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Case Report

Zollinger-Ellison syndrome: case report and topic review

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ABSTRACT

Zollinger-Ellison syndrome (ZES) is characterized by gastrin-secreting neuroendocrine tumors (gastrinomas) in the duodenum or pancreas. It is a rare condition, most patients are diagnosed between the ages of 20 and 50, and a higher incidence in men. Gastrinomas are associated with a high risk of malignancy and the diagnosis is confirmed by the secretin stimulation test and imaging studies such as octreotide scintigraphy. We present the case of a 24-year-old man who presented with melena, asthenia, adynamia and abdominal pain, in addition to a history of peptic ulcer. Laboratory tests revealed low levels of hemoglobin and elevated levels of gastrin. Endoscopy showed a giant ulcer and subsequent surgery revealed stomach-jejunum adhesions, gastric lesions and Meckel's diverticulum. Imaging studies confirmed neuroendocrine tumor activity in the pancreas. ZES leads to sustained hypergastrinemia, causing peptic ulcers and other digestive tract complications. Gastrinomas can arise from a variety of locations and can cause peptic ulcers, malabsorption, and diarrhea. Diagnosis requires elevated fasting serum gastrin levels and hypersecretion of gastric acid. Treatment involves discontinuation of proton pump inhibitors (PPIs) before diagnostic testing and surgical resection of tumors in suitable candidates. The diagnosis of ZES can be complicated due to the unreliability of the assays and the need for secretin testing. Surgical resection is recommended for sporadic gastrinomas without metastasis, while medical treatment may be necessary for postsurgical residual hyperacidity. Patients should undergo imaging studies for tumor localization and regular monitoring for complications and recurrences.

Keywords: Gastrinoma, Zollinger-Ellison, Somatostatin receptor scintigraphy

INTRODUCTION

Zollinger-Ellison syndrome (ZES) is caused by the secretion of gastrin by duodenal or pancreatic neuroendocrine tumors (gastrinomas). The annual incidence of gastrinomas is 0.5 to 2 per million inhabitants. Most patients are diagnosed between the ages of 20 and 50, with (a higher incidence in men than in women. Approximately 80% of gastrinomas are sporadic, but 20-30% occur in association with multiple endocrine neoplasia type 1 (MEN1).[1] MEN 1 is an autosomal dominant disorder characterized by the development of specific endocrine tumors. Sporadic gastrinoma has a high risk of malignancy and typically occurs as a single tumor >2 cm. Gastrinoma associated with MEN 1 carries a low risk of malignancy and usually presents as multiple tumors <2 cm, typically in the duodenum. Gastrinomas are reported to be malignant in 60-90% of patients. Gastrinomas usually present with abdominal pain and gastrointestinal bleeding; diarrhea is also common.[2] More than 90% of patients with gastrinoma have peptic ulcer disease. Most ulcers are located in a typical location (proximal duodenum), but the presence of ulcers in atypical locations or multiple ulcers should prompt evaluation for gastrinoma. Its diagnosis is confirmed with the secretin stimulation test; an increase of 200 pg/ml or more in gastrin after the stimulation test confirms the diagnosis. Currently, the imaging study of choice for diagnosis is octreotide scintigraphy, as gastrinoma cells

contain type II somatostatin receptors to which the analog (octreotide) binds with high affinity.[3-5]

CASE REPORT

A 24-year-old male, who began three days prior to admission with melena, asthenia, adynamia, abdominal pain rated 6/10 on an analog pain scale, as well as a history of burning epigastric pain, nausea, and vomiting for 8 years. As significant medical history, he is a native and resident of Mexico City. Peptic disease since the age of 16 on omeprazole treatment. Surgical history includes appendectomy in 2017. Exploratory laparotomy (LAPE) for intestinal occlusion requiring intestinal resection with entero-entero anastomosis with Billroth II reconstruction + Braun's Omega reconstruction in December 2018. LAPE for intestinal occlusion + gastric perforation with primary closure + adhesiolysis in September 2019.

Physical examination included SV blood pressure (BP): 120/70 mmHg, heart rate (HR): 75 bpm, respiratory rate (RR): 19 rpm, saturated O_2: 98%, temperature: 36.4°C, alert, oriented, cooperative patient, dehydrated oral mucosa, scleral and tegumental icterus, lung fields with present respiratory sounds without added pathological sounds, rhythmic heart sounds without added sounds, flat abdomen, with present peristalsis, soft and depressible, slight deep epigastric tenderness, no signs of peritoneal irritation, no masses or organomegaly, rectal examination with bloody residue, intact limbs, with present peripheral pulses, immediate capillary refill. Laboratory studies showed hemoglobin of 8 g/dl and gastrin levels of 133 mg/l, without electrolyte abnormalities or leukocytosis.

An upper endoscopy was performed, revealing a giant ulcer corresponding to Forrest IIC, which was treated with adrenaline and thermal therapy. Esophageal biopsy showed mild and nonspecific esophagitis, while gastric ulcer biopsy showed superficial chronic gastritis associated with chemical changes, with no evidence of metaplasia, dysplasia, atrophy, or microorganisms.

The patient was evaluated, started on 10 days of total parenteral nutrition, and underwent LAPE + antrectomy + gastrojejunostomy in Roux-en-Y + truncal vagotomy + diverticulectomy of Meckel's diverticulum in March 2023, with the following findings: firm stomach-jejunum adhesions to the wall, lax adhesions loop-loop and loop-wall, previous gastrojejunostomy at the gastric antrum level in Braun's Omega at 20 cm from the Treitz angle, Meckel's diverticulum at 60 cm from the ileocecal valve, bleeding of 700 cc, with approximately 3 hours of surgery time, and the patient was discharged 7 days after the surgical event.

Subsequently, a somatostatin receptor scintigraphy was performed on 26.04.2023: Abnormal uptake of the radiopharmaceutical was observed as punctiform and rounded in the pancreatic head topography, irregular and diffuse abnormal concentration of somatostatin analog in the pancreatic tail topography, an amorphous lesion with poorly defined borders was identified in the pancreatic head, isodense with the pancreatic parenchyma measuring approximately 26×30.8 mm in axial section, a second ovoid lesion was identified in the pancreatic tail, with partially defined borders, isodense, measuring 60.7×66.4×27.3 mm, both lesions with abnormal increase in radiopharmaceutical concentration, concluding abnormal increase in somatostatin receptors in the pancreatic head and tail in probable relation to neuroendocrine tumor activity (Figures 1 and 2).

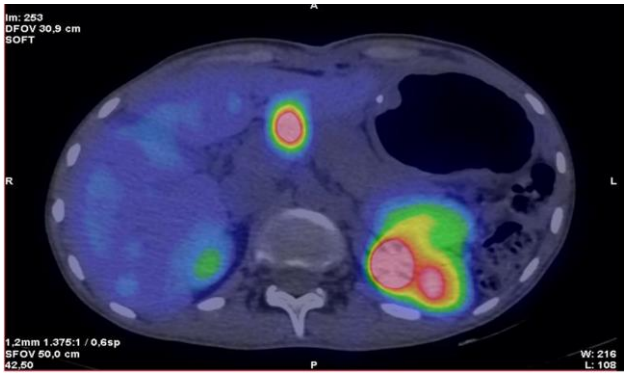

Figure 1: Somatostatin receptor scintigraphy, axial cut.

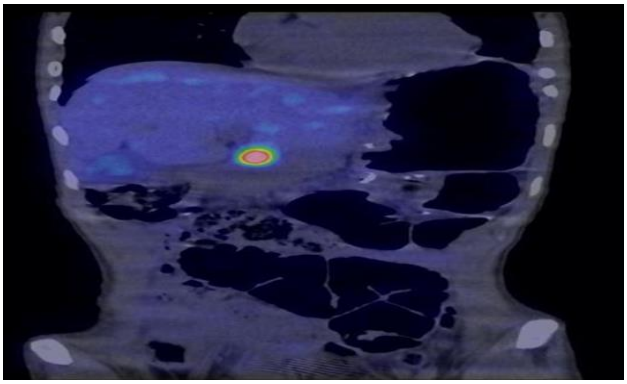

Figure 2: Somatostatin receptor scintigraphy, coronal reconstruction.

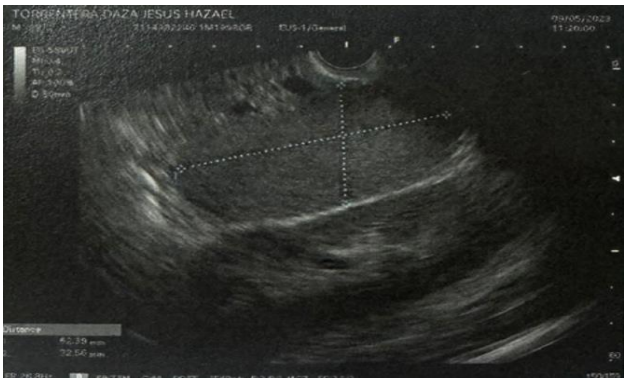

Figure 3: Endoscopic ultrasound, gastrinoma in head of pancreas.

Endoscopic ultrasound on 05 September 2023

In the gastric window, a solid tumor of the head and body of the pancreas with regular borders, homogeneous, measuring 38×60 mm was observed, with normal pancreatic duct, no lymphadenopathy, the lesion respecting the celiac trunk and superior mesenteric artery (Figures 3 and 4).

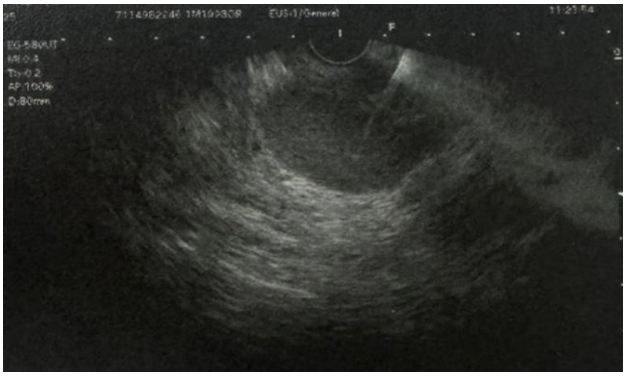

Figure 4: Endoscopic ultrasound, gastrinoma in head of pancreas.

DISCUSSION

ZES has allowed us to understand the biological behaviour of a large portion of pancreatic neuroendocrine tumors and study the consequences of sustained hypergastrinemia on the digestive tract, mainly manifested by hypertrophy of the gastric folds and permanent acid hypersecretion resulting in peptic ulcer disease refractory to conventional treatment with acid suppressants. Although the trophic action of gastrin is very marked on the gastric mucosa, it can also be relevant in the mucosa of the small intestine or colon, with a higher risk of gastric carcinoma postulated in subjects with sustained hypergastrinemia.[6] Gastrin-secreting tumors arise from enteroendocrine cells that develop from embryonic endoderm. Primary location, 30% pancreas, 60-70% duodenum, 5-10% at other locations (stomach, jejunum, liver, spleen, ovary, heart, and lymph nodes). Effects of excess gastric acid may include peptic ulcers (often multiple, large, and located in the distal duodenum and proximal jejunum), malabsorption due to inactivation of pancreatic digestive enzymes by excess acid, inhibition of intestinal absorption of sodium and water, resulting in secretory diarrhea (common in gastrinoma). Regarding diagnosis, we should suspect in patients with severe, refractory, recurrent peptic ulcer, or associated with secondary complications such as severe gastroesophageal reflux disease (GERD), diarrhea, personal or family history of endocrinopathies, prominent gastric folds on endoscopy, hypercalcemia, or hypergastrinemia, not associated with Helicobacter pylori infection or other risk factors such as nonsteroidal anti-inflammatory drug (NSAID) use. The diagnosis of ZES requires demonstrating elevated fasting serum gastrin (FSG) levels and gastric acid hypersecretion: FSG >10 times normal (typically >1000 pg/ml) and gastric pH ≤2 confirm the diagnosis. If FSG is elevated but <10 times normal (typically 100-1,000 pg/ml) and gastric pH ≤2, secretin stimulation test should be performed and basal acid output (BAO) measured (secretin test cannot be performed if the patient is taking proton pump inhibitors [PPIs]), stimulated FSG >120 pg/ml and BAO >15 mEq/hour (>5 mEq/hour if previous acid-reducing surgery) confirms the diagnosis. FSG <100 pg/ml (in the absence of medications that suppress gastric acid secretion) rules out ZES.

Making the diagnosis can be challenging due to the unreliability of many commercial gastrin assays, the lack of availability of the necessary secretin to perform provocative testing, and the widespread use of PPIs. Medications that inhibit gastric acid secretion (PPIs) should be discontinued ≥1 week before diagnostic testing. Discontinuation of PPIs should only be done when the patient is stable and free of peptic disease, and PPIs should not be abruptly discontinued, providing adequate coverage with high-dose histamine type 2 blockers and closely monitoring the patient (daily symptom control). Tests after confirming the diagnosis should include blood tests to detect multiple endocrine neoplasia type 1 (MEN 1), imaging studies to localize tumors, detect metastases, and evaluate complications; imaging studies may include: PET/CT with gallium-68-labeled somatostatin analogs: the most sensitive imaging test for detecting gastrinomas, other studies, such as computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy (SRS), invasive imaging if noninvasive imaging fails to detect the primary tumor, options include endoscopic ultrasound, intraoperative ultrasound, surgical exploration and histopathological evaluation of the tumor if imaging fails to localize the primary tumor. As for surgical treatment; patients with sporadic gastrinoma who do not have evidence of metastatic disease spread should be offered exploratory laparotomy and resection with curative intent, this recommendation stems from the fact that 60-90% of gastrinomas are malignant and, in addition to eliminating (or at least decreasing) the need for antisecretory medical therapy, successful resection of sporadic gastrinomas protects against the possibility of eventual morbidity and mortality from metastasis.[7]

The likelihood of surgical cure is particularly high for extrapancreatic gastrinomas (e.g., those in the duodenum or peripancreatic lymph nodes).[8] Conversely, laparotomy is not routinely recommended for patients with ZES as part of MEN, since the multifocal nature of tumors in this disorder almost uniformly precludes the cure of gastrin hypersecretion.[9,10] Gastric secretion may not return to the normal range after resection of the gastrinoma due to residual excess gastric parietal cell as a consequence of the trophic effect of chronically elevated gastrin levels. Up to 40% of patients will require prolonged antisecretory therapy to control hyperacidity after curative resection, and such patients need ongoing acid hypersecretion control.[11] Vagotomy of parietal cells (proximal gastric) has been recommended performed at the time of tumor

resection to reduce the need for postoperative medical treatment, particularly when complete resection of gastrinoma tissue cannot be achieved, as is the case with our patient.[12]

CONCLUSION

ZES presents a complex interplay of gastrin-secreting tumors and gastrointestinal manifestations, necessitating a comprehensive understanding for effective management. The case report illustrates the diagnostic challenges and treatment considerations inherent in ZES, emphasizing the importance of accurate diagnosis through elevated fasting serum gastrin levels and gastric acid hypersecretion assessments. Surgical resection remains a cornerstone of therapy for sporadic gastrinomas, while medical management plays a crucial role in controlling hyperacidity postoperatively. However, the intricacies of ZES diagnosis and management underscore the necessity of a multidisciplinary approach, encompassing gastroenterologists, surgeons, endocrinologists, and radiologists, to optimize patient outcomes and mitigate the risk of complications and recurrences. Moving forward, continued research and clinical collaboration are imperative to enhance our understanding of ZES pathophysiology and refine therapeutic strategies, ultimately improving patient care and quality of life.

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