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Clinical and Surgical Management of Zollinger-Ellison Syndrome: A Literature Review

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ABSTRACT

Zollinger-Ellison Syndrome is a rare disease caused by tumors called "Gastrinomas", causing high levels of gastrin that produces acid hypersecretion and even gastric ulcers. We present a 20-year-old patient with a 2-month history of pain in the epigastrium accompanied by nausea, vomiting, and weight loss with a history of upper gastrointestinal bleeding from a duodenal ulcer, which on physical examination revealed a tumor in the epigastrium. Contrast-enhanced abdominal CT showed a tumor mass in the tail of the pancreas. She underwent surgery, performing a corporocaudal pancreatectomy and splenectomy, with favorable post-surgical evolution. The anatomopathological study reports pancreatic gastrinoma.

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INTRODUCTION

Zollinger-Ellison Syndrome, described in 1955 by Zollinger and Ellison, is a disease caused by single or multiple gastrin-producing tumors called "Gastrinomas", which are generally located in the head of the pancreas and in the upper part of the small intestine.[1]

It is classified as sporadic and not familial (70-80%) and genetic (20-30%), familial or not, but associated with other tumors such as pituitary or parathyroid, integrating Multiple Endocrine Neoplasia Syndrome type 1 (MEN1) and multiple carcinoids. gastric. The sporadic one is usually due to a solitary, large (greater than 2 cm) and malignant pancreatic gastrinoma, or a benign extrapancreatic gastrinoma, while the genetic one (MEN-1) appears in young people and is usually due to small, multiple duodenal gastrinomas. and benign. It manifests preferentially between the third and fifth decades of life, with a somewhat higher frequency in males, causing elevated levels of serum gastrin that produces acid hypersecretion leading to peptic ulcers, diarrhea, esophagitis, duodenojejunitis, or dyspepsia. [2]

These neoplasms can be subdivided into the following types:

Sporadic Gastrinoma

Patients with Zollinger-Ellison syndrome have a 5-year overall survival ranging from 62 to 75%, 10-year survival is 50%. At diagnosis, some patients will have very small tumors and others will have advanced tumors with lymphatic metastases in up to 40% of cases, which, together with liver metastases, influence survival. Surgery has the ability to alter the natural history of Zollinger-Ellison syndrome. When gastrinomas are resected, patients have a 10-year survival of 60–100%; when the tumor is metastatic, or resection is not possible, 5-year survival is only 40%.[3]

Multiple Endocrine Neoplasia Type 1-Associated Gastrinoma

In Zollinger-Ellison syndrome associated with multiple endocrine neoplasia type 1, 10-year survival averages 83%, compared with sporadic syndrome in which survival to 10 years is from 40 to 65%, with an average of 50%. Survival in patients with the association of both diseases is 90 to 96% at five years, at 10 years it is 75 to 95% and at 20 years it is 58 to 90%. Mortality in these patients is due to the fact that the tumor becomes malignant and develops metastasis in 10% of cases of sporadic gastrinomas and in 45 to 85% of gastrinomas associated with multiple endocrine neoplasia type 1. The most important causes of mortality in Zollinger-Ellison syndrome are complications of hypergastrinemia, such as gastrointestinal bleeding, ulcer perforation, esophageal stricture, and severe malnutrition. [4]

The most important factor determining survival in patients with gastrinomas associated with type 1 multiple endocrine neoplasia is the development of liver metastases, which have a very aggressive behavior compared to lymphatic metastases, which have a more benign behavior. Finally, it has been shown that gastrinomas can have very aggressive behaviors in their presentation or they can behave like benign or slightly aggressive tumors. In multiple endocrine neoplasia type 1, only 14% of tumors have aggressive behavior, compared to 24% of tumors in sporadic Zollinger-Ellison syndrome[4]

CLINICAL PRESENTATION

Sporadic Gastrinoma

Zollinger-Ellison syndrome presents usually in the fifth decade of life; It can do so from childhood to old age, but 90% of cases are diagnosed between 20 and 60 years of age. The current symptoms of Zollinger-Ellison syndrome are not exactly what was originally described. The change is due to the relatively earlier diagnosis of this disease and the indiscriminate use of proton pump inhibitors. The classic description of Zollinger and Ellison included the triad of persistent gastric acid hypersecretion, development of multiple peptic ulcers in unusual locations, such as the second or third portion of the duodenum and proximal jejunum, or recurrent ulcers and non-cell pancreatic tumors. [5]

Currently, the presenting symptoms of Zollinger-Ellison syndrome include diarrhea (71-80%), epigastric pain (65-83%), gastroesophageal reflux, and its complications, such as esophagitis (6-13%) nausea, malnutrition and weight loss. Diarrhea is possibly the most common form of presentation and is described in up to 80% of cases. Due to the non-specific nature of these symptoms, the correct diagnosis of Zollinger-Ellison syndrome, even today, is not early. The most common initial diagnosis in this disease is idiopathic peptic ulcer, in 75% of cases, and diarrheal syndrome, in 20%. The average time to reach the correct diagnosis from the onset of symptoms is 5.9 to 6.4 years 6-8. [6,7]

This average time has remained constant over the last 30 years, however, the current use of proton pump inhibitors, which produce effective suppression of gastric acid secretion, could further delay correct diagnosis. Due to the continuous delay in diagnosis, some recommendations have been proposed and some factors have been identified that, when present, should arouse suspicion of the syndrome. In general, Zollinger-Ellison syndrome should be suspected in any patient presenting with a Helicobacter pylori-negative, refractory peptic ulcer in unusual locations, or in those with endocrine disease, such as hyperparathyroidism or multiple endocrine neoplasia. [8,9]

Multiple Endocrine Neoplasia Type 1-Associated Gastrinoma

Patients with multiple endocrine neoplasia type 1 develop Zollinger-Ellison syndrome at a younger age than those with the sporadic form; the average age of presentation varies between 33 and 39 years. The clinical presentation of multiple endocrine neoplasia type 1 is similar to that of sporadic Zollinger-Ellison syndrome, with diarrhea being the most frequent symptom (66 to 76%), in addition to epigastric pain, heartburn, nausea, vomiting, and weight loss; the main difference is found in the presence of hypercalcemia and nephrolithiasis (47%) caused by hyperparathyroidism. [10]

Even though the high frequency of Zollinger-Ellison syndrome in cases of type 1 multiple endocrine neoplasia is known, the diagnosis in these patients is also not it is precocious. The correct initial diagnosis in the latter is 5%. The period of delay in its diagnosis is similar to that which occurs in sporadic Zollinger-Ellison syndrome (5.5 years). [11]

Diagnostic Algorithm

The diagnosis of Zollinger-Ellison syndrome requires the demonstration of fasting hypergastrinemia associated with hyperchlorhydria 20. Associated with these criteria are other clinical, laboratory, and radiological findings 7-20. The diagnostic study should begin with a fasting serum sample for gastrin at least 72 hours after stopping antisecretory treatment. If the baseline gastrin value is normal, the test is considered negative. When the gastrin value is elevated, gastric acid secretion can be measured, which could be optional. [12]

A secretin stimulation test should then be done; if the serum gastrin value is greater than 200 pg/ml, the patient is considered to have a gastrinoma; some authors consider this test positive with a serum gastrin value greater than 110 pg/ml. When the biochemical diagnosis of gastrinoma is confirmed, radiological studies continue to locate the tumor. Finally, in all patients with Zollinger-Ellison syndrome, multiple endocrine neoplasia type 1 should be studied and ruled out. [13]

When no tumors are identified in the preoperative study in patients with a biochemical diagnosis of gastrinoma, they should undergo surgical exploration in search of the tumor, because in up to 90% of these cases it is possible to find the gastrinoma.[14]

MEDICAL TREATMENT

The goal of medical treatment is to control gastric acid hypersecretion.

Proton pump inhibitors are the first-line treatment, due to both their prolonged action and their potency. They are used in doses once to twice daily in most patients with Zollinger-Ellison syndrome. All drugs in this class (Omeprazole, Lansoprazole, Pantoprazole, Esomeprazole, and Rabeprazole) are effective. [15,16]

Additionally, histamine H2 receptor antagonists are also an option; however, they usually require higher doses than conventional ones. For most patients, it is usually started with doses of proton pump inhibitors equivalent to 60 milligrams per day (mg/day) of omeprazole. This with the aim of suppressing gastric acid hypersecretion, thus allowing ulcer healing and preventing their recurrence. [17]

Standard chemotherapy treatments have produced limited responses and significant toxicity. Somatostatin analogues control symptoms in some cases, but have not yet been shown to have antitumor activity; In addition, treatment with octreotide, which inhibits the release of gastrin, often produces unpredictable clinical responses, which is why it is not considered the first line of treatment. [18]

Targeted therapies have recently been introduced including: Sunitinib (a tyrosine kinase inhibitor) and Everolimus (an mTOR inhibitor); they provide new therapeutic possibilities for patients with advanced or metastatic disease.These drugs directly attack pathways of tumor cell proliferation and angiogenesis; however, they are currently in Phase III clinical trials. [19]

The usual dose to achieve this goal is 40 to 60 mg every 12 hours and, in some cases, doses up to 180 mg on day 20 can be used. Adequate control of gastric acid hypersecretion is confirmed by gastric pH measurement, which should be greater than 4 when the dose is adequate, also, hydrochloric acid secretion can be measured, which should be less than 10 mEq/hour during the last hour before the next dose of pump inhibitors. Numerous studies have shown that long-term treatment with proton pump inhibitors is safe and should be accompanied by supplementation with folic acid and vitamin B12. [20]

It is important to be aware that patients can develop complications secondary to gastric hypersecretion very quickly; consequently, the role of medical treatment in Zollinger-Ellison syndrome should be to prevent possible complications, and to stabilize and maintain the patient with minimal symptoms during the study and definitive diagnosis until the time of surgery. [21]

SURGICAL TREATMENT

The surgical treatment of gastrinomas has evolved from total gastrectomy to specific tumor surgery. Its main objective is to achieve cure or control of the tumor, and to prevent its spread and metastasis. Even with all the diagnostic technology currently available, the preoperative localization of gastrinomas does not reach 100% of the cases and, for this reason, only adequate surgical exploration has the potential to localize 100% of the tumors. [22]

It has been estimated that approximately 60-90% of all gastrinomas are malignant. Tumor progression and the development of metastases are the main determining factors for survival. Consequently, surgery alone offers the patient a 31-50 chance of cure. Routine surgical exploration has been shown and established to increase long-term survival. In 2006, Norton et al., published a study that demonstrated a significant increase in survival in operated patients, with a disease-free survival of 98% at 15 years, compared with 74% survival in those who did not operate. This study and others confirm the need for routine surgical exploration in these patients. [23]

Indications for surgery in sporadic Zollinger-Ellison syndrome All patients with a laboratory diagnosis of sporadic Zollinger-Ellison syndrome have an indication for surgical exploration because up to 30% of gastrinomas are not diagnosed by radiological studies. Although most gastrinomas grow very slowly, 60-90% are malignant, and of these, 25% grow very quickly. [23]

The incidence of lymphatic metastases in duodenal gastrinomas has been reported in up to 40% of cases; pancreatic gastrinomas have hepatic metastases more frequently. It should be noted that up to 15% of gastrinomas not identified on radiological studies are also not identified during surgical exploration. Surgery can achieve definitive cure of gastrinoma in 51–60% of cases in the immediate postoperative period, in 40% of cases at 5 years, and in 34% of cases 10 years postoperatively. [23]

STANDARD SURGICAL TECHNIQUE

The abdomen is approached through a bilateral subcostal laparotomy with an extended Kocher maneuver, exploring the abdominal cavity with special emphasis on the liver, stomach, duodenum, small intestine, mesentery, pancreas, pelvis, and retroperitoneal regions of the upper abdomen. in addition to careful palpation of the duodenum, the head of the pancreas and the uncinate process, trying to identify nodules. [23]

Then proceed to the opening of the gastrocolic ligament and the mobilization of the splenic flexure of the colon, to achieve adequate mobilization of the body and tail of the pancreas to allow bimanual palpation of the organ. Intraoperative ultrasound is useful in identifying small pancreatic nodules and can locate tumors up to 5 mm in diameter. [24]

The duodenum is transilluminated by endoscopy, which also makes it possible to identify submucosal tumors. Tumors of the head of the pancreas must be enucleated or treated by pancreaticoduodenectomy; injuries to the body and tail can be treated by enucleation or distal pancreatectomy. A 3 cm long longitudinal lateral duodenotomy should be performed at the junction of the first and second portions of the duodenum, because it is the most effective method for identifying duodenal lesions by inspection and palpation.[24]

The duodenotomy can be extended proximally and distally; this incision makes it possible to identify all suspicious nodules by palpation. Finally, regional lymphadenectomy of all lymph nodes in the triangle of the gastrinoma should be carried out.Some authors recommend routine measurement of serum gastrin during surgery and before laparotomy closure.[25]

TREATMENT OF METASTATIC DISEASE

Treatment options for liver metastases include surgical resection, radiofrequency ablation, hepatic artery embolism and chemoembolism, liver transplantation, chemotherapy, biotherapy, and radiolabeled somatostatin therapy. Surgical resection of metastases improves patient survival at 5 years

in 70 to 100% of cases. Poor prognostic factors in these cases are age over 50 years and the presence of multiple metastases in both lobes.[26]

CONCLUSIONS

Zollinger-Ellison syndrome is a rare disease, characterized by the presence of acid hypersecretion, gastric-duodenal ulcer disease, and a gastrin-secreting pancreatic or extrapancreatic tumor with difficult primary location. The therapy is initially long-term medical to reduce exposure to acid (high-dose proton pump inhibitors) and surgical treatment is relegated in possible cases when it does not improve with medical treatment, because it is controversial.

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