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ZOLLINGER-ELLISON SYNDROME. CASE REPORT

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Palabras clave: Gastrinoma; Síndrome de Zollinger-Ellison; Neoplasia endocrina múltiple tipo 1.

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ABSTRACT

Introduction: The Zollinger-Ellison syndrome (ZES) is a pathology caused by a neuroendocrine tumor, usually located in the pancreas or the duodenum, which is characterized by elevated levels of gastrin, resulting in an excessive production of gastric acid.

Case presentation: A 42-year-old female patient with a history of longstanding peptic ulcer disease, who consulted due to persistent epigastric pain, melena and signs of peritoneal irritation. Perforated peptic ulcer was suspected, requiring emergency surgical intervention. Subsequently, a tumor lesion in the head of the pancreas was documented and managed with Whipple procedure. The pathology results reported a tumor suggestive of neuroendocrine neoplasm.

Discussion: The Zollinger-Ellison syndrome occurs in 0.1 to 3 people per 1 000 000 inhabitants worldwide and is predominant in women between 20 and 50 years of age. It usually appears as a refractory acid-peptic disease or as a complication of gastric acid hypersecretion. Medical therapy is the standard management, being proton pump inhibitors (PPI) the most effective option. Surgery is recommended for sporadic ZES.

Conclusions: ZES has a low incidence rate. It is rarely considered in the differential diagnosis of chronic epigastric pain and high clinical suspicion is required to achieve adequate management. This article is highly relevant as it presents a confirmed clinical case of ZES in Colombia, highlighting the importance of producing local scientific literature to improve the diagnosis and treatment of this pathology.

RESUMEN

Introducción. El síndrome de Zollinger-Ellison (SZE) es una patología producida por un tumor neuroendocrino habitualmente localizado a nivel duodenal o pancreático, el cual produce niveles elevados de gastrina, derivando en hipersecreción de ácido gástrico.

Presentación del caso. Paciente femenino de 42 años con antecedente de enfermedad ulceropéptica de larga data, quién consulta por epigastralgia persistente y deposiciones melénicas y presenta signos de irritación peritoneal. Se sospecha una ulcera péptica perforada, requiriendo intervención quirúrgica de urgencia. Posteriormente se documenta una lesión tumoral en la cabeza del páncreas, manejada con cirugía de Whipple; en el reporte de patología se detecta un tumor sugestivo de neoplasia neuroendocrina.

Discusión. El SZE se presenta en 0.1-3 personas por cada 1 000 000 de habitantes a nivel mundial, predominantemente en mujeres entre 20 y 50 años de edad. Suele debutar como enfermedad ácido-péptica refractaria o por complicaciones de la hipersecreción gástrica. La terapia médica es el manejo estándar, siendo la más efectiva la que involucra inhibidores de la bomba de protones. En SZE esporádico está recomendada la cirugía.

Conclusiones. El SZE tiene una incidencia baja, raramente se considera en el diagnóstico diferencial de epigastralgia crónica y se requiere alta sospecha clínica para lograr un manejo adecuado. Este artículo es valioso al presentar un caso clínico confirmado de SZE en Colombia, destacando la importancia de producir bibliografía científica local para mejorar el diagnóstico y tratamiento de esta patología.

INTRODUCTION

Zollinger-Ellison syndrome (ZES) is characterized by an increased secretion of gastric acid in the proximal gastrointestinal tract, secondary to the appearance of gastrinomas, which are neuroendocrine tumors located in the duodenum or the pancreas. (1)

The ZES has a wide spectrum of initial presentations and malignancy potentials, so it is important to suspect the presence of the tumor since the first clinical approach. Knowledge about the diagnostic approach and the possible complications and indications to be given to the patient must also be clear. (1) New imaging methods have allowed finding an increasing incidence of this syndrome, which in turn contributes to faster initial treatment. (2)

This paper presents the clinical case of a Colombian patient with ZES, as well as a brief review of the current literature focused on the diagnostic approach to gastric acid hypersecretion and the suspicion of ZES.

CASE PRESENTATION

Female patient of 42 years of age, from Bogotá D.C. (Colombia), housewife, mestizo and from a low-income household, who was admitted to a secondary care hospital due to abdominal pain. The patient presented a clinical profile of 15 days of evolution characterized by epigastric pain associated with multiple episodes of melena; she reported a medical history of refractory ulceroptic disease that appeared 5 years before consultation, which was still pharmacologically treated with omeprazole 20mg every 24 hours, tramadol 50mg every 8 hours and bisacodyl 5mg every 24 hours. She also reported being exposed to wood smoke for 20 years. Her gynecological and surgical history included five pregnancies, four caesarean sections and an ectopic pregnancy that required right oophorectomy.

On physical examination, the patient had tachycardia, but the other vital signs were within normal limits. Hypochromic conjunctiva and dry oral mucosa were found, as well as decreased intestinal sounds and severe abdominal pain in epigastrium on palpation, with signs of peritoneal irritation. Serum hemoglobin was at 9 mg/dL, and electrolytes and glycemia within normal limits.

Perforated peptic ulcer was suspected, so an emergency exploratory laparotomy was performed finding a Forrest III perforated pyloric ulcer. Secondary peritonitis was drained and managed with Graham's patch. Despite the surgery, melena and hematemesis persisted, so a computed axial tomography (CT) and endoscopy of the upper digestive tract were performed, obtaining reports of a mass in the head of the pancreas and Forrest III giant duodenal bulb ulcer, respectively.

Proton pump inhibitors (PPIs) and antibiotic therapy against *Helicobacter Pylori* were initiated. The case of the patient was taken to the surgical board, which decided to perform pancreatoduodenectomy upon concluding that the surgical risk was low and that considering the pathological history, clinical profile, disease evolution and location of the tumor, this was probably a case of gastrinoma that was related to a multiple endocrine neoplasia syndrome (MEN) type 1, so a multifocal nature of the disease was unlikely.

Whipple procedure was performed with usual reconstruction, during which the head of the pancreas, the gallbladder, part of the duodenum, and the lymph nodes located near the head of the pancreas were removed; a mass involving the duodenum, the bowel, the gallbladder, and the lower part of the liver was found (Figure 1).

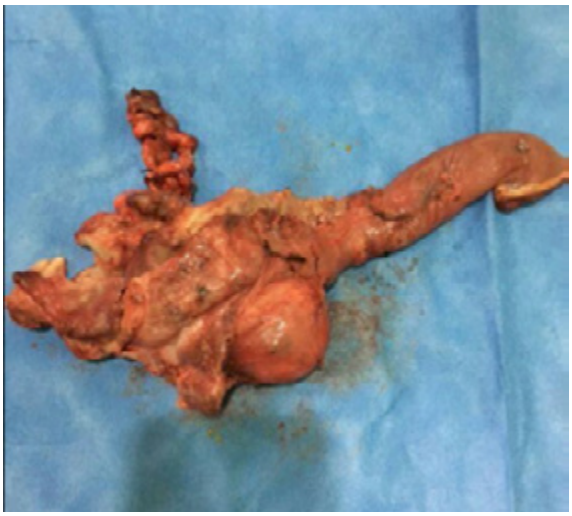

Figure 1. Surgical piece removed –mass involving the duodenum, the bowel, the gallbladder, and the lower part of the liver.

Source: Document obtained during the study.

When the mass was released, a giant ulcer was found in the duodenal bulb with abundant clots and 40% involvement of the duodenal wall and marked fibrosis. Additionally, a 4x3x3cm, regular, soft and apparently encapsulated mass was found on the head of the pancreas immersed in pancreatic tissue and with foci of hemorrhage when cut (Figure 2).

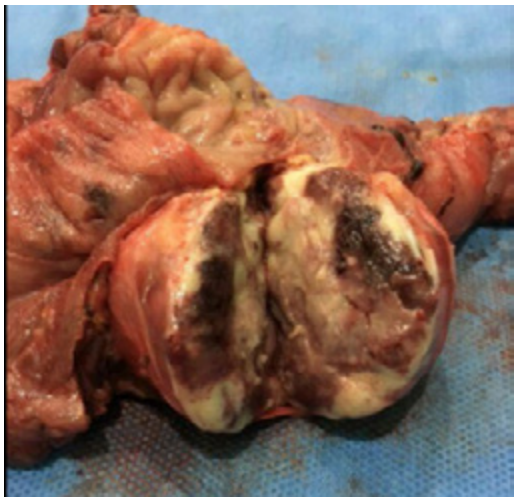

Figure 2. Surgical piece removed: mass in the head of the pancreas with hemorrhagic foci at cut.

Source: Document obtained during the study.

Biopsies were taken from the surgical samples, reporting a histological type of tumor suggestive of neuroendocrine neoplasm, with a solid acinar and trabecular pattern, confined to the head of the pancreas and consistent with gastrinoma. The surgery was successful, there were no complications and the patient had a proper recovery.

Due to administrative procedures, the patient was transferred to a tertiary care hospital in Bogotá D.C., where her treatment continued under the concept of the general surgery service of that institution; this situation prevented an adequate medical follow-up. The prognosis of the patient was considered as favorable in the long term, because besides the satisfactory results of the surgery, not having metastasis of the disease greatly increases survival.

DISCUSSION

The ZES is a pathology caused by a neuroendocrine tumor known as gastrinoma, which is usually located in the duodenum or pancreas. This produces an abnormal increase of the secretion of the hormone gastrin that leads to the hypersecretion of gastric acid in the digestive system in a secondary manner.

The exact incidence of ZES is unknown, but current literature suggests that between 0.1 and 3 people per 1 000 000 inhabitants develop the disease each year. (1) Most patients are diagnosed between 20 and 50 years of age and there is a higher incidence in the female sex.

Gastrinomas originate predominantly in the duodenum and only about 25% occur in the pancreas. (3) About 70-80% of gastrinomas are sporadic, but 20-30% are associated with multiple endocrine neoplasm type 1 (MEN1) with an overall survival rate similar to the sporadic form. (4)

The pathogenesis of gastrinomas remains unknown. Mutations in tumor suppressor genes (p53, retinoblastoma) and oncogenes are rare, and alterations in the m-TOR pathway and abnormal receptor tyrosine kinase activity in tumor growth have also been reported.

Exact cell of origin of gastrinomas remains a controversial issue. Ito *et al.* (5) suggest that pancreatic gastrinomas may originate from islets or duct cells. In the case of duodenal gastrinomas in patients with MEN1, these researchers suggest a higher level of proliferation of duodenal G cells, along with the loss of heterozygosity at the MEN1 locus (11q13) in the G cell. (5)

First of all, it is important to identify the patients with untreated gastric acid hypersecretion, as they can develop complications quickly, and they must be corrected before attempting to establish a diagnosis. (6)

The symptoms of ZES are related to the hypersecretion of gastric acid and the appearance of multiple ulcers distal to the duodenal bulb. In the past, most patients reported refractory peptic ulcers or presented with complications associated with hypersecretion of gastric acid, such as gastric perforation or penetration, bleeding in the digestive tract, and esophageal stricture.

Effective antisecretory drugs, such as PPIs and histamine H2-receptor antagonists (H2Rs), are now available and have led to a significant decrease of this form of presentation.

Symptoms related to ZES are highly variable and include abdominal pain (75%) due to a typical duodenal ulcer or gastroesophageal reflux (GER); diarrhea (73%), being the only manifestation in 3-10% of patients; weight loss (17%); and gastrointestinal bleeding (25%). (7)

Between 1 and 10% of patients with MEN1, especially in metastatic disease, have symptoms associated with a secondary hormonal syndrome (VIPoma, somatostatinoma, glucagonoma, ACTH, etc.) In general, MEN1 patients present with hyperparathyroidism (90-99%), primitive neuroendocrine tumor (PNET) (80-100%), and pituitary adenomas (50-65%) at different ages. The most common functional PNETs are ZES and insulinoma. Hyperparathyroidism can affect the activity of ZES and may even mask its presence if properly controlled, so it is important that all patients with MEN1 are tested for ZES. (5)

The importance of establishing a correct diagnosis of ZES lies in the fact that it requires special treatment. Despite the wide availability of diagnostic tests, there is still a 6-9 year delay in diagnosis. ZES should be suspected in patients with peptic ulcers, ulcers distal to the duodenum, and peptic ulcer disease.

The doses of PPIs and H2Rs antagonists may be different from those generally used in patients with idiopathic peptic disease and may require lifelong treatment. Therefore, in these patients, treatment directed at the gastrinoma should be considered, given its possible malignancy, and should include a periodic evaluation of the location of the tumor and considering surgical resection. (6)

The first study to be performed, if ZES is suspected, is fasting serum gastrin concentration (8), although it is controversial as the literature reports that many of the gastrin assays used worldwide may underestimate or overestimate fasting gastrin concentrations, therefore the results may lead to over- or under-diagnose ZES. In addition, the widespread use of PPIs can mask and delay diagnosis (9-10), as they interferes with the two tests needed to establish it, that is, the measurement of fasting gastrin levels and the evaluation of acid secretion, given their gastric acid suppressor action lasting up to one week.

Hypergastrinemia can be found in many conditions. (2) Hypo/achlorohydria is the most common cause and is frequently observed in patients with atrophic gastritis and chronic pernicious anemia and in whom fasting gastrin levels have been reported even <70 times their normal value or >1000 ng/L. (6)

Shah *et al.* (11) reported the possibility of rapidly developing acid peptic complications associated with ZES by suspending PPIs for at least one week; for this reason, Ito et al. (5) proposed that PPI treatment should be maintained at a lower dose. (6)

The diagnosis of ZES is achieved if the patient has gastrin levels >10 times its normal value or >1000 pg/mL with a gastric pH <2, or fasting gastrin >10 times its normal value with gastric pH <2 and a positive secretin stimulation test. (11,12)

Secretin stimulates the release of gastrin by gastrinoma cells and ZES patients have a significant increase in serum gastrin. In contrast, normal gastric G-cells are inhibited by secretin. A stimulation test with positive secretin in doubtful cases has a sensitivity of 94% and specificity of 100%; however, if the patient is taking PPIs, false positives could be obtained in 15-39% of the cases (12) and false negatives in 6-20%. (13)

This test may also be used to differentiate gastrinomas from other causes of hypergastrinemia, such as atrophic gastritis, kidney failure, or vagotomy. (3) The secretin stimulation test is performed by administering 0.4µg/kg secretin by rapid intravenous infusion for a minute; basal serum gastrin is measured twice before secretin administration and 2, 5, 10, and 30 minutes later. Serum gastrin usually reaches its maximum levels at 10 minutes. Several criteria have been proposed to define a positive test and the most accepted is an increase in gastrin levels of more than 120pg/mL above baseline fasting levels. (14)

On the other hand, 40-90% of gastrinomas are duodenal, both in patients with and without MEN1, and are often so small that they are not clearly seen by imaging tools. They are rarely found in other intra-abdominal sites including lymph nodes, stomach, mesentery, renal capsule, splenic hilum, omentum, ovary, liver, and bile ducts, and may be rarely found in an extra-abdominal location, such as the heart and the lungs. (5) Their location is crucial for surgical management of the organ, active surveillance or modern ablative methods. About 75-90% of gastrinomas are detected in the gastrinoma triangle. (8)

CT and nuclear magnetic resonance with contrast are the most widely used imaging studies; these tools detect 30-50% of primary gastrinomas of 1-2cm; however, their detection rate is low in lesions of size <1cm. Endoscopic ultrasonography has a high spatial resolution, so it is recommended as the method of choice for the detection of very small pancreatic tumors <7mm of diameter. (2,15)

PPIs are the drugs of choice due to their potency and prolonged action, allowing doses of once or twice a day. Intravenous PPIs are the drugs of choice when oral administration cannot be used. RH2 antagonists are also effective, but higher doses and frequencies are required. (5)

Long-term PPI treatment is well tolerated, with <0.1% side effects. Long-term effects of hypoachlorhydria include malabsorption of nutrients and the development of gastric carcinoids by hyperplasia of enterochromaffin cells (EC) of the gastric mucosa. (5)

In patients with sporadic ZES, curative surgery should be attempted if there is no disease that compromises life expectancy or increases surgical risk. The immediate post-operative survival rate is 50-60% and long-term survival rate is 35-40%. (5)

Considering the need for a complete exploration of the abdomen, especially the gastrino-

ma triangle area, the laparoscopic route is not recommended; however, it may be performed in selected cases, such as patients with localized distal pancreatic gastrinoma. (5)

ZES is a disease with a high morbidity and a survival rate of only 50%. The survival of patients, even with active tumors, is >25 years. (16) Between 60 and 90% of gastrinomas are associated with metastasis. Liver metastases are more frequent in patients with pancreatic gastrinomas, and their 10-year survival rate is 15-25%, being one of the most important prognostic factors. Lymph node metastases occur in 43-82% of patients, although lymphadenectomy is routinely recommended in patients with gastrinomas to improve prognosis, prolong recurrence time, and increase survival rates. Metastatic lymphadenopathy has not been shown to have a significant impact on survival. (4)

This case report corresponds to a patient with epidemiological and clinical characteristics frequently reported in the literature, but even so, this is a clinical case that contributes to scientific knowledge as it proposes considering ZES in the differential diagnosis of patients between 20 and 50 years of age who go to the emergency department due to chronic epigastric pain.

CONCLUSIONS

The ZES is a rare entity that requires high clinical suspicion to achieve diagnosis and allow an adequate treatment. Medical therapy is the standard management for patients with this syndrome and the first line of treatment is PPIs at high doses due to their potency and prolonged action. In patients with sporadic ZES without metastases, curative surgery should be attempted, whereas surgical management is not routinely recommended for patients with ZES associated with MEN1, as the multifocal nature of the tumors in this disorder prevents the healing of gastric hypersecretion.

This case report is highly relevant as it presents a confirmed diagnosis in the Colombian environment of a very rare disease, highlighting the importance of producing local scientific literature to improve its diagnosis and treatment. Therefore, it is proposed to consider ZES in the differential diagnosis of patients aged 20 to 50 years who go to the emergency department due to chronic epigastric pain.

The patient received a successful surgical management and achieved a satisfactory early recovery; however, since she was transferred to another institution for administrative reasons, it was not possible to follow her case during hospital stay and long-term medical evolution is unknown.

CONFLICT OF INTEREST

None stated by the authors.

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REFERENCES

1. **Epelboym I, Mazeh H.** Zollinger-Ellison Syndrome: Classical Considerations and Current Controversies. *Oncologist.* 2014;19(1):44-50. http://doi.org/cxsp.
2. **Metz DC.** Diagnosis of the Zollinger-Ellison Syndrome. *Clin Gastroenterol Hepatol.* 2012;10(2):126-30. http://doi.org/fj7bjd.
3. **Lenhart A, Hassan M, Meighani A, Sadiq O, Siddiqui Y.** A Perplexing Case of Abdominal Pain That Led to the Diagnosis of Zollinger-Ellison Syndrome. *Case Rep Gastrointest Med.* 2017;2017: 636952. http://doi.org/f9vq9c.

4. **Rindi G, Arnold R, Bosman FT.** Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman TF, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: International Agency for Research on cancer; 2010. p. 13
5. **Ito T, Igarashia H, Jensen RT.** Zollinger–Ellison syndrome: recent advances and controversies. Curr Opin Gastroenterol. 2013;29(6):650-61. http://doi.org/cxsq.
6. **Ito T, Cadiot G, Jensen RT.** Diagnosis of Zollinger-Ellison syndrome: Increasingly difficult. World J Gastroenterol. *2012;18(39):5495–503. http://doi.org/cxsr.*
7. **Roy PK, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL,** *et al.* Zollinger-Ellison syndrome. Clinical presentation in 261 patients. *Medicine (Baltimore).* 2000;79(6):379-411. http://doi.org/cd3tzg.
8. **Berna MJ, Hoffmann KM, Long SH, Serrano J, Gibril F, Jensen RT.** Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the national institutes of health and comparison with 537 cases from the literature. Evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine (Blatimore).* 2006;85(6):331-64. http://doi.org/bzhkdm.
9. **Rehfeld JF, Gingras MH, Bardram L, Hilsted L, Goetze JP, Poitras P.** The Zollinger-Ellison syndrome and Mismeasurement of gastrin. *Gastroenterology*. 2011;140(5):1444-53. http://doi.org/fcb5s9.
10. **Berna MJ, Hoffmann KM, Serrano J, Gibril F, Jensen RT.** Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the national institutes of health and comparison with 2229 cases from the literature. *Medicine (Baltimore).* 2006;85(6):295-330. http://doi.org/c3fg28.
11. **Shah P, Singh MH, Yang YX, Metz DC.** Hypochlorhydria and achlorhydria are associated with false-positive secretin stimulation testing for zollinger-ellison syndrome. *Pancreas*. 2013;42(6):932-6. http://doi.org/f4989c.
12. **Kuiper P, Biemond I, Masclee AA, Jansen JB, Verspaget HW, Lamers CB.** Diagnostic efficacy of the secretin stimulation test for the Zollinger-Ellison Syndrome: An intra-individual comparison using different dosages in patients and controls. *Pancreatology*. 2010;10(1):14-8. http://doi.org/bdv5w6.
13. **Singh-Ospina N, Donegan D, Rodriguez-Gutierrez R, Al-Hilli Z, Young WF.** Assessing for Multiple Endocrine Neoplasia Type 1 in Patients Evaluated for Zollinger-Ellison Syndrome-Clues to a Safer Diagnostic Process. *Am J Med.* 2017;130(5):603-5. http://doi.org/gbgqww.
14. **Poitras P, Gingras MH, Rehfeld JF.** The Zollinger-Ellison Syndrome: Dangers and Consequences of Interrupting Antisecretory Treatment. *Clin Gastroenterol Hepatol.* 2012;10(2):199-202. http://doi.org/bf4f2q.
15. **Braden B, Jenssen C, D'Onofrio M, Hocke M, Will U, Möller K,** *et al.* B-mode and contrast-enhancement characteristics of small nonincidental neuroendocrine pancreatic tumors. *Endosc Ultrasound.* 2017;6(1):49-54. http://doi.org/f9q7x7.
16. **Smallfield GB, Allison J, Wilcox CM.** Prospective evaluation of quality of life in patients with zollinger-ellison syndrome. Dig Dis Sci. 2010;55(11):3108-12. http://doi.org/cfc76h.