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An Unusual Presentation of Zollinger-Ellison Syndrome

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Key Words

Zollinger-Ellison syndrome · Esophageal strictures · Octreoscan · Positron emission tomography

Abstract

Zollinger-Ellison syndrome is an often progressive, persistent and frequently life-threatening disease, described for the first time as characterized by ulceration of the upper jejunum, hypersecretion of gastric acid and non-beta islet cell tumors of the pancreas; this syndrome is due to the hypersecretion of gastrin. We report a case of Zollinger-Ellison syndrome presenting as severe esophagitis evolving in stenosis, which demonstrates how a delayed diagnosis may induce risk of disease spreading. In this setting new diagnostic approaches, such as somatostatin receptor scanning and positron emission tomography with ⁶⁸Ga-labeled octreotide, could be particularly useful, as well as further new therapeutic options, such as molecular targeted treatments and peptide receptor radionuclide therapy, though surgery is currently the only form of curative treatment, and the role of the therapeutic options mentioned needs to be clarified by forthcoming studies.

Introduction

Zollinger-Ellison syndrome (ZES) is an often progressive, persistent and frequently life-threatening disease, described for the first time as characterized by ulceration of the upper jejunum, hypersecretion of gastric acid and non-beta islet cell tumors of the pancreas; this syndrome is due to the hypersecretion of gastrin [1] secondary to a gastrinoma. This is a neuroendocrine tumor derived from multipotential stem cells of

endodermal origin. It can be sporadic (in 80% of cases) or associated with multiple endocrine neoplasia type 1 (MEN1). 70% of gastrinomas arise from the duodenum, the remainder from the pancreas or less often from lymph nodes adjacent to the pancreas.

MEN1 is an autosomal dominant inherited syndrome caused by mutations of the *MEN1* tumor suppressor gene on chromosome 11q13 [2]. *MEN1* gene mutations are also identified in 33% of sporadic gastrinomas [3]. MEN1 is characterized by the combined occurrence of primary hyperparathyroidism (>90%), pancreaticoduodenal endocrine neoplasms (65–75%) and tumors of the anterior pituitary gland (30–65%). Pancreaticoduodenal endocrine tumors (PETs) are of outstanding interest because malignant PETs represent the most common cause of death within MEN1 syndrome [4, 5]. This is especially true for gastrinomas, despite effective control of acid hypersecretion and its complications by proton pump inhibitors (PPIs) [6, 7].

The incidence of ZES in the United States initially ranged from 0.1 to 1% of patients with peptic ulcer disease [8], but this percentage may be underestimated because patients with ZES often presented with symptoms similar to those of *Helicobacter pylori*-related disease or to those caused by typical peptic ulcer disease related to nonsteroidal anti-inflammatory drugs. In fact these symptoms may be controlled by a standard dose of PPIs, thus such patients are not tested for hypergastrinemia [8].

ZES is usually diagnosed in the fifth decade of life, and although it may occur in children and adolescents or the elderly, it is diagnosed between the age of 20 and 60 in 90%. The male-to-female ratio ranges between 1.5:1 and 2:1. Over 90% of patient with ZES develop peptic ulcers, often solitary ulcers <1 cm in diameter (75% of ulcers in the first portion of the duodenum, 14% in the distal duodenum and 11% in the jejunum). These ulcers recur much more often than in patients with sporadic ulcer disease. Other prominent clinical features are abdominal pain (75%) and diarrhea (73%), which are the most frequent symptoms, while heartburn and weight loss are reported by 44 and 17% of patients. Gastrointestinal bleeding is the initial presentation in 25% of patients, while nephrocalcinosis and renal colic are more frequent in MEN1 compared with sporadic tumors. Metastatic disease is evident at the time of diagnosis in one third of patients with gastrinoma; the liver is the most common site of metastasis [8].

For the diagnosis of ZES there are three tests: fasting serum gastrin concentration, secretin stimulation test and gastric acid secretion studies. Of these, only the first and the second are used routinely. After the diagnosis of ZES is made, the gastrinoma must be located and staged [8]. We report a case of ZES presenting as severe esophagitis evolving in stenosis, which demonstrates how a delayed diagnosis may induce risk of disease spreading.

Case Report

A 61-year-old woman was admitted to our hospital with a 3-year history of nausea and vomiting not related to food and sometimes associated with watery diarrhea. During the last year she had lost about 20% of her body weight (her previous weight was 78 kg, and at admission to our unit her weight was 64 kg). Because of worsening of these symptoms she was admitted to our unit.

In the previous years the patient had been admitted to other hospitals. Esophagogastro-duodenoscopy had been performed 3 years before, showing a large *H. pylori*-positive bulbar ulcer (treated with eradicator triple therapy) and esophagitis. Abdominal ultrasonography and computed

tomography were performed to exclude intestinal disease. These showed some focal hepatic lesions which were interpreted as angiomyolipomatosis. The patient was discharged from the hospital and treated with PPIs and prokinetics, without any clinical benefit.

On admission to our unit, esophagogastroduodenoscopy showed severe esophagitis with large mucosal ulcerations and an esophageal stenosis ([fig. 1](#)). For this reason gastrin and chromogranin levels were determined, resulting in values over the upper normal limits (>1,490 mU/ml and >540 mU/ml, respectively). ZES was then suspected, so abdominal ultrasonography was performed, showing many hepatic focal lesions with a contrastographic pattern of repetitive lesions.

Octreoscan revealed only many enhancing lesions (somatostatin receptor subtype 2 and 5 positive) in the liver. The serrated esophageal stenosis did not allow us to perform endoscopic ultrasonography to try to find any primary lesions of the pancreas. Abdominal magnetic resonance imaging did not detect pancreatic or intestinal lesions, thus a biopsy of the liver lesion was performed and the histology diagnosed a gastrinoma. The immunohistochemical profile showed 80% cell positivity for gastrin (as shown in [fig. 2](#), with a scale bar of 100 μ m) and chromogranin (as shown in [fig. 3](#), with a scale bar of 100 μ m). In addition, no mutation of the *MEN1* gene was found, so MEN1 was excluded.

For this reason total parenteral nutrition and PPI i.v. were started, obtaining a reduction in the frequency of vomiting and diarrhea. An endoscopic pneumatic dilation of the esophageal stenosis was performed, with an improvement of both dysphagia and esophageal canalization. A further endoscopic ultrasonography was performed to detect primary lesions of the pancreas, but the result was negative. The patient was discharged with a high-dose PPI therapy, with the program to perform periodical esophageal endoscopic dilation and to start chemotherapy with octreotide and receptorial radiotherapy with 1,850 MBq of 90Y-Dotatoc.

Discussion

This case reported shows that severe necrotic esophagitis unresponsive to a standard dosage of PPI may be due to ZES [9]. In the literature few cases of necrotic esophagitis have been described [10–12]. The consequence of a delayed diagnosis may be severe esophageal stricture and metastatic disease [13, 14], like in our patient. High doses of PPI together with endoscopic pneumatic dilation led to resolution of esophageal symptoms.

Little is known about the risk of severe esophagitis in ZES. A prospective study has evaluated esophageal involvement and its complications in ZES [8]. The authors show that this complication is more severe in ZES associated with MEN1 than in sporadic ZES and they also identify important factors for the pathogenesis that need to be incorporated into the long-term treatment. In Jensen's series [8], 10 patients out of 215 (0.4%) with sporadic ZES developed esophageal strictures. Our case was a sporadic ZES which developed strictures. It is possible that the delayed diagnosis was the cause of this complication. A high dosage of PPIs together with endoscopic pneumatic dilation kept the patients asymptomatic.

Though the two major modalities for tumor identification are somatostatin receptor scanning (SRS) and single photon emission computed tomography, particularly useful in identifying liver and bone metastases [15], sometimes the identification of gastrinoma is difficult. When a strong clinical suspicion persists despite negative results, other techniques have been used in the past, including dual phase helical computed tomography, magnetic resonance imaging, angiography, arterial stimulation and venous sampling, and fluorodeoxyglucose-positron emission tomography (FDG-PET) [16]. To date, with the improvement of the knowledge

about the pathophysiology of the disease, further techniques could be used for the detection of both primary tumors and metastases. Multi-detector computed tomography could be performed not only to demonstrate small primary tumors and liver metastases, but also tumor-associated desmoplastic fibrosis around the primary tumor and lymph node metastases. Other new approaches performed to visualize neuroendocrine tumors are ^{11}C - and ^{18}F -labeled L-Dopa PET, which show a higher sensitivity (65%) than FDG-PET (29%) and SRS (57%), but a lower sensitivity than morphologic imaging by computed tomography and magnetic resonance imaging (73%) and by ^{11}C -5-hydroxytryptophan-PET. PET with ^{68}Ga -labeled octreotide (such as ^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC and ^{68}Ga -DOTA-TATE) has also been evaluated in a few published reports, also showing a higher sensitivity than SRS. In selected cases tumor localization can only be achieved through laparotomy by direct palpation, duodenal transillumination or intraoperative ultrasound. The precise role of these new approaches in the treatment algorithm of neuroendocrine tumors will hopefully be clarified by forthcoming studies [17].

Disclosure Statement

The authors declare no conflicts of interest.



Fig. 1. Severe esophagitis with a tight lower esophageal stenosis.

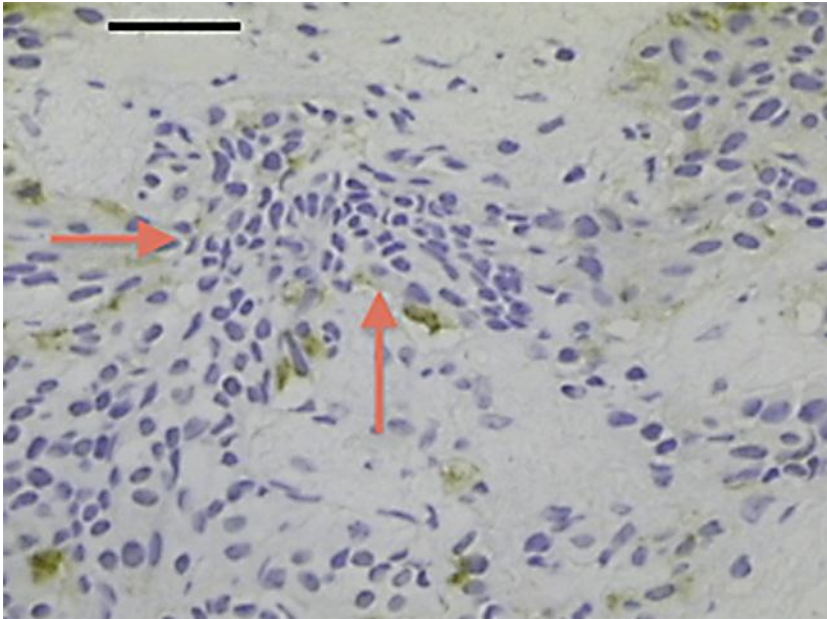


Fig. 2. Liver immunohistochemistry with cell positivity for gastrin (arrows), scale bar = 100 μ m.

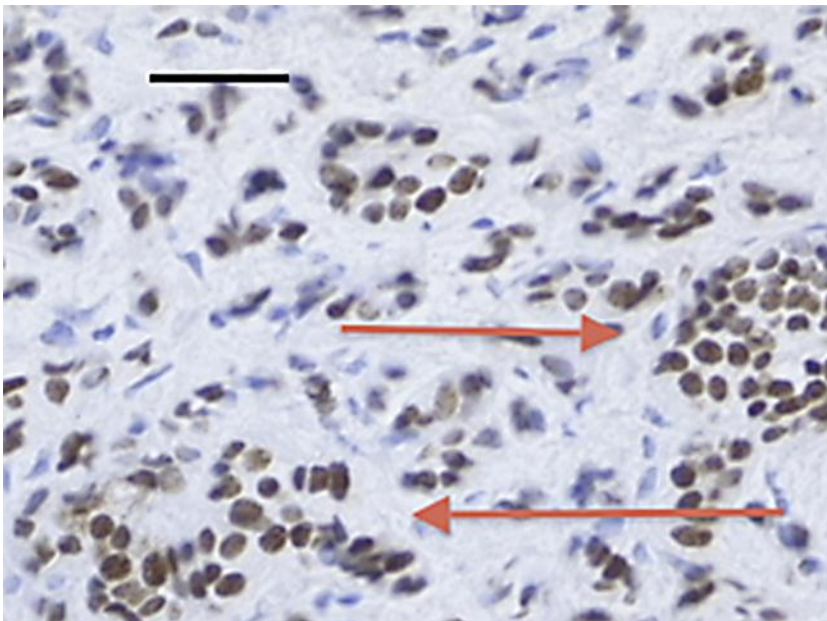


Fig. 3. Liver immunohistochemistry with cell positivity for chromogranin (arrows), scale bar = 100 μ m.

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