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Diagnosis and Surgical Treatment for Primary Liver Gastrinoma: Report of a Case

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Zollinger–Ellison syndrome (ZES) was proposed in 1955 (1) as a new gastrointestinal disease manifesting as peptic ulcers in unusual locations, recurrent stomal ulcer following any type of partial gastrectomy, and persistent gastric hypersecretion associated with an islet cell tumor of the pancreas. It was later confirmed that the islet cell tumor secreted the peptide hormone gastrin as the cause of ZES. The vast majority of gastrinomas are found in what has been referred to as the gastrinoma triangle, while ectopic gastrinoma is very rare, defined as an extrapancreatic, extraduodenal, and extralymphatic primary location (2). Although ovarian and hepatic gastrinomas are well documented among ectopic gastrinomas, they are still uncommon (2–5).

Even with state-of-the-art imaging and functional localization studies including selective arterial secretin injection (SASI) test (6), it is difficult to prove that a hepatic gastrinoma is the primary site and not a metastatic gastrinoma. We were able to diagnose a primary hepatic gastrinoma utilizing all imaging modalities, including functional localization studies and radiological interventions.

CASE REPORT

A 50-year-old male was referred because of a history of a duodenal ulcer and a high serum gastrin level. The medical history and family history were otherwise negative. He had been treated for duodenal ulcer with a histamine-2 receptor antagonist beginning in 1994. In April 1996, the ulcer recurred and a deep ulceration was observed in the duodenal third portion on gastrointestinal endoscopy. A high level of fasting plasma gastrin as well as hypersecretion of the gastric acid (basal acid output, 48.8 mEq/ml; maximum acid output, 67.6 mEq/ml) was recognized. Although his ulcer was cured with a proton pump inhibitor lansoprazloe, the patient was referred to our department for diagnosis and treatment. On admission, the fasting plasma concentration of gastrin was 1500 pg/ml. The plasma concentrations of parathyroid hormone, adrenocorticotropic hormone, prolactin, growth hormone, and somatomdein C (hormones associated with multiple endocrine neoplasm-I) as well as gastrointestinal peptides including insulin, glucagon, and secretin were within normal range. Serum gastrin increased from 1300 pg/ml at baseline to 2000 pg/ml 30 min after systemic injection of secretin at 5 U/kg-hr. A 4.5-cm oval-shaped solitary tumor with rich vascularization was detected in the medial segment of the liver close to the hepatic hilus on computed tomography (CT), ultrasonography (US), magnetic resonance imaging (MRI), and angiography (Figure 1A). No tumor, however, was obvious in the pancreas and duodenum by any of those imaging modalities above. Endoscopic US (EUS) did not reveal any tumor in the pancreas and duodenum. Nevertheless, we assumed that the tumor in the liver must be a metastasis from an occult primary gastrinoma in the pancreas or duodenum too small to detect. Although we performed the SASI test, the primary tumor could not be detected because plasma gastrin in the hepatic vein did not increase after injection of secretin into splenic, gastroduodenal, and superior mesenteric arteries.

We performed transcatheteric arterial embolization (TAE) of the liver two times in an attempt to attenuate the growth of the hepatic tumor, but plasma gastrin continued to increase and the liver tumor increased in size. In an attempt to localize the primary gastrnioma, which we assumed to exist in the pancreas or duodenum, we performed a modified SASI test in which blood samples were drawn from the portal vein at the hepatic hilum instead of the hepatic vein, utilizing a technique of percutaneous transhepatic portal vein puncture. This modified SASI test aimed to avoid the confounding effects of the hepatic tumor on plasma gastrin level when blood samples were drawn in the hepatic vein. On this modified SASI test, no paradoxical increase in plasma gastrin was noted after injection of secretin into peripancreatic arteries.

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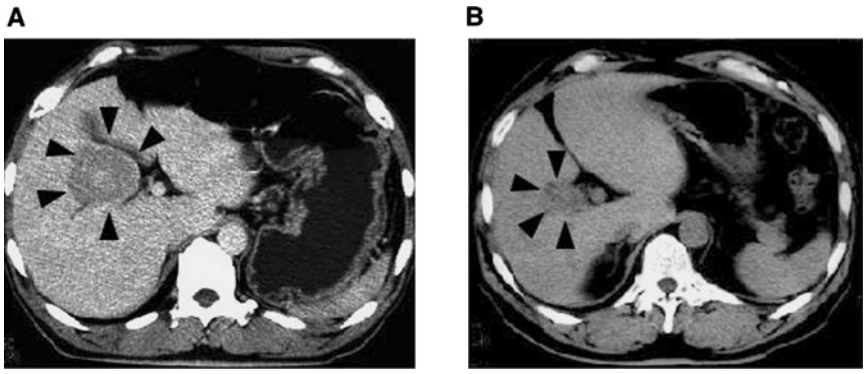

Fig 1. Computed tomography. (A) CT scan at the time of admission demonstrated a 4.5-cm solitary tumor of oval shape in the medial segment of the liver close to the hepatic hilus (arrows). (B) MCT markedly reduced the size of the liver tumor (arrows).

At this time point, the likelihood emerged that the hepatic tumor was the primary tumor and not a metastatic gastrinoma. The patient underwent laparotomy for intraoperative microwave coagulation therapy (MCT) to treat the liver tumor. Other extrahepatic tumor or enlarged lymph nodes were not found in the pancreatoduodenal region despite very careful systematic intraoperative palpation and intraoperative US. When the hepatic tumor became smaller after MCT (Figure 1B) and the fasting plasma gastrin concentration decreased to 250 pg/ml, we carried out a "regular" SASI test again in an attempt to localize the primary gastrinoma. However, selective injection of secretin into the peripancreatic arteries failed to induce a paradoxical increase in serum gastrin in the hepatic vein. The serum concentration of fasting gastrin increased to 480 pg/ml in accordance with regrowth of the hepatic tumor on imaging. We diagnosed the hepatic tumor as a primary gastrinoma and performed an extended right hepatic lobectomy. Histologic examination of the tumor revealed typical endocrine tumor cells with a ribbon-like arrangement along with the fibrous tissue induced by MCT (Figure 2). The tumor cells stained positive for gastrin on immunohistochemical staining. After hepatectomy, the fasting concentration of plasma gastrin declined to normal ranges within 2 months. The secretin test remained normal and CT did not demonstrate any tumor in the liver 6 months after the hepatectomy. Although serum gastrin increased to 300–400 pg/ml thereafter, the result of secretin stimulation test was negative. The patient is doing well 5 years postoperatively.

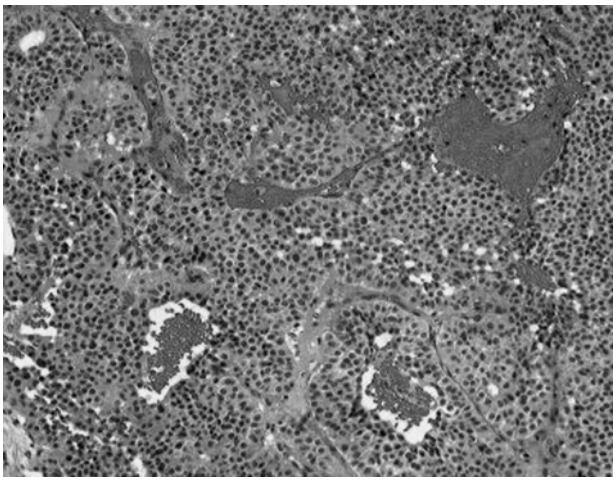

Fig 2. Histological findings. Histological examination of the tumor revealed the typical endocrine tumor cells with a ribbon-like arrangement.

DISCUSSION

Ectopic gastrinoma is rare, and 10 reports of primary hepatic gastrinoma were identified in the literature (2, 5, 7–14). In most of those reports, the final diagnosis of primary hepatic gastrinoma was made based on achieving a normal fasting plasma gastrin and negative secretin test after hepatectomy (7–13). One patient was preoperatively diagnosed as harboring a primary liver gastrinoma from the results of percutaneous transhepatic venous sampling (14).

We performed TAE and MCT to reduce the liver tumor, and after use of all imaging modalities and the SASI test, we were able to make a confident diagnosis of primary hepatic gastrinoma before hepatectomy. The rate of curative resection in ZES is not satisfactory because of the difficulty of accurately localizing the primary tumor. Thus several groups have emphasized the necessity of a standardized surgical exploration of the pancreas and duodenum to make an accurate diagnosis and to increase the rate of curative resection (15, 16). Strong acid suppressors such as histamine-2 receptor antagonists or proton pump inhibitors are able to relieve most symptoms associated with hypersecretion of the gastric acid. Nevertheless, curative resection of the gastrinoma is desirable because at least 50% of gastrinomas are malignant (15). Alongside the development of increasing sensitive imaging modalities, introduction of the SASI test greatly contributed to accurate anatomic localization of the primary tumor in the pancreas and duodenum (6, 17). The SASI test made it possible to identify the feeding artery

to the gastrinoma and thereby increased the rate of curative resection. If gastrinoma exists in the liver, accurate tumor localization with the SASI test appears to be difficult. We were assuming in our patient that the plasma concentration of gastrin increases after secretin injection into any artery, because secretin injected into arteries flows into the liver via the portal vein and stimulates secretion of gastrin. However, an increase in the concentration of gastrin in the hepatic vein was not observed after intra-arterial injection of secretin into the splenic, gastroduodenal, and superior mesenteric arteries. The amount of secretin that reached the hepatic tumor via the portal vein must have been too small to increase the plasma concentration of gastrin in the hepatic vein, which is basically very high.

It was very difficult in our patient to completely exclude the possibility that a primary gastrinoma existed in the pancreas or duodenum with negative imaging modalities and a normal SASI test. We performed a modified SASI test by drawing blood samples from the hilar portal vein instead of the hepatic vein, but did not obtain a positive response after secretin injection into any artery. The negative results of this modified SASI test made us doubt that the hepatic tumor was a primary gastrinoma. However, the fact that plasma gastrin decreased in association with the reduction in size of the hepatic tumor after MCT, as well as negative results of intraoperative palpation and US, led us to conclude that the hepatic tumor was a primary gastrinoma. Although EUS has a high sensitivity to detect gastrinomas, its sensitivity for detection of pancreatic gastrinomas (85%) is higher than that for detection of duodenal gastrinomas (43%) (18). As pancreatic gastrinomas are usually larger than duodenal gastrinomas, pancreatic gastrinomas can be frequently detected by conventional imaging modalities. Therefore, when hepatic gastrinoma became evident, we could not exclude the possible primary duodenal gastrinoma even though EUS did not reveal any tumor. Surgical exploration of the duodenum including duodenotomy should be considered to exclude primary duodenal gastrinoma. Although somatostatin receptor scintigraphy with a high sensitivity to localize gastrinomas should be performed (20), unfortunately it is not available in our country.

We believe that a modified SASI test is useful in determining whether the solitary hepatic tumor is a metastatic lesion or the primary tumor. Resection of a localized hepatic gastrinoma should be performed whenever possible for both a primary hepatic gastrinoma and a solitary hepatic metastasis from a resected extrahepatic gastrinoma, because this procedure provides the excellent 5-year survival of 85% (6). The clinical outcome after hepatic resection for primary liver gastrinomas is generally good, as 11 of 12 patients remain asymptomatic without recurrence 1–5 years postoperatively (2, 5, 7–14).

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