Diagnostic and Treatment Approaches for Refractory Peptic Ulcers

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Refractory peptic ulcers are defined as ulcers that do not heal completely after 8 to 12 weeks of standard anti-secretory drug treatment. The most common causes of refractory ulcers are persistent _Helicobacter pylori_ infection and use of nonsteroidal anti-inflammatory drugs (NSAIDs). Simultaneous use of two or more _H. pylori_ diagnostic methods are recommended for increased sensitivity. Serologic tests may be useful for patients currently taking proton pump inhibitors (PPIs) or for suspected false negative results, as they are not affected by PPI use. NSAID use should be discontinued when possible. Platelet cyclooxygenase activity tests can confirm surreptitious use of NSAIDs or aspirin. Cigarette smoking can delay ulcer healing. Therefore, patients who smoke should be encouraged to quit.

Zollinger-Ellison syndrome (ZES) is a rare but important cause of refractory gastroduodenal ulcers. Fasting plasma gastrin levels should be checked if ZES is suspected. If an ulcer is refractory despite a full course of standard PPI treatment, the dose should be doubled and administration of another type of PPI considered.

Key Words: Peptic ulcer; Ulcer, refractory; _Helicobacter pylori_; Anti-inflammatory agent, non-steroidal; Gastrins

INTRODUCTION

Peptic ulcers were previously considered a chronic recurrent disease. However, a breakthrough in treatment of peptic ulcers followed the discovery of the causative role of _Helicobacter pylori_ infection and introduction of proton pump inhibitors (PPIs) as powerful anti-secretory drugs.

However, because medical advances allow patients with serious diseases to survive longer and because an increasing number of older people use nonsteroidal anti-inflammatory drugs (NSAIDs), our hospital has experienced an increase in the number of peptic ulcer disease cases due to various causes.

PPI is the most powerful remedy for treatment of peptic ulcers. However, some peptic ulcers do not heal completely even with PPI treatment. Refractory ulcers are defined as peptic ulcers that do not heal completely despite 8 to 12 weeks of standard anti-secretory drug treatment. Patients with refractory peptic ulcers are generally believed to have persistent _H. pylori_ infections or resistant strains, and these ulcers typically result from NSAID use, large size, malignancy, refractory response to drug administration, or other acid hypersecretory states. This article describes the diagnosis and treatment of refractory peptic ulcers.

DIAGNOSIS AND APPROACH

Korean diagnostic guidelines

Recent Korean guidelines for treatment of non-bleeding peptic ulcer disease recommend the following steps for treatment of refractory ulcers: The first is drug compliance. If an ulcer fails to heal with a standard dose of an anti-secretory drug, the dose should be doubled and treatment should be continued for an additional 6 to 8 weeks. Second, _H. pylori_ status should be evaluated. False-negative results should be suspected when ulcers test negative for _H. pylori_ infection. Third, clinicians should confirm that patients have discontinued use of NSAIDs. Many patients do not realize that cold remedies or headache medicines contain NSAIDs, so it is important to...
confirm that they are not inadvertently taking medicines containing NSAIDs. Fourth, clinicians should check that patients have quit smoking. Fifth, it is important to determine if there is a family history of gastrinoma, Zollinger-Ellison syndrome (ZES), or type I multiple endocrine neoplasia; their secondary symptoms, including chronic diarrhea or hypercalcemia due to hyperparathyroidism, should be investigated for acid hypersecretion. Sixth, the possibility of primary or metastatic malignancies, infectious diseases such as cytomegalovirus infection, crack cocaine use, and gastroduodenal involvement of inflammatory bowel disease should be considered. About 90% of refractory ulcers heal after 8 weeks of PPI treatment; however, additional or continuous treatment may be necessary in 10% of cases, and surgical treatment may also be considered.

Clinical conditions

Persistent \(H. \text{ pylori}\) infection

Peptic ulcers were previously considered a chronic intractable disease because over 60% of ulcers recurred if their cause was not corrected. Several methods are used to detect \(H. \text{ pylori}\) in the stomach, including culture, rapid urease tests, urea breath tests, histological examination, and stool antigen tests. However, these tests have pitfalls and introduce the potential for diagnostic errors. Recurrence rates have recently decreased with aggressive eradication of \(H. \text{ pylori}\)-positive ulcers. However, false negative test results may result in overlooked \(H. \text{ pylori}\) infections and missed standard treatment opportunities. Use of antibiotics, bismuth preparations, and PPIs reduce \(H. \text{ pylori}\) numbers and can lead to false negative findings in many diagnostic modalities, including rapid urea, urea breath, and stool antigen tests, as well as culture and histological examination. Because PPIs decrease \(H. \text{ pylori}\) numbers and also improve antral histology, an additional biopsy at the corpus is recommended after antral biopsy. In some cases, two or more simultaneous diagnostic methods are recommended. It is not difficult to determine \(H. \text{ pylori}\) status during the first endoscopy. However, determination may become difficult after PPI treatment. In cases of failed eradication or false negative results, serologic tests may be used, as they are not affected by previous PPI use.

Non-\(H. \text{ pylori}\) helicobacter infections may also occur. \(Helicobacter \text{ heilmannii}\) has similar bacteriologic features, but is spread by zoonotic infection. The presenting symptoms of \(H. \text{ heilmannii}\) infection are similar to those of \(H. \text{ pylori}\). Like \(H. \text{ pylori}\), \(H. \text{ heilmannii}\) causes many diseases, including peptic ulcer diseases, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. Due to its low colonization density and the low sensitivity of the rapid urease tests, it is usually diagnosed by biopsy. Once diagnosed, the treatment is same as for \(H. \text{ pylori}\).

NSAIDs and ulcerogenic drugs

NSAIDs delay ulcer healing by depleting prostaglandin, which plays a critical role in mucosal maintenance and protection. NSAID use is more frequently attributed to gastric ulcers, but may also result in duodenal ulcers. NSAIDs have recently emerged as a major cause of peptic ulcers in an increasingly aged population with increased NSAID use, as well as a decreased prevalence of \(H. \text{ pylori}\) previously considered the primary cause of peptic ulcer diseases. There is a high possibility of abuse among patients using NSAIDs. The treatment of choice for ulcers due to NSAIDs use is discontinuation of NSAIDs. However, pain makes it difficult to stop NSAIDs use. Moreover, many patients are often unaware of their use of over-the-counter NSAIDs. There are some reports that the platelet cyclooxygenase (COX) activity test can confirm surreptitious use of NSAIDs or aspirin. The COX activity test reportedly revealed 21.5% more aspirin users than history alone. Selective COX-2 inhibitors have been developed to reduce adverse gastroduodenal effects of NSAIDs. However, delayed healing gastric ulcers in patients taking COX-2 inhibitors was comparable to that of patients taking ordinary NSAIDs. COX-2 inhibitor use is also limited due to risk of cardiovascular complications as well as decreased or complete elimination of selectivity when co-administered with aspirin.

In addition to NSAIDs, many other drugs, including potassium chloride, bisphosphonates, clopidogrel, anti-cancer chemotherapeutic agents, and mycophenolate mofetil can cause peptic ulcers.

Smoking

Smoking may be an important factor in idiopathic refractory ulcers. It is one of the most important causes of refractory ulcers, and is listed in the current Korean guidelines. Smoking reduces prostaglandin synthesis and decreases the barrier function of the gastric mucosa. Cigarette smoking also induces a significant reduction in gastric mucosal blood flow. Peptic ulcers are more common in smokers than in non-smokers due to increased gastrin and gastric acid levels and decreased bicarbonate secretion. Cigarette smoking is positively associated with peptic ulcer pathogenesis and delayed ulcer healing. Several studies have shown that cigarette smoke and its active ingredients can cause mucosal cell death, inhibit cell renewal, decrease blood flow in the gastrointestinal mucosa, and interfere with the mucosal immune system.

Therefore, patients who smoke should be encouraged to quit because continued smoking delays healing of peptic ulcers.
**Crack cocaine**

The inhalable free-base form of cocaine is manufactured by processing the cocaine with ammonia or sodium bicarbonate (baking soda) to remove hydrochloride. This form is heat-stable and melts at 98°C, which allows it to be smoked. Cocaine blocks presynaptic reuptake of norepinephrine and dopamine, and acts as powerful sympathomimetic agent. It also causes increased endothelin production and decreased nitric oxide production. Smoking crack cocaine induces tissue ischemia via contraction of mucosal arterioles. This process is repeated each time smoking occurs, leading to serious stomach and intestinal ulcers. Though it is typically difficult to obtain an accurate history from patients who smoke crack cocaine, this cause should be considered in cases of idiopathic refractory ulcers.

**Zollinger-Ellison syndrome**

ZES is defined as the presence of a gastrin-secreting neuroendocrine tumor that results in hypersecretion of gastric acid; it commonly manifests as peptic ulcer disease, dyspepsia, gastroesophageal reflux, abdominal pain, and diarrhea. The hallmark of this condition is hypergastrinemia in the presence of low gastric pH.

ZES is a rare disease, but is one of the most important causes of refractory gastroduodenal ulcers. The ulcers are not completely healed with standard anti-secretory agent therapy and rapidly recur after treatment cessation. Diarrhea may be due to acid hypersecretion and can be improved with use of anti-secretory agents. While the gastric mucosa is relatively normal, the gastric folds are hypertrophied. This syndrome is characterized by multiple ulcers beyond the duodenal bulb. Due to the gastrin-secreting tumor, fasting plasma gastrin concentrations greater than 1,000 pg/mL or basal acid outputs (BAOs) greater than 15 mEq/hr suggest the presence of ZES. Because use of anti-secretory drugs increases blood gastrin levels, these drugs should be withdrawn before measurement. However, it may be difficult to stop anti-secretory agents in cases of refractory ulcers. The most common causes of gastrin elevation are ZES and atrophic gastritis with hypochlorhydria. Moderate gastrin increases over 10 mEq/hr can make it difficult to diagnose ZES because this level is also seen in atrophic gastritis with hypochlorhydria, in which the gastrin levels increase due to a negative feedback mechanism by the hypochlorhydria. In this case, gastric acid secretion should be checked. If ZES is suspected despite moderate gastrin increase, secretin tests may be helpful. Clinical features may also help differentiate these conditions: acid hypersecretion, gastric wall hypertrophy, multiple duodenal ulcers, and increasing numbers of parietal cells on histological examination characterize atrophic gastritis.

The secretin stimulation test is the best way to diagnose gastrinoma. Blood draws to measure serum gastrin levels should be obtained immediately before intravenous secretin administration and then 1, 2, 5, 10, 15, and 30 minutes later. ZES is diagnosed based on serum gastrin concentrations increasing to ≥120 pg/mL. The gastric acid output test is very complex; however, pH >2 is inconsistent with ZES.

Patients diagnosed with ZES must be tested to determine if the tumor is a type I multiple endocrine neoplasia. Somatostatin receptor scintigraphy is useful to localize the tumor site in about 80% of cases; endoscopic ultrasound also offers high sensitivity and specificity to accurately identify the tumor site.

Gastrinoma is treated by suppressing acid hypersecretion and tumor growth. Gastrinoma resection is the treatment of choice. PPIs are the best treatment for acid hypersecretion in gastrinoma, and should be used in doses sufficient to suppress BAO below 10 mEq/hr.

**Other acid hypersecretion states**

After ruling out *H. pylori* infection and ZES, idiopathic gastric acid hypersecretion should be considered for refractory peptic ulcers with acid hypersecretion. The diagnostic criteria are as follows: an increase in BAO over 10 mEq/hr with a fasting serum gastrin lower than 100 pg/mL or negative secretin test in the case of gastrin over 100 pg/mL. Idiopathic gastric acid hypersecretion can be controlled with strong anti-secretory drugs.

Gastric surgery can result in gastrin-induced acid hypersecretion. After partial gastrectomy with Billroth II anastomosis, a small portion of the antral mucosa containing G-cells may remain in the proximal portion of the duodenum. The gastric antral mucosa at the end of duodenum loop is stimulated by the alkaline duodenal environment to continuously secrete gastrin, a condition known as retained gastric antrum syndrome. This condition may be suspected if peptic ulcers recur after partial gastrectomy with Billroth II anastomosis, and can be differentiated by moderately increased serum gastrin levels and a more prominent increase in BAO over the peak acid output.

**Giant ulcers**

Giant ulcers are defined as gastric ulcers over 3 cm or duodenal ulcers over 2 cm. Because giant ulcers require more time to heal, they typically fulfill the refractory ulcer criteria. In general, larger ulcers require more time to heal than smaller ulcers. Large ulcers are more common in old age, again requiring longer healing times under the same treatment con-
Systemic disease such as Crohn disease and vasculitides

The incidence of Crohn disease has recently increased so much in Korea that it is now a differential diagnosis of refractory ulcers. About 0.3% to 5% of Crohn disease cases involve the upper gastrointestinal tract. Cobblestone appearance, patch hyperemia or multiple erythema, mucosal friability, and protruding hypertrophy may be seen during endoscopic procedures, along with variable ulcer sizes. Though histological abnormalities may be visible on the duodenum and gastric antrum, the granuloma required for confirmation of Crohn disease is only seen in about 7% of cases. About 16% of Crohn disease cases have abnormal endoscopy findings; however, only 7% have gastrointestinal symptoms.

Refractory ulcers are also seen in various vasculitides such as polyarteritis nodosa, Henoch-Schönlein purpura, and eosinophilic gastroenteritis.

Mesenteric ischemia

Blood supply to the stomach and duodenum is important to maintain mucosal integrity and promote ulcer healing. However, it is easy to overlook ischemia as a cause of peptic ulcers. Chronic mesenteric ischemia is an unusual cause of peptic ulcer disease because the gastroduodenal mucosa is supplied by rich vascularization. As the disease is typically asymptomatic until at least two major vessels are involved, it generally manifests only in individuals with a history of severe atherosclerotic disease. The typical symptoms are severe postprandial abdominal pain within 1 hour of ingestion, which subsides 1 to 2 hours later. Patients often limit food intake due to postprandial pain, resulting in substantial body weight loss. The goal of treatment is restoration of blood flow to the gastroduodenal mucosa, typically achieved with a vascular stent or operation.

Infectious diseases

Gastroduodenal infectious diseases such as tuberculosis, syphilis, strongyloidiasis, cytomegalovirus or herpes virus infection, and mucormycosis can present as refractory ulcers. They should be diagnosed and treated with specific anti-microbial agents rather than with PPI.

Chronic diseases

Peptic ulcers are more common among patients with chronic diseases such as liver cirrhosis, chronic renal disease, and diabetes mellitus; these patients often have lower H. pylori eradication success rates and lower PPI efficacy than those without chronic diseases. It is, therefore, necessary to identify underlying chronic diseases, if any, for cases of refractory ulcers.

Radiation therapy

The stomach and duodenum are sometimes involved in the radiation field during treatment of hepatocellular carcinoma, biliary-pancreatic cancer, or lymphoma. Radiation-induced ulcers are difficult to treat and usually fail to heal with conventional anti-acid secretory agents; they may require surgical treatment. Both extracorporeal radiation and transarterial chemoembolization using radioisotopes can cause refractory ulcers.

Malignancy

Endoscopies to screen for gastric cancer are popular in Korea. The aim of this procedure is to identify early cancers that typically present as ulcers. If the initial histological examination for an ulcer fails to diagnose a neoplastic lesion, clinicians concentrate on ulcer treatment. However, in the case of refractory ulcers, biopsies should be repeated if it is difficult to determine if the lesion is cancerous based on gross findings, even if the lesion suggests benign disease. Malignant ulcers may improve transiently with anti-secretory drug treatment, but aggravate with tumor progression. Follow-up endoscopy and repeated biopsy are recommended for benign-appearing ulcers.

Treatment of refractory ulcers

Correction of the causes

Before identification of their cause, peptic ulcers were considered a chronic recurrent disease. Without addressing these causes, healing might be delayed or ulcers could recur. Two or more H. pylori diagnostic methods may offer improved sensitivity. False negative findings should be suspected for cases of H. pylori-negative ulcers. If it is difficult to withhold PPI, physicians should consider serologic tests for H. pylori. NSAIDs should be stopped or changed to COX-2 inhibitors and physicians should survey for use of over-the-counter NSAIDs or NSAID patches. Patients should also refrain from smoking, and physicians should be aware of the signs of acid hypersecretion and the possibility of ZES. If the ulcer cause remains undetermined after following the above procedure, physicians should investigate for possible rare diseases.

Anti-secretory drugs

Anti-secretory drugs are used to improve the current state of ulcers, regardless of their cause. While various medications can be used to treat ulcers, PPIs are the most powerful. If an ulcer is refractory even after a full course of standard PPI
therapy, the dose should be doubled and administration of another type of PPI should be considered.

**Surgical treatment**

Surgical treatment for refractory ulcers has markedly decreased in the PPI era; however, surgery is still necessary on a case-by-case basis. If it is not an emergency, surgery should be selected carefully based on consideration of patient compliance and willingness to change behavior.

**CONCLUSIONS**

The most common causes of refractory ulcers are *H. pylori* infection and chronic NSAID use; however, these factors are also the most common causes of peptic ulcers. Obtaining thorough patient histories and increasing efforts to identify hidden causes are necessary. Histological examination is important for final diagnosis of malignancy and identification of rare diseases such as infection or vasculitides. Therefore, histological examination of biopsy specimens taken during endoscopy is recommended. Finally, patients should be followed-up with a degree of skepticism in order to determine the underlying causes of refractory ulcers.

**Conflicts of Interest**

The author has no financial conflicts of interest.

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