CLINICAL VIGNETTE

Malignant Diarrhea in a 54-Year-Old Male

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Case Presentation

A 54-year-old male presents to the Emergency Department with two and a half weeks of abdominal pain and diarrhea. The abdominal pain is in the right upper quadrant, non-radiating, persistent but not associated with food or bowel movements. He notes occasional bloating and nausea but no vomiting. He reports diarrhea is four to five non-bloody watery bowel movements per day with a mild increase in frequency over the last few weeks. There is no melena. HE also reports severe acid reflux symptoms but no dysphagia. He has tried over-the-counter calcium carbonate, famotidine, and bismuth subsalicylate without relief of his reflux symptoms or abdominal pain. Over the same time period, his weight has decreased from 220 to 197 pounds. He denies fevers, chills, jaundice, icterus or other symptoms.

His past medical and surgical history are notable for atopic dermatitis and a tonsillectomy in childhood. He has no medication allergies and his only other medication is triamcinolone cream. There is no family history of gastrointestinal malignancy or any other gastrointestinal conditions. He denies tobacco and drugs and only uses alcohol socially.

Physical exam is only notable for minimal right upper quadrant tenderness to palpation without a Murphy's sign, rebound or guarding. Bowel sounds are present and his abdomen is soft and nondistended.

Laboratory studies are notable for a mildly elevated white blood cell count of 13,900 per microliter. Hemoglobin is 15.8 g/dL and platelets are normal as well at 360,000 per microliter. The sodium is 139 mEq/L, potassium 3.4 mEq/L, creatinine of 0.7 mg/dL. The albumin is 3.6 g/dL. The remainder of the hepatic panel is normal. Stool studies sent at admission returned negative for bacteria, including clostridium difficile. Ova and parasite testing was also negative.

A CT scan performed in the emergency room revealed a large exophytic, well-defined, slightly lobulated mass arising from the pancreatic body with associated adenopathy and hepatic metastases. The mass was approximately 6.7 by 4 cm. The pancreatic tail was atrophic.

The patient was admitted and upper endoscopy and endoscopic ultrasound were performed. These showed Los Angeles Class C erosive esophagitis, antral gastritis, duodenitis in the duodenal bulb and multiple clean-based ulcers in the second and third portions of the duodenum. Endoscopic ultrasound showed multiple liver metastases along with a single solid heterogeneous mass measuring 37 by 42 mm. The pancreatic duct was 3 mm in size. Fine needle aspiration of the mass was performed with pathology consistent with an intermediate grade neuroendocrine tumor (grade 2). It was positive for chromogranin A, synaptophysin and CD56 and negative for gastrin. Ki67 Index was 13% and mitotic count was 2 per 10 high power fields. Gastric biopsies were negative for Helicobacter pylori.

Additional laboratory results included elevated chromogranin A of 654 (normal range 0-95), gastrin 837 (normal <100) with VIP <50 (normal <75).

Thus, a diagnosis of Zollinger-Ellison Syndrome (ZES) was made.

Discussion

Zollinger-Ellison Syndrome is a condition defined by gastric acid hypersecretion due to secretion of gastrin by a duodenal or pancreatic neuroendocrine tumor (gastrinoma).[1,2] Gastrinomas occur more commonly in men and the peak range is between 20 and 50 years of age.[3] Approximately 70-80% are sporadic with the rest associated with multiple endocrine neoplasia type 1 (MEN-1).[4] Duodenal gastrinomas, usually in the first part of the duodenum, are more likely to be small while pancreatic gastrinomas are more likely to have metastasized to the liver.[5] According to the World Health Organization, they are classified as well-differentiated (low-grade and intermediate grade) or poorly differentiated neuroendocrine carcinoma (high grade).[6]

Pathophysiology of gastrinomas involves high gastrin secretion from the tumor with a resultant high gastric acid output. This is due to the effects of gastrin on parietal cells and enterochromaffin-like (ECL) cells.[3] Diarrhea results from the copious gastric acid secretion with resulting malabsorption and steatorrhea due to inactivation of pancreatic enzymes due to the low pH, and a secretory aspect from inhibition of sodium and water absorption by high serum gastrin levels.[3]

Clinical symptoms include abdominal pain, diarrhea, heartburn and to a lesser extent gastrointestinal bleeding and weight loss.[7] Peptic ulcer disease is present in over 90% of patients with the majority in the first portion of the duodenum.[8,9] Other findings include prominent gastric folds and reflux esophagitis.[7]

Zollinger-Ellison Syndrome should be considered based on the presence of multiple or refractory ulcers, distal duodenal ulcers, peptic ulcer disease in combination with diarrhea (especially if diarrhea improves with proton pump inhibitor [PPI] therapy), and history of MEN-1. Diagnosis is made using fasting serum gastrin concentration (>10 times upper limit of normal) while off of a PPI along with gastric pH (below 2), although gastric pH testing is not used as frequently in clinical practice.[3] If the fasting serum gastrin level does not meet criteria for diagnosis (two-thirds of ZES patients), a secretin stimulation test can be performed as other conditions including PPI use can cause elevated serum gastrin levels.[3] Of note, serum chromogranin A levels are also typically elevated.[10]

Tumor localization is then needed. This can be accomplished via upper endoscopy with or without endoscopic ultrasound along with imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or somatostatin receptor-based imaging (somatostatin receptor scintigraphy [SRS] otherwise known as an octreotide scan). Rarely, laparotomy is needed for tumor localization.

Both medical and surgical management can be used to treat ZES. Medical management consists of acid suppressive therapy with PPIs to reduce peptic ulcer disease and its associated complication. Generally, high dose PPI is recommended to start and can be reduced later. Second line therapy would include somatostatin analogs such as octreotide if PPIs are unsuccessful.[11]

Surgical resection is an option in those with sporadic gastrinoma without evidence of metastatic disease. Cure is reported in up to 50% of these patients with higher likelihood in those with extrapancreatic gastrinomas.[12] Most curable gastrinomas occur within the gastrinoma triangle - the head of the pancreas and the duodenal sweep. Surgery is typically not recommended for those with gastrinomas associated with MEN-1 due to the typically multifocal nature of the tumors and inability to achieve cure of gastrin hypersecretion.[13] Even after curative resection, many patients require PPI due to excess gastric parietal cells.

The two most common sites of metastatic disease are the liver and bone.[14] Treatment typically includes somatostatin analogues. For liver metastases, other options include resection, hepatic artery embolization, radio frequency ablation and cryoablation.

Prognosis is far better for those without liver metastases.[5] Post-treatment surveillance typically includes imaging and serum gastrin levels.[15]

Conclusion

Zollinger-Ellison Syndrome is a rare condition presenting with common symptoms. With current antisecretory therapy and surgery in the carefully selected patient, prognosis in the absence of metastatic disease is good.

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