Zollinger-Ellison Syndrome Successfully Treated with Esomeprazole

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The medical management of patients with Zollinger-Ellison syndrome (ZES) generally requires long-term gastric acid suppression because of profound hypergastrinemia and gastric acid hypersecretion. We describe a 47-year-old man with a history of pituitary prolactinoma who presented for evaluation of refractory diarrhea of 3 years’ duration and occasional nausea and vomiting, but no dyspepsia or heartburn. Esophagogastroduodenoscopy revealed erosive esophagitis, antral erosions and bulbar duodenitis, but no submucosal masses. Esomeprazole 40 mg once daily was prescribed. Shortly thereafter, his diarrhea resolved, but some nausea persisted. After increasing the dose of esomeprazole to 40 mg twice daily, all symptoms resolved and the dose was well tolerated. Fasting serum gastrin concentration, drawn prior to endoscopy and initiation of medical therapy, was markedly elevated (411 pg/mL). Endoscopic ultrasound disclosed multiple pancreatic and duodenal masses. The patient underwent distal subtotal pancreatectomy with resection of a low-grade neuroendocrine carcinoma metastatic to regional lymph nodes. Immunohistochemically, the tumor cells expressed gastrin. Concurrently, total parathyroidectomy for hyperparathyroidism was performed and a final diagnosis of multiple endocrine neoplasia type 1 with ZES was rendered. Treatment with esomeprazole relieved the diarrhea, nausea and vomiting associated with ZES when prescribed at 40 mg twice daily. Esomeprazole should be studied further to determine its efficacy and optimal dosing for this difficult-to-treat patient population.

INTRODUCTION

In 1955, Robert M. Zollinger and Edwin H. Ellison described the classic triad of peptic ulcer disease, gastric acid hypersecretion and islet cell tumors of the pancreas that constitute the syndrome that bears their names (1). Most patients with Zollinger-Ellison syndrome (ZES) require long-term medical management to suppress gastric acid hypersecretion, control symptoms, and reduce the incidence of complications. The introduction of proton pump inhibitors (PPIs) more than one decade ago markedly changed the approach to the medical treatment of ZES (2). The decrease in gastric acid produced by earlier PPI generations has been improved with the development of a new PPI generation that provides more effective acid suppression and symptom control (3–5). Of the currently available PPIs, esomeprazole has been shown in head-to-head pharmacodynamic studies to offer the highest degree of acid suppression compared with other PPIs at standard doses (6,7). This degree of efficacy may be particularly advantageous in the treatment of some patients with ZES.

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Although 1 of the 2 patients originally described by Zollinger and Ellison complained of chronic diarrhea (1), its recognition as a typical or predominant symptom of ZES has been receiving more attention (8–11). Indeed, in a few patients, diarrhea may be the only symptom of ZES, but it is unusual. In a clinical review of more than 200 patients, diarrhea alone was observed among fewer than 8% of patients (10,12). Delay in diagnosis is common among patients with ZES regardless of their presentation. However, recognition of diarrhea as a possible manifestation of ZES may shorten diagnostic delay because diarrhea is frequently among the early symptoms (10).

We describe the medical and surgical management of a patient who presented with diarrhea and later complained of nausea and vomiting. At endoscopy, erosive esophagitis in the absence of heartburn was another unusual feature of this patient, who was ultimately found to have ZES as one component of his multiple endocrine neoplasia type 1 (MEN-1).

CASE REPORT

A 47-year-old obese white male was referred for evaluation of progressive diarrhea of 3 years’ duration that was refractory to standard medical management. The diarrhea was typically worse in the early morning, causing the patient to awaken at approximately 4 a.m. The patient also complained of occasional nausea and vomiting of more recent onset, but no dysphagia, dyspepsia, heartburn or abdominal pain. Colonoscopy performed elsewhere 4 months earlier was normal. The patient had a 13-year history of type 2 diabetes mellitus, an 18-year history of hypertension, a 3-year history of pituitary prolactinoma, and recently discovered hyperparathyroidism. There was no history of peptic ulcer disease.

Concurrent medications included cabergoline to control secretion of prolactin, metformin, glipizide, recombinant human insulin, quinapril, atenolol and hydrochlorothiazide. There was no history of prior use of antacids, histamine H₂-receptor blocker, or PPIs. His paternal family history was remarkable for MEN-1.

Esophagogastroduodenoscopy revealed erosive esophagitis, gastric antral erosions, and bulbar duodenitis with erosions and shallow ulcerations, but no visible submucosal lesions. Esomeprazole at a dose of 40 mg once daily was initiated. Diarrhea resolved soon thereafter. However, mild nausea persisted and esomeprazole was increased to 40 mg twice daily. All gastrointestinal symptoms were then resolved and esomeprazole was well tolerated.

Serum chemistry studies drawn prior to endoscopy revealed a fasting gastrin level of 411 pg/mL (normal 0–111) and a vasoactive intestinal peptide level of 9 pg/mL (normal 0–60). Radiographic studies (endoscopic diagnostic ultrasonography and computed axial tomography) revealed several discrete masses in the pancreas and duodenum. Single-photon emission computed tomography imaging of the abdomen with In-111 pentetreotide (OctreoScan®, Mallinkrodt Inc., St. Louis, Missouri) demonstrated increased uptake in the body of the pancreas, compatible with gastrinoma. Fine needle aspiration of one of the pancreatic masses disclosed a cellular population of neoplastic cells cytologically diagnostic of islet cell tumor. Immunocytochemical studies of the tumor cells demonstrated the expression of several neuroendocrine markers, including chromogranin A, synaptophysin, and neuron-specific enolase, which further confirmed the light microscopic impression.

Immediately preoperatively, esomeprazole was discontinued, and the patient underwent laparotomy with intraoperative ultrasonography followed by radical distal subtotal pancreatectomy. Approximately 7 tumors within the head, neck, body, and tail of the pancreas were identified intraoperatively and excised. Two masses detected deep within the head of the pancreas could not be removed. Three duodenal tumors were also located and excised.

Pathologic examination disclosed low-grade neuroendocrine carcinoma in the duodenal tumors with metastases involving 2 regional lymph nodes. The tail of the pancreas contained multiple islet cell tumors and diffuse endocrine cell hyperplasia. No single tumor was larger than 1.5 cm in maximal dimension. Immunohistochemical staining for gastrin showed diffuse reactivity within the various duodenal tumors but only scattered immunoreactive cells within the 2 involved lymph nodes. Postoperatively, the fasting serum gastrin level decreased to 237 pg/mL. Because complete resection of the neuroendocrine tumor burden could not be accomplished, a return to normal gastrin output was
neither anticipated nor observed, and the patient was continued on PPI therapy.

During the interval when hypergastrinemia was under investigation, the patient also had an evaluation for hypercalcemia. A diagnosis of hyperparathyroidism was rendered and the patient underwent total parathyroidectomy with autotransplantation of parathyroid tissue into the left forearm. Thus, all 3 classic components of the MEN-1 triad were identified (pituitary adenoma, parathyroid hyperplasia or adenoma, and islet cell tumor of the pancreas).

**DISCUSSION**

ZES is sporadic in 80% of patients and attributable to MEN-1 in the remaining 20% (10,13,14). In most patients with hereditary disease, the genetic defect is a tumor suppressor gene (15) localized to chromosome 11q13 (16), and usually inherited as an autosomal dominant trait (17).

Gastrinoma is the most common islet cell neoplasm among patients with MEN-1 (13,18). In a recent review of the surgical findings in 151 patients with ZES, the duodenum was the most frequent location (49%) of the tumor, but the pancreas was also a common site (24%); however, the location was sometimes unknown (9%) (13). Because there are no reliable histologic criteria for malignancy, detection of metastatic disease provides the only conclusive evidence of malignancy. “Neuroendocrine carcinoma” is the currently preferred term for a malignant islet cell tumor.

As this case demonstrates, it is not always feasible to completely excise the tumor due to multifocality or metastases. Indeed, in one series, 51% of patients with sporadic gastrinomas but only 16% of patients with MEN-1-associated gastrinomas were free of disease immediately postoperatively (13). Almost one half of patients with MEN-1 will have tumors in both the pancreas and the duodenum (19). Although surgical resection generally results in a reduction of serum gastrin levels (18), a biochemical cure in the form of normalization of gastrin levels cannot be expected in most patients with MEN-1 postoperatively.

Metastases to the lymph nodes or the liver from gastrinomas are identified at the time of surgery twice as frequently among patients with MEN-1 relative to patients with sporadic disease (13). The incidence of lymph node metastases among MEN-1 patients with multiple pancreatic tumors has been reported to be as high as 70% (19). However, the presence of lymph node metastases does not predictably portend a worsened prognosis, whereas the presence of liver metastases appears to be associated with a significantly shortened survival (14,20,21). Patients with advanced localized disease (multiple primaries or tumors 6 cm or larger) who undergo resection are generally not cured but have survival rates similar to those with limited disease and those without identifiable tumor. Therefore, surgical resection has been advocated for all patients with MEN-1 unless systemic illness or widespread metastases are present (22).

Despite the plethora of symptoms that can occur in patients with ZES, the initial presentation is often non-specific and rarely leads to an immediate diagnosis. In fact, the mean delay in diagnosis is approximately 5 years regardless of whether the disease is sporadic or MEN-1-related (10). Moreover, there is no indication that the time interval from onset of symptoms to diagnosis is decreasing. When one group of investigators stratified the duration of symptoms before diagnosis by time periods (pre-1980, 1980–1989, 1990–1999), they found no indication that the lag-time was shortening (10).

Diarrhea is a common symptom of ZES. In one reported series, 76% of 261 carefully evaluated patients complained of diarrhea (10). However, diarrhea is typically not the sole symptom in patients with ZES, yet when present, the character and timing of the diarrhea are somewhat characteristic. Typically, a mild to moderate amount of diarrhea occurs early in the morning without a relationship to meals (10). In our patient, diarrhea was the only presenting symptom, and only later did nausea and vomiting develop.

The reported frequency of esophageal involvement in ZES varies widely, ranging from 1% to 60% (12,23), and is largely dependent upon the rigor of the diagnostic evaluation. Erosions and ulcerations are frequently identified endoscopically in patients with ZES (24,25), and may be severe. The severity of esophagitis is directly related to the extent and duration of esophageal gastric acid exposure (26,27). In our patient, the absent of heartburn was unusual, given the presence of esophageal erosions. However, (continued on page 62)
because the severity of heartburn does not correlate with the severity of esophagitis (28) aggressive acid-suppressive treatment is often warranted. PPIs are the medical treatment of choice for patients with ZES. Indeed, because of the profound and persistent hypergastrinemia and gastric acid secretion, higher doses of a PPI and more frequent dosing are often required to control the symptoms of ZES (10, 29–31). The selection of a PPI to manage ZES should be based on a combination of efficacy and safety. Pharmacokinetic and pharmacodynamic characteristics of esomeprazole suggest that it has an increased acid inhibitory effect compared with standard doses of other PPIs (32). Esomeprazole 40 mg once daily maintains intragastric pH >4 for a significantly longer time period and displays less interpatient variability than twice the standard dose of omeprazole (40 mg) (3). Our patient with ZES received twice the standard dose of esomeprazole and experienced amelioration of all symptoms without adverse effects. Esomeprazole should be studied further to determine its efficacy profile and optimal dosing in patients with ZES.

References
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