Primary Calcified Gastrinoma of the Liver

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The liver is a rare site for primary neuroendocrine tumors including gastrinomas. We are aware of only 12 cases of hepatic gastrinoma reported in the English literature (1–12), some of these reports focused on the liver as the primary site of gastrinoma (7–12). Calcification within a hepatic mass is most commonly seen in hepatocellular carcinoma (HCC) and metastases from colorectal cancer (13), but is rare in liver metastases of endocrine tumors (14). To the best of our knowledge, only two cases of calcified hepatic metastases have been documented in Zollinger-Ellison syndrome (ZES) (15, 16). We present a case of primary hepatic gastrinoma with calcification that had never been reported before.

CASE REPORT

A 27-year-old Taiwanese woman was a hepatitis B surface antigen (HBsAg) carrier. She had had selective truncal vagotomy and pyloroplasty in October 1989 for pyloric stenosis complicating a repeated bleeding duodenal ulcer. After surgery, epigastralgia associated with coffee-ground vomitus recurred. Panendoscopy showed diffuse ulcerations with bleeding at the distal esophagus and a deformed duodenal bulb with an active ulcer. She had received blood transfusions frequently during this period. As a routine survey for hepatocellular carcinoma (HCC), liver sonography was performed. It revealed noncirrhotic hepatomegaly. Incidentally, a confluent mass with central necrosis totaling 10 cm in diameter over the right lobe of liver was found. Percutaneous needle biopsy diagnosis showed trabecular type HCC. She refused surgical intervention, transcatheter arterial embolization, and chemotherapy. Liver sonography or computed axial tomography (CT) every four to six months showed that the tumor size gradually increased to 15 cm with several daughter nodules in a three-year period. Another percutaneous liver biopsy was performed because hepatic gastrinoma was highly suspected. The histological studies revealed neuroendocrine tumor. She finally decided to allow surgery five months later.

Physical examination before operation showed that the patient was anicteric, there were no spider angiomata, palmar erythema, ascites, or splenomegaly; the liver was enlarged with a span of 18 cm on the right middle clavicle line, and had a hard surface that measured 8 cm below the right costal margin. Laboratory studies disclosed the following values: hemoglobin, 10.9 g/dl; leukocytes, 14.9 × 109/liter; platelet 180 × 109/liter; albumin, 4.0 g/dl (normal 3.5–4.7 g/dl); globulin, 2.9 g/dl (normal 2.8–3.3 g/dl); total bilirubin, 0.8 mg/dl (normal <1.3 mg/dl); serum aspartate transaminase (AST), 24 IU/liter (normal <34 IU/liter); serum alanine transaminase (ALT), 14 IU/liter (normal <36 IU/liter); alkaline phosphatase (ALP), 86 IU/liter (normal 28–94 IU/liter); γ-glutamyltranspeptidase (γ-GT) 10 IU/liter (normal <26 IU/liter); prothrombin time 11.8 sec (control 12.7 sec); α-FP, 5 ng/ml. HBsAg and antibody to hepatitis B e antigen (anti-HBe) were positive by radioimmunounassay (RIA), antibody to hepatitis delta virus (anti-HDV) was negative by RIA, antibody to hepatitis C virus (anti-HCV) was positive by enzyme immunoassay (Abbott HCV EIA). Carcinoembryonic antigen (CEA) was 2.39 ng/ml (normal <5 ng/ml); CA-19.9, 18.3 units/ml (normal <33 units/ml); CA-125, 8.55 units/ml (normal <35 units/ml); gastrin, 778 pg/ml; calcitonin, 6.85 pg/ml (normal <10 pg/ml); growth hormone, 6.96 ng/ml (normal <5 ng/ml); insulin, 19.7 μIU/ml (normal 4–25 μIU/ml); prolactin, 7.14 ng/ml (normal 3–14 ng/ml) and ACTH, 11.8 pg/ml (normal 10–60 pg/ml). Urinary 5-hydroxyindoleacetic acid (5-HIAA) daily was 3.4 mg (normal <10 mg/24 hr). Panendoscopy showed esophagitis and esophageal and duodenal ulcer scars with a deformed bulb. Studies of small intestine and colon were negative. Endoscopic ultrasonography (EUS) demonstrated normal pancreas without tumor detected. Both liver sonography and CT scan showed hepatomegaly with hypodense masses, central necrosis, intra-tumor calcification and daughter nodules, totalling 15 cm in diameter, over the right lobe of liver, with a 3-cm hypodense tumor in left lobe of liver (Figure 1). The pancreas was normal. Celiac angiography showed hypervascular masses occupying the whole right lobe of liver with areas of hypo-
vascularity representing central necrosis (Figure 2) and a smaller tumor at the left lobe of liver. Laparotomy revealed a large mass occupying nearly the entire right lobe of liver and two daughter tumors at the left lobe of liver. There was considerable induration around the bulb of the duodenum consistent with chronic duodenal ulcer disease. No discrete lesion was found in pancreas. Right lobectomy and partial segmentectomy (segments 2 and 4) were performed. Grossly, the masses measured $10 \times 13 \times 15$ cm. They were pink, soft with focal calcifications and cystic changes. Histologically, the hepatic tumor showed a trabecular or festoonlike arrangement of uniform round cells with granular cytoplasm in fibrovascular or hyaline stroma (Figure 3). Focal calcification was noted. Immunohistochemical staining showed strong reactivity for gastrin in many of the tumor cells (Figure 4). Electron microscopic examination showed round secretory granules of variable sizes ranging from 150 to 300 nm in diameter (Figure 5). Serum gastrin levels were normal 2 weeks, 6 months, and 42 months after surgery. The patient has done well since surgery without proton pump inhibitors or $H_2$ receptor antagonists. No tumor has been found by repeated abdominal CT scan and ultrasonography.

**DISCUSSION**

The liver is one of the most common sites of metastatic endocrine tumors, so that a complete preoperative work-up and transoperative search are mandatory to rule out any other possible origin. In the present case, no extrahepatic primary tumor was found before, during, or after surgery. Although an occult extrahepatic source cannot be totally excluded, the fact that the serum gastrin level dropped dramatically after surgery and has remained within normal limits for 42 months after resection of the large solitary hepatic tumor indicates that the tumor is a primary hepatic gastrinoma.

Of note is that the present liver tumor was misdiagnosed as a HCC clinically and histologically before surgery. In an HBV-endemic and HCC-prevalent area like Taiwan (17), HCC is the most likely diagnosis in a patient positive for HBsAg and/or anti-HCV with a large liver tumor. In fact, the histologic recognition of a primary neuroendocrine tumor of the