กลุ่มอาการโซลลิงเจอร์-เอลลิสัน: สาเหตุที่พบไม่บ่อยแต่ควรคิดถึงเมื่อพบแผลในทางเดินอาหารส่วนต้นร่วมกับมีอุจจาระร่วงเรื้อรัง : รายงานผู้ป่วย

ฐากูร กาญจโนภาส[1], อรุณชัย แซ่ฉั่ง[2*], กีรติ อัครปฏิมา[2], ชีพ เจริญลาภ[3], ทรงกลด ภักดีจิตร[4], อรรถพล รัตนสุภา[2]
[1]*หน่วยงานอายุกรรม โรงพยาบาลหาดใหญ่*
[2]*หน่วยระบบทางเดินอาหาร หน่วยงานอายุกรรม โรงพยาบาลหาดใหญ่*
[3]*หน่วยงานพยาธิวิทยา โรงพยาบาลหาดใหญ่*
[4]*หน่วยรังสีร่วมรักษา หน่วยงานอายุกรรม โรงพยาบาลหาดใหญ่*

Zollinger-Ellison Syndrome: An Uncommon Cause of Peptic Ulcer Disease and Chronic Diarrhea : A Case Report

Thagoon Kanjanopas[1], Arunchai Chang[2*], Keerati Akarapatima[2],
Cheep Charoenlap[3], Songklod Pakdeejit[4], Attapon Rattanasupa[2]
[1]*Department of Internal Medicine, Hatyai Hospital, Songkhla, Thailand*
[2]*Division of Gastroenterology, Department of Internal Medicine, Hatyai Hospital, Songkhla, Thailand*
[3]*Department of Anatomical Pathology, Hatyai Hospital, Songkhla, Thailand*
[4]*Division of Intervention Radiology, Department of Radiology, Hatyai Hospital, Songkhla, Thailand*

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บทคัดย่อ

หลักการและวัตถุประสงค์: กลุ่มอาการโซลลิงเจอร์-เอลลิสัน (Zollinger-Ellison syndrome; ZE syndrome) เป็นภาวะที่พบได้น้อยที่เกิดจากโรคเนื้องอกกลุ่ม neuroendocrine tumor ชนิด แกสตรินโนมา (gastrinoma) ซึ่งหลั่งฮอร์โมนแกสตรินออกมามากเกินผิดปกติ ผู้ป่วยมักมาด้วยอาการสำคัญคือแผลในทางเดินอาหารส่วนต้นร่วมกับอุจจาระร่วงเรื้อรัง

วิธีการศึกษา: เป็นรายงานผู้ป่วย (case report study) โดยนำข้อมูลกรณีศึกษาจากเวชระเบียนผู้ป่วยในระบบฐานข้อมูลคอมพิวเตอร์ในหอผู้ป่วยอายุรกรรม โรงพยาบาลหาดใหญ่

ผลการศึกษา: ผู้ป่วยหญิงอายุ 55 ปี 1 ราย มาด้วยอาการปวดท้องเป็นๆ หายๆ ร่วมกับอุจจาระร่วงเรื้อรัง ผลการส่องกล้องทางเดินอาหารส่วนต้นพบติ่งเนื้อขนาดเล็กในกระเพาะอาหารจำนวนมากร่วมกับแผลในลำไส้เล็กดูโอดีนัมบริเวณ post-bulbar area จำนวนมาก ผลการตรวจด้วยคลื่นแม่เหล็กไฟฟ้าพบก้อนเนื้อในบริเวณสามเหลี่ยมแกสตริโนมา (gastrinoma triangle) ร่วมกับมีแพร่กระจายบริเวณตับ ผู้ป่วยได้รับการยืนยันวินิจฉัยทางจุลพยาธิวิทยาว่าเป็นแกสตริโนมาระยะลุกลามและตอบสนองดีต่อการรักษาตามอาการอย่างเหมาะสม

สรุป: กรณีศึกษาผู้ป่วยรายนี้แสดงให้เห็นถึงความสำคัญทางคลินิกถึงกลุ่มอาการโซลลิงเจอร์-เอลลิสัน โดยผู้ป่วยมักมีแผลในทางเดินอาหารส่วนต้นร่วมกับอุจจาระร่วงเรื้อรังเพื่อนำไปสู่การวินิจฉัยและการรักษาที่เหมาะสม

คำสำคัญ: กลุ่มอาการโซลลิงเจอร์-เอลลิสัน, แกสตริโนมา, อุจจาระร่วงเรื้อรัง, แผลในทางเดินอาหารส่วนต้น, กลุ่มอาการเนื้องอกของต่อมไร้ท่อ ชนิดที่ 1

Abstract

Background and Objective: Zollinger-Ellison syndrome (ZES) is an extremely rare condition caused by a neuroendocrine tumor, namely gastrinoma, associated with gastric acid overproduction. The typical presentations include recurrent peptic ulcers accompanied by chronic diarrhea.

Method: We present a case report using the information extracted from medical records at Hatyai Hospital.

Results: A 55-year-old woman presented with intermittent epigastric pain and chronic diarrhea. Upper endoscopy revealed multiple small gastric polyps accompanied by multiple ulcers in the postbulbar region. Magnetic resonance imaging showed a hypervascular tumor located in the gastrinoma triangle with liver metastasis. The condition was diagnosed as an aggressive gastrinoma based on the histopathology. The patient's symptoms responded well to supportive treatment.

Conclusion: The present case emphasizes the importance of having high clinical suspicion of ZES, especially in patients presenting with peptic ulcer disease and chronic diarrhea, which may help in the early diagnosis of the patient and provide appropriate treatment.

Keywords: Zollinger-Ellison syndrome, gastrinoma, chronic diarrhea, peptic ulcer disease, multiple endocrine neoplasia-type 1

*Corresponding author: Arunchai Chang E-mail: busmdcu58@gmail.com

Introduction

Zollinger-Ellison syndrome (ZES) is a rare entity caused by the hypersecretion of gastrin produced by duodenal or pancreatic neuroendocrine tumors (NETs), namely gastrinoma. High gastrin levels trigger the overproduction of gastric acid, resulting in the classic manifestation of recurrent peptic-related diseases and chronic diarrhea. We present a case of intermittent epigastric pain and chronic diarrhea that was subsequently diagnosed as ZES secondary to malignant gastrinoma.

Case Presentation

A 55-year-old woman presented with chronic intermittent epigastric pain and diarrhea over a 2-month period. Her comorbid conditions included dyslipidemia and hypertension, which were well-controlled by lifestyle modifications. There was no history of nonsteroidal anti-inflammatory drug (NSAIDs) usage. The patient experienced chronic epigastric pain and had undergone esophagogastroduodenoscopy and colonoscopy three years previously, which were unremarkable. Her symptoms partially responded to omeprazole and mebeverine; however, she was subsequently lost to follow-up. Her father had a history of hypertension but was otherwise healthy. The patient's mother and younger brother were healthy.

Physical examination of the patient was unremarkable, except for the pale conjunctivae. The hemoglobin level of the patient was reduced (9.7 g/dL). Her biochemical laboratory results and chest radiographs were otherwise normal. The HIV antibody test results were negative. Notably, stool tests for ova, parasites, fats, *Clostridium difficile*, and cultures for enteric pathogens were negative.

Endoscopic examination revealed an enlarged gastric fold with multiple small gastric polyps in the gastric fundus and body. Multiple small clean-based ulcers were present in the second and third duodenal sections (Figure 1). Histologically, fundic gland polyps were detected without evidence of *Helicobacter pylori (H. pylori)* infection or malignancy, and a rapid urease test was negative for *H. pylori* activity. Magnetic resonance imaging (MRI) of the whole abdomen revealed a mildly lobulated, well-defined mass between the duodenum, and the superior aspect of the pancreatic head (2.6 cm × 2.1 cm) with enhancement on the arterial phase and washout on the porto-venous phase. Multiple liver masses (0.8–1.8 cm) were observed with arterial enhancement and washout in the portal and delayed phases, with increased rugal folds and mild gastric wall thickening (Figure 2).

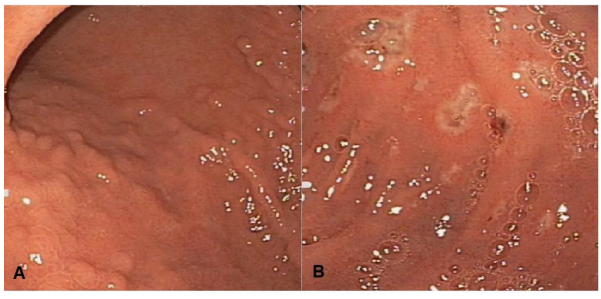

Figure 1 Upper endoscopy images demonstrate (A) multiple small polyps located in the gastric region; (B) multiple small clean base duodenal ulcers in the third sections of the duodenum.

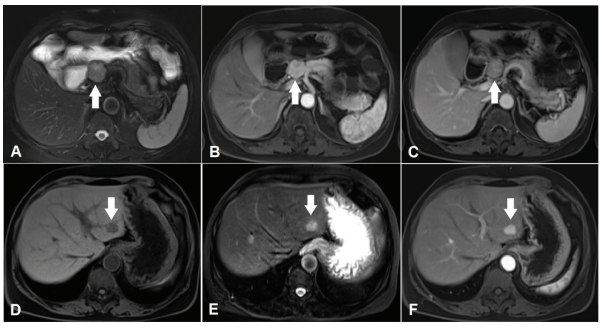

Figure 2 Magnetic resonance images of the whole abdomen, axial T2-weighted (A) fat-suppressed images, axial arterial phase, (B) and PVP (C) T1-weighted fat-suppressed image demonstrates a mildly lobulated, slightly hyperintense mass (arrow) epicentered between the duodenum and superior aspect of the pancreatic head. The mass exhibits enhancement on the arterial phase and washout on the portovenous phase. Axial T1-weighted (D), T2-weighted (E), fat-suppressed image and axial arterial phase T1-weighted image (F), and hyperintense liver mass (arrow) with arterial enhancement. Increased gastric rugal folds and mild gastric wall thickening was noted.

A hepatic lesion specimen was obtained via ultrasound-guided percutaneous liver biopsy. Pathological results revealed nests and glandular patterns of uniform polygonal shaped tumor cells containing bland nuclei, fine nuclear chromatin, and abundant pale pink granular cytoplasm. No mitotic figure or tumor necrosis was observed. The tumor cells demonstrated diffuse, moderate-to-strong granular immunoreactivity for chromogranin, gastrin, synaptophysin, and AE1/AE3. The majority of cells demonstrated moderate membrane immunoreactivity for CD56, with a Ki-67 proliferative index of 1 (Figure 3). The histological and immunohistochemical findings were consistent with those of grade 1 well-differentiated NET. The serum gastrin level was significantly

elevated (2253 ng/L; reference range: 13–115 ng/L) 4 weeks after the discontinuation of proton pump inhibitors (PPIs). Investigations for multiple endocrine neoplasia-type 1 (MEN1), including serum calcium, parathyroid hormone, prolactin level, morning cortisol, thyroid function test, and brain MRI, including the pituitary were unremarkable.

The patient was diagnosed with ZES secondary to aggressive gastrinoma. Systemic chemotherapy or targeted therapy, sunitinib, and interval MRI were proposed, but were not administered because the patient did not consent. Clinical epigastric pain and diarrhea were well controlled with high-dose omeprazole (80 mg/day) and loperamide, and her hemoglobin level was stable during the 3-year follow-up.

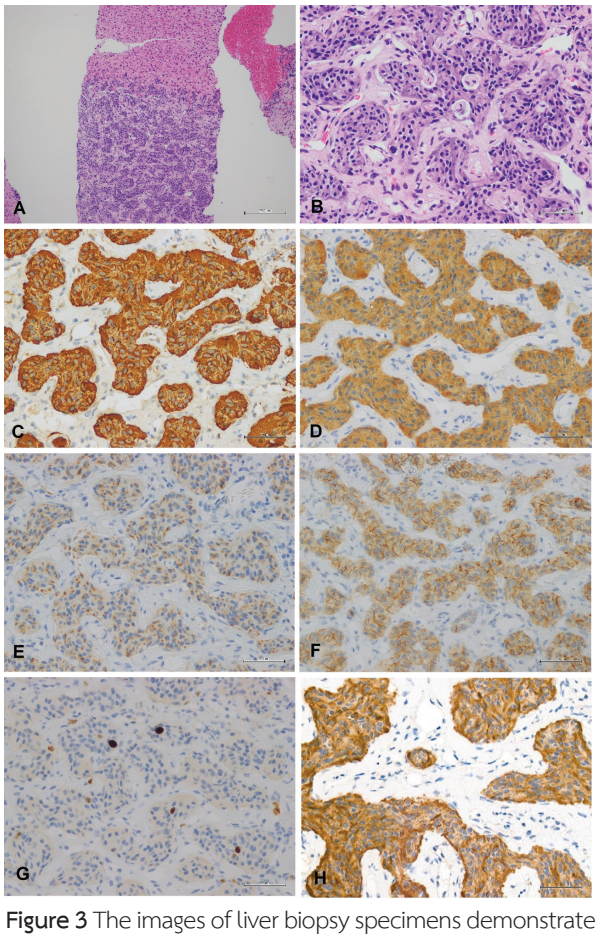

Figure 3 The images of liver biopsy specimens demonstrate (A) nests and glandular patterns of uniform polygonal shaped tumor cells; (B) Tumor cells displaying bland nuclei, fine nuclear chromatin, and abundant pale-pink granular cytoplasm, mitotic count = 0/10 HPF, without identifiable tumor necrosis; (C) diffuse, strong granular immunoreactivity for chromogranin in the cytoplasm of tumor cells; (D, E) diffuse, moderate granular immunoreactivity for synaptophysin, and AE1/AE3 in the cytoplasm of tumor cells; (F) diffuse, moderate membrane immunoreactivity for CD56 in the tumor cells; (G) Ki67 proliferative index was 1% in tumor cells; and (H) diffuse strong granular immunoreactivity for gastrin in the cytoplasm of tumor cells.

Discussion

ZES was first described in 1955 by Zollinger and Ellison in a report of two patients with severe refractory peptic ulcer disease. They proposed a diagnostic triad of unusual primary site peptic ulcers, gastric acid hypersecretion, and the presence of pancreatic non-specific islet cell tumors[1]. Gastrin was identified as an essential hormone in the pathogenesis of ZES in the 1960s[2] and binds to the cell surface receptors on gastric parietal and chief cells, stimulating HCl production via two mechanisms:1) histamine production from enterochromaffin-like (ECL) cells and 2) direct parietal cell stimulation[3]. The terms gastrinoma and ZES were used interchangeably. However, gastrinoma is more specifically a pathological term describing any tumor containing gastrin determined by immunohistochemistry, whereas ZES is more descriptive of the clinical syndrome of peptic ulcer disease and chronic diarrhea resulting from the hypersecretion of gastric acid.

Gastrinoma is a rare entity, occurring in less than one case per million per year, with a mean age of 41–54 years and a male/female ratio of 1.3–1.5:1[4-6]. MEN1, an autosomal dominant inherited disease, is the cause of ZES in 20–30% of cases; hence, it is advisable to screen for MEN1 in cases of suspected gastrinoma[7,8]. In our patient, the blood chemistry of the parathyroid hormone and prolactin hormone was unremarkable. Therefore, we diagnosed a sporadic case of gastrinoma with liver metastasis.

Roy et al.[5] reported 261 cases of ZES; abdominal pain and diarrhea were the most common clinical manifestations; both symptoms were observed in 75% of the patients. Non-specific symptoms suggestive of ZES included the recurrence/persistence of ulcer-like symptoms refractory to medication and complications of peptic ulcer disease[9]. The complications of peptic ulcer disease were less common than those in previous reports (~33%)[10]. Diarrhea in ZES may be caused by the osmotic load from gastric secretions, interception of sodium and water reabsorption by enterocytes resulting from high levels of gastrin, and fat maldigestion from pancreatic enzyme inactivation by the enteric acid environment[8,11]. Patients diagnosed with ZES develop diarrhea in up to 72% of cases, and approximately 20% of patients of ZES present with diarrhea alone[9].

Endoscopic findings revealed multiple small fundic gland polyps and multiple ulcers in the duodenum, particularly beyond the duodenal bulb. An association between hypergastrinemia and fundic gland polyps has been established[12,13]. In this patient, the reason for

hypergastrinemia was difficult to ascertain; it may have arisen from gastrinoma, the long-term use of PPIs, or both. The awareness of ZES should be considered in cases of multiple ulcers located in unusual sites and *H. pylori*-or NSAID-negative subjects[1]. Upper endoscopy may be beneficial to exclude secondary complications, such as esophageal stricture and perforation resulting from long-standing acid hypersecretion[8].

The serum fasting gastrin level is an initial screening test for ZES. Gastrin levels exceeding 10 times the upper limit of normal (ULN) and gastric pH <2 were considered as a diagnosis[14]. The gastrin levels may be increased in certain conditions, such as hypo- and achlorhydria, including atrophic gastritis, use of PPIs, hyperchlorhydria, including *H. pylori* infection, pyloric stenosis, renal failure, antral G-cell syndromes, and short bowel syndrome, which may complicate the diagnosis[11]. The fasting gastric pH was not obtained in our case, whereas a significantly elevated fasting gastrin level (>10 times the ULN) and a pathologically confirmed gastrin-stained neuroendocrine tumor confirmed the diagnosis of gastrinoma. The PPIs were discontinued 4 weeks before the measurement of fasting gastrin levels in accordance with expert recommendations to withdraw PPIs 1 week before measuring the fasting gastrin level. However, the discontinuation of PPI therapy is associated with complications, such as esophageal perforations, strictures, and the recurrence of chronic diarrhea[3], which notably did not occur in this patient.

In most patients, the primary tumor usually arises from the area within the gastrinoma triangle, defined by the junction of the neck and body of the pancreas (as the medial border), the junction of the second and third sections of the duodenum (as the inferior border), and the junction of the cystic and common bile ducts (as the superior border)[15]. The epicenter of our patient's tumor was located between the duodenum and superior aspect of the pancreatic head, which was in the middle of the gastrinoma triangle. A tumor size >2 centimeters (cm) with liver metastasis suggests a pancreatic origin; previous studies reported that sporadic duodenal gastrinoma usually originates from the first section of the duodenum and is usually <1 cm in diameter. Sporadic pancreatic gastrinomas mostly have a diameter of ≥2 cm[16]. Generally, more than 50% of gastrinomas are malignant, and hepatic metastases are present in 25 to 50% of patients with ZES at the time of diagnosis[17]. Liver metastases occur more frequently in patients whose tumor originated from the pancreas than in those with a duodenal origin.

Several centers utilize computed tomography (CT) scanning and magnetic resonance imaging (MRI) for the initial imaging of NETs. They detect large tumors (>2.5 cm) with a sensitivity exceeding 70%, but frequently do not detect smaller tumors (<1.5 cm)[18]. Somatostatin receptor scintigraphy has enhanced sensitivity compared to CT and MRI and can detect primary pancreatic tumors even when morphological imaging shows no lesions. Recently, endoscopic ultrasonography (EUS) has played a more prominent role in the detection of tumors because subcentimeter tumors in the pancreas and duodenum can be visualized[19, 20].

Two principal therapeutic objectives in ZES patients are to control the gastric acid hypersecretion and tumor growth[21]. High-dose PPIs remain the standard for the symptomatic treatment of ZES, and the recommended oral starting dose of omeprazole is 60–80 mg/day[22]. The monitoring for vitamin B12 deficiency in patients undergoing long-term PPI treatment is recommended, especially in the elderly and in patients with previous malabsorption[23].

There are also various approaches for the surgical management of patients, depending on the type of ZES. All the patients with sporadic gastrinoma without metastatic disease should be considered for surgical approach as a potential cure[21]. MEN1 associated gastrinomas generally present with multiple small tumors in the duodenum, frequently with positive lymph node metastases. Thus, surgery is recommended for MEN1/ZES patients with larger tumors (>2 cm). Pancreaticoduodenectomy is reserved for specific, selected cases[23, 24]. Hypercalcemia from primary hyperparathyroidism may exacerbate symptoms and, if present, should be managed by resection of the parathyroid before gastrinoma[21]. For patients with liver metastasis at presentation similar to ours, multimodal therapies, including chemotherapy, molecular targeted therapies, hepatic artery embolization, and radiotherapy may be proposed. However, no level 1 data exist regarding their efficacy[8, 19, 21]. Although the patient refused specific therapy, her symptoms were well-controlled with appropriate supportive treatment. The patient was followed up for 2 years and did not show any progression of the disease, which corresponded to a Ki-67 index of 1%, associated with a good survival rate[25].

Conclusion

This case underscores the importance of high clinical suspicion of ZES, particularly if ulcer-like symptoms become persistent or refractory to medication. Endoscopic, laboratory, and histological findings

demonstrated the classical features of the disease and confirmed the diagnosis of aggressive gastrinoma.

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Compliance with ethical standards: The study protocol was reviewed and approved by the institutional review board of Hatyai Hospital (protocol number 62/2563) and complied with the Declaration of Helsinki.

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Consent: Informed consent was obtained from the patient for this case report.

Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this article.

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