Case of the Month: June’s Diagnosis

Gastrinoma

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The first 3 respondents in each time zone to identify February’s Case of the Month correctly are:

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In summary, this is a 52-year-old hypertensive woman who presented with left-sided abdominal pain and diarrhea, and was found to have multiple gastric and duodenal ulcers. The patient improved on proton-pump inhibitors, but withdrawal of proton-pump inhibitors led to a recurrence of symptoms, and recurrent duodenal ulcers. There were no significant findings on physical examination, and a serum gastrin level taken initially was normal. Radiological studies were remarkable for diffusely thickened gastric folds in the face of a distended stomach, and a hypervascular 1cm nodule within the liver.

Both of these radiologic findings have specific differential diagnoses. Thickened gastric folds are associated with malignancy (usually lymphoma, but poorly-differentiated signet ring cell gastric carcinoma is also a possibility), Menetrier's disease, Zollinger-Ellison syndrome and gastritis. Hypervascular nodules within the liver are found with primary liver disorders (hepatocellular carcinoma, hemangioma or focal nodular hyperplasia), or metastatic lesions to the liver (typically highly vascular tumors such as renal cell carcinoma, carcinoid tumor, melanoma, islet cell tumor, choriocarcinoma, or breast carcinoma).

Two classic clinical differential diagnoses are useful for evaluating this case; that of refractory peptic ulcer, and that of gastroduodenal ulcers associated with diarrhea. The differential diagnosis for refractory peptic ulcer disease includes Helicobacter pylori infection, retained gastric antrum, antral G cell hyperplasia, gastric malignancy, surreptitious use of non-steroidal anti-inflammatory drugs (NSAIDs) and gastrinoma. Helicobacter pylori infection is acquired by the fecal-oral route in childhood, and leads to gastritis via the effects of specific bacterial cytotoxic factors (cagA, vacA) and production of ammonium hydroxide, which leads to the production of cytokines that injure the gastric mucosa. The diagnosis may be established using a rapid urease test, histologic biopsy, or culture; the latter is useful for detecting resistance to antibiotics. This patient's biopsies were negative, which argues against Helicobacter pylori infection. A retained antrum applies only to patients who have had prior Billroth II resections. In this procedure, the patient has undergone a gastrojejunostomy, and the antrum is separated from the acid-producing body of the stomach. In the absence of down-regulation by the effects of gastric acid in its lumen, the antrum hypersecretes gastrin, leading to hyperacidity and refractory ulcers. Since this patient did not undergo this specific surgical procedure, this possibility can be easily eliminated. Antral G-cell hyperplasia reflects an increased number of gastrin producing G-cells in the stomach. It is a very rare cause of recurrent peptic disease, and approximately 50% of cases are probably due to occult Helicobacter pylori infection. A secretin stimulation test can be useful for distinguishing G-cell hyperplasia from a neoplasm of gastrin-producing cells, a gastrinoma. A gastric malignancy, such as adenocarcinoma or lymphoma, is always a concern with a patient with a refractory gastric ulcer; however, this patient's biopsies were negative, and the ulcers also involved the duodenum, where malignancy would be most unusual. Surreptitious use of NSAIDs is thought to cause approximately 40% of "refractory" peptic ulcer disease. Patients may not report that they are using NSAIDs, or be unaware that the over-the-counter medications that they are taking contain these agents. NSAIDs cause gastric toxicity by their topical irritant effects, and by their inhibition of prostaglandin synthesis due to their inhibition of cyclooxygenase 1. This can easily be ruled out by measuring serum salicylate levels. The final cause of refractory peptic disease is a gastrinoma. We will defer discussion of this until later.

The differential diagnosis for gastroduodenal ulcers in the face of diarrhea includes lymphoma, Crohn’s disease, vasculitis, infection and gastrinoma. Enteropathy associated T-cell lymphomas typically cause large, shallow ulcerations leading to secretory diarrhea, and/or malabsorption. The facts that the patient lacked constitutional symptoms, the gastric biopsies were negative, and the most recent upper endoscopy was normal, argue against this diagnosis. Crohn’s disease may affect any part of the gastrointestinal tract. However, upper
GI tract involvement is much less common than disease in the ileum and colon, and gastroduodenal ulceration typically occurs concomitantly with lower GI tract involvement. These facts, and the fact that the gastric biopsies did not show granulomas, argue against Crohn's disease. Vasculitis may cause gastroduodenal ulcers and diarrhea; specific ones to consider include Behcet's disease and Wegener's granulomatosis. Behcet's is unlikely due to the lack of oral or genital ulcerations, while Wegener's does not typically lead to severe intestinal involvement. Infection should always be considered. Specific agents to consider include Histoplasmosis, Cytomegalovirus or Herpes simplex virus. The absence of systemic involvement, the absence of a history of immunocompromise, as well as the absence of constitutional symptoms argue against these infections. This brings us to the possibility of gastrinoma, which also emerged from the refractory peptic ulcer disease differential diagnosis as a leading possibility.

Gastrinoma is a rare, non-β islet cell tumor that secretes gastrin. It is thought to be the cause of 0.1%-1% of peptic ulcer disease. Gastrinoma leads to the characteristic Zollinger-Ellison Syndrome (ZES) that was first described in 1955 as peptic ulcer disease, gastric acid hypersecretion and the presence of a pancreatic tumor. The typical symptoms at presentation for Zollinger-Ellison syndrome include abdominal pain, reflux and diarrhea. The abdominal pain in ZES is typically epigastric, and results from peptic ulcer disease. Of patients with ZES with ulcers, 75% of patients have solitary ulcers, but distal involvement of the duodenum and jejunum occurs in the other 25%. Interestingly, however, 20% have no evidence of peptic ulcer disease at presentation. Gastroesophageal reflux leads to dysphagia and stricture formation in some of these patients. Diarrhea may be the sole presenting symptom in 20% of the patients, and is largely due to the excessive amounts of gastric acid secretion. Patients with ZES secrete an average of 314 ml an hour of gastric acid as opposed to the normal 55 ml per hour. The diarrhea results from malabsorption due to villus blunting from the injurious effects of the acids, and inactivation of pancreatic enzymes and precipitation of bile salts by the gastric acid. Specific clinical clues to that suggest ZES include recurrent and persistent ulcers despite acid-suppressive therapy, persistent diarrhea of unknown etiology, and multiple ulcers (specifically distal ulcers) in the upper gastrointestinal tract. Histologically, the stomach in ZES shows a thickened wall (Figure 1) due to marked Parietal cell hyperplasia (Figure 2), including Parietal cells abnormally localized to the superficial gastric pits (Figure 3).

The diagnosis of ZES can be made through several modalities. A fasting serum gastrin level is the best screening test, and is elevated in 99% of patients. It is diagnostic if the gastrin level is > 1000 and the gastric pH is < 3. Basal acid secretion is useful when the gastric acid is > 15 meq per hour (normal range is 1.3-4.2). A gastric pH of > 3 excludes the diagnosis of ZES. In equivocal cases, a secretin stimulation test has a sensitivity of approximately 85%. In a patient with a gastrinoma, secretin stimulation results in a paradoxical rise in serum gastrin levels, which does not happen in patients with antral G-cell hyperplasia. Secretin was unavailable at the time this patient presented, but has recently again become available for clinical use.

Several radiologic studies can be useful to localizing gastrinomas. 90% or so of gastrinomas occur in a triangle which is centered upon the head of the pancreas, and includes the
gastric antrum and duodenum. An abdominal CT scan has a sensitivity of approximately 50%, whereas, an MRI has a sensitivity of 45%. Selective angiography has a sensitivity of 40%, and is useful for detecting the hypervascular pattern of the gastrinoma. Endoscopic ultrasound (EUS) has one of the highest sensitivities of these studies, reaching 85%. However, the best study for detecting gastrinoma may be the somatostatin receptor scintigraphy study. This study takes advantage of the fact that neuroendocrine tumors typically have somatostatin receptors upon them. Therefore, an octreotide scan, which uses an analog of somatostatin, is highly successful in localizing these neoplasms.

Once one establishes a diagnosis of Zollinger-Ellison syndrome, it is important to remember that 20% of patients with ZES have the multiple endocrine neoplasia-1 syndrome (MEN-1). This is an autosomal dominant disorder with high penetrance, which is characterized by a classic triad of tumors involving the parathyroid, endocrine pancreas and anterior pituitary. Virtually all patients with MEN-1 have hyperparathyroidism, so it is important to screen patients with ZES by checking their serum calcium levels. In this patient, the serum calcium was normal.

In summary, this patient’s clinical course is most compatible with a gastrinoma. Given the presence of a liver lesion, the most important concern is that the liver lesion represents a metastasis from an occult primary, though primary hepatic gastrinomas have been reported.

**CLINICAL COURSE:**

This patient had additional serum gastrin levels drawn, all of which came back elevated. The highest value was 900 picograms/mL. Importantly, all of these were taken while the patient was not taking proton pump inhibitors, since these agents can cause a mild elevation of serum gastrin due to blockage of acid secretion which diminishes feedback onto the G-cells. The patient underwent an octreotide scan which revealed a solitary left hepatic mass. An upper endoscopy with endoscopic ultrasound revealed an acid pH, despite the fact that the patient was taking proton-pump inhibitors. This helped to rule out the possibility that the gastrin elevation was due to atrophic gastritis, which would yield a neutral pH. Importantly, however, no pancreatic or duodenal masses were detected on the ultrasound in the classic gastrinoma triangle.

The patient was then taken to the operating room for an intraoperative exploration. Careful visual examination and palpation, guided by intraoperative ultrasound, failed to reveal any tumors aside from that which was identified in the left lobe of the liver. The patient then underwent an uncomplicated left hepatectomy. This procedure entailed gaining control of the blood supply to the left lobe of the liver (portal vein and hepatic artery), gaining control of the left hepatic vein which carries the liver’s outflow of blood to the vena cava, the transecting then hepatic parenchyma to remove the left lobe with the tumor (Figure 4-8). The mass was identified in segment four of the liver, adjacent to the left hepatic duct.

Histologic examination of the resection specimen revealed a 2cm well-circumscribed, tan tumor mass within the liver parenchyma. Microscopic examination revealed a circumscribed tumor composed of epithelioid cells with a nested and trabecular pattern of growth (Figure 9). The nuclei of the tumor cells were uniform with "salt and pepper" type chromatin, which is typical of neuroendocrine neoplasms, and neither mitoses nor necrosis were identified (Figure 10). The neuroendocrine nature of the tumor was confirmed by immunostaining for chromogranin (Figure 11).
These findings are that of a low-grade neuroendocrine neoplasm within the liver. On pathologic grounds, this tumor could be a primary hepatic carcinoid tumor, a metastatic carcinoid tumor from the gastrointestinal tract or a metastatic pancreatic islet cell tumor.

**Clinical Follow-up**

The patient’s postoperative course was unremarkable. The patient left the hospital after one week, with normal liver function tests. The gastrin level returned to normal at one month, after which the patient was asymptomatic off of proton pump inhibitor therapy.

In summary, this is a patient who presented with the Zollinger-Ellison syndrome. The complete recovery of the patient after resection of the hepatic lesion suggests that this was in fact a rare primary hepatic gastrinoma. It is still possible that this patient has within her an occult primary gastrinoma, and that the hepatic lesion was a metastasis. If this were true, one would expect the patient’s symptoms to recur in the future. This patient will require complete long-term follow-up to determine which of these possibilities is the case.