Surgical Management of Zollinger-Ellison Syndrome; State of the Art

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KEYWORDS

• Gastrinoma • Surgery • Diagnosis • Localization
• Outcome • MEN-1

Zollinger-Ellison Syndrome (ZES) was originally described in 1955.[1] It is a syndrome of acid hypersecretion caused by a gastrin-producing tumor (gastrinoma). Since the recognition of this disease entity, diagnosis and treatment strategies have changed greatly. The purpose of this review is to describe the current standard in diagnosis and surgical management of ZES and to outline some controversies that have arisen recently.

EPIDEMIOLOGY

The incidence of ZES in the United States is one to three new cases per million per year, making it a rare condition.[2] Eighty percent of gastrinomas occur sporadically, while 20% are associated with Multiple Endocrine Neoplasia Type 1 (MEN-1).[3] ZES causes 0.1% to 1% of peptic ulcer disease.[4] Men are slightly more likely to develop ZES.[5] The mean age at which symptoms begin is 41 years.[6] Patients with MEN-1–associated ZES are likely to present at a younger age; in the third decade of life.[7] ZES occurs in approximately 25% of patients with MEN-1.[8]

PRESENTATION

The presenting signs and symptoms of ZES have also changed with earlier recognition and diagnosis. Initially, it was described as gastric acid hypersecretion, ulcers in unusual locations (jejunum), recurrent ulcers, and nonbeta islet cell tumors of the pancreas.[9] Subsequent studies of large numbers of patients with ZES have demonstrated that common presenting symptoms include abdominal pain, diarrhea, heartburn, nausea, and weight loss.[6] Diarrhea is a common problem as approximately 80% of patients

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with ZES have this symptom. Given the nonspecific nature of these symptoms, and the rarity of ZES as compared with more common disorders, such as gastroesophageal reflux disease or routine peptic ulcer disease, there is commonly a significant delay in the diagnosis of ZES. The most common initial diagnosis for patients with ZES is idiopathic peptic ulcer disease.[8] The mean time from onset of symptoms to diagnosis of ZES is 5.9 years.[6] Although the time to diagnosis has remained constant over the past 30 years, there is some evidence that it may prove even more challenging with the widespread use of proton pump inhibitors (PPI).[10] PPI provide very effective acid suppression, which may defer the diagnosis even further.[11,12]

The presentation of ZES in MEN-1 may differ somewhat from patients with sporadic ZES. A recent NIH study demonstrated a higher incidence of severe esophageal disease including Barrett's esophagus in patients with MEN-ZES.[13] Despite the high frequency of ZES in MEN-1, the diagnosis is still usually delayed. Only 5% of patients with MEN-1 are initially diagnosed correctly, compared with 2% of patients with sporadic ZES.[8]

Given the continued delay in diagnosis of ZES, recommendations have been made regarding factors which should increase a clinician's suspicion for the syndrome. Patients who present with the triad of abdominal pain, diarrhea and weight loss, patients who have recurrent or refractory ulcers, patients with prominent gastric rugal folds on endoscopy, or patients with MEN-1 and gastrointestinal symptoms should be tested for ZES.[8] In addition, symptoms of acid hypersecretion associated with diarrhea should indicate the possibility of ZES.[2]

At the time of diagnosis, some patients will have minimal or nonimageable tumor while others may have advanced disease (ie, greater than 40% have lymph node metastases). The duodenum is the most common site of a primary gastrinoma, while the pancreas is the second most common site (**Fig. 1**). Lymph node metastases do not affect survival, while liver metastases do. Hepatic metastases (**Fig. 2**) occur more commonly with pancreatic gastrinomas than duodenal. They may occur in up to 60% of pancreatic cases and less than 10% of duodenal cases.[14]

DIAGNOSIS

Suspicion for the diagnosis of ZES should be aroused when any of the above factors are present. Once the clinician suspects ZES, diagnostic workup should begin with

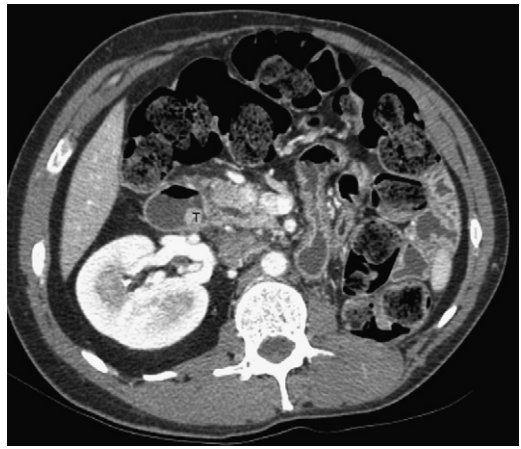

Fig. 1. A large duodenal gastrinoma which is visible on CT.