

A case of primary intrahepatic gastrinoma

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Gastrinoma is an uncommon but important cause of peptic ulcer disease. These tumors are most commonly located in the duodenum or pancreas. We present a case of a primary intrahepatic gastrinoma. Only 20 such cases have been previously reported in the literature. Metastatic hepatic gastrinomas are much more common, but it is important to differentiate between a primary and metastatic lesion because of the worse prognosis associated with a metastatic lesion.

Case report

A 51-year-old female with a previous history of gastric and duodenal ulcers (with biopsy-proven *Helicobacter pylori*) presented in June 2010 with symptoms of abdominal pain and chronic diarrhea. She had persistent symptoms after confirmed eradication of *H. pylori*. Enteroscopy showed diffuse fissuring, with an overlying mosaic appearance in the fundus and proximal stomach. The duodenum and jejunum appeared atrophic, with scattered nonbleeding ulcers. Biopsies showed chronic inactive gastritis in the stomach and mild villous shortening in the duodenum and jejunum. Tests for *H. pylori*, CMV, and HSV were negative. A test of the serum gastrin level was above 5000 pg/mL, an extremely elevated value. The patient was placed on high-dose proton-pump inhibitor therapy, and a search for a suspected gastrinoma began with computed tomography (CT) of the abdomen and pelvis.

CT images were obtained during the delayed phase after IV contrast administration. Likely because images were not obtained during the arterial phase, a 3.4 x 3.0-cm ovoid lesion in the caudate lobe, later identified on contrast-enhanced magnetic resonance imaging (MRI), was not ini-

tially seen on the CT. In retrospect, this lesion is more clearly seen on MRI and can be faintly seen on CT (Fig. 1).



Figure 1. 51-year-old female with primary intrahepatic gastrinoma. Delayed, contrast-enhanced axial CT shows a subtle mass (red asterisk) in the caudate lobe that is isodense to the liver parenchyma with possible faint rim enhancement.

On the MRI, the mass is most conspicuous in the arterial phase, where it demonstrates a hypervascular appearance (Figs. 2A and 2B). No other enhancing lesions were seen.

Somatostatin-receptor scintigraphy (Octreoscan) was performed to look for additional tumor foci. Octreotide is a somatostatin analogue that binds to somatostatin receptors that can be found in a gastrinoma. The sensitivity of Octreoscan for detecting a gastrinoma depends highly on the

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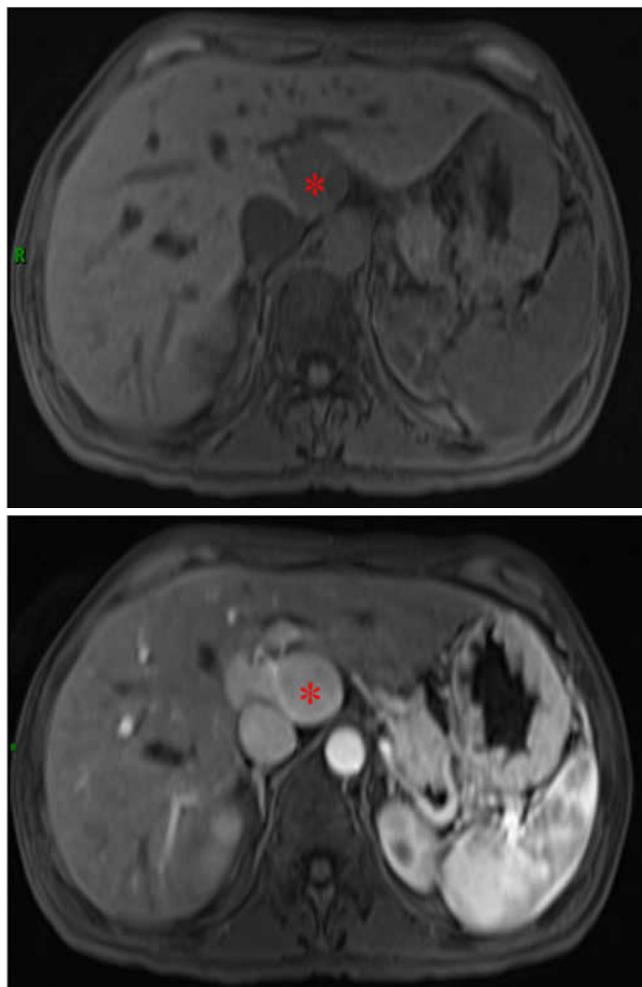


Figure 2. 51-year-old female with primary intrahepatic gastrinoma. T1 images, before (A) and after (B) gadolinium enhancement, show an oval, solid lesion within the caudate lobe of the liver measuring 3.4 x 3.0 cm (red asterisk). The lesion is most conspicuous on arterial dominant-phase-enhanced images, where it demonstrates a hypervascular appearance.

size of the tumor, with a 30% sensitivity for tumors smaller than 1.1 cm but 96% for tumors larger than 2.0 cm (1). The Octreoscan showed a focal area of intense uptake in the upper abdomen, almost in the midline, corresponding to the solid lesion seen on the MRI. (Fig. 3). No other areas of increased radiotracer uptake were seen.

Since no lesions outside the caudate lobe were identified on CT, MRI, or Octreoscan, the patient was referred for an intraoperative search for a possible primary lesion. The pancreas was thoroughly explored by opening the lesser sac to further visualize the head, neck, and body of the pancreas. In addition, the gastrinoma triangle, hepatoduodenal ligament, and surrounding areas were explored. No mass was able to be visualized or palpated. The duodenum was carefully examined, and there was no evidence of any ab-

normalities within the wall of the duodenum. The duodenum had previously been examined by endoscopic ultrasound without finding an abnormality. Open abdominal

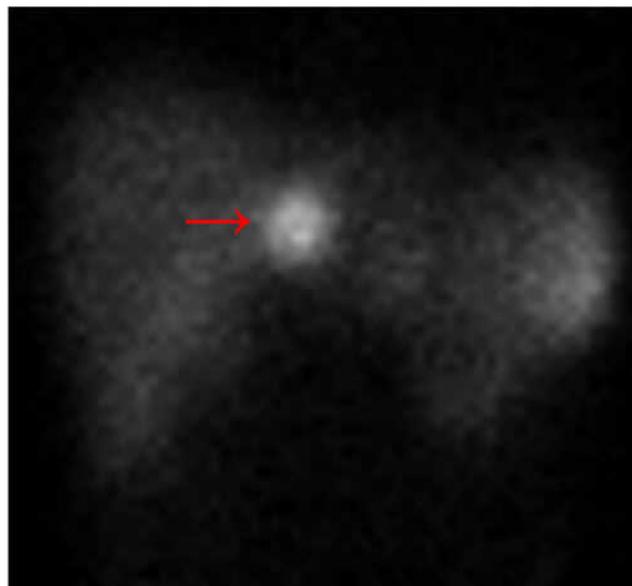


Figure 3. 51-year-old female with primary intrahepatic gastrinoma. Focal area of intense uptake in the upper abdomen almost in the midline (red arrow) corresponds to the solid lesion seen on the MRI. No other areas of increased uptake are seen.

ultrasound was then carried out by the attending radiologist, and no extrahepatic gastrinoma was identified. After resection of the caudate lesion, surgical pathology samples revealed a well-differentiated neuroendocrine carcinoma. The resection margins were negative for tumor (see pathology images in Figs. 4A and 4B). Immunohistochemical stains for chromogranin and synaptophysin were positive, further indicative of a neuroendocrine tumor.

Following the patient's tumor resection, she was seen in the gastroenterology clinic in order to monitor for signs of recurrence. It was initially feared that a small primary lesion in the duodenum or pancreas that was simply too small to be seen on imaging or intraoperatively had been missed, or that not all tumor had been resected. Therefore, the patient had serial secretin-stimulation tests (SST) performed. This test can be used to differentiate patients with gastrinomas from those with the many other causes of increased serum gastrin. Secretin stimulates the release of gastrin by gastrinoma tumor cells; thus, patients with these tumors show a rise in serum gastrin in response to a secretin administration. However, normal gastric G cells are inhibited by secretin, and therefore serum gastrin levels do not rise in patients with other causes of hypergastrinemia (2).

The SST is usually performed by administering 0.4 mcg of secretin per kg body weight intravenously over a minute.

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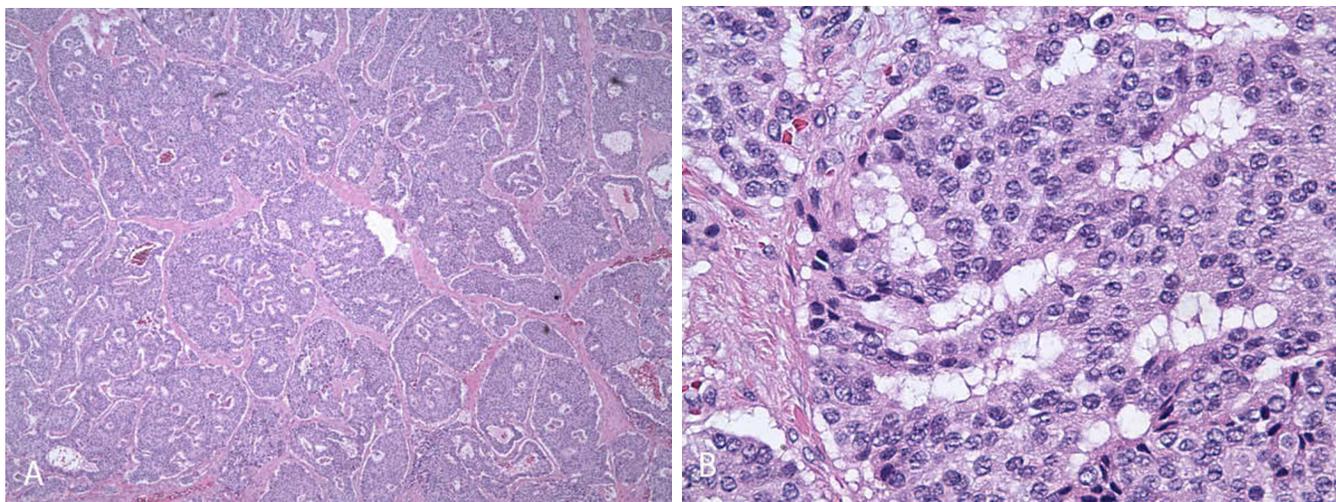


Figure 4. 51-year-old female with primary intrahepatic gastrinoma. A. Low-magnification view (4X) of the resected caudate lobe lesion demonstrates a pseudoglandular pattern of growth, one of the typical patterns for neuroendocrine tumors. B. High-magnification (40X) view of the lesion shows that the cell population is uniform, with finely granular, eosinophilic cytoplasm containing a low nuclear-to-cytoplasmic ratio. The nuclei are oval, with a dispersed chromatin ("salt and pepper") pattern.

Baseline serum gastrin is measured before the secretin is administered and at 2, 5, 10, 15, and 30 minutes later. One large study performed at the National Institutes of Health (NIH) concluded that the optimal cutoff for a positive SST was a rise of ≥ 120 pg/mL in serum gastrin, which was associated with the highest sensitivity and specificity (94% and 100%, respectively) for detecting a gastrinoma (3).

Although our patient did have a slight rise in gastrin concentrations from one month to six months following resection, both tests were negative using the standard set by the NIH trial, with only a 77 pg/mL rise in serum gastrin concentration following secretin administration at 6 months following surgery. The patient will require continued followup, but so far she remains negative for residual or recurrent gastrinoma.

Discussion

Zollinger-Ellison Syndrome (ZES), a disorder marked by severe peptic-ulcer disease and diarrhea, is caused by the hypersecretion of gastric acid in response to a gastrin-producing endocrine tumor. ZES typically affects patients who are between the ages of 35 to 65, with men being more frequently affected, by a 3:2 ratio. Approximately 20% of patients with ZES have multiple endocrine neoplasia (MEN) type 1, which is characterized by pancreatic endocrine tumors, pituitary adenomas, and parathyroid hyperplasia. Therefore, a diagnosis of ZES should raise the suspicion of these other entities.

The clinical presentation of ZES can be similar to peptic-ulcer disease from other causes, but symptoms that do not respond well to medical therapy with proton-pump inhibitors or *H. pylori* eradication should be viewed as suspicious for ZES. When ZES is suspected, a fasting serum gastrin level is usually ordered, and a level above 1000 pg/mL

is almost diagnostic of a gastrinoma. However, other causes can result in elevated serum gastrin, including the use of proton-pump inhibitors. When the diagnosis remains in doubt, a SST can be performed, as outlined above.

Once gastrinoma is clinically suspected, imaging should be performed to localize the tumor. On CT, a gastrinoma appears as a hypervascular mass that may demonstrate cystic areas with or without necrosis and calcifications. MRI also demonstrates a hypervascular mass that is T1-hypointense and T2-hyperintense. These imaging findings are characteristic of gastrinomas regardless of where the tumor arises. Octreoscan is more specific for gastrinoma than CT or MRI, but with the aforementioned size limitations.

Since 60% of gastrinomas turn out to be malignant, surgical resection of the primary tumor is recommended if there is no evidence for metastatic disease. Regardless of any evidence for metastatic disease, patients with ZES need medical therapy with high-dose proton-pump inhibitors to treat their symptoms related to acid hypersecretion (4).

Gastrinomas arise from amine-precursor uptake and decarboxylation (APUD) cells, which are multipotent, primitive neuroendocrine cells found in the central and peripheral nervous system, pulmonary mucosa, and gastrointestinal tract (5). In a gastrinoma, APUD cells undergo inappropriate differentiation to form G cells that produce gastrin. These cells are normally found in the gastric antrum. Gastrinomas are frequently found outside this location, and when this occurs they are called ectopic. The common locations for ectopic gastrinomas are in the duodenum and pancreas, with over 85% of primary gastrinomas being found in these locations. Neuroendocrine cells can also be found in bile ducts, which explains the rare occurrence of intrahepatic gastrinomas (6).

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Metastatic hepatic gastrinomas are much more common than primary lesions, but it is important to differentiate between these two entities because of the worse prognosis associated with a metastasis. Patients with a metastatic gastrinoma lesion in the liver were found to have a decreased overall survival in one study (7). In contrast, patients with a resected primary lesion in any location that remained disease-free at 6 months (as our patient currently is) as defined by a negative SST were found to have an 88% probability of being disease-free at 3 years post resection (8). It is important for the radiologist to know the pathogenesis of these tumors, and to know that a gastrinoma may arise primarily at all locations where APUD cells are found. Also, because of the prognostic implications, it is important to identify all foci of tumor with gastrinomas when possible to direct the patient to the appropriate course of treatment.

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