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Primary Hepatic Carcinoid Tumor with a Paranuclear Clear Zone : A Case Report

Carcinoid tumors having distinct paranuclear clear zones seen on hematoxylin and eosin stain are rare and few cases have been reported in the literature. Furthermore, primary hepatic carcinoid tumor with a paranuclear clear zone is extremely rare. We recently experienced a case from a 48-year-old man who presented a large single mass, 12 cm in largest diameter, in the right lobe of the liver. Histologically, the tumor revealed characteristic organoid pattern with central hyaline degeneration. The tumor cells had a prominent paranuclear vacuolated clear zone. On immunohistochemistry, tumor cells were diffusely positive for synaptophysin and focally stained for chromogranin A. Ultrastructural examination revealed paranuclear aggregation of intermediate filaments and membrane-bound clear vesicles, which corresponded to the paranuclear vacuolated clear zone.

Key Words : *Carcinoid tumor; Intermediate filaments; Liver*

Young Ha Oh, Gyeong Hoon Kang, On-Ja Kim

Department of Diagnostic Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Address for correspondence
Gyeong Hoon Kang, M.D.
Department of Diagnostic Pathology, Asan Medical Center, University of Ulsan College of Medicine, 388-1, Poongnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel : (02) 224-4550, Fax : (02) 472-7898

INTRODUCTION

Carcinoid tumors are commonly seen in the gastrointestinal tract and metastatic carcinoid tumors to the liver are not infrequent, but cases of primary hepatic carcinoid tumor have been reported very rarely (1-5). Based upon the few documented cases (6, 7), primary hepatic carcinoid tumors appear likely to have a more favorable prognosis than other primary liver cancers and carcinoids metastatic to the liver (6, 7). The diagnosis of a primary hepatic carcinoid tumor may be difficult because of both the rarity of the tumor and its histologic similarity with a well differentiated, hepatocellular carcinoma. Differential diagnosis between these two types of tumor is very important for appropriate treatment.

In 1991, a striking feature of paranuclear clear zone in hepatic carcinoid tumor was first described (5). Paranuclear clear zone or intracytoplasmic inclusion had rarely been described in carcinoid tumor (5, 8, 9). The purpose of this report is to add a case of primary hepatic carcinoid tumor accompanying prominent paranuclear vacuolated clear zone.

CASE REPORT

A 48-year-old man visited a local clinic with mid-epigastric pain and abdominal fullness. Over the previous eight years, the patient had complained of gradually increasing abdominal fullness. Gastrofiberscopy revealed diffuse erosion of the gastric mucosa. Abdominal ultrasound demonstrated a single huge mass in the right lobe of the liver, measuring 13 cm in largest diameter. He was transferred to Asan Medical Center for further evaluation and surgical treatment for the mass. There was no history of other medical or surgical illness. Physical examination revealed a firm palpable hepatic mass approximately 4 finger breath in size, which was tender and moved with respiration. The physical examination was otherwise normal. The chest X-ray and electrocardiogram were normal. A dynamic computed tomogram (CT) also showed a large solid and cystic mass and it was avascular on selective hepatic arteriography. No mass was identified in the gastrointestinal tract. Laboratory values were as follows: Hemoglobin, 15.8 g/dl; hematocrit, 44.4%; white blood cell count, 7,500/μl; platelet count, 219,000/μl; total bilirubin, 1.3 g/dl; total cholesterol, 178 mg/dl; serum aspartate aminotransferase (SGOT), 18 IU/ml; serum glutamic pyruvic transaminase (SGPT), 12 IU/ml; creatinine 1.2 mg/dl; prothrombin time, 106%. The hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) were negative. Right lobectomy of liver was performed. The patient had an uneventful postoperative course and remains asymptomatic and well 5

months after the operation.

PATHOLOGY

The right hepatectomy specimen contained a large, ovoid, 12×8×5 cm sized mass which abutted the hepatic capsule. The cut surface showed an non-capsulated but well demarcated, reddish-tan colored mass. There was extensive hemorrhagic and hyaline degeneration with irregular fibrosis, especially in the central portion (Fig. 1). The remaining liver parenchyma was unremarkable. Microscopically, the tumor revealed mostly hemorrhagic and hyaline degeneration in the central portion. In the peripheral portion, the tumor cells were arranged in small nests, strands, and ribbons, and separated by delicate fibrovascular tissue. The tumor cells had moderate eosinophilic cytoplasm and round, relatively uniform nuclei with inconspicuous nucleoli (Fig. 2A). Some nuclear atypia including mild nuclear irregularity and hyperchromasia was also observed. Mitotic figures were not found. Among the tumor nests, there were occasional multinucleated giant cells. These histologic features had no similarity to those of hepatocellular carcinoma. Numerous tumor cells in both well-preserved and degenerative areas showed a striking feature of paranuclear vacuolated clear zone (Fig. 2B). The surrounding liver parenchyma was normal and did not accompany the features of chronic liver disease.

Immunohistochemical stains were positive for cytokeratin (Dako, Carpinteria, CA, U.S.A.) and neuron specific enolase (Dako, Carpinteria, CA, U.S.A.), and negative for factor VIII (Dako, Carpinteria, CA, U.S.A.), CD34 (Immunotech, Marseille Cedexa, France), α-fetoprotein (Dako, Carpinteria, CA, U.S.A.), and vimentin (Zymed, S. San Francisco, CA, U.S.A.). Synaptophysin (Dako, Carpinteria, CA, U.S.A.) stain was diffusely positive, and chromogranin (Dako, Carpinteria, CA, U.S.A.) was focally but strongly positive for tumor cells especially in the peripheral viable area (Fig. 3), although, inconspicuous in central degenerative area. The striking light microscopic feature of paranuclear vacuolated clear zone was intensely stained by cytokeratin. These histologic and immunohistochemical findings were consistent with the diagnosis of carcinoid tumor.

By electron microscopy the tumor cells contained sparse neurosecretory granules ranging from 200 to 300 nm, and other abundant cytoplasm including numerous mitochondria, rough endoplasmic reticulum, and lysosomes. In addition, most of the tumor cells represented eccentric nuclei and membrane-bounded empty vesicles intermingled with aggregation of the intermediate filaments (Fig. 4). These features corresponded to the para-

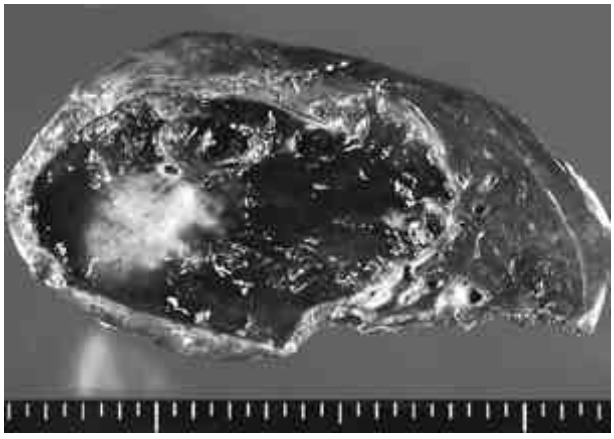

Fig. 1. A 12 cm-sized huge mass shows extensive hemorrhage and hyaline degeneration and is well demarcated from the hepatic parenchyma.

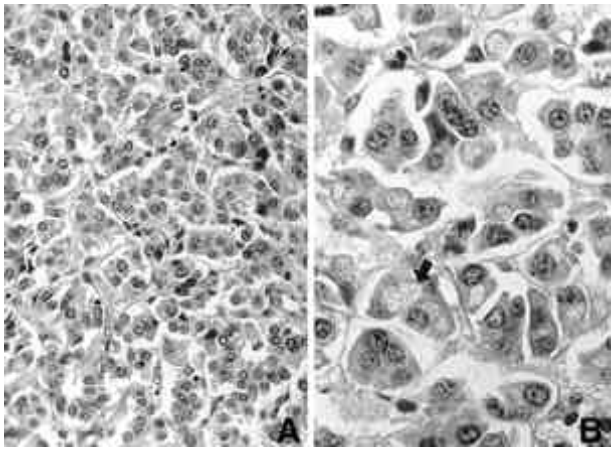

Fig. 2. A: The tumor cells are arranged in nests or strands and have moderate eosinophilic cytoplasm and relatively uniform nuclei with inconspicuous nucleoli. B: Most tumor cells demonstrate striking features of paranuclear vacuolated clear zone (arrow).

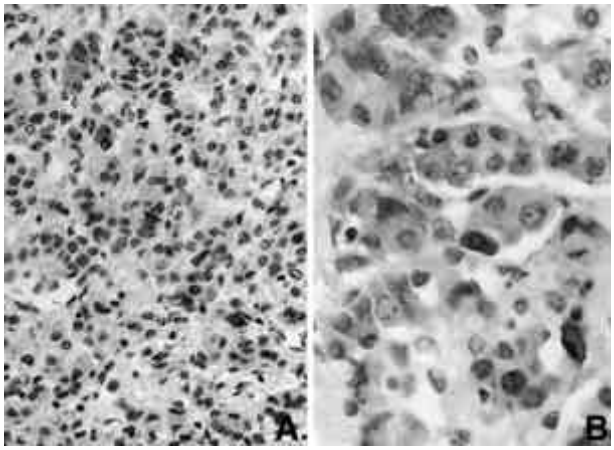

Fig. 3. Tumor cells are diffusely positive for synaptophysin (A) and focally but strongly positive for chromogranin (B).

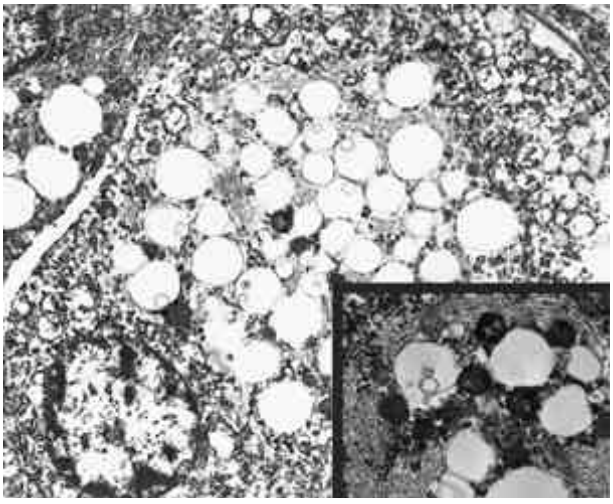

Fig. 4. Ultrastructural examination of tumor cells shows paranuclear aggregation of intermediate filaments and membrane-bound empty vesicles, intermingled with other cytoplasmic organelles such as mitochondria and lysosomes (×2,500). Inset: Another paranuclear aggregates (×8,000).

nuclear vacuolated clear zone seen on light microscopic examination. Some lysosomes and mitochondria were admixed with intermediate filaments and membrane-bounded empty vesicles.

DISCUSSION

Carcinoid tumor is a benign or low-grade malignant neoplasm, generally well differentiated, with minimal pleomorphism, and very common in the gastrointestinal tract. However, primary hepatic carcinoid tumors have been rarely reported (1-5). Some of the primary carcinoid tumors reported in the liver have been described as hepatocellular carcinomas or cholangiocarcinomas with a carcinoid or neuroendocrine component (6, 10, 11). It has been suggested that primary carcinoid tumors of the liver arise from argentaffin cells present in the intrahepatic biliary epithelium (10).

The diagnosis of this carcinoid tumor was supported by light microscopic, immunohistochemical, and ultrastructural findings. Light microscopic examination demonstrated extensive degenerative areas and focally characteristic trabecular or ribbon-like pattern of monotonous tumor cells with inconspicuous mitotic activity in the peripheral viable area. Mild nuclear atypia including nuclear irregularity and hyperchromasia in this case were thought to represent severe degenerative effects. Immunohistochemically, the tumor cells were diffusely positive for NSE and synaptophysin, and focally but strongly positive for chromogranin with cytoplasmic granularity. Ultrastructural examination also demonstrated sparse neurosecretory granules. Possibilities of hepatocellular carcinoma or cholangiocarcinoma with carcinoid features should be considered for differential diagnosis. The present case, however, showed neither hepatocellular nor cholangiocellular differentiation in any focus; there were no diagnostic features of hepatocelluar carcinoma such as nuclear pleomorphism with distinct nucleoli or intranuclear inclusions, intracytoplasmic bile, cytoplasmic alpha-fetoprotein, and sinusoid formation; diagnostic features of cholangiocellular carcinoma such as mucus production or glandular or duct-like structures were absent. Additionally, the remaining liver parenchyme was normal without cirrhosis or incomplete septal fibrosis, which are commonly associated in hepatocelluar carcinoma. We concluded that all these features and long-term history were consistent with the diagnosis of carcinoid tumor.

The demonstration of a hepatic origin for a neuroendocrine carcinoma or carcinoid tumor of the liver may be very difficult. The liver is a frequent site of metastasis from intestinal carcinoid tumors which can be difficult to detect. In the present case, no abnormal findings were detected in the gastrointestinal tract with complete preoperative workup or intraoperative observation. Furthermore, the large size and solitary nature of the tumor and continuous symptom of upper abdominal fullness over a period of 8 years favor a carcinoid tumor arising in the liver.

In 1991, a striking feature of paranuclear clear zone in the primary hepatic carcinoid tumor was first described by Sioutos et al. (5). Additionally, cytoplasmic inclusion or pallor zone was reported in a few cases of carcinoid tumor (8, 9). In the reported cases, the paranuclear clear zone corresponded to a paranuclear mass or aggregation of intermediate filaments on electron microscopic examination (5, 8, 9). In our present case, most tumor cells revealed paranuclear vacuolated clear zones. Ultrastructurally, this clear zone corresponded to an admixture of paranuclear aggregation of intermediate filaments and membrane-bound empty vesicles as described in the cases of Sioutos et al. (5). In addition, some lysosomes and mitochondria were also intermingled with intermediate filaments and membrane-bound empty vesicles. It has been suggested that the cytoplasmic inclusions may represent degenerative changes or microfilament inclusions originating from cytoplasmic constituents of cytoskeletal actomyosin (5, 8, 9). However, Sioutos et al. (5) argued against origin from actomyosin and favored origin from cytokeratin. Paranuclear accumulation of intermediate filaments were also described in pancreatic islet cell tumor, mixed salivary tumors, basal cell carcinoma, and epithelioid leiomyoma, indicating that paranuclear accumulation of intermediate filaments may not be confined to any particular type of cell (9, 12). In our current case,

there was diffuse and massive hemorrhagic and hyaline degeneration especially in the central portion of the tumor. These findings support the contention that the cytoplasmic inclusion represents degenerative changes of the neoplastic tumor cells.

It is important to understand that carcinoid or neuroendocrine tumors may rarely arise in the liver to ensure that these lesions are not misinterpreted as hepatocellular carcinoma or other highly malignant neoplasm. Furthermore, our case demonstrated a striking feature of paranuclear clear zone that is rarely seen in carcinoid tumor. Although the origin of the paranuclear clear zone is unkown, diffuse degeneration in our case supports the opinion that cytoplasmic inclusion represents a degenerative or regressive process.

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