Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis

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Literature review current through: **Sep 2023.**
This topic last updated: **Nov 30, 2021.**

INTRODUCTION

Zollinger-Ellison (ZES) syndrome is characterized by gastric acid hypersecretion resulting in severe acid-related peptic disease and diarrhea [1,2]. The clinical manifestations and diagnosis of ZES will be reviewed here. The management of ZES is discussed separately. (See "Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)".)

EPIDEMIOLOGY

Zollinger-Ellison syndrome (ZES) is caused by secretion of gastrin by duodenal or pancreatic neuroendocrine tumors (gastrinomas). The annual incidence of gastrinomas is 0.5 to 2 per million population [3-5]. Most patients are diagnosed between the ages of 20 and 50, with a higher incidence in males as compared with females [6]. Approximately 80 percent of gastrinomas are sporadic, but 20 to 30 percent occur in association with multiple endocrine neoplasia type 1 (MEN1) [7,8]. (See "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis".)

Although gastrinomas are one of the most common functional pancreatic neuroendocrine tumors, only 20 to 25 percent of gastrinomas arise in the pancreas [6,9]. Approximately 50 to 88 percent of patients with sporadic ZES, and 70 to 100 percent of patients with ZES associated with MEN1, have duodenal gastrinomas [8]. Duodenal gastrinomas are predominantly found in

the first part of the duodenum. As compared with pancreatic gastrinomas, duodenal gastrinomas are usually small (<1 cm), are often multiple, and are less likely to have metastasized to the liver at diagnosis (0 to 10 versus 22 to 35 percent) [6,7,10,11]. In 5 to 15 percent of patients, gastrinomas arise in non-pancreatic, non-duodenal abdominal (stomach, peripancreatic lymph nodes, liver, bile duct, ovary), and extra-abdominal (heart, small cell lung cancer) locations [12-14].

CLASSIFICATION, NOMENCLATURE, AND HISTOLOGY

The World Health Organization (WHO) classifies neuroendocrine tumors (NETs) arising within the digestive system based upon the extent to which they resemble their normal non-neoplastic counterparts (table 1). (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on '2010 and 2019 World Health Organization classification'.)

Histologically, most gastrinomas are well-differentiated NETs with few mitoses and a histologic appearance that is similar to that of other pancreatic NETs. The cells are arranged in a solid, trabecular, gyriform, or glandular pattern, with fairly uniform nuclei, salt-and-pepper chromatin, and finely granular cytoplasm. As with other pancreatic NETs, the degree of malignancy cannot be predicted by morphologic appearance alone. The cells produce abundant neurosecretory granules, as reflected in the strong and diffuse immunohistochemical expression of neuroendocrine markers such as synaptophysin and chromogranin. Gastrin is the predominant peptide within the secretory granules of gastrinoma cells, but other neuroendocrine peptides such as vasoactive intestinal peptide and glucagon can sometimes be identified as well. The designation of the tumor as a gastrinoma is based upon the presence of a clinical syndrome that results from tumor production and secretion of gastrin, and not by its morphologic appearance or the presence of gastrin in the secretory granules. Of note, not all patients with ectopic gastrin secretion have the symptoms associated with Zollinger-Ellison syndrome, as in many cases, the hormone is not processed to biologically active gastrin [15]. If a tumor stains for gastrin or secretes gastrin but does not produce symptoms of Zollinger-Ellison syndrome, it should not be considered a gastrinoma. (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on 'Functionality and nomenclature'.)

PATHOPHYSIOLOGY

Excessive gastrin secretion from a gastrinoma results in high gastric acid output (usually four- to sixfold, and up to over 10-fold) due to the trophic action of gastrin on parietal cells and histamine-secreting enterochromaffin-like (ECL) cells (picture 1) [15]. In addition, gastrin stimulates parietal cells largely via the release of histamine. (See "Physiology of gastric acid secretion".)

Chronic diarrhea in Zollinger-Ellison syndrome results from the following [6]:

- The high volume of gastric acid secretion that cannot be fully reabsorbed by the small intestine and colon.
- The rate of gastric acid secretion exceeds the neutralizing capacity of pancreatic bicarbonate secretion, resulting in an exceptionally low pH of intestinal contents. The low pH inactivates pancreatic digestive enzymes, interfering with the emulsification of fat by bile acids, and damaging intestinal epithelial cells and villi. Maldigestion and malabsorption both result in steatorrhea.
- Extremely high serum gastrin concentrations inhibit the absorption of sodium and water by the small intestine, thereby adding a secretory component to the diarrhea.

CLINICAL MANIFESTATIONS

Clinical presentation — Peptic ulcer disease (73 to 98 percent), heartburn (52 to 55 percent), diarrhea (60 to 75 percent), weight loss (7 to 53 percent), and complications from acid hypersecretion (bleeding, stricture, fistulization, perforation) are the most common symptoms in patients with Zollinger-Ellison syndrome (ZES) (figure 1) [15,16]. Sixty to ninety percent of gastrinomas are malignant [8]. The mean time to diagnosis is six years [16].

Approximately 1 to 10 percent of patients, especially with metastatic disease or multiple endocrine neoplasia type 1 (MEN1), have symptoms due to a second hormonal syndrome (eg, VIPoma, somatostatinoma, glucagonoma, ACTH) [17]. (See "Epidemiology and clinical manifestations of Cushing syndrome", section on 'Frequency and severity of symptoms' and "Somatostatinoma: Clinical manifestations, diagnosis, and management", section on 'Clinical manifestations' and "VIPoma: Clinical manifestations, diagnosis, and management", section on 'Clinical features' and "Glucagonoma and the glucagonoma syndrome", section on 'Clinical features'.)

Endoscopic features — Over 90 percent of patients with ZES develop peptic ulcers [18]. Patients with ZES, like those with sporadic peptic ulcer disease, often present with solitary ulcers

less than 1 cm in diameter. Approximately 75 percent of ulcers are in the first portion of the duodenum, 14 percent in the distal duodenum, and 11 percent in the jejunum [19]. Ulcers are more likely to be refractory to proton pump inhibitor therapy and to recur as compared with patients with sporadic ulcer disease. Furthermore, in ZES, ulcers often occur in unusual locations (eg, beyond the first or second fold of the duodenum). Over 90 percent of patients with ZES often have prominent gastric folds. Patients may also have evidence of reflux esophagitis. However, strictures of the esophagus, pylorus, or duodenum are present in less than 10 percent of patients [16]. In the setting of MEN1, duodenal gastrinomas are typically multifocal, small (<0.5 cm), and associated with lymph node involvement in 40 to 60 percent [15].

DIAGNOSIS

Zollinger-Ellison syndrome (ZES) should be suspected in patients with multiple or refractory peptic ulcers; ulcers distal to the duodenum; peptic ulcer disease and diarrhea, enlarged gastric folds, or multiple endocrine neoplasia type 1 (MEN1) (table 2) [20]. ZES should also be suspected in patients with peptic ulcer disease and a family history of peptic ulcer disease or MEN1, or in patients with diarrhea that is responsive to proton pump inhibitors (PPIs). The diagnosis is established by demonstrating an elevated basal or stimulated gastrin concentration (in the setting of a low gastric pH).

Evaluation — Initial evaluation in a patient with suspected ZES is with measurement of fasting serum gastrin concentration and measurement of gastric pH. In patients with elevated gastrin levels/low gastric pH that are not diagnostic for ZES, we perform a secretin stimulation test. The calcium infusion study (intravenous infusion with calcium gluconate) is usually reserved for patients with gastric acid hypersecretion in whom there is a strong clinical suspicion of gastrinoma despite a negative secretin stimulation test [21]. Importantly, the diagnosis of ZES can be difficult to make, as evidenced by the fact the average time from onset of symptoms to diagnosis is >5 years. The symptoms can be nonspecific and/or masked by PPI use [22]. Gastric antral/body biopsy for atrophic gastritis combined with parietal cell and intrinsic factor antibodies can also be useful for confirming situations of "appropriate" hypergastrinemia.

In patients in whom PPIs cannot safely be stopped, modern criteria for ZES have been proposed [8]. An elevated gastrin level, combined with a history of current or recent peptic ulcer disease, and improvement of diarrhea on a PPI supports a diagnosis of ZES, particularly in the setting of a positive biopsy for a well differentiated neuroendocrine tumor (in a patient with or without MEN1). The diagnosis is less clear without a tissue diagnosis and with only a history of positive somatostatin receptor imaging (with or without MEN1).

In patients with a positive imaging study and fasting hypergastrinemia without peptic ulcer disease or diarrhea, a lack of atrophic gastritis and the absence of parietal cell and intrinsic factor antibodies suggests gastrinoma. However, it is important to note that atrophic gastritis can be missed with this approach as detection depends on biopsy location and number, and parietal cell and intrinsic factor antibodies are not always positive.

Furthermore, the use of somatostatin imaging (eg, 68Ga-DOTATATE positron emission tomography [PET]/computed tomography [CT] or 111In-DTPA-octreotide with single-photon emission CT [SPECT]/CT) for diagnosis is of limited value, as it can detect any benign or malignant process overexpressing somatostatin receptors, and there can be uptake in nonneoplastic conditions like arthritis, infections, thyroid disease, granulomatous diseases [8].

Serum gastrin concentration — Fasting serum gastrin should be measured in any patient suspected of having ZES [6]. A serum gastrin value greater than 10 times the upper limit of normal (1000 pg/mL) in the presence of a gastric pH below 2 is diagnostic of ZES. Higher levels are more likely with pancreatic (compared with duodenal) tumors, larger tumor size, and with metastatic disease [6]. Measurement of gastric pH on a single specimen is important to exclude secondary hypergastrinemia due to achlorhydria (eg, atrophic gastritis, pangastritis-associated *Helicobacter pylori* infections, renal failure, vagotomy, and ingestion of gastric acid antisecretory drugs [eg, PPIs]). In such cases the serum gastrin level can exceed 1000 pg/mL, but the gastric pH is >2. Importantly, these "appropriate" hypergastrinemic conditions are much more common and need to be distinguished from inappropriate causes, such as ZES [8]. While assessment of gastric pH is classically required for the diagnosis of ZES, case series suggest that assessment of gastric acidity is underutilized. This is likely due to the inability to stop PPIs or unfamiliarity with gastric pH testing).

Approximately two-thirds of patients with ZES have serum gastrin concentrations less than 10 times the upper limit of normal (between 110 and 1000 pg/mL) [6]. This degree of hypergastrinemia is nonspecific and can also be present in patients with increased gastric acid secretion (eg, antral G-cell hyperplasia, gastric outlet obstruction, and retained gastric antrum). Patients receiving PPIs generally have elevated serum gastrin levels. Fasting serum gastrin levels can fluctuate even within the same patient, and elevated levels should be rechecked (see 'Differential diagnosis' below). Importantly, no level of hypergastrinemia can distinguish appropriate from inappropriate hypergastrinemia; high levels can be seen in the setting of atrophic gastritis or PPI use [8]. However, persistently normal fasting serum gastrin values are exceedingly uncommon in ZES [8].

Commercial immunoassay kits in current use vary in their accuracy [22,23]. In one study that evaluated 12 different commercial assay kits, four of the kits returned falsely low results in 20 to

80 percent of patients [23]. False negatives are most likely to occur at relatively low gastrin concentrations, with most assays accurately detecting patients with ZES whose serum gastrin concentrations are greater than 400 pmol/L (845 pg/mL).

Secretin stimulation test — The secretin stimulation test is used to differentiate patients with gastrinomas from other causes of hypergastrinemia (eg, in the setting of gastrin, <10-fold upper limit of normal and gastric pH ≤2). Although, some have questioned the test's utility since achlorhydria can lead to false positives [8]. Secretin stimulates the release of gastrin by gastrinoma cells, and patients with ZES tumors have a dramatic rise in serum gastrin. In contrast, normal gastric G cells are inhibited by secretin.

The secretin test should not be performed in a patient on PPIs. False-negative responses have been reported in 6 to 20 percent of patients [24]. However, other studies suggest that false-negative results caused by PPIs may be low in frequency, particularly in patients with a high pretest probability of ZES [25]. False-positive results occurred in 15 to 39 percent of patients with achlorhydria induced by PPIs or due to chronic atrophic gastritis [26]. However, if PPIs are discontinued abruptly, patients with ZES are at high risk to develop complications (such as acute bleeding and perforation) during the interim week [27]. As such, discontinuation of a PPI in a patient suspected of having ZES should be done by an experienced provider. Before this is attempted, an endoscopy should be performed to exclude active ulcer disease. If ulceration is present, suppressive PPI therapy should be used until active disease is healed before stopping PPI therapy [8]. One week prior to the secretin study we substitute PPIs with high-dose H2 receptor antagonists (eg, cimetidine 300 to 600 mg every six hours) until 12 to 30 hours prior to the test [8]. Oral antacids are then taken as needed until midnight prior to the study. Patients should be advised to seek immediate medical attention for nasogastric aspiration if they develop significant exacerbation of ZES symptoms (eg, vomiting, pain, diarrhea) during the taper period [28].

The secretin stimulation test is performed by administering 0.4 micrograms/kg by rapid infusion intravenously over one minute; a baseline fasting serum gastrin is measured twice before the secretin is administered and 2, 5, and 10 minutes later. Several criteria have been proposed to define a positive test; an increase in gastrin levels of greater than 120 pg/mL over basal fasting levels has a sensitivity and a specificity of 94 and 100 percent, respectively (others use an absolute increase greater than 110 or 200 pg/mL, or a 50 percent increase in gastrin levels) [21,22,29]. Serum gastrin levels usually peak by 10 minutes (figure 2).

The secretin stimulation test should not be performed in patients with active severe manifestations of ZES. This includes patients with severe abdominal pain, vomiting and diarrhea to the point of dehydration, or endoscopic findings of thickened gastric folds or multiple ulcers,

as they are at particular risk for life-threatening consequences of discontinuing acid suppression. In such patients, tumor localization studies should be performed. (See 'Tumor localization' below.)

Other — Other tests that are supportive of the diagnosis of ZES but are less commonly performed include the following [8]:

- **Serum chromogranin A** – Serum chromogranin A is elevated in most patients with gastrinomas, and the level of elevation tends to correlate with tumor volume [30]. In contrast to other neuroendocrine tumors, very high levels of chromogranin A can be seen in gastrinomas without liver metastases [31]. Chromogranin A levels are usually normal or near normal in patients with high gastrin levels secondary to chronic atrophic gastritis. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts", section on 'Stomach'.)

  However, serum chromogranin A is less sensitive for a gastrinoma as compared with fasting serum gastrin levels. In addition, elevated chromogranin A is not specific to gastrinomas and is a general marker for well-differentiated neuroendocrine tumors [32]. Elevated chromogranin A levels may be seen in a number of other conditions including PPI use [33,34].

- **Gastric acid secretion studies** – Gastric acid secretion studies to measure basal acid output, which were once pivotal in establishing the diagnosis of ZES, are no longer performed due to their technical difficulty [26]. Basal acid output is measured by the passage of a nasogastric tube into the dependent portion of the stomach with aspiration and quantification of gastric juice production over a one-hour period. A basal acid output of >15 mEq/hour is supportive of the diagnosis of ZES.

DIFFERENTIAL DIAGNOSIS

- **Antral G-cell hyperplasia** – Antral G-cell hyperplasia is a rare entity associated with increase in the number of G cells and characterized by a marked hypergastrinemia. Peptic ulcers can also be seen in patients with antral G-cell hyperplasia. However, unlike Zollinger Ellison syndrome (ZES), antral G-cell hyperplasia is characterized by a poor response to secretin stimulation test, and absence of gastrinoma on imaging.

- **Retained antrum syndrome** – Retained antrum syndrome should be suspected in patients with recurrent peptic ulceration after gastrectomy. In such cases, peptic ulcer recurrence results from incomplete excision of the gastric antrum from the duodenum.

Gastrin elevation in patients with retained antrum syndrome is only modest as compared with patients with ZES, and hypergastrinemia is reversible with excision of the retained antral remnant.

TUMOR LOCALIZATION

After the diagnosis of Zollinger-Ellison syndrome (ZES) is made, the gastrinoma must be located and staged. (See "Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)" and "Multiple endocrine neoplasia type 1: Management".)

- Tumor localization begins with an upper endoscopy if not already performed, cross-sectional imaging with helical, contrast-enhanced, triple-phase computed tomography (CT) or magnetic resonance imaging (MRI), and somatostatin receptor-based imaging (somatostatin receptor scintigraphy [SRS]) using 111-In pentetreotide, or integrated PET/CT using Gallium-68-DOTA-0-Phe^{1}-Tyr^{3}-Octreotate (Gallium Ga-68 DOTATATE) or Gallium-68-DOTA-0-Phe^{1}-Tyr^{3}-Octreotide (Gallium Ga-68 DOTATOC) [35,36]. Because of its greater sensitivity, Ga-68 DOTATATE or Ga-68 DOTATOC PET imaging may be preferable to conventional SRS with 111-In pentetreotide [37,38]. (See 'Endoscopic features' above and "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Somatostatin-receptor-based imaging'.)

- If CT/MRI and somatostatin receptor-based imaging are negative, and surgery is being considered, an endoscopic ultrasound (EUS) should be performed because of its greater sensitivity in detecting small tumors. EUS also permits fine-needle aspiration for histological identification. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Endoscopic ultrasonography'.)

- We reserve invasive testing to localize the tumor with angiography or selective arterial stimulation and venous sampling with secretin injection for patients who are strongly suspected of having a gastrinoma in whom imaging is negative [39]. The sensitivity for pancreas tumors is 75 to 100 percent, and the specificity is 95 percent; the sensitivity for duodenal tumors is 38 to 63 percent [22].

- However, in some cases tumor localization can only be achieved at laparotomy by direct palpation, duodenal transillumination, or intraoperative ultrasound. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Intraoperative localization techniques' and 'Evaluation' above.)

STAGING SYSTEM

Two staging systems are available for pancreatic neuroendocrine tumors such as gastrinomas, one from the combined American Joint Committee on Cancer/Union for International Cancer Control (UICC) [40], and another proposed by the European Neuroendocrine Tumor Society (table 3) [40,41]. Both staging systems are highly prognostic for both relapse-free and overall survival [42-44]. The newest update of the TNM staging classification (8th edition, 2017) has a staging system for neuroendocrine tumors of the pancreas (table 4) that is separate from that used for exocrine pancreatic tumors [45]. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Staging system'.)

ADDITIONAL EVALUATION

We suggest biochemical studies to screen for multiple endocrine neoplasia type 1 (MEN1) in patients with Zollinger-Ellison syndrome (ZES), as 20 to 25 percent of patients have MEN1 and because up to 40 percent of MEN1/ZES patients have no family history [13].

- All patients with ZES should have serum parathormone levels, ionized calcium levels, and prolactin levels at diagnosis and periodically thereafter [13]. Screening for MEN1-associated tumors is discussed separately. (See 'Epidemiology' above and "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis", section on 'Monitoring for MEN1-associated tumors'.)

- Individuals with a family history of MEN1, suspicious clinical or laboratory findings (eg, renal colic or nephrolithiases, history of hypercalcemia), or multiple MEN1 tumor types (parathyroid gland, anterior pituitary, and enteropancreatic) should undergo evaluation for MEN1 syndrome. The management of patients with MEN1 is discussed separately. (See "Multiple endocrine neoplasia type 1: Management".)

- All patients with gastrinoma should at least be considered for testing for an inherited genetic syndrome. Data suggest that 17 percent of patients with seemingly sporadic pancreatic neuroendocrine tumors harbor germline alterations in any one of a variety of genes (including *MUTYH, CHEK2*, and *BRCA2*, as well as *MEN1* and *VHL*).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Well-differentiated gastroenteropancreatic neuroendocrine tumors".)

SUMMARY AND RECOMMENDATIONS

- Zollinger-Ellison syndrome (ZES) is caused by secretion of gastrin by duodenal or pancreatic neuroendocrine tumors (gastrinomas). The annual incidence of gastrinomas is 0.5 to 2 per million population. Most patients are diagnosed between the ages of 20 and 50, with a higher incidence in males as compared with females. While most gastrinomas are sporadic, 20 to 30 percent occur in association with multiple endocrine neoplasia type 1 (MEN1) syndrome. Approximately 50 to 88 percent of sporadic ZES patients, and 70 to 100 percent of ZES and MEN1, have duodenal gastrinomas. (See 'Epidemiology' above and 'Classification, nomenclature, and histology' above.)

- Excessive gastrin secretion from a gastrinoma results in high gastric acid output. Chronic diarrhea results from failure of resorption of the increased gastric acid, inactivation of pancreatic enzymes, damage to intestinal epithelium, and inhibition of the absorption of sodium and water. (See 'Classification, nomenclature, and histology' above and 'Pathophysiology' above.)

- Abdominal pain (75 percent) and diarrhea (73 percent) are the most common symptoms in patients with ZES. Nearly half of patients have heartburn due to gastroesophageal reflux (figure 1). Other symptoms include weight loss (17 percent) and gastrointestinal bleeding (25 percent). (See 'Clinical presentation' above.)

- Over 90 percent of patients with ZES develop peptic ulcers. Patients with ZES often present with solitary ulcers less than 1 cm in diameter. Approximately 75 percent of ulcers are in the first portion of the duodenum, 14 percent in the distal duodenum, and 11 percent in the jejunum. Ulcers in ZES may be refractory to proton pump inhibitors and recur much more often as compared with patients with sporadic ulcer disease. On upper endoscopy, patients with ZES may have prominent gastric folds and evidence of reflux esophagitis. However, strictures of the esophagus, pylorus, or duodenum are present in less than 10 percent of patients. (See 'Endoscopic features' above.)

- ZES should be suspected in patients with multiple or refractory peptic ulcers; ulcers distal to the duodenum; peptic ulcer disease and diarrhea, enlarged gastric folds, an endocrinopathy or MEN1 (table 2). ZES should also be suspected in patients with peptic

ulcer disease and a family history of peptic ulcer disease or MEN1. The diagnosis is established by demonstrating an elevated basal or stimulated gastrin concentration, ideally assessed off a PPI (if safe) and in the setting of a gastric pH <2. (See 'Diagnosis' above.)

- Tumor localization begins with an upper endoscopy if not already performed, cross-sectional imaging with helical, contrast-enhanced, triple-phase computed tomography (CT) or magnetic resonance imaging (MRI), and somatostatin receptor-based imaging using somatostatin receptor scintigraphy (SRS) with 111-In pentetreotide or integrated PET/CT using Gallium Ga-68 DOTATATE or Ga-68 DOTATOC. Because of its greater sensitivity, Ga-68 DOTATATE or Ga-68 DOTATOC PET/CT is preferred over conventional SRS with 111-In pentetreotide, where available. If CT or MRI and somatostatin receptor-based imaging are negative, and surgery is being considered, endoscopic ultrasound should be performed to localize the tumor. We reserve invasive testing to localize the tumor with angiography or selective arterial stimulation and venous sampling with secretin injection for patients who are strongly suspected of having a gastrinoma in whom imaging is negative. However, in some cases, tumor localization can only be achieved at laparotomy, by direct palpation, duodenal transillumination, or intraoperative ultrasound. (See 'Tumor localization' above.)

- All patients with gastrinoma should at least be considered for testing for inherited genetic syndromes. Approximately 20 to 30 percent of patients develop ZES in the setting of MEN1 syndrome. As such, all patients with ZES should be screened for MEN1 syndrome with serum parathormone levels, ionized calcium levels, and prolactin levels at diagnosis, and periodically thereafter. Individuals with a family history of MEN1, suspicious clinical or laboratory findings (eg, renal colic or nephrolithiases, history of hypercalcemia), or multiple MEN1 tumor types (parathyroid gland, anterior pituitary, and enteropancreatic) should undergo evaluation for MEN1 syndrome. (See 'Additional evaluation' above and "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Dr. Stephen E. Goldfinger, MD, for his past contributions as an author to previous versions of this topic review.

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Topic 2627 Version 27.0

GRAPHICS

Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatobiliary organs, World Health Organization (WHO), 2019

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm^2)	Ki-67 index* (percent)
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type (SCNEC)	Poorly differentiated	High[Δ]	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High[Δ]	>20	>20
MiNEN	Well or poorly differentiated[¶]	Variable[¶]	Variable[¶]	Variable[¶]

NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; SCNEC: small cell neuroendocrine carcinoma; LCNEC: large cell neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-nonneuroendocrine neoplasm.

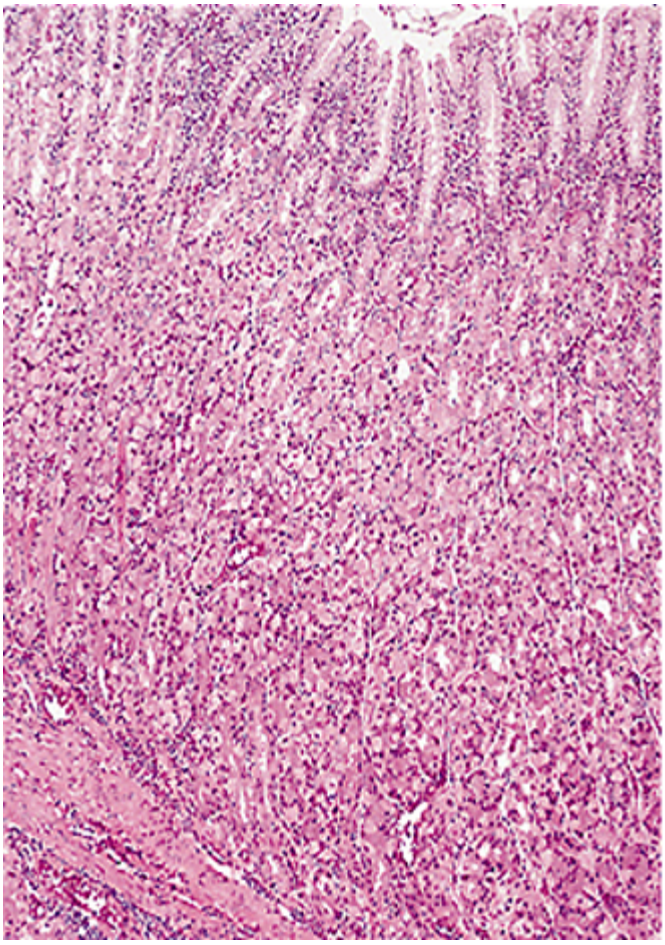
* Mitotic rates are to be expressed as the number of mitoses/2 mm^2 (equalling 10 high-power fields at 40× magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm^2 (ie, in a total area of 10 mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher grade category.

¶ In most MiNENs, both the neuroendocrine and nonneuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

Δ Poorly differentiated NECs are not formally graded but are considered high grade by definition.

Graphic 122325 Version 10.0

Zollinger-Ellison syndrome

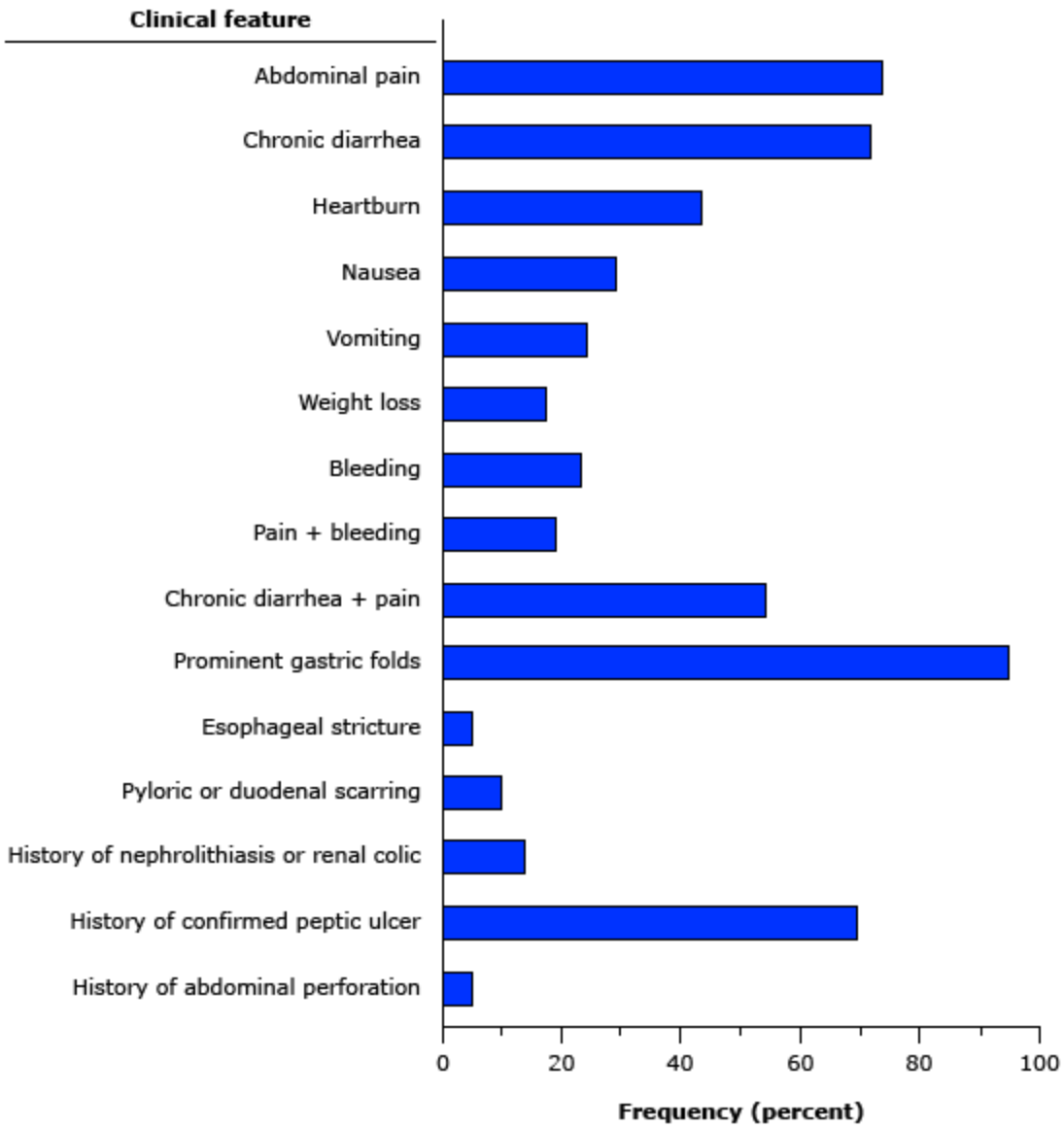


Low power light micrograph of a gastric body biopsy from a patient with Zollinger-Ellison syndrome. The mucosa has an abnormally thick pit compartment and an expanded glandular compartment with much of the expansion due to an excess of parietal cells.

From: Lewin KJ, Appelman HD. Tumors of the esophagus and stomach. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 18, 1996, Washington, DC. Armed Forces Institute of Pathology.

Graphic 78549 Version 3.0

Presenting symptoms and signs in patients with Zollinger-Ellison syndrome



The presence or absence of clinical symptoms or signs at the initial assessment in 261 patients with Zollinger-Ellison syndrome (ZES). Prominent gastric body folds, esophageal stricture, and pyloric or duodenal scarring were determined by upper gastrointestinal endoscopy; a confirmed peptic ulcer was assessed by upper gastrointestinal endoscopy or radiographic studies.

Data from: Roy PK, Venzon DJ, Shojamenesh H, et al, Medicine (Baltimore) 2000; 79:379.

Graphic 82168 Version 5.0

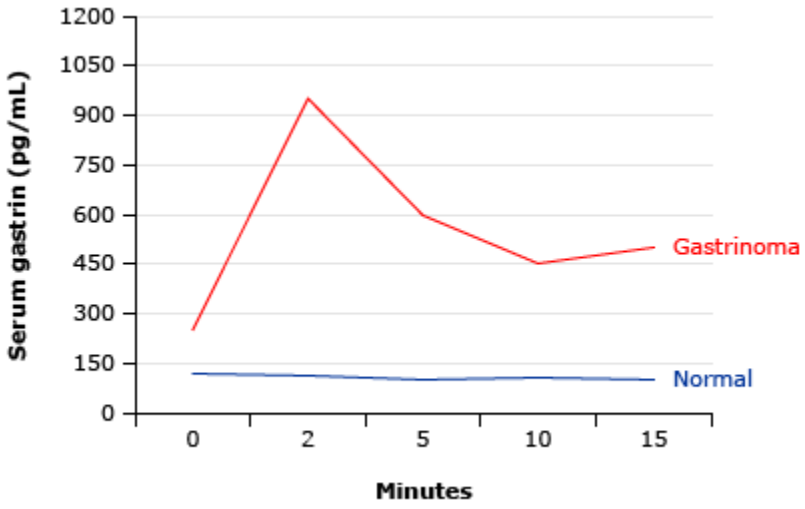
Clinical features associated with peptic ulcer disease in patients with gastrinoma

Clinical presentation
Esophageal reflux disease, especially when severe
Association with diarrhea, steatorrhea, or weight loss (due to the high rate of acid secretion and secondary disruption of digestion enzyme and absorptive function)
Clinical findings
Multiple ulcers
Peptic ulcers in *Helicobacter pylori*-negative, NSAID-negative subjects
Ulcers beyond the duodenal bulb
Increased gastric folds on upper GI series or endoscopy
Findings suggestive of multiple endocrine neoplasia type I (see Family history)
Family history
Extensive family history of ulcer disease
Family history or other findings suggestive of multiple endocrine neoplasia type I
Hypercalcemia or nephrolithiasis due to primary hyperparathyroidism
Hypoglycemia due to insulinoma
Functioning or nonfunctioning pituitary tumor
Diarrhea due to VIPoma
Natural history and response to treatment
Ulcers resistant to medical therapy
Frequent recurrences
Ulcer recurrences after surgical treatment

NSAID: nonsteroidal antiinflammatory drug; GI: gastrointestinal.

Graphic 50291 Version 5.0

Secretin test for gastrinoma



Marked hypersecretion of gastrin occurs after the administration of secretin in a patient with a gastrinoma (Zollinger-Ellison syndrome) compared to the lack of response in normal subjects.

Graphic 66223 Version 2.0

ENETS staging system for pancreatic neuroendocrine tumors

TNM			
T - primary tumor			
For any T, add (m) for multiple tumors			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor limited to pancreas and size <2 cm		
T2	Tumor limited to the pancreas and size 2-4 cm		
T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct		
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)		
N - regional lymph nodes			
NX	Regional lymph node cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M - distant metastases			
MX	Distant metastasis cannot be assessed		
M0	No distant metastases		
M1	Distant metastasis		
Stage			
Disease stages			
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

TNM: tumor, nodes, metastasis.

Reference:

1. Sobin LH, Wittekind C (Eds). TNM classification of malignant tumours. Wiley-Liss, New York, 2002.

Reproduced from: Rindi G, Kloppel H, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 449:395. Copyright © 2006; with kind permission from Springer Science + Business Media B.V.

Graphic 86409 Version 4.0

Neuroendocrine tumors of the pancreas TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Tumor cannot be assessed
T1	Tumor limited to the pancreas,* <2 cm
T2	Tumor limited to the pancreas,* 2 to 4 cm
T3	Tumor limited to the pancreas,* >4 cm; or tumor invading the duodenum or common bile duct
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)
* *Limited to the pancreas* means there is no invasion of adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery). Extension of tumor into peripancreatic adipose tissue is NOT a basis for staging. *NOTE:* Multiple tumors should be designated as such (the largest tumor should be used to assign T category): ▪ If the number of tumors is known, use T(#); eg, pT3(4) N0 M0. ▪ If the number of tumors is unavailable or too numerous, use the *m* suffix, T(m); eg, pT3(m) N0 M0.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group**

			is...
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	II
T4	N0	M0	III
Any T	N1	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer control.

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Graphic 111355 Version 9.0

Contributor Disclosures

Emily Bergsland, MD Grant/Research/Clinical Trial Support: Merck [Carcinoid/pNET]. All of the relevant financial relationships listed have been mitigated. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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