Combined Primary Neuroendocrine Carcinoma and Hepatocellular Carcinoma of the Liver

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We report a unique case of combined primary neuroendocrine carcinoma (NEC) and hepatocellular carcinoma (HCC) of the liver in a 65-year-old male patient. The patient underwent segmental resection of the liver and regional lymph node dissection for a tumor mass that measured 7.5 cm in diameter in the right lobe, with regional lymphadenopathy. Histologically, the hepatic tumor was composed of predominantly small-cell NEC, but admixed with a small island of moderately differentiated HCC. We speculate that the NEC originated from a poorly differentiated tumor clone of an HCC that underwent neuroendocrine differentiation, and that this tumor was now at the end stage of the transitional period from HCC to NEC, based on the small amount of disappearing HCC. Ki-67 and p53 expression were higher in the NEC than in the HCC, and the lymph nodes showed only metastatic NEC. Therefore, this kind of tumor had a more aggressive clinical course in accordance with being an NEC rather than a conventional HCC. Three months after operation, the patient had multiple recurrent tumor nodules within the liver, spreading the metastasis to the adrenal glands and para-aortic lymph nodes. The patient died 1 year after operation. [*J Chin Med Assoc* 2009;72(8):430–433]

Key Words: combined, hepatocellular carcinoma, liver, neuroendocrine carcinoma

Introduction

Although the liver is the most frequent metastatic site of extrahepatic neuroendocrine carcinoma (NEC), a diagnosis of primary hepatic NEC is rarely made.[1–3] Primary mixed NEC and hepatocellular carcinoma (HCC) is even rarer.[4–8] It can present as a collision tumor that shows 2 histologically separate parts without a transitional area or it can present as a combined tumor in which both types of tumor intermingle with each other and are continuous.[8] We herein describe a unique case of combined primary NEC and HCC of the liver within a single tumor nodule, in which the NEC component comprised more than 99% of the tumor area, and only a small nest of moderately differentiated HCC was embedded within the NEC. Its pathogenesis and prognosis are also discussed.

Case Report

A 65-year-old male patient was referred to our hospital due to intermittent epigastric pain for 4 weeks, after which a hepatic tumor was found by ultrasonography. The patient had a 15-year history of chronic hepatitis B and a 5-year history of diabetes mellitus. Abdominal computed tomography revealed a lobulated mass, 7.5 cm in maximal diameter, in the right lobe, and enlarged lymph nodes in the upper retroperitoneum. Angiography showed a hypervascular patch over S4-8, compatible with HCC. Upper gastrointestinal endoscopy revealed esophageal varices and superficial gastritis. Chest X-ray was normal.

Test for serum hepatitis B surface antigen (HBsAg) was positive, while test for hepatitis C antibody (anti-HCV) was negative. Laboratory data including white

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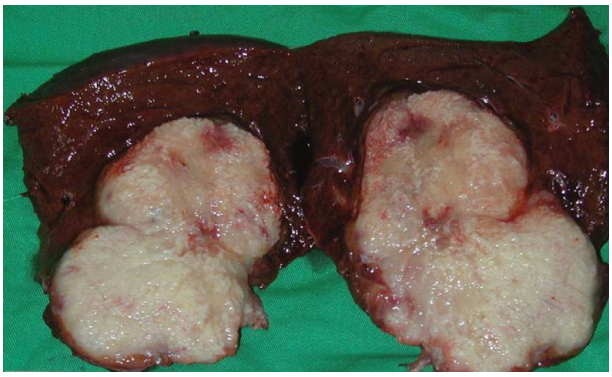

Figure 1. Resected liver specimen shows a well-defined tumor with heterogeneous gray-white and brown cut surface.

blood cell count, hemoglobin, hematocrit, platelet count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, total bilirubin, direct bilirubin, electrolytes and renal function test were all within normal ranges. Plasma levels of tumor markers, including α-fetoprotein, carcinoembryonic antigen and CA19-9, were within normal ranges.

With suspected hepatic malignancy and regional lymph node metastasis, the patient underwent segmental resection of the hepatic tumor and regional lymph node dissection. The resected specimen of the liver measured 9 × 8 × 3 cm, and there was a well-defined and heterogeneous gray-white to brown friable tumor, 7.5 cm in diameter (Figure 1). The residual liver was firmer than usual but without cirrhotic change.

Microscopically, the tumor consisted of predominantly small- to medium-sized neoplastic cells arranged in solid sheets accompanied by geographic necrosis (Figure 2A). Tumor cells were separated by dense fibrovascular septa and were intimately associated with blood vessels. Tumor cells had round to oval nuclei with inconspicuous nucleoli and scanty cytoplasm. Nuclear molding change and mitoses were frequently seen (Figure 2B). The morphological picture was reminiscent of NEC. In addition, a small island of polygonal tumor cells with abundant eosinophilic granular cytoplasm and round nuclei in a trabecular structure with variable cell thickness or pseudoglandular pattern, consistent with moderately differentiated HCC, were found floating in the main tumor parts (Figure 2C). The HCC component measured about 5 × 2 mm and made up less than 1% of the whole tumor volume. The majority of the HCC was separated from the NEC by a thin fibrous capsule, but there was a small focus of HCC transition into the NEC with breakthrough of the fibrous capsule of the HCC (Figure 2D). The residual liver tissue revealed chronic hepatitis without cirrhotic change.

Immunohistochemically, the small round cells were strongly positive for neuron-specific enolase and CD56, and focally positive for chromogranin-A and synaptophysin. Hepatocyte-specific antigen antibody (OCH1E5), α-fetoprotein, TTF-1, CDX2, and leukocyte common antigen were negative. The immunohistochemical findings supported a diagnosis of NEC. Tumor cells of the HCC were diffusely positive for OCH1E5 and focally positive for CD56 (Figure 3). Immunostaining for p53 protein expression and Ki-67 proliferative index were significantly higher in the NEC than in the HCC.

Study of the lymph nodes revealed metastatic NEC without an HCC component. Thus, a diagnosis of primary combined NEC and HCC with regional lymph node metastasis of NEC was made. Three months after the operation, follow-up abdominal CT showed multiple recurrent tumors, measuring up to 16.5 × 13 × 8 cm in diameter, in both lobes of the liver, with diffuse portal vein thrombosis accompanied by metastasis reaching bilateral adrenal glands and para-aortic lymph nodes. The patient died 1 year after operation.

Discussion

There are 2 types of primary mixed NEC and HCC in the liver. It can present as a combined-type tumor in which both NEC and HCC components intermingle with each other and cannot be clearly separated in the transitional area within a single tumor nodule.[7] A collision tumor, less frequent than the combined type, shows 2 grossly separated tumor nodules composed of histologically different tumors.[4,8] Immunohistochemically, some tumor cells of the HCC in the combined tumor may be immunoreactive for neuroendocrine markers;[7] however, the HCC component of the collision tumor revealed no neuroendocrine features. In this patient, only a small HCC component floated within the NEC component. Most of the HCC component was separated by a thin fibrous capsule, but there was focal transition into the NEC. The HCC was focally immunoreactive for the neuroendocrine marker CD56. Therefore, the tumor had combined primary NEC and HCC.

The origin of the neuroendocrine components of mixed NEC and HCC is still controversial. Two hypotheses have been postulated: (1) malignant transformation of hepatic stem cells;[2,5] and (2) neuroendocrine differentiation of HCC cells under certain circumstances.[4,7] In our case, the second theory is favored because the HCC component were focally positive for the neuroendocrine marker CD56. Therefore, if a poorly-developed tumor clone of HCC underwent

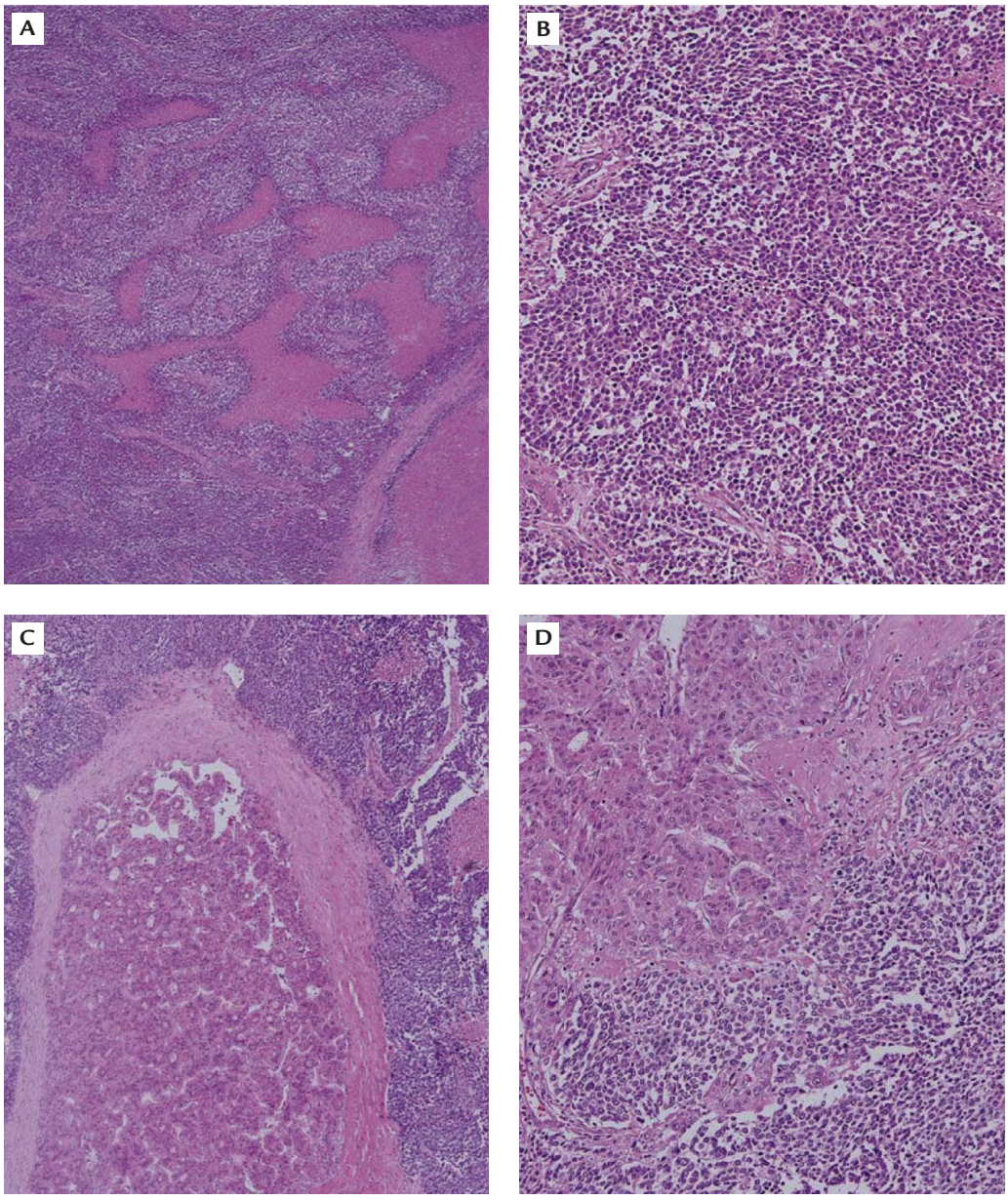

Figure 2. (A) The neoplastic cells of the neuroendocrine carcinoma (NEC) are arranged in a solid pattern accompanying geographic necrosis (hematoxylin & eosin [H&E]; original magnification, 40×). (B) Tumor cells of the NEC have round to oval molded nuclei with scanty cytoplasm and frequent mitoses (H&E; original magnification, 400×). (C) Moderately differentiated hepatocellular carcinoma (HCC) is predominantly separated from NEC by a thin fibrous capsule (H&E; original magnification, 40×). (D) Focal transitional area between HCC and NEC is observed (H&E; original magnification, 200×).

neuroendocrine differentiation and was transformed into an NEC, it is possible that the original HCC was completely replaced by the NEC.[4] Yamaguchi et al[7] also found the expression of p53 protein and Ki-67 proliferative index to be significantly higher in the NEC component than in the HCC component. This finding further confirms that NEC has higher proliferative activity and malignant potential than ordinary HCC.

Based on the 3 features observed in our patient—the HCC component comprised less than 1% of the whole tumor, p53 protein expression and Ki-67 proliferative index were higher in the NEC than in the HCC, and HCC focally transitioned into the NEC with breakthrough of the fibrous capsule of the HCC—we can speculate that a poorly differentiated part of the HCC underwent neuroendocrine differentiation, proliferated and transformed into an NEC.[4] Because of its highly proliferative activity and malignant potential, it gradually replaced the original HCC component. The tumor was now at the end stage of the transitional

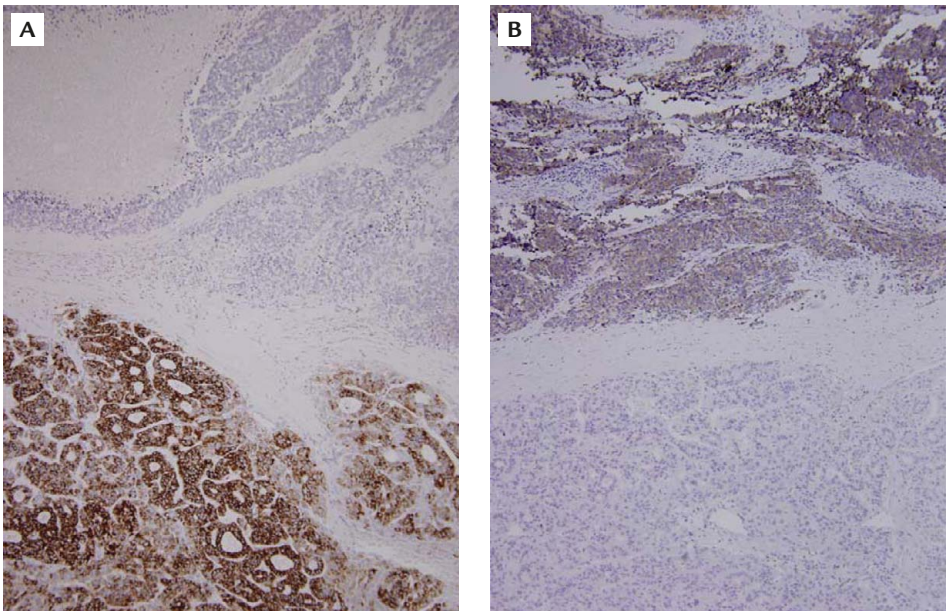

Figure 3. (A) Hepatocellular carcinoma (HCC) is strongly positive for hepatocyte-specific antigen, while neuroendocrine carcinoma (NEC) is nonreactive for hepatocyte-specific antigen (original magnification, 100×). (B) HCC is negative for synaptophysin, but NEC is immunoreactive for synaptophysin (original magnification, 100×).

period from HCC to NEC. Thus, it is reasonable that we only found a residual disappearing HCC component. Thus, we believe, in the long run, it would have transformed into a complete NEC.

Most patients with primary hepatic NEC die within 1 year with or without tumor resection,[4] whereas the actuarial 1- and 5-year survival rates are 67% and 18%, respectively, after partial hepatectomy for patients with HCC.[9] The prognoses for combined- or collision-type NEC and HCC are uncertain due to the few reported cases. However, p53 protein expression and Ki-67 proliferative index were higher in the NEC component than in the HCC component, and the metastatic tumors always consist of NEC only. We believe that primary mixed NEC and HCC run aggressively, with behavior similar to that of primary hepatic NEC rather than conventional HCC.

References

1. Pilichowska M, Kimura N, Ouchi A, Lin H, Mizuno Y, Nagura H. Primary hepatic carcinoid and neuroendocrine carcinoma: clinicopathological and immunohistochemical study of five cases. *Pathol Int* 1999;49:318–24.
2. Kaya G, Pasche C, Osterheld MC, Chaubert P, Fontolliet C. Primary neuroendocrine carcinoma of the liver: an autopsy case. *Pathol Int* 2001;51:874–8.
3. Yasuda E, Takeshita A, Murata S, Ihaku Y, Nitta T, Akutagawa H, Egashira Y, et al. Neuroendocrine carcinoma of the liver associated with dermatomyositis: autopsy case and review of the literature. *Pathol Int* 2006;56:749–54.
4. Ishida M, Seki K, Tatsuzawa A, Katayama K, Hirose K, Azuma T, Imamura Y, et al. Primary hepatic neuroendocrine carcinoma coexisting with hepatocellular carcinoma in hepatitis C liver cirrhosis: report of a case. *Surg Today* 2003;33:214–8.
5. Barsky SH, Linnoila I, Triche TJ, Costa J. Hepatocellular carcinoma with carcinoid features. *Hum Pathol* 1984;15:892–4.
6. Artopoulos JG, Destuni C. Primary mixed hepatocellular carcinoma with carcinoid characteristics. A case report. *Hepatogastroenterology* 1994;41:442–4.
7. Yamaguchi R, Nakashima O, Ogata T, Hanada K, Kumabe T, Kojiro M. Hepatocellular carcinoma with an unusual neuroendocrine component. *Pathol Int* 2004;54:861–5.
8. Garcia MT, Bejarano PA, Yssa M, Buitrago E, Livingstone A. Tumor of the liver (hepatocellular and high grade neuroendocrine carcinoma): a case report and review of the literature. *Virchows Arch* 2006;449:376–81.
9. Closset J, Van de Stadt J, Delhaye M, El Nakadi I, Lambilliotte JP, Gelin M. Hepatocellular carcinoma: surgical treatment and prognostic variables in 56 patients. *Hepatogastroenterology* 1999;46:2914–8.