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Current Management of the Zollinger-Ellison Syndrome

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Keywords

• Zollinger-Ellison • Gastrinoma • Gastrin • Ulcer
• Gastroesophageal reflux disease • Diarrhea • Octreotide

Key points

- Zollinger-Ellison Syndrome (ZES) should be considered in patients with upper gastrointestinal tract symptoms (gastroesophageal reflux disease, peptic ulcer disease) with or without secretory diarrhea, or in those with peptic ulcer disease and primary hyperparathyroidism or family history suspicious for multiple endocrine neoplasia type 1 (MEN1).
- The initial workup should include a measurement of serum gastrin, serum calcium, gastric pH, and/or basal acid output when off antacid medications.
- Gastric acid hypersecretion should be controlled with proton-pump inhibitors.
- Localization studies including positron emission tomography, somatostatin receptor scintigraphy, computed tomography, magnetic resonance imaging, and endoscopic ultrasonography should be performed initially to evaluate for metastases and identify surgically resectable disease.
- In patients with MEN1, surgical correction of hyperparathyroidism (3½-gland parathyroidectomy) should precede surgical resection of the primary tumor, as patients have multiple tumors and are seldom cured; however, surgical resection is recommended for pancreatic neuroendocrine tumors larger than 2.5 cm because of malignant potential.
- All patients with localized sporadic gastrinoma should undergo surgical exploration for tumor resection, regardless of the results of imaging studies.

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INTRODUCTION

Zollinger-Ellison Syndrome (ZES) is caused by gastrinoma, which is the second most common functional pancreatic neuroendocrine tumor (PNET). Gastrin hypersecretion from gastrinoma leads to increased production of gastric acid and severe peptic ulcer disease. In their landmark description, Robert Zollinger and Edwin Ellison correlated the triad of pancreatic tumors, hypersecretion of gastric acid, and unusual peptic ulcer disease in a series of patients at Ohio State University in 1955 [1]. Zollinger and Ellison correctly attributed the patients' intractable peptic ulcer disease to their pancreatic tumors that we now know were gastrinomas.

Gastrinoma has a yearly incidence of approximately 1 to 3 cases per million people in the United States [2]. ZES is the underlying cause in approximately 0.1% to 1% of patients with peptic ulcer disease [3]. Patients with ZES commonly present with signs and symptoms of peptic ulcer disease, gastroesophageal reflux disease (GERD), and secretory diarrhea. Because of the widespread availability of accurate immunoassays to measure serum concentrations of gastrin, gastrinoma is increasingly diagnosed and treated at an early stage of disease. Nevertheless, the mean time from symptoms to diagnosis is up to 8 years in many studies, underscoring the need for increased awareness of ZES [4]. In 80% of cases ZES occurs sporadically; however, approximately 20% of patients have the familial form associated with multiple endocrine neoplasia type 1 (MEN1). Fifty percent of patients with MEN1 have ZES, making gastrinoma the most common functional neuroendocrine tumor in MEN1. As a result, MEN1 must always be excluded during the workup of ZES. A significant family history of ulcers and peptic ulceration occurring at a young age are clues to familial gastrinoma. In addition, peptic ulcers in association with hyperparathyroidism and/or nephrolithiasis, pituitary tumors, benign thyroid tumors, benign and malignant adrenocortical tumors, lipomas, and cutaneous angiofibromas all may indicate MEN1.

CHARACTERISTICS

Size and location

Approximately 80% of gastrinomas are found within the gastrinoma triangle. The gastrinoma triangle is the anatomic area bounded by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum laterally, and the neck of the pancreas medially [5]. Gastrinomas are 3 times more likely to occur in the duodenum than in the pancreas, with the highest proportion in the first portion of the duodenum, becoming progressively less common toward the distal duodenum (Fig. 1) [6]. Duodenal gastrinomas (mean size 0.95 cm) are often smaller than pancreatic tumors (mean size 2.1 cm) [7]. In MEN1, both pancreatic and duodenal gastrinomas are multiple. Primary gastrinomas have been reported in several ectopic anatomic sites including the jejunum, stomach, liver, spleen, mesentery, ovary, heart, and lymph nodes [8]. Gastrinomas have been found in extrapancreatic, extraintestinal lymph nodes with no identifiable primary pancreatic or duodenal