally, the PHNET can be diagnosed only after the extrahepatic primary sites are excluded (17). In recent research, CDX2 and TTF-1 were reported as markers of gastrointestinal and pulmonary NETs, respectively (18,19). Further, they were proposed to be valuable for separating metastatic NETs of unknown origin (18); however, this is still contradictory. In our research, TTF-1 was 44.4% positive and CDX2 was negative in 9 patients, which was different from the reported results (18,19). Thus, it is important in our research that no extrahepatic primary lesions were found by US, CT, MRI, or PET examinations preoperatively or during the follow-up period. Although we strictly excluded ex-
trahepatic primary site by such modalities, there may still be a proportion of patients with metastatic disease of unknown primary origin that becomes evident in time. Thus, to make the final and exact diagnosis, it is necessary to make the follow-up period as long as possible to strictly exclude occult extrahepatic primaries, considering the slow progression of the tumor.

Surgery is confirmed to be the primary treatment modality for PHNET (1,20), especially when a single lesion is confirmed or single lobe is located. The modality for PHNET (1,20), especially when a single lesion is confirmed or single lobe is located. The five-year survival rate after operation was reported to be 74%, with a recurrence rate of 18% [15]. However, another report showed an unsatisfactory result, with a five-year survival rate of 56.3% and a five-year recurrence rate of 40% [21]. In a recent report, liver transplantation was offered in 2 patients and the outcome was optimistic after 95 and 45 months of follow-up (22,23). In our research, all 5 surgically treated patients with finished follow-up had survived to date, revealing a 100% two-year survival rate. Thus, total resection of the tumor makes the prognosis promising. TACE is performed when the lesions are unresectable or the patient’s general condition and functional hepatic reserves do not permit surgery. It was reported that TACE is effective in controlling symptoms and prolonging disease-free survival. Chemotherapy and RFA are applied in patients with unresectable lesions or in those not suitable for TACE treatment, though the effects of chemotherapy and RFA alone are less promising. Chemotherapy has poor satisfactory response and more side effects, and usually causes gastrointestinal reaction and inhibition of hematopoiesis. Nonetheless, combined with surgery, a multimodality treatment including chemotherapy, TACE and RFA should be used pre- or postoperatively to improve the survival.

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