

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Prateek Sharma, MD

## Are All Esophageal Ulcers Caused by Gastroesophageal Reflux Disease?



Nayantara Coelho-Prabhu, MD  
Professor of Medicine  
Consultant, Division of Gastroenterology and Hepatology  
Mayo Clinic  
Rochester, Minnesota

**G&H** What are some important clinical differences between gastroesophageal reflux disease and esophageal ulcers?

**NC** Esophageal ulcers can occur as a result of gastroesophageal reflux disease (GERD), but they can develop from various other causes such as infections, drug-induced injury, and malignancy. Not all GERD causes esophageal ulcers, and not all esophageal ulcers are from GERD. In terms of symptoms, usually patients with GERD complain of heartburn; sometimes they have acid regurgitation. Esophageal ulcers, on the other hand, present more often with dysphagia, odynophagia, or bleeding, which may be in the form of hematemesis, melena, or anemia. Bleeding is more often seen in patients who are on long-term anticoagulation.

**G&H** How might the evaluation of a suspected esophageal ulcer differ in a patient with a history of GERD vs a patient without GERD?

**NC** The American Society for Gastrointestinal Endoscopy recommends that endoscopy be performed as soon as possible in GERD patients with alarm symptoms, such as dysphagia, weight loss, and gastrointestinal bleeding. In addition to erosive esophagitis or ulcers, patients with a history of GERD may have peptic strictures or Barrett esophagus, which can be a consequence of longstanding GERD in some patients. Patients who have difficulty swallowing and a history of ulcers, esophagitis, or longstanding GERD should undergo esophagogastroduodenoscopy to rule out a benign or malignant stricture.

Patients without GERD will probably present with either dysphagia or odynophagia as a symptom of their

esophageal ulcer. It is important to take a detailed medical history because immunocompromised conditions (eg, from medications or chemotherapy) can increase the risk of certain infections in the esophagus that can cause ulcers. An upper endoscopy should still be performed whether or not the patient has a history of longstanding GERD because some patients have asymptomatic GERD and most of these patients will have an alarm feature such as dysphagia or odynophagia.

**G&H** What is the current diagnostic approach to esophageal ulcers?

**NC** Taking an adequate history—a gastrointestinal-based history as well as a global history—is the first step, followed by an upper endoscopy with good visualization to examine the esophagus. If the esophagus looks entirely normal and the patient has dysphagia, esophageal biopsies should be obtained to rule out eosinophilic esophagitis. Ulcer location is important to consider. Esophagitis ulcers are contiguous with the stomach, whereas reflux esophagitis is usually more circumferential or will be just a few stripes of inflammation. Otherwise, there will be a breakdown of the mucosa throughout. The literature is not very clear on whether to biopsy acute esophagitis that manifests as inflammation in a circumferential pattern. Usually, the practice at our center is to treat patients who have Los Angeles (LA) grade C or higher esophagitis with a high-dose proton pump inhibitor (PPI) and follow up in 4 to 8 weeks to confirm that the esophagitis has healed and there is no underlying Barrett esophagus.

A discrete ulcer should always be biopsied. Large ulcers should be biopsied both at the base and the edge of the ulcer because different infections can be found at

different sites. Biopsies have the best yield for cytomegalovirus when samples are taken toward the center of the ulcer (which should be done gently). Herpes simplex virus, on the other hand, is more likely on the periphery of the ulcer. Both of those areas should be biopsied separately from the

**For an ulcer that is nondiagnostic, at our center, we treat the patient but then repeat the biopsy in 4 to 8 weeks because there may be more than one etiology.**

rest of the esophagus. One should not presume that kissing ulcers (ulcers on opposite walls of the esophagus), which are the textbook presentation of drug-induced esophagitis, are in fact pill-induced, and biopsy should still be done to rule out either infection or malignancy. Of course, an ulcerated mass must also be biopsied.

#### **G&H** In what ways can an esophageal ulcer be misdiagnosed?

**NC** During endoscopy, one misdiagnosis may be a flat cancer that has ulcerated. Squamous cell carcinoma can occur anywhere throughout the length of the esophagus and can sometimes be a flat ulceration rather than a nodule that one might see in adenocarcinoma, which more often extrudes into the lumen. It is important to remember that squamous cell carcinomas can be flat. Another possibility is infection. Although rare in the United States but not in other countries of the world, esophageal tuberculosis can occur and requires multiple biopsies of the site for diagnosis. For an atypical ulcer, an endoscopic ultrasound should be considered to determine the depth of inflammation or involvement in the layers of the esophagus wall. For an ulcer that is nondiagnostic, at our center, we treat the patient but then repeat the biopsy in 4 to 8 weeks because there may be more than one etiology. Especially when the ulcer is at the distal esophagus, it could be an adenocarcinoma growing in the esophageal wall that is not apparent except for surface ulceration.

#### **G&H** What are the most common causes of esophageal ulcers?

**NC** GERD is the most common cause, affecting about two-thirds of patients with esophageal ulcers. GERD

ulceration is often contiguous from the stomach because of the reflux and its continuation up the distal esophagus. An ulceration only in the midesophagus is much less likely to be GERD. Drug-induced esophagitis is probably the second most common cause owing to specific antibiotics, potassium pills, and nonsteroidal anti-inflammatory drugs. This type of esophagitis usually develops within the midesophagus where there is compression from either the aortic arch or the tracheal bifurcation.

These are the most common causes according to published epidemiologic studies from 2003. Potentially, as the population has become more obese, GERD may account for even a higher population of patients. The rates may also depend on the local population. In our tertiary referral center, GERD is the top cause. However, infectious esophagitis from cytomegalovirus or herpes simplex virus is also very common in our population, which includes many patients with cancer on immunotherapies and inflammatory bowel disease patients who are immunosuppressed.

#### **G&H** When is an esophageal ulcer considered a failure of GERD treatment?

**NC** According to the American College of Gastroenterology clinical guideline for the diagnosis and management of GERD, nonhealing GERD is diagnosed when patients who after a reasonable course of therapy with a PPI still have esophagitis. If they discontinue the PPI and have recurrence of esophagitis, then they would be considered to have PPI-dependent GERD. When an esophageal ulcer does not heal or develops while the patient is on a PPI, that is considered a failure of GERD management. Because different PPIs have different efficacy, it is important to try another PPI if one fails. Before moving on to other PPIs or non-PPI medications, such as vonoprazan (Voquezna, Phantom Pharmaceuticals), that can be used for patients recalcitrant to PPIs, or to genetic testing (for specific stress-induced protein genes that examine how fast someone may break down certain PPIs), consider that adherence may be a factor. Are they taking the PPI correctly? Are they taking it 20 minutes before meals? Other factors should be considered as well. Are they obese? Do they take a medication that slows down their gastric emptying, predisposing them to more reflux? Could they have gastroparesis as a cause of reflux? Could it be a structural problem? Do they have a large hiatal hernia? It is important to think about these different factors when managing a nonhealing ulcer despite standard therapy.

#### **G&H** When a cause cannot be identified, what further testing might help?

**NC** The point to remember is always biopsy, unless an LA grade C or D esophagitis is apparent, where biopsy is possible, but the yield is going to be quite low. If the patient has not been on PPIs, for example, treat them, bring them back, and reassess. Repeating the endoscopy and biopsies may help because it is possible to find dysplasia, precancerous cells, or even cancer in just one segment. Biopsies can also rule out conditions like eosinophilic esophagitis. Esophageal manometry may be considered when motility of the esophagus could be an issue, such as when the esophagus is not clearing adequately or the lower esophageal sphincter is lax, which can happen in cases like scleroderma in patients who have constant reflux.

I think it is important to document how much reflux patients are having. There is debate about whether to do this testing on or off the PPI. Essentially, ambulatory pH monitoring with placement of a Bravo capsule that sits 6 cm above the gastroesophageal junction is helpful for measuring acid reflux, although not as helpful for non-acid reflux. The amount of reflux overall and whether it is acidic or nonacidic can be determined with a probe pH monitor, which measures how high the reflux travels through the esophagus. Esophageal manometry can be done at the same time as the 24-hour probe, as long as patients can tolerate a probe going down the back of their nose, which most people can.

Other tests to consider include mucosal impedance testing, gastric pH, structural abnormality testing, a barium esophagram to rule out a hiatal hernia, and a gastric emptying study in the case of suspected gastroparesis.

### **G&H** What are the main complications of esophageal ulcers and how are they diagnosed?

**NC** As for benign complications, esophageal strictures as a result of ulceration are quite common. They usually develop at the lower end of the esophagus. They can be ring-like, but long-term inflammation from GERD and esophagitis can cause a long segment of stricturing, which can be quite difficult to treat. A barium esophagram can identify where the tapering of the esophagus is; however, strictures should be diagnosed and treated with endoscopy. It is very important to biopsy extensively esophageal strictures that develop as a result of GERD because they can still have adenocarcinoma in them.

Strictures that require frequent dilation do not have to be biopsied at every endoscopy; however, repeating biopsies after every 2 or 3 endoscopies can help catch an underlying etiology. It is also important to remember to retroflex in the stomach and look at the gastric cardia, which can sometimes have tumors that cause stricture

formation. A good retroflex examination of the cardia can ensure that there is no nodularity or abnormality on the stomach side causing what would be considered an esophageal stricture. Esophageal strictures do happen quite commonly after GERD and when benign are quite responsive to treatment with an endoscopic balloon or with a bougie.

Cancer is a concern with a nonhealing ulcer anywhere in the gastrointestinal tract, but especially in the esophagus. As mentioned, squamous cell carcinoma can occur anywhere in the esophagus, and Barrett esophagus, a precursor to adenocarcinoma, can sometimes protrude into the lumen, but sometimes can be in the wall. Often, when the inflammation heals, the underlying Barrett esophagus is then visible. Esophageal adenocarcinoma generally occurs in the lower third of the esophagus. It is important to always biopsy a nonhealing ulcer.

### **G&H** Which practice pearls on esophageal ulcers are most important?

**NC** There are a few important points to highlight. First, if patients present with alarm symptoms, they must have an early endoscopy. Second, if they have active esophagitis, they must have a repeat endoscopy with extensive biopsies. The setting of active esophagitis is where missed adenocarcinomas and Barrett esophagus are often seen. Third, all esophageal ulcers should be biopsied except for new esophagitis, which is treated and examined again in 4 to 8 weeks. Perforation should not occur if the endoscopist does not push too hard, and good pieces of tissue can be obtained for the pathology.

### **Disclosures**

*Dr Coelho-Prabhu has no relevant conflicts of interest to disclose.*

### **Suggested Reading**

- Higuchi D, Sugawa C, Shah SH, Tokioka S, Lucas CE. Etiology, treatment, and outcome of esophageal ulcers: a 10-year experience in an urban emergency hospital. *J Gastrointest Surg.* 2003;7(7):836-842.
- Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2022;117(1):27-56.
- Muthusamy VR, Lightdale JR, Acosta RD, et al; ASGE Standards of Practice Committee. The role of endoscopy in the management of GERD. *Gastrointest Endosc.* 2015;81(6):1305-1310.
- Pasha SF, Acosta RD, Chandrasekhara V, et al; ASGE Standards of Practice Committee. The role of endoscopy in the evaluation and management of dysphagia. *Gastrointest Endosc.* 2014;79(2):191-201.
- Spechler SJ. Clinical manifestations and esophageal complications of GERD. *Am J Med Sci.* 2003;326(5):279-284.