Surgical Treatment of Zollinger-Ellison Syndrome in Multiple Endocrine Neoplasia, Type 1

To the Editor: After a case description of Zollinger-Ellison syndrome (ZES) in the setting of multiple endocrine neoplasia, type 1 (MEN 1), the conclusions of Drs Liang and Mueller1 are somewhat concerning for those involved in the day-to-day care of patients with MEN 1. The authors state that patients with MEN 1/ZES are not candidates for surgical intervention because their disease is multicentric, nonlocalized with imaging, and well controlled with antisecretory medication, and their long-term survival is high. Management of MEN 1/ZES is controversial, and care must be taken to avoid broad all-inclusive statements.

The illusion of wellness in patients taking antisecretory medication coupled with previous low surgical cure rates has led many to consider ZES a medical disorder. MEN 1/ZES is more indolent than its sporadic counterpart.2 Symptoms are often well controlled with medication after subtotal parathyroidectomy. Nonetheless, the highest cause-specific mortality in MEN 1 comes from pancreaticoduodenal tumors.3 All gastrinomas have malignant potential; at diagnosis, 30% to 40% have metastasized. Although patients can live for years with this malignant process, many will die prematurely of this cancer.2 Recent data indicate that 50% of patients with MEN 1 develop malignancy by their mid-40s and nearly 80% by age 60 years. Although an aggressive operative approach may not eliminate development of malignant disease, it may delay its life-threatening uncontrolled manifestations.4

In the past 2 decades, surgeons have appreciated that the duodenum and not the pancreas is the most common site for gastrinomas.2 Between 70% and 90% of sporadic and more than 90% of MEN 1 gastrinomas are duodenal in origin. Tumors are submucosal and are frequently less than 1 cm, rendering them too small for imaging. These microadenomas may not even be palpable through the bowel wall and may be found only after duodenotomy and meticulous mucosal evaluation.5 Despite their size, these tumors may be the sole source of hypergastrinemia and may be potentially curable after local excision and regional lymphadenectomy.2 When tumors are not cured, palliation can be effective. Localizing studies are not as helpful in MEN 1/ZES except for ruling out liver metastases and for identifying adrenocortical tumors and small concomitant pancreatic neuroendocrine tumors.3 Direct manual palpation by an experienced physician coupled with intraoperative real-time ultrasonography are the most accurate localizing modalities.2

An increasing number of medical centers favor aggressive prophylactic surgical extirpation in selected patients to include functioning and nonfunctioning islet cell tumors throughout the pancreas.3 Endocrine surgeons advocate many types of pancreatic/duodenal resections for attempted cure or optimal palliation. Most important is the removal of duodenal primary tumors because they are the principal source of gastrin overproduction. Duodenal gastrinomas, in contrast to those of pancreatic origin, have a propensity to spread to regional lymph nodes. Regional lymphadenectomy, including lymph nodes along the duodenum, pancreas, and hepato-duodenal ligament, is important. One possibility for lower surgical cure rates is inadequate lymph node dissection.5 These operations have extremely acceptable morbidity when performed by experienced surgeons and offer the only chance of cure. Although cure rates are lower than in sporadic disease, euagastremia can be achieved.3

This patient had a family history of metastatic gastrinoma. Such patients should have both genetic and surgical consultation. New evidence exists for genotype-phenotype relationships for MEN 1/ZES. Truncating nonsense or frameshift mutations in C- or N-terminal regions of the MENV gene appear to lead to significantly higher rates of malignant tumors (55% vs 10%).3 Masking symptoms with proton pump inhibitors and discharging without structured follow-up and screening does little to alter the malignant potential of MEN 1/ZES. All too often, we see patients who present with locally advanced or systemic disease while in the prime of their lives.

Mark J. Truty, MD
Geoffrey B. Thompson, MD
Mayo Clinic College of Medicine
Rochester, Minn


In reply: We greatly appreciate the letter by Drs Truty and Thompson, who articulate important points regarding surgical consultation and treatment of patients with MEN 1/ZES. Physicians who provide primary care and medical consultations commonly assess and care for patients with symptoms due to gastric hyperacidity. Needless to say, it can be challenging to discern which patients should undergo expensive and potentially invasive evaluations for possible MEN 1/ZES. In fact, establishing a diagnosis of MEN 1/ZES can be challenging and delayed, not only because of its relatively common symptoms but also because of the widespread (eg, over-the-counter) availability of H2 receptor antagonists and proton pump inhibitors (PPIs), which as Drs Truty and Thompson point out, may mask the symptoms. The purpose of our article was to describe a patient with MEN 1/ZES, when to consider the diagnosis, and the diagnostic approach to, and medical management of, this rare condition.

The goals of treatment for patients with MEN 1/ZES are (1) treatment and prevention of peptic disease due to hyperacidity (which affects more than 90% of patients and can be devastat-
ing) and (2) treatment of malignancy-associated aspects of the gastrinoma. In patients with known gastrinoma, treatment with PPIs effectively addresses the first goal.¹ The answer to our multiple choice question 5 was meant to emphasize that, of the choices given, treatment with PPIs is the best next treatment. However, treatment with PPIs does not address the second goal of treating the malignancy-associated aspects of the gastrinoma. Drs Truty and Thompson provide a helpful surgical perspective regarding this goal, particularly the rationale of why some recommend aggressive surgical approaches. We appreciate their emphasizing the fact that all gastrinomas have malignant potential and acknowledge that this was not emphasized in our article. However, we did not categorically state that patients with MEN 1/ZES were not candidates for surgical intervention. Like Drs Truty and Thompson, we pointed out that treatment of patients with MEN 1/ZES is controversial, with some authors recommending routine exploration and tumor resection, some recommending exploration based on tumor size, and others recommending nonoperative approaches. Our statement that “surgery should not be performed routinely in patients with MEN 1/ZES” was not meant to imply that patients with MEN 1/ZES are never surgical candidates, but rather that the surgical management of MEN 1/ZES is controversial, unlike in sporadic ZES, for which surgical exploration should be performed routinely for attempted cure.²

Indeed, a subset of patients with MEN 1/ZES experience aggressive tumor growth associated with decreased survival. In a prospective study done by Gibril et al.,³ 57 patients with MEN 1/ZES were monitored for a mean of 8 years; 23% developed liver metastases and 14% had a gastrinoma showing aggressive growth. Survival was significantly decreased (P=.0012) in patients with aggressive tumor growth compared with those with nonaggressive tumor growth, whether or not the latter group had liver metastases. The 5-year survival of patients with nonaggressive tumor growth (with or without liver metastases) was 100%. Clinical factors that were significantly predictive of aggressive tumor growth were age younger than 35 years at the time of MEN 1 diagnosis, age 27 years or younger at onset of ZES symptoms, age 33 years or younger at the time of ZES diagnosis, duration of ZES symptoms less than 2.1 years before diagnosis, fasting gastrin levels of 10,000 pg/mL or greater, pancreatic tumor size greater than 3 cm, presence of liver or bone metastases, and presence of gastric carcinoid. In this study, exploratory laparotomy was performed if the tumor size was 2.5 cm or greater. Notably, in the retrospective study of 39 patients by Hausman et al.,¹ the mean age at initial operation was 37 years, and in the retrospective study of 21 patients by Bartsch et al.,⁴ the median age at initial diagnosis was 35 years. One wonders whether, in light of the findings of Gibril et al.,³ the relatively young age of patients in the retrospective studies may partly account for the relatively high rates of malignant disease.

Our patient was 68 years old, had serious comorbid disease (coronary artery disease), and had none of the aforementioned clinical factors predictive of aggressive tumor growth. In addition, our patient had nonlocalizable disease on computed tomography, endoscopic ultrasonography, and somatostatin receptor scintigraphy. Some authors do not recommend routine exploratory laparotomy for patients with MEN 1/ZES and small (<2.0-2.5 cm) tumors because such patients have excellent survival rates at 15 years.² Other authors suggest a more aggressive approach, in which all patients with MEN 1/ZES, regardless of tumor size or results of imaging or endoscopic studies, undergo exploratory laparotomy.¹ ³ This is an area of controversy that both we and Drs Truty and Thompson highlighted. Further research, including long-term prospective studies with sufficient numbers of patients that include assessments of novel risk factors such as those that link genotype-phenotype relationships with tumor aggressiveness in MEN 1/ZES⁵ should help address this controversy.

In our article, we emphasized the need for clinicians to obtain a careful family history for patients with MEN 1/ZES. We agree that referral of these patients and their families to a geneticist and an endocrine surgeon should be considered. However, given current knowledge, a decision to proceed with surgery should take into account the patient’s entire clinical picture and health care values and goals. We agree that a wise approach is to reserve aggressive surgery for selected patients.² Regardless of the approach, patients should be informed of the risks, benefits, and expected outcomes of the proposed treatment and alternatives to the treatment. After lengthy discussions with our patient regarding his clinical findings and his health care values and goals, he declined further evaluation and referrals at our institution and was dismissed to the care of his local primary care physician and endocrinologist.

Complete Heart Block Associated With Mitral Annular Abscess

To the Editor: Aortic and mitral valve abscesses have been well described in the literature as causes of cardiac conduction abnormalities. Mitral valve endocarditis is associated primarily with atrial fibrillation or with first-degree or second-degree heart blocks. We describe an unusual case of complete heart block (CHB) associated with mitral annular abscess in the setting of endocarditis.