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CASE REPORT | STOMACH

Postsurgical Presentation of Zollinger–Ellison Syndrome After Resection of Endometrioid Neuroendocrine Tumor

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ABSTRACT

Zollinger–Ellison syndrome is a functional neuroendocrine tumor with inappropriate gastrin secretion and hyperchlorhydria causing severe peptic ulcer disease and chronic diarrhea. Although 70% of primary gastrinomas occur in the region of the duodenum, the diagnosis and localization of gastrinomas can be challenging because of small lesions that may arise functionally as lymph node metastases at initial presentation. We report a 76-year-old woman presenting with Zollinger–Ellison syndrome several months after surgical resection of endometrioid small cell neuroendocrine carcinoma and endometrioid adenocarcinoma.

INTRODUCTION

The diagnosis of Zollinger–Ellison syndrome (ZE) can be challenging. Common sites for primary gastrinoma include the duodenum and pancreatic/peripancreatic region,[1,2] but there is a paucity of information regarding ZE arising in the context of gynecologic cancer. One case series reported 25 cases of endometrial neuroendocrine tumors, of which 15 were associated with endometrioid adenocarcinoma, and 4 were small cell neuroendocrine tumors mixed with endometrioid adenocarcinoma.[3] Here, we report a case of delayed presentation of gastrinoma in a patient with a coexisting endometrioid small cell neuroendocrine carcinoma and endometrioid adenocarcinoma.

CASE REPORT

A 76-year-old white woman presented initially with heavy vaginal bleeding. Enhanced computerized tomography (CT) scan revealed an enlarged uterus measuring 6.2 × 5.4 cm. The patient underwent uneventful robotic-assisted total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and bilateral sentinel lymph node dissection. Pathological examination revealed stage IB mixed endometrioid adenocarcinoma and small cell neuroendocrine carcinoma. Gastrin immunostaining was negative in all tissue examined (both small cells and endometroid carcinoma). Four cycles of cisplatin 50 mg/m^2 and etoposide 80 mg/m^2 were given as standard chemotherapy for International Federation Of Gynecology And Obstetrics grade 2 endometrial cancer followed by radiation treatment with brachytherapy. International Federation Of Gynecology And Obstetrics Grading System is validated international federation of gynecology and obstetrics system used for endometrial cancer staging.[4]

The patient presented 3 months after completing chemotherapy (1 month after radiation treatment with brachytherapy) with melena in addition to chronic watery diarrhea. The patient denied aspirin or nonsteroidal anti-inflammatory drug use and was not taking a proton pump inhibitor (PPI) for the past 12 months. The patient denied a history of either gastrointestinal bleeding or abdominal pain. Esophagogastroduodenoscopy demonstrated multiple nonbleeding superficial gastric ulcers with clean ulcer bases (Forrest Class III) in the gastric antrum and prepyloric region (Figure 1). There were no ulcers identified in the duodenum (Figure 2). Gastric pH was not obtained at this examination. Serum gastrin level was obtained because of clinical suspicion for potential ZE in the setting of multiple gastric ulcers without significant risk factors for peptic ulcer disease. An elevated serum gastrin level (538 pg/mL) was noted on the day after esophagogastroduodenoscopy with the patient not on PPI therapy. Somatostatin receptor-based imaging

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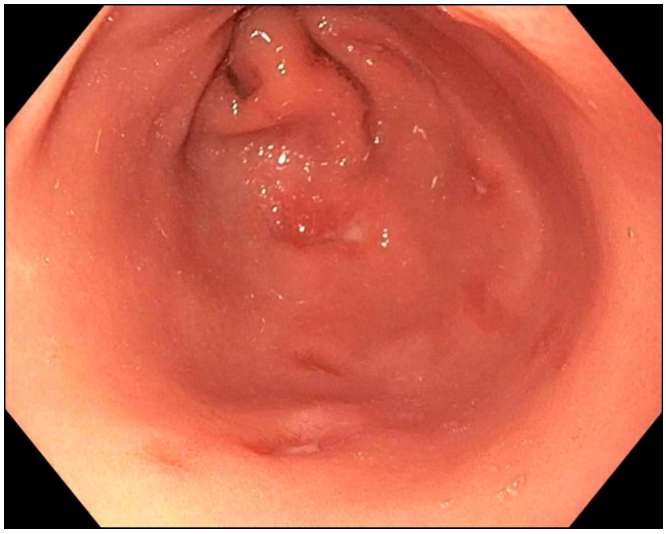

Figure 1. Multiple nonbleeding superficial gastric ulcers with clean ulcer bases (Forrest Class III) in the gastric antrum and prepyloric region.

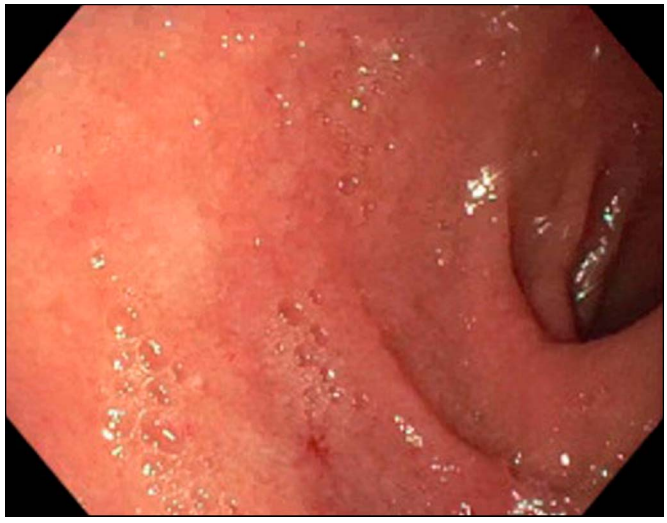

Figure 2. Normal endoscopic duodenal examination.

(Ga-68 Dotatate-positron emission tomography [PET]/CT) revealed avid left paraesophageal node uptake measuring 11 × 8 mm (Figure 3). The patient was started on pantoprazole 40 mg twice a day. Stool *Helicobacter pylori* antigen test was negative. Serum calcium (9.2 mg/dL), renal function, and parathyroid hormone were within normal limits.

After 5 months, follow-up upper endoscopic examination demonstrated 2 persistent (2–3 mm) clean-based ulcerations in the gastric antrum on the posterior gastric wall (Figures 4 and 5). Gastric fluid demonstrated pH of 1 despite taking pantoprazole 40 mg twice a day for 4 months. Endoscopic ultrasound examination demonstrated an ill-defined 14 × 70-mm heterogenous lymph node in the approximate location of the lymph node noted on the PET scan which was sampled by fine-needle aspiration, revealing scant lymphoid tissue insufficient for pathologic diagnosis (Figure 6).

The diagnosis of ZE was supported by elevated serum gastrin (538 pg/mL) and abnormal somatostatin receptor scan uptake with gastric pH < 2 and persistent gastric ulcers despite high-dose PPI for more than 2 months. Unfortunately, the tissue sampling from the left paraesophageal node yielded insufficient material for microscopic examination. Somatostatin receptor-Dotatate-PET/CT scan showed no abnormal uptake elsewhere, and we speculate that the primary lymph node represents the primary gastrinoma site. The patient's chronic diarrhea and endoscopic appearance of her gastric ulcers substantially improved after high-dose PPI therapy. Follow-up gastrin level was trending down (307 pg/mL) after 4 months of PPI therapy as of May 2020.

Our patient elected to pursue medical management because of her advanced age and multiple comorbidities, including endometroid tumor, recent radiation and chemotherapy exposure, body mass index of 41.9 kg/m^2, and type 2 diabetes. Our patient is scheduled for follow-up visits with biochemical laboratory studies including fasting serum vitamin B 12, ionized calcium, parathyroid hormone, and gastrin levels every 3–6 months. Surveillance imaging studies (abdominal CT or magnetic resonance imaging) will be conducted annually, with somatostatin receptor scintigraphy repeated at least every 3 years.[5]

DISCUSSION

Here, we describe a case of ZE presenting several months after surgical resection of endometrioid small cell neuroendocrine carcinoma and endometrioid adenocarcinoma.

Primary gastrinoma is frequently detected as lymph node metastasis at first presentation and often within a lymph node in the "gastrinoma triangle."[1,6] Other primary gastinoma sites include stomach, mesentery, ovaries, heart, lung, hepatobiliary tract, and jejunum.[1,6] In cases where the tumor can be localized, surgical exploration may increase diagnostic yield, prevent advanced disease progression, and improved survival rate.[7]

Most guidelines for evaluation for patients with suspected ZE recommend obtaining fasting serum gastrin (off PPI) followed by gastric pH measurement. The accepted criteria for a diagnosis of ZE include fasting serum gastrin more than 10-fold above normal ($<$100 pg/mL) and a gastric pH $<$2.[7,8] The lack of consistency in establishing standardized ZE criteria primarily reflects widespread use of PPIs and limited access to gastric pH testing.[9] In patients with limited access for gastric acid assessment, alternative criteria include active ulcer disease combined with positive somatostatin receptor scintigraphy, cytology or biopsy for neuroendocrine tumor, or a positive secretin test.[9] In some cases, diarrhea responsive to PPI or histamine H_2 receptor antagonist therapy may be an adjunctive criterion.[9]

Long-term acid suppression is recommended in ZE patients to prevent severe peptic ulcer disease.[5] In sporadic ZE patients

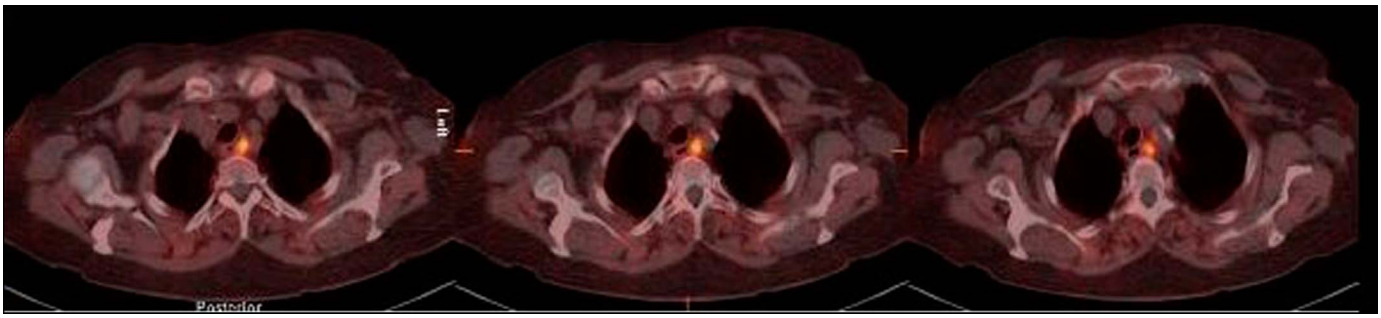

Figure 3. Somatostatin receptor-based imaging (Ga-68 Dotatate-positron emission tomography/computerized tomography) revealed avid left paraesophageal node uptake measuring 11 × 8 mm.

without multiple endocrine neoplasia, type 1, current guidelines recommend surgical exploration for complete tumor removal if possible, in patients without medical contraindication.[4,10] In a single institution experience, there was no significant difference in survival between subjects with primary lymph node vs nonprimary lymph node gastrinomas. In addition, patients with primary lymph node gastrinoma were less likely to develop persistent/recurrent disease (9.1% vs 42.9%, $P = .04$).[11] In our case, the decision to pursue medical management reflected the patients' limited life expectancy and her medical comorbidities, including (recent history of endometrioid tumor, chemoradiation exposure, obesity, and type 2 diabetes). In general, however, primary tumor localization is an important step to determine whether surgical resection is feasible,[5] and somatostatin receptor-based imaging, and endoscopic ultrasonography may guide localization of the primary site and determining metastatic burden.[10,12]

To the best of our knowledge, the coincidence of multiple neuroendocrine neoplasms involving the gastrointestinal tract and endometrium has not been described. Owing to its variable clinical presentation, high mortality, and challenging primary lesion identification, clinicians should consider ZE as a potential diagnosis in a patient with multiple gastric or duodenal ulcers. In addition, it is essential to consider the possibility of ZE even in complex situations such as our patient because of the potential to change therapeutic strategies and its impact on the overall prognosis. In our case, the presumptive diagnosis of ZE was based on a combination of fasting serum gastrin concentration, gastric pH, and somatostatin receptor–based imaging. Our case reflects the challenges in establishing a diagnosis of ZE without formally identifying a primary lesion. ZE should be considered in a patient with NET presenting with melena and diarrhea but without evident risk factors for gastrointestinal bleeding or *Helicobacter pylori* infection.

DISCLOSURES

Author contributions: A. Almuhaidb wrote the manuscript, reviewed the literature, and revised the manuscript for intellectual content. NO Davidson edited the manuscript, revised the manuscript for intellectual content, and is the article guarantor.

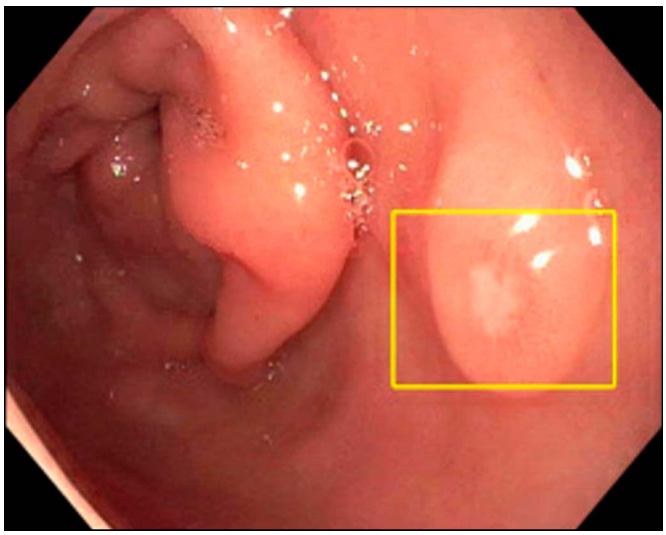

Figure 4. Persistent clean-based ulcerations in the gastric antrum on the posterior gastric wall.

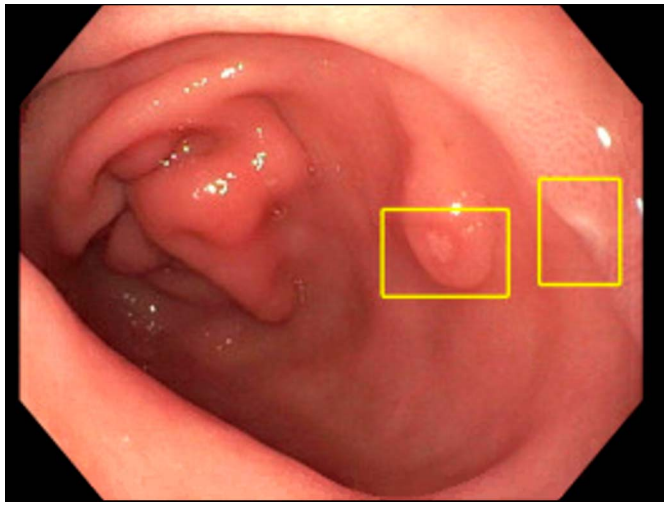

Figure 5. Persistent clean-based ulcerations in the gastric antrum on the posterior gastric wall.

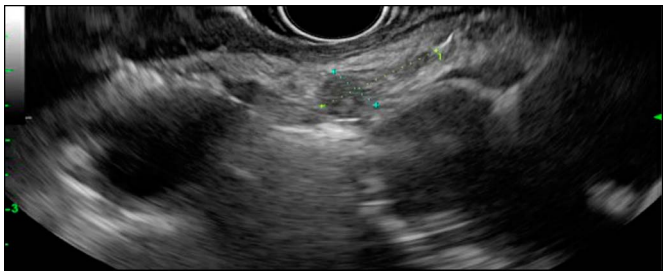

Figure 6. Ill-defined 14 × 7-mm heterogenous lymph node/endoscopic ultrasound examination.

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Informed consent was obtained for this case report.

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