Introduction

Gastrinoma was first recognized as a disease entity, the Zollinger-Ellison syndrome (ZES), in 1955.[1] Initial management of this syndrome was historically directed at the end organ (the stomach) and necessitated total gastrectomy. In recent years, management has changed as a result of the development of medications to control acid hypersecretion, the ability to preoperatively confirm the diagnosis, and the availability of more effective techniques to adequately localize tumors. Currently, attention is directed at management of the primary tumor rather than gastric ulceration. This review outlines the current management of the patient with gastrinoma and specifically addresses diagnosis, imaging studies, nonoperative management, operative management, and patient follow-up.

Diagnosis

While most individuals experience some degree of intermittent hyperacidity requiring symptomatic treatment (eg, antacids), only a small percentage of these people will have a gastrinoma. In essence, a gastrinoma should be suspected if a patient presents with unusual symptoms, such as a peptic ulcer and diarrhea, familial ulcer disease, recurrent ulcer, ulcers of the distal duodenum or jejenum, ulcer disease in conjunction with hypercalcemia, or an ulcer that fails to heal on conventional doses of an H₂-blocker or omeprazole (Fig 1). In addition, a patient being considered for an “ulcer” operation should have at least a baseline fasting serum gastrin level measured in order to exclude gastrinoma as a possible cause. This is also the first step in establishing a diagnosis of gastrinoma.

If symptoms suggest a gastrinoma, both fasting serum hypergastrinemia of more than 100 pg/mL and an elevated basal acid output (BAO) of more than 15 mEq/h must be present to establish the diagnosis of ZES. If either of these tests is inconclusive, a secretin stimulation test should be performed to confirm the diagnosis. This test involves administering intravenously a secretin bolus of 2 U/kg and monitoring subsequent serum levels of serum gastrin over 30 minutes. An increase in the serum gastrin level of 200 pg/mL or greater at 10 minutes is indicative of the presence of gastrinoma. It is rare for a patient with ZES to have a normal fasting serum gastrin level (false negative).

Several disorders, however, can cause hypergastrinemia (false positive). Hypergastrinemia in association with low BAO can be seen in patients on therapy with H₂-blockers or omeprazole (which should be discontinued prior to measurement of the gastrin level), vagotomy, renal failure, or achlorhydria associated with pernicious anemia or atrophic gastritis. Hypergastrinemia and elevated BAO are seen in patients with gastric outlet obstruction, in those with antral G-cell hyperplasia, in patients with the retained antrum syndrome, or in those who have had a recent massive small bowel resection. Hypergastrinemia has been recently reported to be associated with hyperchlorhydria in patients with Helicobacter pylori infections.[2] Eradication of the H pylori led to a decrease in serum gastrin levels. All of these conditions can be distinguished from gastrinoma by a negative secretin provocative test.

Another important consideration in the diagnosis of gastrinoma is the presence of other endocrine abnormalities, particularly multiple endocrine neoplasia syndrome type 1 (MEN 1). The natural history and treatment of patients with gastrinoma and MEN 1 differ from those of patients with sporadic gastrinoma. Since approximately 20% to 60% of patients with gastrinoma have the MEN 1 syndrome, it is important to make this diagnosis.[3-6] The initial presenting symptom is usually hypercalcemia, although one third of patients may present with the ZES as their initial manifestation of MEN 1.[7]
Imaging Studies

When biochemical evidence of gastrinoma has been established, an attempt to locate the primary tumor should be made. Other important considerations include evaluation for local resectability and the presence of metastatic disease. The first imaging study should be an abdominal computed tomography (CT) scan (Fig 2). A CT scan not only can demonstrate the primary tumor, but also can provide information regarding both the possibility of resectability and the presence of metastatic disease. However, up to 50% of gastrinomas may not be detected by CT scan, especially tumors that are smaller than 3 cm or extrapancreatic tumors.[8] Even with dynamic CT scanning, which improves the accuracy of CT scans in this respect with a sensitivity rate of 75% to 80%, many small tumors may be missed.[8,9] Magnetic resonance imaging has a reported sensitivity of 83% in detecting metastatic gastrinoma in the liver but only a 25% sensitivity in localizing the primary tumor.[10]

The best traditional modality for the diagnosis of both primary and metastatic disease is selective angiography. Unfortunately, this test is invasive and overlooks small tumors.[11] The addition of selective secretin injection and venous sampling to selective angiography improves the accuracy of this modality but increases the morbidity, the expense, and the length of time needed for the procedure.[12] It also requires experienced and dedicated interventional radiologists.

More recently, two tests have been introduced into the diagnostic armamentarium: endoscopic ultrasonography (EUS) and the octreotide scan. Since most gastrinomas contain somatostatin receptors, they can theoretically be imaged with octreotide, the somatostatin analog. EUS is capable of identifying tumors as small as 2 to 3 mm in the duodenal wall[13] and has a reported sensitivity of 80% to 85% with a specificity of 95%.[14,15] While EUS is a more effective test for the localization of primary tumors, the octreotide scan is superior for identifying metastatic tumors. The octreotide scan is less useful for primary tumor localization.[16] Most reported series with this test have been small, however, and its actual usefulness is yet to be determined.

Nonoperative Management

Effective medical therapy is currently available for the acid hypersecretion found in patients with gastrinoma. In fact, patients with ZES rarely die of the complications of peptic ulcer disease, but rather they die of progression of their gastrinoma. While it makes intuitive sense that removal of the primary gastrinoma will prolong survival (and a recent study from the National Institutes of Health appears to confirm this[17]), many patients still present with unresectable disease as a result of local tumor invasion, extensive metastases, or poor overall health. Most of these patients can maintain excellent acid secretory control with increasing doses of H₂-blockers or omeprazole. However, a patient with ZES is usually given acid-reducing drugs at a dose that is twice that given to the patient with uncomplicated peptic ulcer disease. The goal is to maintain a BAO of less than 10 mEq/h in the uncomplicated patient and a BAO of less than 5 mEq/h in the patient with reflux esophagitis or previous gastric surgery.

The issue, therefore, becomes the availability of a treatment to inhibit the growth of tumor in those patients deemed unresectable. Chemotherapy is usually streptozotocin-based, with the "best" regimen being a combination of streptozotocin, fluorouracil, and doxorubicin.[18,19] However, while partial response rates of up to 40% have been observed, survival does not appear to be affected. Selective embolization with or without chemotherapy is sometimes used to eradicate liver lesions and has been found to decrease gastrin levels and medication doses, but this also does not appear to affect survival.[20,21] Octreotide has been used to treat some patients with metastatic disease, but the benefit of this treatment remains unproven.[22]

Gastrinomas in patients with MEN 1 are thought to be multiple occurring throughout the pancreas. Since total pancreatectomy would be the only way to cure these patients, most were managed nonoperatively in the past. Since correction of hyperparathyroidism usually results in a decrease in serum gastrin, it is well accepted that parathyroidectomy for the correction of primary hyperparathyroidism should be the initial surgical procedure in these patients. This approach leads to a decrease in the symptomatology of ZES, as well as decreases in the fasting serum gastrin levels and the BAO.[23]

Recent reports indicate that patients with MEN 1 and gastrinoma may have extrapancreatic primaries and may benefit from surgical removal of the primary tumor.[24,25] Surgery, however, is still reserved for a select few of these individuals.

Operative Management

Not all patients who come to the operating room with the diagnosis of ZES have preoperative tumor localization. Also, many patients, even those with no evidence of metastatic disease on preoperative studies, may have miliary disease at the time of laparotomy. Thus, the first step should be laparoscopy for identification of metastatic disease. Identification of the primary tumor may require intraoperative ultrasonography, direct palpation of the duodenum, and even intraoperative endoscopy and transillumination of the duodenal wall.[13] and has a reported sensitivity of 80% to 85% with a specificity of 95%.[14,15] While EUS is a more effective test for the localization of primary tumors, the octreotide scan is superior for identifying metastatic tumors. The octreotide scan is less useful for primary tumor localization.[16] Most reported series with this test have been small, however, and its actual usefulness is yet to be determined.

The surgical options for resection of the primary tumor include enucleation, duodenal resection, or pancreatic resection. A select few patients may benefit from a pancreaticoduodenectomy, but only if all gross tumor can be removed. There is increasing evidence to suggest that the removal of metastatic disease may prolong survival in some patients. While controversial, this approach appears most beneficial to patients with solitary, localized metastatic disease.[29,30]

A few patients have primary tumors that cannot be identified at the time of operation. Again, the treatment of these patients is controversial, but we believe that a "blind" resection should not be performed. Most of these patients can be managed medically. Patients who have failed medical management may undergo highly selective vagotomy to facilitate medical management and should be followed for the development of resectable disease at a later date. Total gastrectomy is rarely indicated.

Follow-up

Follow-up of the patient with gastrinoma that has been resected is directed at the diagnosis and treatment of recurrence. Again, measurement of the fasting serum gastrin level is the best screening test to follow these patients. Symptoms of recurrence including recurrent peptic ulceration, diarrhea, or abdominal pain are also important findings. If recurrent disease is identified, reoperation may be considered and undertaken if all disease can be fully resected. For the unresectable patient, management is similar to that described for nonoperative management.

Conclusions

The management of the patient with gastrinoma has shifted to the early diagnosis and subsequent removal of the tumor (Fig 3). Diagnosis is usually established earlier due to physician awareness, readily available diagnostic tests, and better imaging modalities. Surgery still plays a major role for potential cure and relief of symptoms. Even in patients with metastatic disease, tumor resection and even debulking may be effective in symptom-free, long-term survival.
Although no potentially curative nonoperative options are currently available, medical management can control the majority of symptoms from hyperacidity and hypergastrinemia. Since the majority of patients can now be spared the complications of peptic ulcer disease and the morbidity of total gastrectomy, attention is directed at high-quality, long-term survival. In those patients with gastrinoma as part of MEN 1, nonoperative management of the gastrinoma appears to be the best treatment with operative treatment directed at the primary hyperparathyroidism.

References

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