




Radiological Features of Zollinger–Ellison Syndrome: A Report of Two Cases

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Abstract

Keywords

- ▶ Zollinger–Ellison syndrome
- ▶ peptic ulcer
- ▶ diarrhea
- ▶ gastrinomas

Hypersecretion of gastrin from duodenal or pancreatic gastrinomas results in a rare clinical entity called Zollinger–Ellison syndrome (ZES). It mostly presents with abdominal pain and diarrhea. ZES may be sporadic or occur in association with multiple endocrine neoplasia type 1. Usually, ZES manifests between 20 and 50 years.

We report two cases of patients who presented with abdominal pain, vomiting, watery diarrhea, and significant weight loss.

Introduction

The incidence of Zollinger–Ellison syndrome (ZES) is 0.5 to 2 per million population.¹ Ectopic secretion of gastrin from gastrinomas causes damage to gastrointestinal (GI) mucosa resulting in ZES. Gastrin causes excess production of gastric acid (hyperchlorhydria) which in turn results in severe recurrent ulcers of the esophagus, stomach, duodenum, and jejunum.² In total, 70% of gastrinomas are sporadic. Gastrinomas are associated with multiple endocrine neoplasia type 1 (MEN1) in 20 to 30% of cases.¹ MEN1 is characterized by the occurrence of primary hyperparathyroidism (>90%), pancreaticoduodenal endocrine neoplasms (65–75%), and tumors of the anterior pituitary gland (30–65%).² ZES associated with MEN1 have a younger age at presentation, reduced incidence of peptic ulcer and GI bleeding, and a markedly increased incidence of renal calculi due to hyperparathyroidism.³ In total, 65% of gastrinomas

are malignant, and up to 30 to 40% of patients will have metastatic disease at initial presentation.⁴ Liver metastases occur much more frequently with pancreatic gastrinomas (22–35%) than duodenal gastrinomas (0–10%).⁵ We report two similar cases presenting with vomiting and watery diarrhea associated with significant weight loss.

Case 1

A 68-year-old male presented with vomiting and watery diarrhea. He had significant weight loss of 12 kg during the time period of 10 months. On physical examination, he appeared cachectic. Abdomen was mildly distended. Laboratory analysis showed normal hemoglobin, total protein, and albumin. Liver and renal functions were normal.

Ultrasound scan showed markedly distended stomach with fluid and debris and stomach wall thickening. Plain

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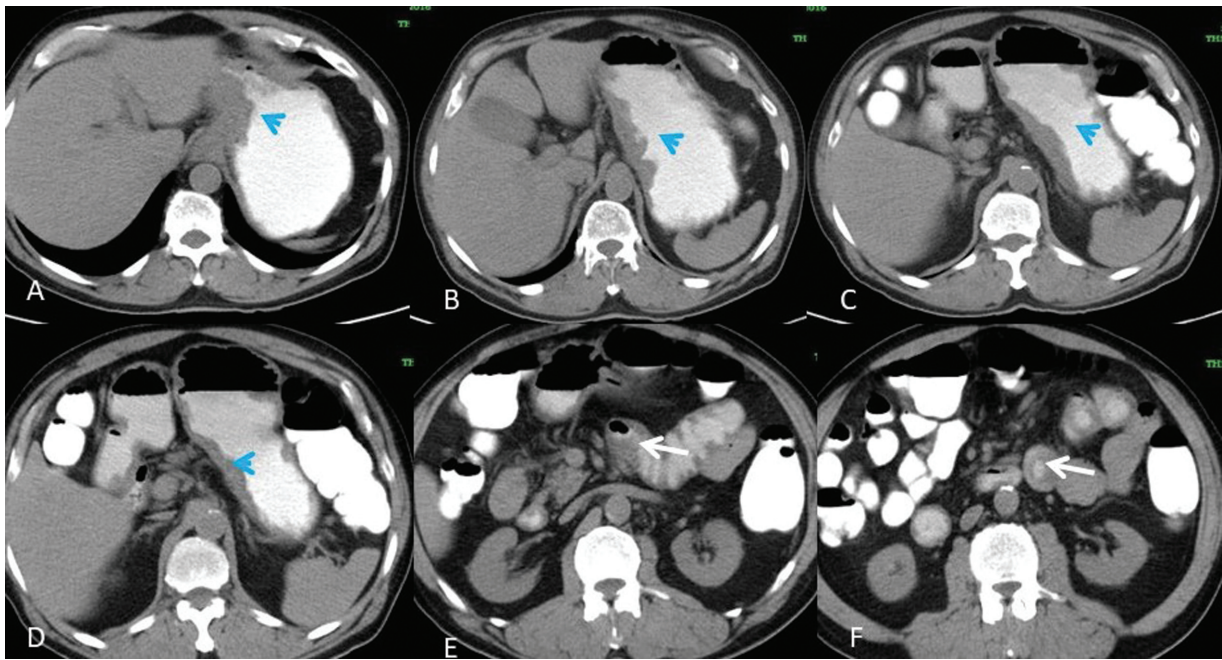


Fig. 1 (A–F) Plain CT showing extensive diffuse mucosal fold thickening involving the entire stomach, predominantly fundus and body (arrowheads). Panels (E) and (F) showing mild dilatation of duodenum and jejunum with mucosal fold thickening (arrows). CT, computed tomography.

computed tomography (CT) scan showed extensive diffuse mucosal fold thickening involving the entire stomach, predominantly fundus and body, along with mild dilatation of duodenum and jejunum (►Fig. 1).

Contrast-enhanced CT (CECT) images with iodinated oral contrast showed thickened enhancing stomach wall prominently in the stomach fundus and body region (►Fig. 2). Arterial, venous, and delayed phase CECTs showed well-defined, oval-shaped lymph node (4.3×3.0 cm) adjacent to

the lateral wall of duodenum with heterogeneous enhancement (►Fig. 3). Mild progressive enhancement of the node was noted in delayed images.

Upper GI endoscopy showed thick gastric mucosal folds with antral predominant gastritis and superficial ulcers in the duodenum, jejunum, stomach, and gastroesophageal junction (►Fig. 4). Hypertrophic gastritis, lymphoma, and ZES were considered as the differential diagnoses. Endoscopic biopsy from the gastric fundus and body showed mild

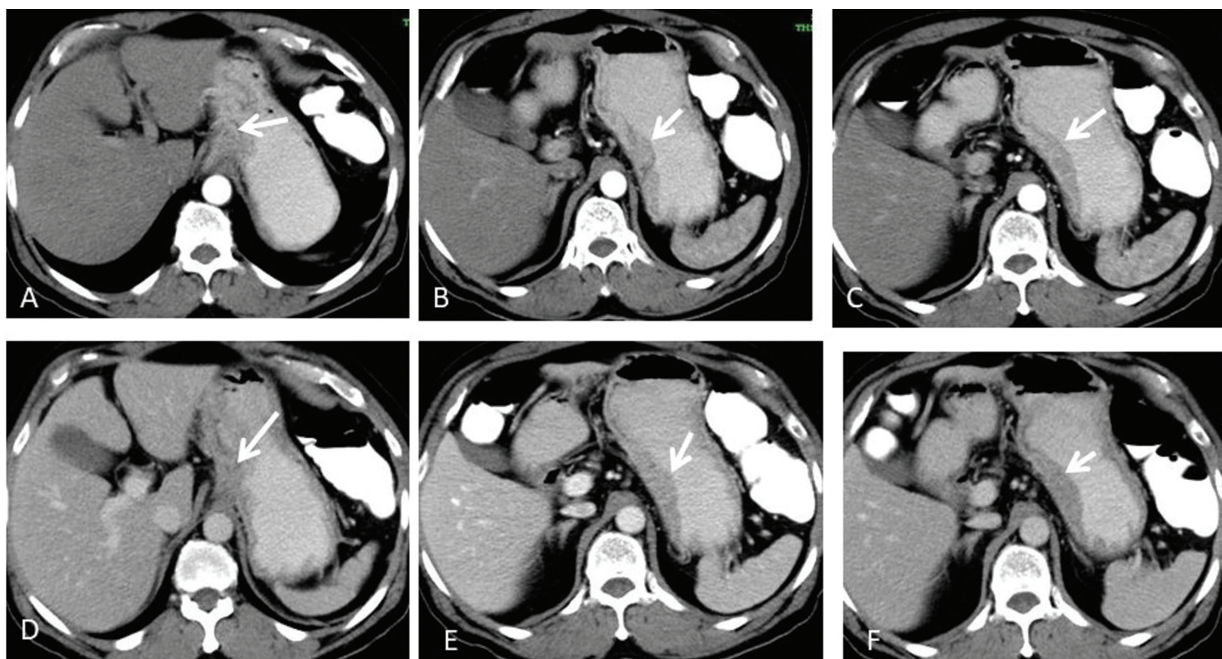


Fig. 2 Axial CECT—arterial phase (A, B, C) and venous phase (D, E, F)—showing thickened enhancing stomach wall prominently in the proximal stomach—fundus and proximal body region (arrow). CECT, contrast-enhanced computed tomography.

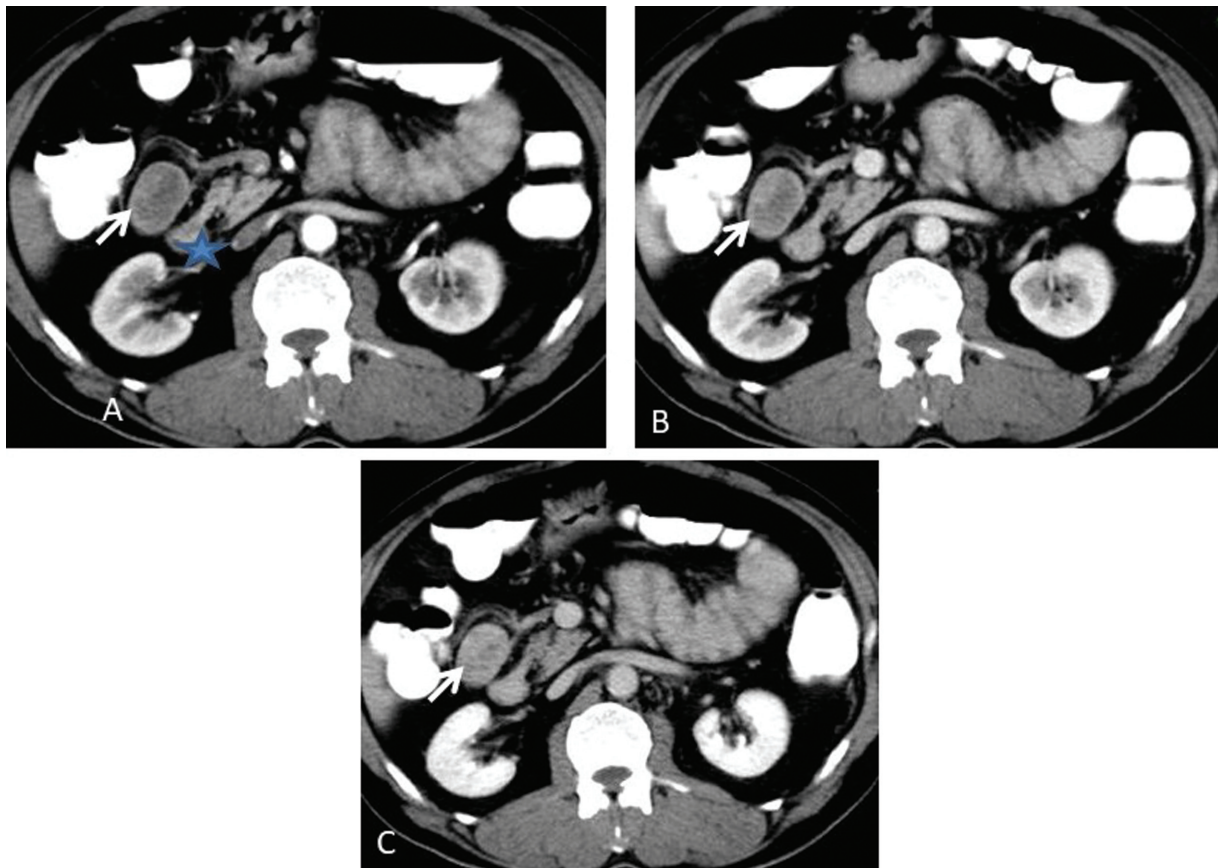


Fig. 3 Axial CECT—arterial (A), venous (B), and delayed phase (C)—showing well-defined oval-shaped lymph node (4.3 × 3.0 cm) adjacent to the duodenum with heterogeneous enhancement. Mild progressive enhancement of the node noted in delayed images (arrow). The asterisk “*” indicates duodenum. CECT, contrast-enhanced computed tomography.

chronic gastritis. Biopsy from D2 segment of duodenum showed superficial ulceration and focal duodenitis.

The serum gastrin level was 390 pg/mL (normal range: 13–115) and serum chromogranin A level was more than 650 ng/mL (normal value < 100).

Gallium-68 Dotatoc positron emission tomography (PET)-CT showed uptake in the somatostatin receptor expressing lymph node adjacent to the second part of duodenum. Mild abnormal uptake was also noted along the posterior wall of body of stomach. No other avid lymph nodal/other suspicious lesions were noted elsewhere in the whole body.

Endoscopic ultrasound showed diffuse stomach wall thickening with oedematous submucosa. No focal lesion was detected in the stomach. Endoscopic ultrasound (EUS)-guided biopsy of paraduodenal lymph node was consistent with neutrophil extracellular trap (NET).

The patient did not respond to proton-pump inhibitors (PPIs) and ultimately underwent total gastrectomy with en bloc dissection of paraduodenal lymph node. Gastrectomy specimen showed cerebriform rugae with parietal cell hyperplasia consistent with ZES (►Fig. 5).

Histopathology with immunohistochemistry from the paraduodenal lymph node confirmed neuroendocrine tumor, grade 2, composed of uniform cells forming small acini in a richly vascular stroma (►Fig. 6). There was evidence of lymphoid tissue in the periphery of the lesion; the neoplastic

cells were positive for synaptophysin and chromogranin with Ki 67 index of 4%.

The patient became symptom free after the surgery, serum gastrin level was normalized, and is on regular follow-up.

Case 2

A 50-year-old male presented with history of epigastric pain, vomiting, and watery diarrhea for the past 18 years, with aggravation of symptoms for the past 1 year. His biochemical and laboratory parameters were normal.

Esophagogastroduodenoscopy showed multiple small less than 1 cm sessile polyps carpeted against mucosa in the body and fundus of stomach and in the duodenum. There was thickening of gastric mucosal folds. Biopsy showed multiple fundic gland polyps of stomach and polypoid duodenal mucosa with gastric heterotopia. Colonoscopy was normal.

Plain CT scan (►Fig. 7) and CECT images (►Fig. 8)—arterial phase (►Figs. 7–8[A–C]) and venous phase (►Fig. 7–8[D–F])—showed grossly thickened gastric folds.

CECT—arterial (►Fig. 9A), venous (►Fig. 9B), and delayed phase (►Fig. 9C, D)—showed well-margined, thick-walled cystic lesion of size 2.0 cm in the pancreatic tail with peripheral enhancement. Calcific speck was noted in the

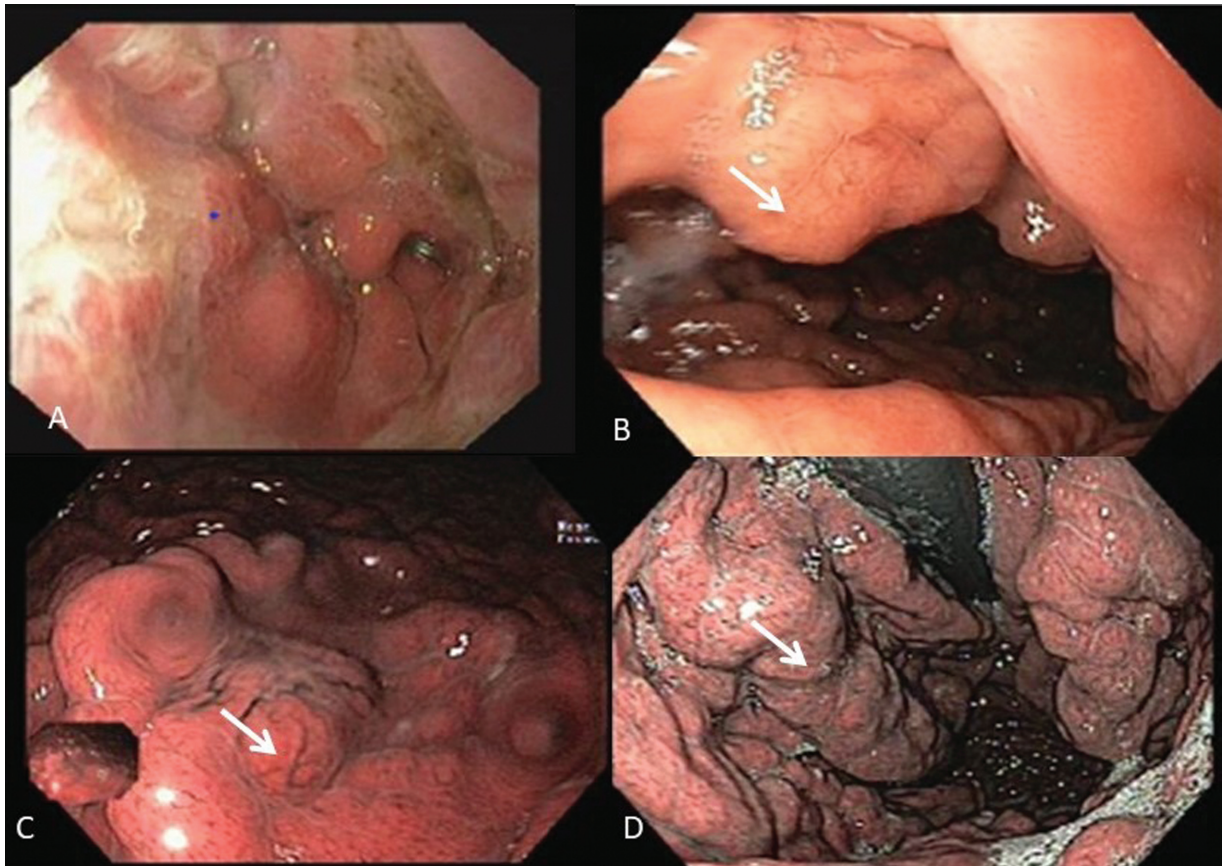


Fig. 4 Upper GI endoscopy showing esophageal ulcer, antral predominant gastritis with thickened gastric folds (arrows). GI, gastrointestinal.

periphery of the lesion on plain CT scan (A). The possibility of neuroendocrine tumor was considered in view of symptoms.

The serum gastrin level was 817 pg/mL (normal range: 13–115) and serum chromogranin level was more than 850 ng/mL (normal value < 100).

The patient was a known case of pituitary macroadenoma, now on medication with normal prolactin level of 5 (normal range of prolactin: 2.2–18.5 ng/mL). His serum calcium levels were within normal limits. He was evaluated

for MEN1. Serum parathyroid hormone was 71 (normal: 15–68 pg/mL). He underwent Technetium parathyroid scintigraphy, which was negative for parathyroid lesion.

The patient underwent laparoscopic enucleation for endocrine tumor in the tail of pancreas. Histopathology was consistent with neuroendocrine tumor grade II. Immunohistochemistry showed capsulated neoplasm composed of islands and nests of round cells with coarse granular chromatin and scanty cytoplasm. The cells were mostly

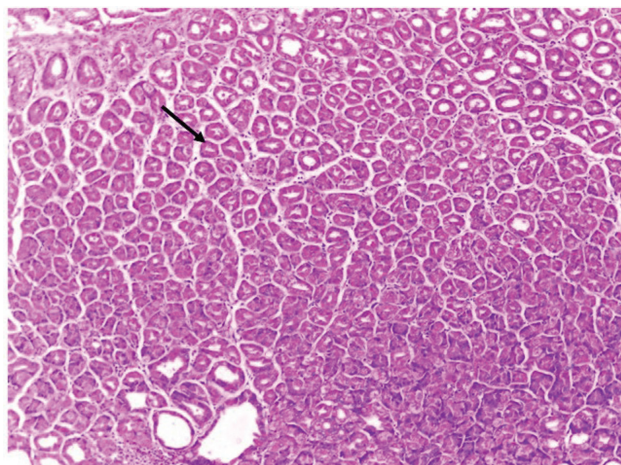


Fig. 5 H&E staining—gastrectomy specimen—showing gastric mucosa with parietal cell hyperplasia (arrow).

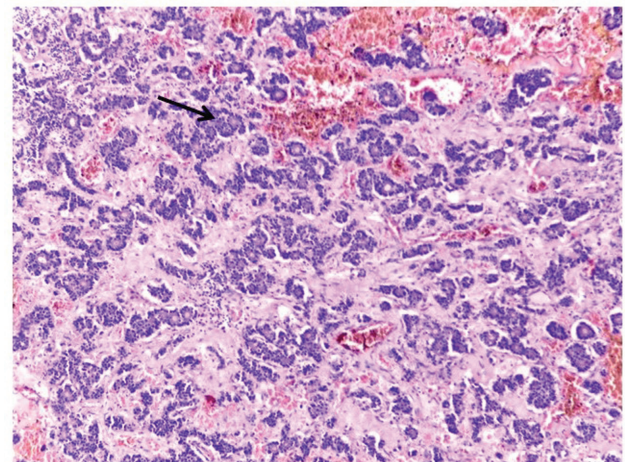


Fig. 6 H&E staining—resected paraduodenal lymph node—showing neuroendocrine tumor, grade 2 composed of uniform cells (arrow) forming small acini in a richly vascular stroma.

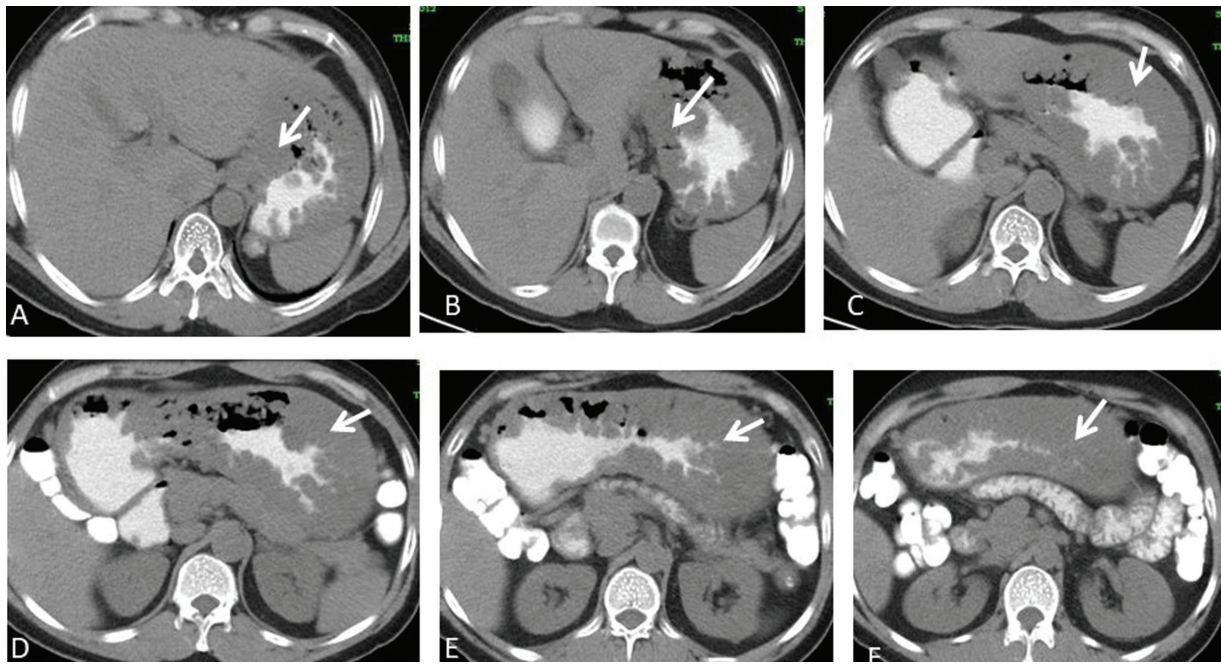


Fig. 7 (A–F) Plain CT showing grossly thickened gastric folds involving fundus and body of stomach (*arrow*). CT, computed tomography.

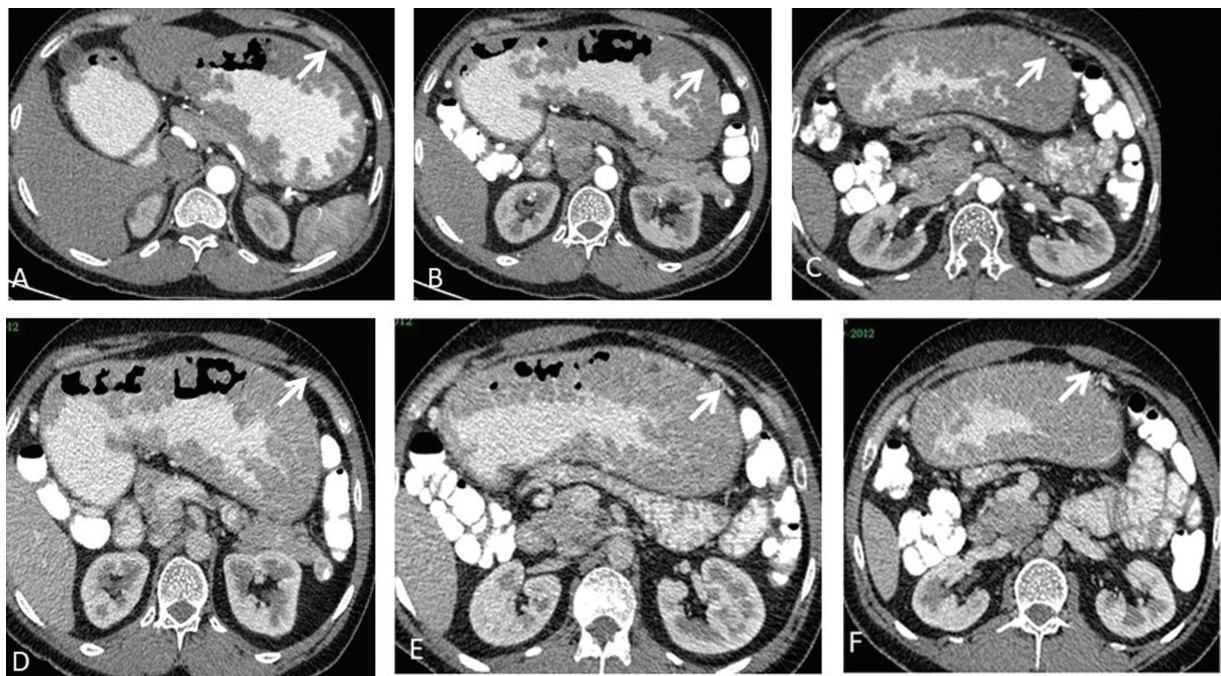


Fig. 8 CECT—arterial phase (A, B, C) and venous phase (D, E, F)—showing grossly thickened gastric folds (*arrow*). CECT, contrast-enhanced computed tomography.

monomorphous with occasional mitotic figures $\sim 2/10$ high-power-field. No vascular emboli were seen. The periphery showed a strip of pancreatic tissue into which there was no capsular invasion. The neoplastic cells were positive for synaptophysin, chromogranin, and cytokeratin. The $K_i 67$ proliferation index was 4%. There were no angiolymphatic emboli.

We have presented two similar cases with diffuse stomach wall thickening due to ZES, one due to gastrin secreting neuroendocrine tumor in a lymph node in paraduodenal

location and the second case due to a gastrinoma in the pancreatic tail region.

Discussion

Hypersecretion of gastrin by a gastrinoma results in a clinical syndrome called ZES. ZES most commonly presents with abdominal pain (75%) and diarrhea (73%).⁶ Peptic ulcers and hyperplastic gastric folds are the hallmarks seen in more than

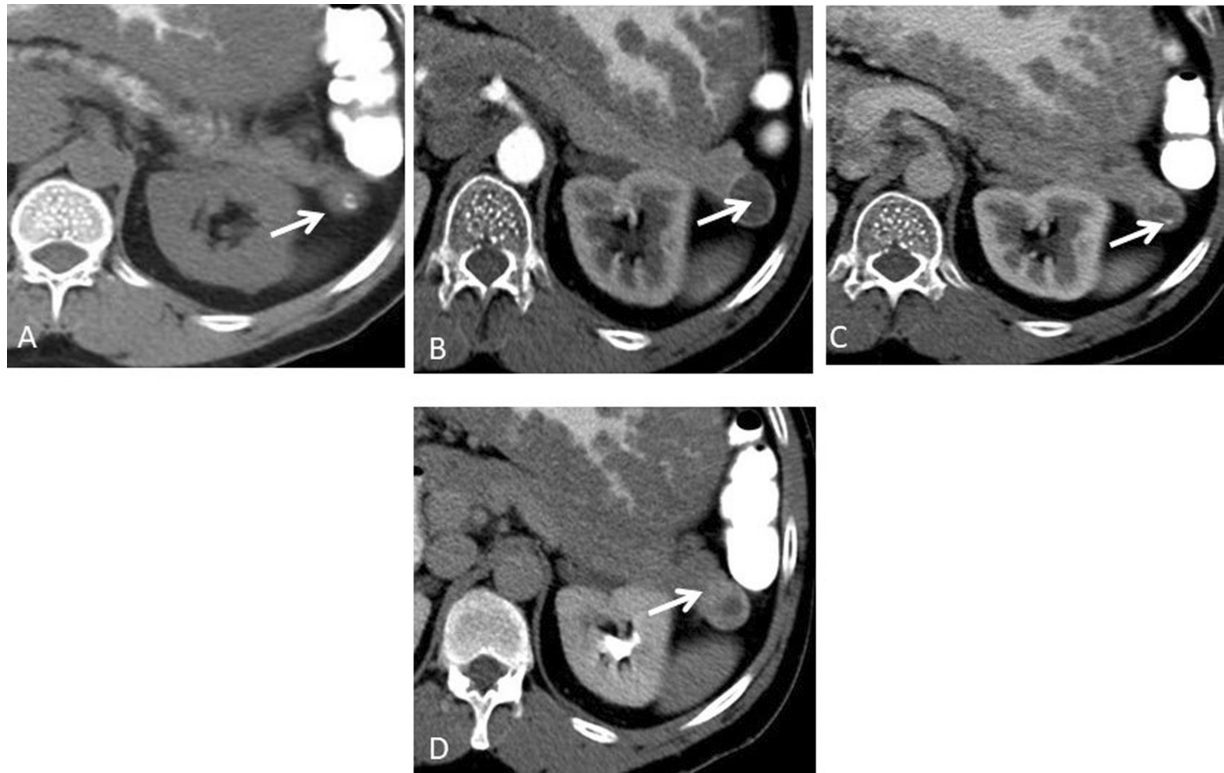


Fig. 9 CECT—arterial (A), venous (B), and delayed phase (C, D)—showing well-margined thick-walled ~2 cm sized cystic lesion (arrow) in the pancreatic tail with peripheral enhancement. Calcific speck noted in the periphery of the lesion on plain scan (A). CECT, contrast-enhanced computed tomography.

90% of the patients with ZES.⁶ The peptic ulcers are often solitary, <1 cm in diameter, and mostly occur in duodenum and jejunum—75% of ulcers in the first part of the duodenum, 14% in the distal duodenum, and 11% in the jejunum.⁷ If there is persistent hypergastrinemia, there could be further complications—peptic ulcers may bleed or perforate.⁷

The vast majority of gastrinomas are present within the “gastrinoma triangle,” which is bounded by junction of cystic duct/CBD (common bile duct), 2/3rd part of duodenum, and pancreatic head/neck junction as shown in ►Fig. 10. Around 60 to 80% of gastrinomas are located in the duodenum and 10 to 40% in the pancreas.⁷ Gastrin-producing NETs without ZES are not considered as gastrinomas.⁵

The gastrinoma triangle (Passaro’s triangle) is a triangular area which is bounded by junction of cystic duct/CBD, 2/3rd part of duodenum, and pancreatic head/neck junction. Gastric acid hypersecretion and decreased absorption of sodium and water due to hypergastrinemia are the reasons for diarrhea in ZES.

Usually there is a long mean delay in diagnosis as patients generally present with nonspecific symptoms mimicking acid-peptic disease.⁸ Diagnosis of gastrinomas is done by endoscopy and relevant blood tests, and localization is done by various imaging modalities.

Fasting serum gastrin levels and serum chromogranin A levels are elevated and are diagnostic of gastrinomas.³ Fasting serum gastrin levels more than 10 times the upper limit of normal (>1,000 pg/mL) in the presence of low gastric pH (<2) are diagnostic of ZES.¹ Secondary hypergastrinemia can

be associated with other conditions like atrophic gastritis, renal failure, and PPIs.⁹

Chromogranin A is an important marker of neuroendocrine tumors in general and gastrinoma in particular.¹⁰ False-positive increases of serum chromogranin A levels can occur in patients with liver disease, renal failure, gastric atrophy, or due to PPI therapy.⁹ However, serum chromogranin A levels are helpful when serum gastrin levels are only moderately elevated.

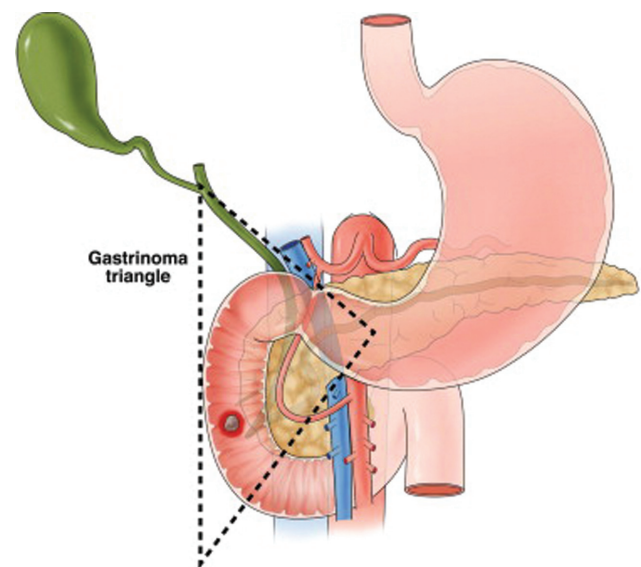


Fig. 10 Gastrinoma triangle.

CT, magnetic resonance imaging (MRI), EUS, somatostatin receptor scintigraphy (SRS), and Ga68 DOTA PET scans are the imaging modalities to localize gastrinoma in ZES.⁸ EUS is an extremely sensitive (93%) and specific (95%) test for diagnosing small pancreatic NETs and has been shown to be superior to CT, MRI, and other invasive diagnostic measures such as angiography and secretin stimulation test.^{10,11} It helps to detect pancreatic lesions as small as 2 or 3 mm in diameter as well as to perform guided fine needle aspiration.¹² Prior to the development of functional imaging studies, angiography and sampling for hormone gradients were widely used for diagnosis in patients with neuroendocrine tumors.⁸

The neuroendocrine tumors have somatostatin receptors and hence octreotide scan, using In-111 radiolabeled somatostatin analogue, was the technique of choice before the advent of Ga68 DOTA PET. Although an Octreoscan is a sensitive test for the localization gastrinomas, its sensitivity for identifying a primary tumor is no higher than 70% so that negative testing cannot exclude the presence of ZES.⁹

The current imaging modality of choice is Ga68-DOTA PET scan using DOTA TATE/DOTA NOC/DOTA TOC. It has shown better sensitivity than SRS and is useful in staging, treatment response assessment, and recurrence evaluation.

Regarding management, ZES is treated medically with high-dose PPIs (omeprazole 60 mg or pantoprazole 120 mg daily) as PPIs effectively control the symptoms in most of the patients.⁷ Somatostatin analogues should be used if symptoms persist despite PPI.⁶ Localization of gastrinoma is done by imaging modalities as described above. Once localization is done, surgery is the treatment for patients with gastrinoma and without evidence of metastases. Total gastrectomy for treatment is no longer absolutely required.¹³ It is done if the patient presents with complication of hypersecretion with GI bleed or perforation due to peptic ulcers which cannot be controlled with other measures.¹³ It is also done when a gastrinoma is not localized or if the primary is unresectable.¹³ The first patient underwent total gastrectomy as there was faint uptakes in the posterior stomach wall on Ga68 DOTA PET scan suspecting an additional microgastrinoma in the stomach wall as gastrinomas can be multiple. However, even after detailed pathological evaluation, there was no evidence of any lesion in the gastric wall. The primary neuroendocrine tumor/gastrinoma in our case was gastrinoma in a paraduodenal lymph node which is a rare occurrence. Although literature search showed primary gastrinomas in lymph nodes, it could represent metastatic deposits resulting from a primary microgastrinoma which has not been detected.¹⁴ These patients should undergo long-term follow-up as the occult primary disease may become evident at a later time. Hence the argument that the lymph node gastrinoma presented here may still be a metastasis of an undetected duodenal microgastrinoma cannot be completely negated.¹⁵ Extensive sampling of the proximal part of the duodenum, the region where most of the microgastrinomas can be found is essential to rule out a small primary.¹⁶ The second case was a typical case of cystic

neuroendocrine tumor/gastrinoma with small lesion in the pancreatic tail localized by CT scan.

Conclusion

ZES is a rare entity, presenting with features of acid peptic disease and hence the diagnosis is often delayed. Increased awareness of this disorder in patients who present with chronic GI symptoms along with familiarity of endoscopic findings is essential for prompt diagnosis and appropriate treatment. Thickened gastric folds in endoscopy along with ulcers in unusual locations like duodenum and jejunum should alert one toward the diagnosis of ZES. Cross-sectional imaging with Ga68 DOTA PET is currently the imaging modality of choice for tumor localization. A workup for MEN1 should also be done for those with ZES.

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Conflict of Interest

None.

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