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REVIEW ARTICLE

Severe and Refractory Peptic Ulcer Disease: The Diagnostic Dilemma

Case Report and Comprehensive Review

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The recognition of *Helicobacter pylori* infection as a cause of peptic ulcer disease, medical regimens to eradicate the organism, and the widespread use of proton pump inhibition to suppress gastric acid secretion have revolutionized the management of peptic ulcer disease. As a result, successful medical management of peptic ulcer disease has largely supplanted the need for gastric surgery by general surgeons. Surgery is reserved for complications of the disease, refractory disease, or rare causes of ulcer disease such as gastrinoma and Zollinger–Ellison syndrome. In this report, we describe a case of intractable peptic ulcer disease that progressed to gastric outlet obstruction despite maximal medical therapy. We review the diagnostic studies utilized to evaluate the potential etiologies of peptic ulcer disease and the difficulty in diagnosing gastrinoma and Zollinger–Ellison in the setting of potent medical acid suppression therapy.

KEY WORDS: peptic ulcer disease; *Helicobacter pylori*; gastrin; Zollinger–Ellison syndrome; hypersecretion.

Regimens to identify and eradicate *Helicobacter pylori* infection and the widespread use of proton pump inhibition to suppress gastric acid secretion have resulted in successful medical management of peptic ulcer disease in the vast majority of patients (1–3). Surgical management of peptic ulcer disease is now limited to treatment of more emergent complications of the disease (hemorrhage, perforation, gastric outlet obstruction), intractability, and rare causes of ulcer disease such as gastrinoma and Zollinger–Ellison Syndrome (ZES). Indications for elective peptic ulcer surgery include resection of ulcers suspicious for malignancy, failure to heal despite maximal medical therapy, intolerance or noncompliance with medical therapy, and relapse while on maximal medical therapy. In this report we describe a patient with persistent abdominal pain, nausea, and emesis from intractable peptic ulcer disease that progressed despite maximal medical therapy.

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CASE REPORT

A 43-year-old female was evaluated at the Gastroenterology Clinic for persistent epigastric abdominal pain related to a known duodenal ulcer. Her medical history was notable for heavy tobacco use, prior alcohol use, and a history of depression. Her epigastric pain had been present for 20 years but had worsened over the past 5 years, and pain was unrelated to meals. Despite warnings against it, she intermittently used nonsteroidal anti-inflammatory medication (NSAIDs) for pain control. She had been treated twice previously for *Helicobacter pylori* infection.

Diagnostic esophagogastroduodenoscopy (EGD), *H. pylori* antigen testing, and computed tomography of the abdomen and pelvis were performed. EGD revealed a single, nonbleeding superficial ulcer in the gastric antrum, extending to the pylorus, and a large duodenal bulb ulcer. Tissue biopsy was taken for *Campylobacter*-like organism (CLO) testing to identify the presence of H. pylori, and separate biopsies to rule out carcinoma were all negative. Repeat blood testing for *H. pylori* was negative at this time. CT scan of the abdomen and pelvis demonstrated antral and pyloric wall thickening but no adjacent masses or lymphadenopathy. Acid suppression therapy with a proton

pump inhibitor (PPI) was increased (rabeprazole, 40 mg po bid) and the patient was scheduled for an interval EGD in 8 weeks to assess ulcer healing.

She returned to the emergency department 2 weeks later with a complaint of 24 hr of increasing epigastric pain, nausea, and emesis. She did report one episode of a small amount of coffee ground emesis; nasogastric lavage was negative. She was admitted to the medicine service, made NPO, and started on intravenous PPI therapy, and intravenous antiemetics and analgesics were administered as needed. EGD again confirmed the prepyloric ulcer, with no evidence of interval healing or stigmata of recent bleeding. A new finding was a severely strictured, friable region in the distal bulb that would not permit the endoscope to pass. A general surgery consult was obtained for evaluation of gastric outlet obstruction.

The evaluation of the etiology of the severe peptic ulcer disease in this patient included multiple diagnostic studies. An upper gastrointestinal (GI) series was performed to evaluate gastric empyting, and radiographically demonstrated a linear ulceration of the prepyloric area, normal duodenal caliber distal to ulceration, no constricting lesions, and normal emptying distal to ulcer. Fasting gastrin level, neuroendocrine markers, and octreotide scan were performed for evaluation of gastrinoma or ZES as a cause of intractable peptic ulcer disease. Fasting gastrin level was within normal range (37 pg/ml; normal, 0–42 pg/ml), but a gastrin level obtained 1 week prior was elevated at 115 pg/ml. Pancreatic polypeptide and chromogranin level A were also tested and were in the normal range.

Since PPIs and *H. pylori* are major causes of hypergastrinemia, it is difficult to determine the meaning of a high fasting serum gastrin concentration and to rule out ZES in these patients, in which case the surgical therapy would be altered. To obtain a more accurate fasting gastrin, a plan to discontinue PPI therapy and convert to high-dose histamine receptor antagonist (ranitidine, 450 mg every 6 hr) for 10 days was initiated. At this point, ranitidine would be held for 30 hr, and repeat fasting gastrin level and EGD performed. If the serum gastrin was elevated in the face of an acidic pH in the gastric lumen, then this would be more suggestive of a gastrinoma. An octreotide scan was also scheduled. The patient did achieve some pain relief and needed to leave to attend to personal matters; a PICC line was placed for home TPN support, a date for interval endoscopy was set, and plans were made for elective gastric surgery in 4 weeks.

The patient returned to the emergency department, 10 days following discharge, with continued epigastric pain, nausea, and emesis related to ingestion of solid foods. She stated that she used NSAIDs when the oral narcotics worsened her nausea. She was admitted to the general surgery service. Repeat EGD revealed a gastric pH of 4 and gastric outlet obstruction. Laparotomy confirmed a large postpyloric duodenal ulcer eroding into the pancreas. Distal to this lesion there was complete obstruction of the duodenum secondary to cicatrisation. Truncal vagotomy, antrectomy, Roux-en-Y gastrojejunostomy, and cholecystectomy were performed. Postoperative surgical pathology revealed the stomach and proximal duodenum with moderate acute and chornic inflammation, ulceration, fibrosis, and granulation tissue, with focal intestinal metaplasia present in the gastric epithelium. There was no evidence of *H. pylori* and no evidence of malignancy.

The patient's postoperative course was complicated by catheter-related fungemia (*Candida albicans*) associated with the use of total parenteral nutrition and *C. difficile* colitis. At her 2-month follow-up visit, she continued to have mild diarrhea, but her upper GI symptoms fully resolved and she was tolerating a postgastrectomy diet.

DISCUSSION

The management of peptic ulcer disease has changed markedly over the last decade. The widespread use of effective antisecretory therapies, including PPIs, and the recognition and successful eradication of Helicobacter pylori infection have made this a disease that can be cured by medical management in most cases (4). Surgical intervention had once been the dominant form of definitive therapy, but is now reserved for emergent, life-threatening complications of peptic ulcer disease such as bleeding, perforation, and obstruction (5). Intractability, failure to comply with or tolerate medical therapy, and rare cases of gastrinoma or ZES are indications for elective surgery for peptic ulcer disease.

Helicobacter pylori is associated with 95% of duodenal and 70% of gastric ulcers, and eradication of *H. pylori* reduces the relapse rate of ulcers. A recent Cochrane evidence-based review of 53 randomized controlled trials of short- and long-term treatment of peptic ulcer disease in *H. pylori*-positive adults examined the magnitude of this effect. Patients received at least 1 week of *H. pylori* eradication compared with ulcer-healing drug, placebo, or no treatment. In duodenal ulcer healing, *H. pylori* eradication therapy was superior to ulcer-healing drug (34 trials, 3910 patients; relative risk [RR] of ulcer persisting = 0.66; 95% confidence interval [CI] = 0.58, 0.76) and no treatment (2 trials, 207 patients; RR = 0.37; 95% CI = 0.26, 0.53). In gastric ulcer healing, no significant differences were detected between eradication therapy and ulcer-healing drug (13 trials, 1469 patients; RR = 1.32; 95% CI = 0.92, 1.90). This confirmed that a 1- to 2-week course of *H. pylori* eradication therapy is an effective treatment for *H. pylori*-positive peptic ulcer disease (6).

Furthermore, it is well accepted that in patients with uncomplicated peptic ulcers, *H. pylori* eradication therapy does not need to be followed by subsequent antisecretory treatment. A recent 5-year, prospective, controlled study randomized 82 patients with *H. pylori*-associated bleeding peptic ulcers to one of four 16-week maintenance treatment groups after successful *H. pylori* eradication with a 1-week PPI-based triple therapy and an additional 3-week treatment with 20 mg of omeprazole daily for ulcer healing. The four experimental groups were as follows: Group A received 15 ml of an antacid suspension four times daily; group B received 300 mg of colloidal bismuth subcitrate four times daily; group C received 20 mg of famotidine twice daily; and group D, the

control group, received placebo twice daily. Follow-up included a urea breath test labeled with carbon-13, biopsy-based tests, and repeat endoscopic examination. During a mean follow-up of 56 months, there was no peptic ulcer recurrence among the three treatment groups, and all of the patients remained free of *H. pylori* infection during the study period. This study documented that in patients with bleeding peptic ulcers, antiulcer maintenance treatment was not necessary to prevent ulcer recurrence after successful *H. pylori* eradication and ulcer healing. In addition, the 1-week PPI-based triple therapy had the efficacy to ensure long-term eradication of *H. pylori* in a region of high prevalence (7).

Patients with complicated and/or refractory peptic ulcer disease are the more challenging patients to evaluate and treat. A recent analysis regarding admission rates for peptic ulcer disease in the United Kingdom during 1972–2000 determined that emergency admission rates as a whole changed little, a decline in the young being offset by an increase in the elderly. Hemorrhage was the most common reason (approximately 115 per million population for duodenal ulcer and 87 per million for gastric ulcer) throughout (compared with perforation [80 and 21] and pain [90 and 68]) (8).

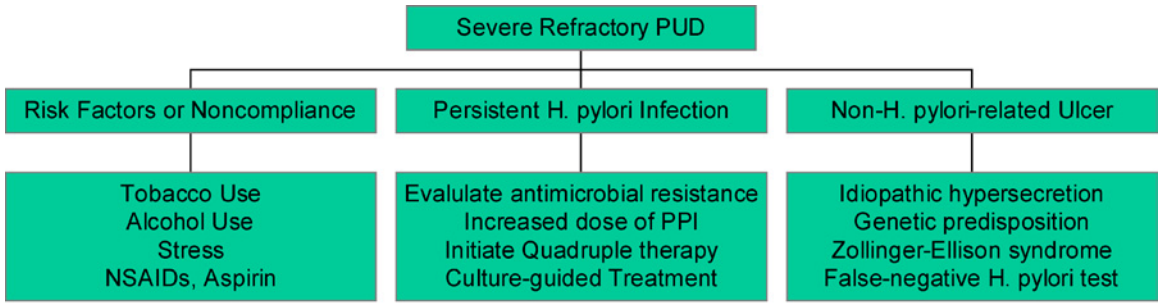
This case report illustrates, however, the difficulties encountered in the diagnostic evaluation of patients with refractory peptic ulcer disease. Potential etiologies of persistent or worsening peptic ulcer disease include the following: patient risk factors and noncompliance, persistent *H. pylori* infection, and non-*H. pylori*-related infection, related to underlying idiopathic gastric hypersecretion, or ZES and gastrinoma (Figure 1). Recent data and studies regarding each of these potential etiologies of refractory peptic ulcer disease are reviewed below.

Patient Risk Factors and Noncompliance

Although curative treatment of *H. pylori* infection markedly reduces the relapse of peptic ulcers, the ulcers that do recur have not been well characterized until recently. A multicenter study involving 4940 peptic ulcer patients who were *H. pylori* negative after successful eradication treatment were followed for up to 48 months. The crude peptic ulcer recurrence rate was 3.02% (149/4940). The annual recurrence rates of gastric, duodenal, and gastroduodenal ulcer were 2.3%, 1.6%, and 1.6%, respectively. Exclusion of patients who took NSAIDs produced annual recurrence rates of 1.9%, 1.5% and 1.3%, respectively. The recurrence rate was significantly higher in gastric ulcer. Recurrence rates of patients who smoked, consumed alcohol, and used NSAIDs were significantly higher in those with gastric ulcer recurrence compared to duodenal ulcer recurrence, and relapsed ulcers recurred at the same site as, or sites adjacent to, the previous ulcers (9).

Persistent or recurrent peptic ulcer disease may occur due to specific patient risk factors or noncompliance with medical therapies. Patient risk factors for peptic ulcer disease include smoking or alcohol use, stress, and use of NSAIDs (10). A population-based prospective cohort study ($n = 2416$ Danish adults) confirmed that the main risk factors for peptic ulcer disease were *H. pylori* infection (odds ratio [OR], 4.3; 95% CI, 2.2–8.3), tobacco smoking (OR, 3.8; CI, 1.7–9.8), and stress with use of minor tranquilizers (OR, 3.0; CI, 1.4–6.6). In patients with documented *H. pylori,* tobacco and alcohol use both increased the risk of peptic ulcer disease, whereas moderate leisure-time physical activity protected against peptic ulcer disease in Danish adults (11).

Multiple studies support a causal relationship between smoking and peptic ulcers in men and women. A CDC



PUD = peptic ulcer disease
PPI = proton pump inhibitor
H. pylori = Helicobacter pylori

Fig 1. Algorithm in the diagnostic workup of refractory peptic ulcer disease (PUD). *H. pylori, Helicobacter pylori*; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

study (the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study) used data from a nationally representative prospective study of U.S. adults to evaluate the impact of smoking on the incidence of peptic ulcers in women ($n = 2851$) who had not been diagnosed as having a peptic ulcer prior to the baseline interview (12). Among these women, 140 (4.9%) developed peptic ulcer disease. During 12.5 years of follow-up, the estimated cumulative incidence of ulcers was 10.0% for current smokers, 6.4% for former smokers, and 5.4% for never smokers. After adjusting for age, education, regular aspirin use, coffee consumption, and use of alcohol, current smokers were 1.8 times more likely to develop ulcers than never smokers (95% CI, 1.2 to 2.6); the risk of peptic ulcer increased as the amount smoked increased.

Since tobacco use and alcohol use are independent risk factors for peptic ulcer disease, and interfere with patient compliance and rate of ulcer healing, cessation should be considered in patients with refractory or severe peptic ulcer disease (13).

NSAIDs are widely used for their anti-inflammatory, analgesic, and antipyretic effects, and low-dose aspirin (also an NSAID) is used for cardiovascular prophylaxis. The main concern limiting use of these drugs is their GI toxicity. GI side effects include ulcers (found at endoscopy in 15%–30% of patients using NSAIDs regularly), complications such as upper GI bleeding (annual incidence of 1.0%–1.5%), and development of upper GI symptoms such as dyspepsia (occurring in up to 60% of patients taking NSAIDs). Histamine-2 receptor antagonists (H2RAs) are not effective at preventing NSAID-induced gastric ulcers when used at standard doses, although they can decrease upper GI symptoms. Misoprostol effectively decreases NSAID-induced ulcers and GI complications but is used infrequently in the United States—perhaps because of issues of compliance (multiple daily doses) and side effects (e.g., diarrhea, dyspepsia). Once-daily PPI therapy also decreases the development of NSAID-associated ulcers and recurrent NSAID-related ulcer complications; it also decreases upper GI symptoms in NSAID users. In patients using aspirin, the addition of a cyclooxygenase-2-specific inhibitor appears to significantly increase GI risk to the level with a nonselective NSAID; aspirin plus a nonselective NSAID appears to increase GI risk still higher. Patients taking low-dose aspirin who have risk factors for GI complications (including concomitant nonselective NSAID therapy) should therefore receive medical cotherapy, such as a PPI (14).

Clinical trials have reproducibly demonstrated that the healing of NSAID-associated gastric and duodenal ulcers is accelerated with the use of acid suppressive agents (e.g., H2RAs and PPIs), even with the continued use of the NSAID. The risk of developing gastroduodenal ulcers or ulcer complications with the continued and long-term use of NSAIDs is now well recognized as an important problem commonly encountered in daily clinical practice. Clinical trials have shown that coprescription of misoprostol, high-dose H2RAs or PPIs can effectively prevent or reduce the rate of gastroduodenal mucosal damage associated with the use of nonselective NSAIDs. Approaching the problem in a different way, COX-2-selective inhibitors circumvent the problem; based on their mechanism of action, these agents are less ulcerogenic in the upper GI tract compared with nonselective NSAIDs (15).

Most recently, a study examined whether prophylaxis with lansoprazole could prevent relapse of ulcers after eradication of *H. pylori* in patients with NSAID-related peptic ulcers. Patients who presented with peptic ulcers and were found to be infected with *H. pylori* while receiving NSAIDs were recruited into the study. They received 30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin twice daily for 1 week, followed by 30 mg lansoprazole daily for 4 weeks. Patients with healed ulcers and *H. pylori* eradicated were given naproxen, 750 mg daily, and randomly assigned to receive lansoprazole, 30 mg daily, or no treatment for 8 weeks. At the end of the 8-week treatment period, significantly fewer patients (1/22; 4.5%; 95% CI, 0–23) in the lansoprazole group compared with the group that received *H. pylori* eradication alone (9/21; 42.9%; 95% CI, 22–66) developed recurrence of symptomatic and complicated ulcers (log rank test, $P = 0.0025$). Lansoprazole significantly reduced the cumulative relapse of symptomatic and complicated ulcers in patients requiring NSAIDs after eradication of *H. pylori* (16).

While a tremendous amount of research supports the use of preventive therapies and interventions to reduce and/or avoid NSAID- or aspirin-associated ulcers and ulcer complications in the upper GI tract, these strategies are often underutilized, not optimally dosed, and/or associated with poor patient compliance. This reinforces the need for continued clinician and patient education to improve outcomes of care.

Persistent *H. pylori* Infection

H. pylori is the primary cause of peptic ulcer disease (17). *H. pylori* infection is curable with regimens of multiple antimicrobial agents, but antimicrobial resistance is a leading cause of treatment failure (18). Current treatment for *H. pylori* infections generally includes two or more antimicrobials (amoxicillin, clarithromycin, nitroimidazoles, tetracycline, etc.), but treatment fails in 10%–20% of all cases, often because of drug resistance.

A recent study examined 67 *H. pylori* isolates from patients unsuccessfully treated with amoxicillin, clarithromycin, metronidazole, and levofloxacin. Clarithromycin and metronidazole resistance were identified in 91% and 82.1% of the isolates, respectively; importantly, 52 (77.6%) were resistant to both drugs. All 67 isolates were susceptible to amoxicillin and tetracycline. The choice of antibiotic treatment for refractory *H. pylori* infections should be based on in vitro susceptibility data, and physicians should consider local resistance patterns when treating these infections empirically (19).

The efficacy of a culture-guided treatment approach for the eradication of persistent *H. pylori* infection was analyzed in 94 consecutive patients in whom *H. pylori* infection had persisted after two eradication attempts. Susceptibility analysis was performed for amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin. Patients were then treated with a culture-guided, third-line regimen: 89 patients with a 1-week quadruple regimen including omeprazole, bismuth, doxycycline, and amoxicillin, and 5 patients with a 1-week triple regimen containing omeprazole, amoxicillin, and levofloxacin or clarithromycin. Ninety-four subjects (100%) were resistant to metronidazole, 89 (95%) to clarithromycin, 29 (31%) to levofloxacin, and 5 (5%) to tetracycline. No resistance to amoxicillin was found in any patient. Overall, *H. pylori* eradication was obtained in 90% of subjects. The quadruple regimen was effective in 81 patients (92% by per protocol and 91% by intention-to-treat analysis). Four patients (80% by both per protocol and intention-to-treat analysis) were *H. pylori*-negative after the triple regimen. This study confirmed that the culture-guided, third-line therapeutic approach is effective for the eradication of *H. pylori*. Furthermore, the 1-week doxycycline- and amoxicillin-based quadruple regimen is a good third-line "rescue" treatment option (20).

The *Helicobacter pylori* Antimicrobial Resistance Monitoring Program is a prospective, multicenter U.S. network that tracks national incidence rates of *H. pylori* antimicrobial resistance. Of 347 clinical *H. pylori* isolates collected from December 1998 to 2002, 101 (29.1%) were resistant to one antimicrobial agent, and 17 (5%) were resistant to two or more antimicrobial agents. Eighty-seven (25.1%) isolates were resistant to metronidazole, 45 (12.9%) to clarithromycin, and 3 (0.9%) to amoxicillin. On multivariate analysis, black race was the only significant risk factor ($P < 0.01$; hazard ratio, 2.04) for infection with a resistant *H. pylori* strain (21).

Owing to rising drug-resistant *H. pylori* infections, currently recommended PPI-based triple therapies are losing their efficacy, and regimens efficacious in the presence of drug resistance are needed. A recent meta-analysis examined the efficacy, safety, and adherence of first-line quadruple *H. pylori* therapies in adults. Quadruple therapy containing a gastric acid inhibitor, bismuth, metronidazole, and tetracycline was enhanced when omeprazole was included, when treatment duration lasted 10–14 days, and when therapy took place in the Netherlands, Hong Kong, and Australia. Treatment efficacy decreased as the prevalence of metronidazole resistance increased. Even in areas with a high prevalence of metronidazole resistance, this quadruple regimen eradicated more than 85% of *H. pylori* infections when it contained omeprazole and was given for 10–14 days. Furthermore, in the presence of clarithromycin resistance, this quadruple regimen eradicated 90%–100% of *H. pylori* infections, while the currently recommended triple therapy containing clarithromycin, amoxicillin, and a PPI eradicated only 25%–61% ($P < 0.001$). Adherence and adverse events for quadruple therapy were similar to currently recommended triple therapies. This study questions whether quadruple therapy with a PPI, a bismuth compound, metronidazole, and tetracycline should be recommended as first-line anti-*H. pylori* therapy (22).

In patients who present with persistent or worsening peptic ulcer disease, it is important to assess for active *H. pylori* infection and to determine whether antimicrobial resistance is present. Bacteriological methods are necessary for detection of the putative antimicrobial resistance of *H. pylori*. The main cause for failure of *H. pylori* eradication therapy is resistance to clarithromycin, which is due to point mutations. In these patients with resistant isolates, the provision of alternative therapeutic regimens for the successful eradication of *H. pylori* infection is mandatory.

High-dose PPI/amoxicillin therapy can also be used as an alternative strategy for retreatment of *H. pylori* after failure to eradicate the infection. A recent prospective cohort study included 17 *H. pylori*-positive patients who had failed to clear *H. pylori* infection after 1 week of treatment with usual doses of PPI, amoxicillin, and clarithromycin. The sensitivity of *H. pylori* to clarithromycin and amoxicillin and the CYP2C19 genotype status of each patient were determined, and treatment with rabeprazole (10 mg qid) and amoxicillin (500 mg qid) for 2 weeks was started. Eleven patients were infected with a clarithromycin-resistant strain of *H. pylori.* Twelve patients had the homozygous extensive metabolizer genotype, five had the heterozygous extensive metabolizer genotype, and there were none with the poor metabolizer genotype of CYP2C19. All patients were successfully cleared of their *H. pylori* infection without any adverse effects, irrespective of CYP2C19 genotype status (100%; 95% CI, 76–100). High-dose dual therapy with rabeprazole (10 mg

qid) and amoxicillin (500 mg qid) for 2 weeks was a useful treatment strategy after failure of eradication of *H. pylori* by the usual triple PPI/amoxicillin/clarithromycin therapy (23).

The future development of new anti-*H. pylori* therapies presents enormous challenges to clinical pharmacologists, not only in identifying novel targets, but also in ensuring adequate drug delivery to the unique gastric mucous niche of *H. pylori*. Several lines of evidence from experimental animal models of infection have clearly demonstrated the feasibility of a prophylactic and therapeutic vaccine against *H. pylori*. However, comparatively few clinical studies have been carried out to evaluate whether the positive results obtained in animals can be reproduced in humans. The preliminary results obtained with single component, mucosally delivered vaccines have shown very limited results thus far. Very good immunogenicity and safety profiles are now being obtained with parenterally delivered, aluminium hydroxide-adjuvanted multicomponent candidate vaccines. Improved vaccine formulations, antigen preparation, adjuvants, and delivery systems have to be designed and tested for safety and immunogenicity. These studies are also needed for deciphering those aspects of the effector immune responses that correlate with protection against *H. pylori* infection and disease (24).

Non-*H. pylori*-Related Ulcer

The proportion of ulcers that are not associated with *H. pylori* infection is increasing, especially in the United States and Australia (25). The increase in this type of ulcer warrants an analysis of the diagnostic and treatment approaches to *H. pylori*-negative ulcers. Review of the medical literature documents that up to 52% of duodenal ulcers and 47% of gastric ulcers are not caused by *H. pylori* infection. The cause of *H. pylori*-negative ulceration appears to be multifactorial. Contributing factors include covert NSAID use, false-negative *H. pylori* tests, genetic predisposition, and, in rare cases, Crohn's disease or ZES. *H. pylori*-negative ulcers tend to be associated with hypersecretion and can have serious clinical sequelae. *H. pylori*-negative ulcers are often refractory to treatment, and may have an aggressive clinical course, possibly because they lack the beneficial effect of *H. pylori* infection on antisecretory therapy. PPIs appear to effectively treat both *H. pylori*-positive and *H. pylori*-negative ulcers (26). Furthermore, the recent availability of intravenous PPIs has simplified therapy in patients that cannot receive enteral therapy, such as this patient with partial gastric outlet obstruction and when there is question or concern for adequate absorption of enteral PPIs.

In patients with hypersecretion as the etiology of the non-*H. pylori*-related ulcer, the potential etiologies include idiopathic gastric hypersecretion or ZES and/or gastrinoma. The diagnostic evaluation in these patients is difficult, however, since most of these patients have hypergastrinemia due to chronic treatment with acid suppressive therapy and medical regimens for eradication of *H. pylori*. PPIs are potent acid suppressants which, at normal doses, can result in hypergastrinemia. In fact, there is a significant inverse correlation between the fasting serum gastrin concentration and the gastric acid profile in patients with gastroesophageal reflux and peptic ulcer disease. An elevated fasting serum gastrin concentration while on PPI therapy suggests that gastric acid secretion is adequately suppressed (27). Additionally, gastric outlet obstruction may be a contributing etiology of elevated serum gastrin.

Therefore, the use of PPIs could delay or mask the diagnosis of gastrinoma (28). In this case, an attempt was made to eliminate PPI therapy as a possible cause of hypergastrinemia, prior to surgical intervention. It was critical to determine the etiology of the worsening ulcer disease and hypergastrinemia in this patient. A short course of high-dose H-2 receptor antagonist therapy was initiated prior to repeat gastrin measurements. It is important to note, however, that this strategy is not recommended in the treatment of acute peptic ulcer disease, since it has been well established that ulcer healing rates are superior with PPI therapy (29).

A recent study investigated whether the widespread use of PPIs masks or complicates the diagnosis of gastrinoma. Data from two centers with different referral criteria for suspected gastrinomas were analyzed (Gastroenterology Unit, Rome, Italy, and National Institutes of Health, Bethesda, MD, USA). The number of referrals and the number of new patients with gastrinoma diagnosed in the years prior to the widespread use of PPIs (1986–1992) were compared with the numbers since PPIs became widely available (1993–1998). The decrease in referral rate ($P = 0.0009$) and the decrease in the annual rate of gastrinoma diagnosis ($P = 0.0020$) at both centers correlated with the increased use of PPIs. At the Italian center, there was a 62% decrease in annual referrals ($P < 0.0001$) in the post-PPI period, relative to the pre-PPI period, whereas there was an increase in the rate of referral of other GI endocrine tumors. The number of new cases of gastrinoma diagnosed decreased by 40%. At the U.S. center, the referral rate decreased by 28% ($P = 0.024$) in the post-PPI period. There was also a 43% decrease in the number of new cases diagnosed annually in the post-PPI period ($P = 0.0012$). There was a 2.6-fold increase in the post-PPI period in the percentage of referrals with a false diagnosis of gastrinoma as the cause

of hypergastrinaemia ($P = 0.0040$). These data support the conclusion that, since PPIs have been released, the diagnosis of gastrinoma has been masked and will probably be delayed, with the result that patients with gastrinoma will be diagnosed at more advanced stages in their disease course (30). Physicians must therefore maintain a high index of suspicion for this disease and not mask a potential malignancy with prolonged control of acid-related symptoms without taking steps to diagnose gastrinoma.

Furthermore, differentiation of idiopathic gastric hypersecretion versus gastrinoma or ZES can be difficult and frequently requires multiple diagnostic studies. This workup is necessary, however, since the medical and surgical therapy of these patients differs. Patients with "idiopathic" ulcers are characterized by postprandial hypersecretion of acid and hypergastrinemia with accelerated gastric emptying. Any patient with intractable or recurrent peptic ulcer disease requires diagnostic evaluation for ZES or gastrinoma.

ZES is characterized by severe peptic ulcer disease due to gastric acid hypersecretion that results from gastrin-secreting tumors (gastrinomas) of the GI tract. Gastrin stimulates the parietal cell to secrete acid directly and indirectly by releasing histamine from enterochromaffin-like cells and induces hyperplasia of parietal and enterochromaffin-like cells. ZES should be suspected in patients with severe erosive or ulcerative esophagitis, multiple peptic ulcers, peptic ulcers in unusual locations, refractory peptic ulcers, complicated peptic ulcers, peptic ulcers associated with diarrhea, and a family history of multiple endocrine neoplasia type 1 (MEN-1) or any of the endocrinopathies associated with MEN-1. In about 75% of patients the tumors are sporadic, and 25% of patients have MEN-1. Patients with ZES have two problems that require treatment—the hypersecretion of gastric acid and the gastrinoma itself. Although most gastrinomas grow slowly, 60% to 90% are malignant and 25% show rapid growth.

The clinical signs and symptoms of patients presenting with ZES can be myriad. A prospective evaluation of the initial presenting symptoms in 261 patients with ZES was performed over a 25-year period at the National Institutes of Health. Twenty-two percent of the patients had MEN-1 with ZES. Mean age at onset was 41.1 ± 0.7 years, with MEN-1 patients presenting at a younger age than those with sporadic ZES ($P < 0.0001$). A mean delay to diagnosis of 5.2 ± 0.4 years occurred in all patients. Abdominal pain and diarrhea were the most common symptoms, present in 75% and 73% of patients, respectively. Heartburn and weight loss, which were uncommonly reported in early series, were present in 44% and 17% of patients, respectively. GI bleeding was the initial presentation in a quarter of the patients. Patients rarely presented with only one symptom (11%); pain and diarrhea was the most frequent combination, occurring in 55% of patients. An important presenting sign that should suggest ZES is prominent gastric body folds, which were noted on endoscopy in 94% of patients; however, esophageal stricture and duodenal or pyloric scarring, reported in numerous case reports, were noted in only 4%–10%. A correct diagnosis of ZES was made by the referring physician initially in only 3% of the patients. The most common misdiagnoses made were idiopathic peptic ulcer disease (71%), idiopathic gastroesophageal reflux disease (7%), and chronic idiopathic diarrhea (7%). These results demonstrate that abdominal pain, diarrhea, and heartburn are the most common presenting symptoms in ZES and that heartburn and diarrhea are more common than previously reported. The presence of weight loss, especially with abdominal pain, diarrhea, or heartburn, is an important clue suggesting the presence of gastrinoma. The presence of prominent gastric body folds, a clinical sign that has not been appreciated, is another important clue to the diagnosis of ZES. Patients with MEN-1 presented at an earlier age; however, in general, the initial symptoms were similar to those of patients without MEN-1. Gastrinoma extent and location have minimal effects on the clinical presentation. Overall, neither the introduction of successful antisecretory therapy nor the widespread publication of information about ZES, attempting to increase awareness, has shortened the delay in diagnosis or reduced the incidence of patients presenting with peptic complications. The introduction of successful antisecretory therapy, however, has likely led to patients presenting with less severe symptoms and fewer complications (31).

The initial diagnostic test for ZES should be a fasting serum gastrin level when antisecretory medications are discontinued. Patients with ZES have significantly increased serum gastrin concentrations, frequently between 150 and 1000 pg/ml. If the gastrin level is elevated, gastric acidity should be assessed through pH or gastric analysis. It should be noted that hypochlorhydria causes feedback stimulation of antral gastrin secretion. In suspected cases of ZES with mild hypergastrinemia, the secretin stimulation test may be useful.

Serologic markers helpful in reaching a diagnosis of gastrinoma are also available, as serum chromogranin A has been shown to be a general marker for neuroendocrine tumors. It is elevated in gastrinoma, and the elevation has been reported to correlate with tumor volume (32). It is less sensitive and specific than fasting serum gastrin for the diagnosis of ZES but can be a confirmatory test. Chromogranin A is considered the most accurate marker in the diagnosis of gastroenteropancreatic (GEP) endocrine

tumors. Pancreatic polypeptide has also been proposed to play this role but then not used due to its low sensitivity. A recent study examined whether the assessment of pancreatic polypeptide would improve the diagnostic reliability of chromogranin A in patients ($n = 68$) with GEP tumors. By combining the two markers a significant gain in sensitivity vs. chromogranin A alone was obtained: overall in GEP tumors (96% vs. 84%; $P = 0.04$), in nonfunctioning (95% vs. 75%; $P = 0.02$), and in pancreatic (94% vs. 74%; $P = 0.04$). Therefore, the combined assessment of both pancreatic polypeptide and chromogranin A leads to a significant increase in sensitivity in the diagnosis of GEP tumors (33).

The secretin stimulation test can differentiate patients with gastrinomas from those with other causes of hypergastrinemia, such as idiopathic gastric hypersecretion. By an unknown mechanism, gastrinoma cells are responsive to secretin administration, but normal gastric G cells are actually inhibited by it. A rise in serum gastrin by 200 pg/ml is considered positive and is 90% sensitive and specific for the presence of gastrinoma. Secretin, however, is difficult to obtain for the conduct of this diagnostic test.

Calcium infusion has been advocated as a provocative test for the diagnosis of some endocrine tumors of the pancreas and GI tract (gastrinoma, insulinoma, intestinal carcinoids). The release of gastrin from gastrinoma tissue is very sensitive to alterations in the serum calcium level, and the calcium infusion test is recommended in ZES when the results of the secretin stimulation test are equivocal (34).

Initial treatment for ZES should be oral high-dose PPIs. Maintenance po pantoprazole therapy at a dose of 80–240 mg/day in divided doses was both effective and generally well tolerated for patients with ZES ($n = 26$) and idiopathic hypersecretion ($n = 9$) in a recent study (35). If parenteral therapy is needed, intermittent bolus injection of pantoprazole is recommended (36).

Imaging for gastrinoma localization can be accomplished via computed tomography or magnetic resonance imaging, but perhaps the best modality with highest sensitivity and specificity for localization is via somatostatin receptor scintigraphy with 111-In-pentetreotide and spectroscopy (37). Somatostatin receptor scintigraphy, which images the entire body at one time, is more sensitive for detecting gastrinomas than any conventional imaging study (38). Since this test became available, all liver metastases detected at exploration have been detected by the test, and it is therefore the initial localization study of choice. This study, however, has limited sensitivity for detection of the primary gastrinoma.

In a recent prospective study, 55 patients with a recent diagnosis of endocrine gastroenteropancreatic tumors (22 intestinal carcinoids, 17 gastrinomas, 10 nonfunctioning pancreatic tumors, and 6 insulinomas), were examined with somatostatin-receptor scintigraphy, computed tomography, and ultrasonography. Results of the three imaging modalities were compared with findings at surgical exploration. Of 17 gastrinomas, 9 were detected by somatostatin-receptor scintigraphy, but computed tomography and ultrasonography localized only 7. Metastases from the gastrinoma were localized by somatostatin-receptor scintigraphy in all cases; computed tomography and ultrasonography detected metastases in only 6 of 9 patients. Somatostatin-receptor scintigraphy is superior to computed tomography and ultrasonography for determining the extent of the disease in patients with gastrinomas. However, the problem of detecting *primary* tumors in these patients is not solved by somatostatin-receptor scintigraphy (39). Endoscopic ultrasound may have a similar sensitivity for identifying primary tumors. A combination of both somatostatin receptor scintigraphy and endoscopic ultrasound detects more than 90% of gastrinomas.

The role of surgery in patients with the ZES is controversial (40). Total gastrectomy and antisecretory surgery is rarely required. In patients without metastasis and without MEN-1, surgical cure is possible in 30%. It has been suggested that patients with gastrinomas larger than 2.5 cm, irrespective of whether they have MEN-1, should undergo surgical resection in an effort to decrease the risk for metastasis (41). A recent study examined the outcomes of 151 ZES patients who underwent surgical intervention. Of these patients, 123 had sporadic gastrinomas and 28 had MEN-1 with an imaged tumor of at least 3 cm in diameter. Tumor localization studies and functional localization studies were performed routinely. All patients underwent surgery according to a similar operative protocol, and all patients who had surgery after 1986 underwent duodenotomy. The 151 patients underwent 180 exploratory operations. The mean ($\pm$SD) follow-up after the first operation was 8 ± 4 years. Gastrinomas were found in 141 of the patients (93%), including all of the last 81 patients to undergo surgery. The tumors were located in the duodenum in 74 patients (49%) and in the pancreas in 36 patients (24%); however, primary tumors were found in lymph nodes in 17 patients (11%) and in another location in 13 patients (9%). The primary location was unknown in 24 patients (16%). Among the patients with sporadic gastrinomas, 34% were free of disease at 10 years, compared with none of the patients with MEN-1. The overall 10-year survival rate was 94%. This study concluded that all patients with ZES who do not have MEN-1 or metastatic disease should be offered surgical exploration for possible cure (42).

CONCLUSION

Optimal management of severe or refractory peptic ulcer disease requires a multidisciplinary team approach, utilizing primary care providers, gastroenterologists, and general surgeons. Medical management has become the cornerstone of therapy. Identification and eradication of *H. pylori* infection combined with acid reduction regimens can heal ulceration as well prevent recurrence. Severe, intractable, or recurrent peptic ulcer disease and associated complications mandate a careful and methodical evaluation and management strategy to determine the potential etiologies and necessary treatment (medical or surgical) required.

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