TREATMENT PANCREATIC NEUROENDOCRINE TUMOR (GENERAL POINTS)

Treatment of pNETs requires two different strategies. First, treatment must be directed at the hormone-excess state such as the gastric acid hypersecretion in gastrinomas or the hypoglycemia in insulinomas. Ectopic hormone secretion usually causes the presenting symptoms and can cause life-threatening complications. Second, with all the tumors except insulinomas, >50% are malignant (Table 113-2); therefore, treatment must also be directed against the tumor per se. Because in many patients these tumors are not surgically curable due to the presence of advanced disease at diagnosis, surgical resection for cure, which addresses both treatment aspects, is often not possible.

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)

A gastrinoma is an NET that secretes gastrin; the resultant hypergastrinemia causes gastric acid hypersecretion (Zollinger-Ellison syndrome [ZES]). The chronic hypergastrinemia results in marked gastric acid hypersecretion and growth of the gastric mucosa with increased numbers of parietal cells and proliferation of gastric ECL cells. The gastric acid hypersecretion characteristically causes peptic ulcer disease (PUD), often refractory and severe, as well as diarrhea. The most common presenting symptoms are abdominal pain (70–100%), diarrhea (37–73%), and gastroesophageal reflux disease (GERD) (30–35%); 10–20% of patients have diarrhea only. Although peptic ulcers may occur in unusual locations, most patients have a typical duodenal ulcer. Important observations that should suggest this diagnosis include PUD with diarrhea; PUD in an unusual location or with multiple ulcers; PUD refractory to treatment or persistent; PUD associated with prominent gastric folds; PUD associated with findings suggestive of MEN 1 (endocrinopathy, family history of ulcer or endocrinopathy, nephrolithiases); and PUD without *Helicobacter pylori* present. *H. pylori* is present in >90% of idiopathic peptic ulcers but is present in <50% of patients with gastrinomas. Chronic unexplained diarrhea also should suggest ZES.

Approximately 20–25% of patients with ZES have MEN 1 (MEN1/ZES), and in most cases, hyperparathyroidism is present before the ZES develops. These patients are treated differently from those without MEN 1 (sporadic ZES); therefore, MEN 1 should be sought in all patients with ZES by family history and by measuring plasma ionized calcium and prolactin levels and plasma hormone levels (parathormone, growth hormone).

Most gastrinomas (50–90%) in sporadic ZES are present in the duodenum, followed by the pancreas (10–40%) and other intraabdominal sites (mesentery, lymph nodes, biliary tract, liver, stomach, ovary). Rarely, the tumor may involve extraabdominal sites (heart, lung cancer). In MEN 1/ZES the gastrinomas are also usually in the duodenum (70–90%), followed by the pancreas (10–30%), and are almost always multiple. About 60–90% of gastrinomas are malignant (Table 113-2) with metastatic spread to lymph nodes and liver. Distant metastases to bone occur in 12–30% of patients with liver metastases.

Diagnosis The diagnosis of ZES requires the demonstration of inappropriate fasting hypergastrinemia, usually by demonstrating hypergastrinemia occurring with an increased basal gastric acid output (BAO) (hyperchlorhydria). More than 98% of patients with ZES have fasting hypergastrinemia, although in 40–60% the level may be elevated less than tenfold. Therefore, when the diagnosis is suspected, a fasting gastrin is usually the initial test performed. It is important to remember that potent gastric acid suppressant drugs such as proton pump inhibitors (PPIs) (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) can suppress acid secretion sufficiently to cause hypergastrinemia; because of their prolonged duration of action, these drugs have to be tapered or frequently discontinued for a week before the gastrin determination. Withdrawal of PPIs should be performed carefully because PUD complications can rapidly develop in some patients and is best done in consultation with GI units with experience in this area. The widespread use of PPIs can confound the diagnosis of ZES by raising a false-positive diagnosis by causing hypergastrinemia in a patient being treated with idiopathic PUD (without ZES) and lead to a false-negative diagnosis because at routine doses used to treat patients with idiopathic PUD, PPIs control symptoms in most ZES patients and thus mask the diagnosis. If ZES is suspected and the gastrin level is elevated, it is important to show that it is increased when gastric pH is ≤2.0 because physiologically hypergastrinemia secondary to achlorhydria (atrophic gastritis, pernicious anemia) is one of the most common causes of hypergastrinemia. Nearly all ZES patients have a fasting pH ≤2 when off antisecretory drugs. If the fasting gastrin is >1000 pg/mL (increased tenfold) and the pH is ≤2.0, which occurs in 40–60% of patients with ZES, the diagnosis of ZES is established after the possibility of retained antrum syndrome has been ruled out by history. In patients with hypergastrinemia with fasting gastrins <1000 pg/mL (<10-fold increased) and gastric pH ≤2.0, other conditions, such as *H. pylori* infections, antral G-cell hyperplasia/hyperfunction, gastric outlet obstruction, and, rarely, renal failure, can masquerade as ZES. To establish the diagnosis in this group, a determination of BAO and a secretin provocative test should be done. In patients with ZES without previous gastric acid–reducing surgery, the BAO is usually (>90%) elevated (i.e., >15 mEq/h). The secretin provocative test is usually positive, with the criterion of a >120-pg/mL increase over the basal level having the highest sensitivity (94%) and specificity (100%). Unfortunately the diagnosis of ZES is becoming increasing more difficult. This is due not only to the widespread use of PPIs (leading to false-positive results as well as masking ZES presentation), but also recent studies demonstrate than many of the commercial gastrin kits that are used by most laboratories to measure fasting serum gastrin levels are not reliable. In one study, 7 of the 12 tested commercial gastrin kits inaccurately assessed the true serum concentration of gastrin primarily because the antibodies used had inappropriate specificity for the different circulating forms of gastrin and were not adequately validated. Both underestimation and overestimation of fasting serum gastrin levels occurred using these commercial kits. To circumvent this problem, it is either necessary to use one of the five reliable kits identified or, alternatively, to refer the patient to a center with expertise in making the diagnosis in your area, or if this is not possible, to contact such a center and use the gastrin assay they recommend. An accurate gastrin assay is essential for accurate measurement of fasting serum gastrin level as well as for assessing gastrin levels during the secretin provocative test, and thus, the diagnosis of ZES cannot reliably be made without one.

TREATMENT ZOLLINGER-ELLISON SYNDROME

Gastric acid hypersecretion in patients with ZES can be controlled in almost every case by oral gastric antisecretory drugs. Because of their long duration of action and potency, which allows dosing once or twice a day, the PPIs (H^+, K^+-ATPase inhibitors) are the drugs of choice. Histamine H_2-receptor antagonists are also effective, although more frequent dosing (q 4–8 h) and high doses are required. In patients with MEN 1/ZES with hyperparathyroidism, correction of the hyperparathyroidism increases the sensitivity to gastric antisecretory drugs and decreases the basal acid output. Long-term treatment with PPIs (>15 years) has proved to be safe and effective, without development of tachyphylaxis. Although patients with ZES, especially those with MEN 1/ZES, more frequently develop gastric NETs (carcinoids), no data suggest that the long-term use of PPIs increases this risk in these patients. With long-term PPI use in ZES patients, vitamin B_{12} deficiency can develop; thus, vitamin B_{12} levels should be assessed during follow-up. Epidemiologic studies suggest that long-term PPI use may be associated with an increased incidence of bone fractures; however, at present, there is no such report in ZES patients.

With the increased ability to control acid hypersecretion, more than 50% of patients who are not cured (>60% of patients) will die from tumor-related causes. At presentation, careful imaging studies are essential to localize the extent of the tumor to determine the appropriate treatment. A third of patients present with hepatic