Case Report
Primary hepatic neuroendocrine carcinoma: clinicopathologic analysis of surgical treatment of 12 cases from a single institutional experience

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Abstract: Primary hepatic neuroendocrine carcinoma (PHNEC) is a kind of rarer disease than gastrointestinal derived neuroendocrine carcinoma. Therefore, it is difficult to make an accurate diagnosis and determine a proper therapeutic decision. 12 PHNEC patients were admitted to our hospital from November 2011 to June 2015. CT/ MRI, B-ultrasound and laboratory examination were performed before liver resection. The patients' clinical data were recorded and all patients were followed up. All patients received liver resection including right/left hepatectomy or mesohepatectomy. PHNEC was confirmed pathologically in the 12 patients, immunohistochemical staining in these tumor cells was positive for CgA and Syn and negative for CEA and AFP. The mean follow-up time was 13 (1-45) months, and 3 patients died due to disease aggression or recurrence during the period. PHNEC is rare and easy to be diagnosed as hepatocellular carcinoma, and careful screening to exclude gastrointestinal tumors is needed preoperatively. Radical resection with clear margin is the best choice for PHNEC, and provides favorable prognosis.

Keywords: Neuroendocrine, carcinoma, hepatectomy, immunohistochemistry, carcinoid

Introduction

Neuroendocrine carcinoma is usually derived from neuroendocrine system such as gastrointestinal tract and pancreas. They are commonly characterized by some general markers (i.e., chromogranin, neuron-specific enolase) and hormone secretion products like gastrin, serotonin, ACTH, insulin, etc [1]. There were some clinical reports indicated that carcinoid still has the behavior of invasion and metastasis. Liver was still the main target for metastatic neuroendocrine carcinoma (NEC). However, (PHNEC) is extremely rare compared to NEC, accounting less than 0.3% of all endocrine tumors of the digestive system [2, 3]. Therefore, it is difficult to reach a proper diagnosis and determine a therapeutic approach. In 1907, Oberndorfer firstly described PHNEC as carcinoid resembling adenocarcinoma, but exhibiting a benign fashion. Fewer than 100 cases of PHNET have been reported in the English-language literature so far [4]. We herein present 12 cases in this paper.

Methods

Twelve patients were admitted to our hospital between November 2011 and June 2015. Their clinical presentation, clinicopathologic features, radiological images, type of surgical treatment, prognosis and follow-up time were collected and analyzed retrospectively. Pathological features were assessed by tumor location, size, resection margin, vascular invasion, lymph node invasion and cellular atypia. All the patients were evaluated by immunohistochemical staining to confirm the diagnosis of PHNEC.

Hepatectomy was performed in all patients. Liver resection volume was determined by tumor location, tumor number and proximal to main branches of portal vein. Resection type included segmentectomy, hemihepatectomy and trisegmentectomy. All patients with single or multiple tumors received radical excision.

Survival data and follow-up information were collected by reviewing the patients’ medical records and telephone interview. The study pro-
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tocol was approved by the Institutional Review Board.

Results

Patients’ characteristics

The 12 patients included 4 female and 8 male, with an average age of 58 years old (range 44-78 years). Abdominal dull pain was complained in 6 patients, abdominal discomfort in 1 patient, distension in 1 patient and 4 patients had no symptom. 4 patients were tested positive for hepatitis B virus infection.

All patients were followed up for average 13 months (range from 1 to 45 months) after the initial treatment of PHNEC, no extrahepatic lesion was found radiologically during follow-up period, except for intrahepatic recurrence in 2 patients. 3 patients died from disease aggression or recurrence in the follow-up period. The clinical features of the 12 patients were listed in Table 1.

Preoperative assessment and diagnosis

All patients were AFP(-) and CEA(-) except one with CA19-9(+) (patient 5). Computed tomography and/or magnetic resonance imaging scan were performed for diagnosis before surgery (Figure 1), digestive endoscopy was used to exclude gastrointestinal originated tumors. 10 patients had single lesion, 1 patient had 3 lesions and 1 patient had 4 lesions in the liver, no extrahepatic lesion was found on imaging modality. The average diameter of all lesions was 9.4 cm (3-15 cm).

Surgical treatment

All the 12 patients underwent surgical exploration. The surgical procedures included left segmentectomy (1, 8.3%), left hemihepatectomy (3, 25.1%), left trisegmentectomy (2, 16.7%), extended left hemihepatectomy (1, 8.3%), mesohepatectomy (2, 16.7%), right segmentectomy (1, 8.3%), right hemihepatectomy (1, 8.3%) and extended right hemihepatectomy (1, 8.3%) (Figure 2). The mean operation time was 3.5 hours (range 2-6.5 hours). The average intraoperative blood loss was 210 mL (range 120-1100 mL). All the patients received R0 resection without surgical mortalities. Post-surgical complications occurred in 2 patients. 1 patient had wound infection 5 days after surgery. Another patient had lung infection 3 days postoperatively. These patients were conservatively managed with dressing exchange and antibiotics therapy respectively. The median hospital stay was 9 days (range 6 to 17 days).

Pathological features

We observed various types of primary hepatic neuroendocrine tumor in our study, including well differentiated neuroendocrine carcinoma, carcinoid tumors and poor differentiated neuroendocrine carcinoma. Pathological examination showed that tumor cells were diverse and a large number of tumor cells arranged in vessel-like structure, with little interstitial elements (Figure 3).
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Light microscope showed that their nuclei were round in shape, arranged irregularly and clustered flakily. The immunohistochemical staining of tumor cells was positive for Syn and CgA, but negative for AFP and CEA. The Ki 67 is almost expressed in all of the neoplastic cells. Immunohistochemical data are summarized in Table 2. Final diagnosis was neuroendocrine tumour with regard to WHO 2010.

Immunohistochemical studies were performed in 12 patients. Results were typically positive for chromaffin granule protein A (CgA, 12/12, 100%), synaptophysin (Syn, 11/11, 100%), pan cytokeratin (PCK, 3/3, 100%), epithelial membrane antigen (EMA, 4/4, 100%). In addition, cluster differentiation 56 (CD56) was detected in 8 patients and the positive rate was 6/8 (75%). Cytokeratin 19 (CK19) was detected in 6/8 (75%), transcriptional intermediary factor-1 (TIF-1) in 1/3 (33%), alpha-fetoprotein (AFP) in 3/9 (33%), and hepatocyte paraffin antigen-1 (Heppar-1) in 0/3 (0%). Ki-67 was detected in 11 patients and the index ≤2% was found in 1/11, 4 in 11 patients’ index was between 2% and 20%, 6 patients’ index ≥20%.

Figure 1. CT and MRI scan images of patients with PHNEC. Magnetic resonance imaging showed a long T1 signal mass in the right liver (A and B); computed tomography showed a single mass in the left hepatic lobe, clear boundary and uneven density with low density necrotic area inside. In enhancement scan, no enhancement was observed in the mass in the arterial phase (C); A decline in enhancement was observed in the portal venous phase (D); an annular enhancement was observed in the arterial phase and a decline in the portal venous phase respectively (E and F).
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Follow up

The 12 patients had been followed up, including routine laboratory tests, abdominal US, and CT or MRI every 3 months after surgery. The follow-up time was for a mean duration of 13 months (range 1 to 45 months), 9 patients were alive with 3 dead. Chemotherapy or radiotherapy was not given to any of the patients.

Discussion

Neuroendocrine carcinoma usually originated from gastrointestinal tract and pancreas, they were likely to metastasize to liver to form secondary neuroendocrine carcinoma [5, 6]. However, primary hepatic neuroendocrine carcinomas (PHNEC) developed from the liver were rare because liver has few enterochromaffin cells [7].

According to the World Health Organization 2010 criteria of neuroendocrine carcinoma [8], neuroendocrine carcinomas were classified into 3 categories: Well-differentiated neuroendocrine tumors (i.e., carcinoid), moderately differentiated neuroendocrine carcinomas (i.e., atypical carcinoid) and poorly differentiated neuroendocrine carcinomas (i.e., small cell neuroendocrine carcinoma) [9]. The origin of PHNEC is not well known, but it has been hypothesized that they may originate from dispersed neuroendocrine cells in the hepatic biliary system, or chronic inflammation initiated biliary epithelium intestinal metapla-

Figure 2. Gross anatomic images of PHNEC. Primary hepatic neuroendocrine carcinoma protruded from the surface of liver (A), which was resected with cutting edge observed (B), the resected tumor was grey with maximal diameter of 15 cm (C), the tumor margin was clear and well capsuled, with grey yellow tissue and multifocal hemorrhage inside (D).

Figure 3. Pathologic examination of PHNEC. HE staining showing tumor cells lined up, surrounded by cuboidal cells, cancer boundary was clear (original magnification ×400) (A); immunohistochemistry showing CgA staining positive (original magnification ×400) (B); NSE staining positive cell (original magnification ×400) (C); Syn staining positive cell (original magnification ×400) (D).
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sia which developed to neuroendocrine tumors [1, 10].

Symptoms and signs were not significant in the early stage of PHNEC. The clinical symptoms were atypical, such as upper abdominal pain or fullness, as well as weight loss. Only a few of patients complained of a typical carcinoid syndrome such as skin flushing or diarrhea [11]. Patients often deny history of hepatitis or cirrhosis, and AFP level is negative. In addition, conventional tumor markers, such as CEA, CA19-9 and CA125 were often negative [12].

Pathological examination especially immunohistochemical results are important for the diagnosis of PHNEC. Positive expression of Syn and CgA indicated the diagnosis of neuroendocrine tumor [13, 14], which was consistent with 11 patients in our study. Ki-67 is positive for all tested patients, the difference is the Ki-67 percentage which represents the proliferation ability of neuroendocrine tumor cells, for example, Ki-67 index more than 20% means high proliferation capacity of tumor cells. Immunohistochemical AFP is positive in 3 patients in contrast to negative serum AFP level indicated that AFP was expressed in tumor cells but not in serum. The mechanism is still unclear and remains to be investigated further.

Early diagnosis and resection of hepatic lesions are the best treatment for PHNEC [15]. Radiofrequency ablation, transhepatic artery chemotherapy embolism and microwave are selective treatment for patients without indication for radical surgery [4, 16]. It is reported that Liver transplantation was also considered in certain cases [17, 18]. Previous studies have showed that somatostatin, as well as its analogs, may exhibit beneficial effects in the treatment of PHNEC [19, 20].

The prognosis of PHNEC is involved with a number of aspects, such as proliferation index, degree of differentiation, pathological subtype, tumor number as well as metastasis. The same with other malignant tumors, early diagnosis and radical treatment are crucial to achieve a long term survival.

Disclosure of conflict of interest

None.

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References


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Table 2. Immunohistochemical features of PHNEC (n=12)
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