

## THE ENDOSCOPICALLY ABNORMAL ESOPHAGUS

The endoscopic abnormalities that may be seen in association with esophageal disorders are numerous, varying from subtle alterations in the esophageal mucosal surface to large ulcers or masses. This discussion will be focused on a few commonly encountered entities in which clinical, endoscopic and histologic correlation are critical for establishing a correct diagnosis. These include gastroesophageal reflux disease (GERD), eosinophilic esophagitis and Barrett's esophagus.

### Gastroesophageal Reflux Disease

The most recent practice guidelines for diagnosis and management of gastroesophageal reflux disease support establishing a presumptive diagnosis of GERD without endoscopic evaluation in the setting of typical symptoms such as heartburn and regurgitation (1). Empiric medical therapy with a proton pump inhibitor is recommended; therefore, most patients that are being evaluated for GERD endoscopically are already on PPI therapy at the time of biopsy. Endoscopic examination is recommended in any patient with "alarm" symptoms, or in those at high risk for development of complications. Alarm symptoms include dysphagia, non-cardiac chest pain, or a lack of a response to PPI therapy. Although the presence of GERD-related symptoms does not provide a high level of sensitivity or specificity for predicting esophageal abnormalities on upper endoscopy, it may be reasonable to screen select individuals for Barrett's esophagus by endoscopy. Epidemiologic risk factors for BE have been well established and include age over 50, symptoms for > 5-10 years, obesity, and male sex. Recent data suggest that selectively screening patients that fall into this high risk group may be reasonable (2).

The endoscopic appearance of the esophagus varies with disease severity. Approximately one third of patients with chronic GERD symptoms are endoscopically normal (3). Areas of patchy erythema and red streaks are the first endoscopic abnormalities. Later erosions and ulcers develop; these predominate distally and taper off proximally. As the disease progresses, the ulcers become confluent, even circumferential. Strictures or BE characterize severe chronic disease. Several endoscopic classifications have been developed to evaluate the esophageal mucosa. The two most common are the Savary-Miller MUSE system and "Los Angeles" classifications (4,5). The use of these grading systems among gastroenterologists varies, likely depending on the practice setting. Among esophageal biopsies seen in our practice in 2010, 27.9% included an LA grade, and 12.2% a Savary-Miller grade (6).

### Savary-Miller Classification

Grade	Features
I	One or more supravestibular reddish spots with or without exudates
II	Erosive and exudative lesions in the distal esophagus that may be confluent, but not circumferential
III	Circumferential erosions in the distal esophagus covered by hemorrhagic and pseudomembranous exudates
IV	Presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia

## Los Angeles Classification

Grade	Features
A	One or more mucosal breaks $\leq$ 5 mm in length
B	At least one mucosal break $>$ 5 mm long, but not continuous between the tops of adjacent mucosal folds
C	At least one mucosal break which is continuous between adjacent mucosal folds, but not circumferential ( $<$ 75% of periphery)
D	Mucosal breaks that involve at least three-quarters of the luminal circumference

*Note: Ulcers, strictures, Barrett's metaplasia, and other findings are reported as an adjunct to each grade.*

## Reflux Esophagitis

GERD affects patients of all ages, even children and small infants, but is most common among patients over age 65 (7). GERD affects from 3% to 4% of the population, and its incidence has increased in the past few decades. The annual cost of managing the disease in the United States is estimated at 9 billions dollars (8). GERD is equally present among men and women, but there is a male predominance of esophagitis and Barrett esophagus. GERD affects whites more frequently than members of other races.

Conditions predisposing to GERD include smoking, decreased physical activity, increased intra-abdominal or intragastric pressure, including pregnancy, ascites, body mass index and obesity; and delayed gastric emptying. Postmenopausal estrogen therapy has been associated with GERD symptoms (9, 10). Motility disorders including diabetes, alcoholic neuropathies, and scleroderma also predispose to GERD. Patients with hiatal hernias and strictures are especially prone to develop GERD. It also follows surgical procedures.

### *Clinical Features*

Transient mild reflux affects most individuals including children and adults. The degree of reflux must be severe for individuals to become symptomatic. Adults present with diverse symptoms including heartburn, regurgitation, bitter-tasting fluid in the mouth, dysphagia, odynophagia, nausea, vomiting, hiccups, anginalike chest, and hoarseness. The regurgitation can cause a spectrum of conditions, including asthma, chronic cough, chronic laryngitis or pharyngitis, subglottic stenosis, and dental disease. Rare patients present with bleeding from esophageal ulcers. Complications peak between ages 50 and 70 years (11).

As discussed above, the majority of patients with GERD symptoms are treated with proton pump inhibitor (PPI) therapy, often prior to being seen by a gastroenterologist (12). A recent survey found, however, that as many as 40% of patients receiving PPI treatment have residual symptoms (13). As a result, many of the patients undergoing endoscopy and biopsy for GERD symptoms are those that are refractory to PPI therapy. Such patients may have additional disorders superimposed on GERD. The differential diagnosis of esophageal disorders that may be associated with refractory symptoms in patients treated with PPIs is summarized below.

## **Disorders Associated with Residual Symptoms in Patients Treated with PPIs**

### Esophageal Disorders

#### Reflux Related

- Incorrect medication dose timing
- Medication non-compliance
- Residual pathologic acid secretion
- Rapid PPI metabolism
- Hypersecretory state
- Anatomic abnormalities
- Defective LES function
- Hypersensitivity of esophagus to small amounts of refluxed material

#### Non-reflux related

- Achalasia
- Esophageal spasm
- Scleroderma
- Eosinophilic esophagitis
- Pill esophagitis
- Infectious esophagitis

### Non-Esophageal Disorders

- Gallbladder disease
- Cardiovascular disease
- Musculoskeletal disorders
- Malignancy (GI and non-GI)

## ***Histologic Features***

Biopsies are performed to confirm the diagnosis of GERD; to document complications, including esophagitis, BE, or tumor development; and to rule out the presence of coexisting infections. Since esophagitis tends to be a patchy process, it is easy to miss diagnostic changes on a single biopsy. The current wisdom is that biopsies should be taken in the area just distal to the Z line to detect carditis (see below), just proximal to the Z line to detect esophagitis, and 3 cm proximal to the Z line to detect the hyperplastic changes that are more predictive of the presence of GERD than more distally derived biopsies.

Various histologic features should be assessed when examining the biopsy for GERD (see below). No single feature represents an absolute criterion for the presence of GERD, but each is helpful in establishing the diagnosis. In the absence of a known drug history or the presence of specific microorganisms, biopsies, particularly distal biopsies showing esophagitis, are most likely to be due to GERD.

### *Epithelial Hyperplasia*

The normal basal cell layer is only one to four cells high; it should not constitute more than 15% of the epithelial thickness. In the setting of GERD, the basal zone increases from 10% to more than 50%; papillary height can increase to more than 50% to 75% of the total epithelial thickness (14). This change affects patients with an endoscopically normal mucosa as well as those with endoscopic evidence of esophagitis. Regenerative changes are characterized by

nuclear enlargement, hyperchromasia, and mitoses that remain limited to the basal layer. Prominent nucleoli may be present.

Although recognition of the basal layer of the squamous epithelium is not difficult, determination of its uppermost limit often is. One definition that may be helpful (15) is that the upper limit of the basal zone is that point where the majority of epithelial cell nuclei are separated by a distance less than the diameter of one nucleus. In addition, accurate assessment of the thickness of the basal layer requires evaluating well-oriented specimens. The basal height should not be assessed near vascular papillae. It may be helpful to divide the epithelial thickness into thirds. When the lower third is divided in half, the basal cells should be confined to its lower half. In less optimally oriented specimens, basal zone thickness can be evaluated if one sees at least three to four papillae arranged in parallel to one another and not cut tangentially. In tangentially cut sections, a helpful feature is an increase in the number of papillae, which can be evaluated in an en face section. In this setting one may see overlapping capillaries. Since the biopsies may be small or have minimal or no lamina propria or they may be inappropriately oriented and therefore difficult to evaluate for basal hyperplasia and papillary elongation, we recommend that the biopsies be examined at three levels to increase their diagnostic accuracy.

The sensitivity of hyperplasia as a diagnostic feature of GERD is only 60% to 70% (16). Basal cell hyperplasia is a reversible change that disappears with treatment. Hyperplasia also complicates other forms of esophagitis so that it is not specific for GERD.

#### *Papillary Height*

Papillary elongation is most often defined as papillae extending more than two-thirds of the distance to the epithelial surface. The degree of papillary elongation correlates with severity of reflux (17), but is not a specific feature of GERD. Evaluation of papillary height, like basal layer thickness, requires a well-oriented biopsy in which the entire thickness of the epithelium is visible.

#### *Dilated Intercellular Spaces*

Dilated intercellular spaces occur in patients with both erosive and non-erosive GERD (18-20). In light microscopic studies, dilated intercellular spaces are defined as an increase in the distance between squamous epithelial cells. This distance varies from greater than 0.47 to 2.4  $\mu\text{m}$  depending on the study (18-22). Dilated intercellular spaces are seen predominantly in the basal layer, and are thought to occur as a result of stretching and detachment of desmosomes (20). The prevalence of dilated intercellular spaces in biopsies from patients with GERD ranges from 67-94% depending on whether or not clinical symptoms, endoscopically identifiable lesions or pH monitoring abnormalities are present (23).

#### *Inflammation*

*Intraepithelial lymphocytes.* Small numbers of lymphocytes populate both the normal mucosa and the lamina propria so that their presence does *not* aid in making a diagnosis of esophagitis. However, they are very conspicuous in patients with GERD (24). Biopsies with esophagitis average greater than six lymphocytes per hpf (25). They are part of the inflammatory response in GERD but are not an independent marker of reflux esophagitis.

*Neutrophils.* The presence of isolated neutrophils, either in the squamous epithelium or in the lamina propria, serves as evidence for acute esophagitis of many etiologies, and are most

commonly observed in erosive GERD. Neutrophils are present in the epithelium of from 10-40% of patients with reflux esophagitis, making them a relatively insensitive marker (26-28). They tend not to appear until the inflammation becomes severe and the epithelium ulcerated. They generally decrease in number the further one goes away from the erosion or ulcer. When numerous neutrophils are identified in an esophageal biopsy, the possibility of other ulcerating conditions including infection and pill-mediated injury should be considered.

*Eosinophils.* The normal number of eosinophils present in the esophagus is still somewhat controversial. However, many feel that eosinophils are normally absent (26, 29). Some, however, have found a modest number (usually less than 5 per high power field) may be seen (27). It is likely that these differences arise from differing definitions of normal controls versus GERD. Influx of eosinophils into the epithelium occurs early in the course of reflux esophagitis and may be seen in the absence of basal cell hyperplasia. Other causes for mucosal eosinophilia include the entities listed in the Table below.

### **Eosinophil-Associated Esophageal Disorders**

#### **Primary eosinophilic disorders**

Eosinophilic esophagitis

#### **Secondary eosinophilic disorders**

Eosinophilic gastroenteritis

Hypereosinophilic syndrome

#### **Secondary noneosinophilic disorders**

Infection

Pill esophagitis

Gastroesophageal reflux disease

Tumors

Vasculitis

Connective tissue disorders

One can easily appreciate eosinophils in small endoscopic biopsies, even when the biopsies are not well oriented. They affect up to 60% of adults with severe disease but the intraepithelial eosinophils may be focal in nature, necessitating a search for them on serial sections; their presence does not correlate with disease severity (29, 30). Eosinophils are not a sensitive marker for GERD, since they are only found in 40% to 50% of individuals with GERD (23, 28, 30). Significant esophageal eosinophilia (>15 intraepithelial eosinophils per hpf) may sometimes be seen in patients with GERD, but should prompt the pathologist to consider the diagnosis of eosinophilic esophagitis as discussed later.

### ***Erosions and Ulcers in Gastroesophageal Reflux Disease***

The mucosal changes of reflux esophagitis range from the changes already described to acute esophagitis, erosions and superficial ulcers. The epithelium close to erosions or ulcers often contains neutrophils, eosinophils, and many lymphocytes. The erosions or ulcers often contain granulation tissue, an inflammatory exudate, and fibrinoid necrosis in the ulcer base. Lymphoplasmacytic infiltrates, often forming lymphoid aggregates, tend to cluster around erosions and ulcers. Epithelium at the ulcer margin is usually attenuated. Marked basal cell

hyperplasia may occupy the entire mucosal thickness and there may be marked acanthosis. These changes may be accompanied by occasional bizarre epithelial or stromal cells.

Erosions or ulcers may be isolated or confluent; they commonly coexist with one another. The damaged mucosa present in reflux esophagitis becomes prone to secondary infection. For this reason, both ulcers and adjacent tissues need to be carefully examined for the presence of coexisting fungal or viral infections.

*Esophageal peptic ulcers* develop in the setting of reflux esophagitis; they resemble peptic ulcers occurring elsewhere. These may erode through the muscular layers, resulting in perforation. Peptic ulcers appear large, oval, and well circumscribed with elevated borders and deep necrotic centers. As these heal strictures may develop. This occurs in about 10% of patients with severe reflux esophagitis. Fibrosis is usually present and may extend into the submucosa or beyond, sometimes extending into the periesophageal tissues. Although peptic strictures nearly always involve the distal esophagus, they occasionally develop more proximally. Proximal strictures average 2 to 4 cm in length. Extensive strictures may complicate severe reflux esophagitis as well as nasogastric intubation in patients with reflux esophagitis or Zollinger-Ellison syndrome. Strictures are also common in patients with eosinophilic esophagitis, the major disorder in the differential diagnosis of reflux esophagitis.

## **Eosinophilic Esophagitis**

Eosinophilic esophagitis (EoE) is a chronic disorder that is well known in children. It has recently become recognized with increased frequency in adults, in whom it was, until recently, likely underdiagnosed. EoE occurs worldwide, having been reported from all continents except Africa (31). Eosinophilic esophagitis appears to be increasing in incidence in both children and adults (32-35). Although the exact incidence of EoE is not known, epidemiologic studies suggest that it occurs with a frequency comparable to inflammatory bowel disease (31). Eosinophilic esophagitis is more common in males in all age groups (36). EoE has a strong familial association; 10% of parents whose children have EoE have a history of esophageal strictures, and 8% have biopsy-proven EoE (32).

### ***Pathogenesis of Eosinophilic Esophagitis***

The etiology of EoE is related to hypersensitivity to food-associated and airborne allergens. Most patients have personal and/or family histories of allergic disorders, including asthma, food allergies, or atopic dermatitis. Skin prick testing shows that the majority EoE patients are sensitized to multiple foods rather than a single food allergen (37, 38). Patients with EoE show a highly conserved gene expression profile that is independent of age, gender or atopic status (39). This so-called EoE transcriptome includes numerous genes, with eotaxin-3 representing the most highly induced gene (39-41). Eosinophil activation and degranulation in the esophagus is thought to result in much of injury that occurs in EoE. Eosinophils granules contain numerous substances that are cytotoxic including eosinophil-derived neurotoxin, eosinophil peroxidase, eosinophil cationic-protein and major basic protein (42-45). Eosinophils also produce numerous cytokines and chemokines that have the ability to modulate many aspects of the immune response (46). Transforming growth factor-beta produced by eosinophils leads to fibroblast recruitment, likely resulting in the fibrosis that characterizes EoE in its later stages.

IgE expressing B lymphocytes and mast cells also contribute to the injury that occurs in EoE (47, 48).

### ***Clinical Features***

The presenting symptoms of EoE vary depending on patient age. Adults typically present clinically with solid food dysphagia and food impaction. Children under age two typically present with feeding refusal, food intolerance, vomiting, abdominal pain or other vague symptoms often thought secondary to GERD such as respiratory problems (49, 50). Children may also present with failure to thrive, growth retardation and developmental delay (51, 52). Peripheral eosinophilia is present in approximately 50% of patients (53, 54). Many patients with eosinophilic esophagitis are referred to gastroenterologists for refractory GERD symptoms unresponsive to acid blockade.

### ***Endoscopic Findings***

Endoscopically, the esophagus is abnormal in approximately two-thirds of patients with EoE (55); the remainder show no endoscopic alterations. Strictures are common and involve both focal as well as long-segment (small-caliber) esophagus. Corrugation, multiple esophageal rings, webs, vertical furrows, mucosal granularity, mucosal fragility, white specks or exudates, and polypoid lesions are other common findings. Some patients have white mucosal patches resembling those observed in *Candida* infection. These white patches correspond to eosinophilic microabscesses and exudates involving the mucosal surface. The rings may result from contraction of the fibers of the muscularis mucosae, perhaps in response to activation of acetylcholine by secretions from mast cells and eosinophils (56). A recent study has proposed an endoscopic classification and grading scheme for EoE (57), but this is not yet in widespread use.

### ***Diagnosis of Eosinophilic Esophagitis***

The diagnosis of eosinophilic esophagitis requires consideration of both pathologic and clinical factors. It is defined by the following criteria: 1) Clinical symptoms of esophageal dysfunction, 2) Eosinophil predominant inflammation on esophageal biopsy, consisting of a peak value of  $\geq 15$  eosinophils per high power field, 3) Mucosal eosinophilia is limited to the esophagus and persists after a trial of proton pump inhibitor (PPI) therapy, 4) Secondary causes of esophageal eosinophilia are excluded. A response to treatment, either dietary elimination or corticosteroid administration, supports, but is not required for diagnosis (58).

### ***Histologic Features***

Histologically, esophageal biopsies demonstrate often marked epithelial basal hyperplasia and extensive infiltration of the epithelium by eosinophils. The changes occur not just in the distal esophagus as in GERD, but also in the mid and upper esophageal mucosa. Eosinophils in EoE are typically more numerous in the superficial portion of the squamous epithelium, and frequently occur in small aggregates of 4 or more cells to form eosinophilic microabscesses. It is important to note that the histologic changes are commonly patchy in this disorder, and therefore, multiple biopsies should be taken and examined (58, 59).

Recent consensus recommendations for the diagnosis of EoE state that intraepithelial eosinophils should be counted in the most intensely inflamed portion of the biopsy specimen, and that at least 15 eosinophils per high power field be present before the diagnosis is suggested (60, 61). It is important to note, that these consensus recommendations also state that the

diagnosis of EoE should only be made in the proper clinical context, and therefore, close communication between the pathologist and gastroenterologist is necessary to establish the diagnosis.

The differential diagnosis of esophageal eosinophilia centers around eosinophilic esophagitis, PPI-responsive esophageal eosinophilia, reflux esophagitis, hypereosinophilic syndrome, and eosinophilic gastroenteritis. In contrast to EoE, GERD is usually characterized by lower numbers of intramucosal eosinophils, usually 7 or fewer per high power field (62, 63). As discussed above, however, large numbers of eosinophils (>20/hpf) may occasionally be present in adult patients with GERD, and occasionally in patients with other esophageal disorders (64, 65). Therefore, absolute eosinophil counts cannot be used to establish a definitive diagnosis of EoE. In addition, many patients appear to have features of both EoE and GERD, making definite distinction between the two entities difficult.

Definitive diagnosis requires correlation with clinical factors, most importantly response to proton pump inhibitor therapy (58). There are two clinical scenarios in which patients with esophageal eosinophilia respond to PPI therapy. The first situation is one in which the patient has classic symptoms of GERD and erosive esophagitis or Barrett's esophagus on endoscopy (65, 66). These patients likely have GERD contributing to esophageal eosinophilia, and treatment of the reflux results in a reduction in eosinophil numbers. The second situation is one in which the patient presents with symptoms or endoscopic findings typical of EoE, but their symptoms and their esophageal eosinophilia regress following PPI therapy. These patients are diagnosed as having *PPI-responsive esophageal eosinophilia*. The reason for the PPI response in these individuals is not well understood, and likely results from the complex interplay of many different factors. It is currently unknown whether these patients have a variant of GERD, an EoE variant, or a separate process from either EoE or GERD. Long-term follow-up on these patients is currently lacking, although one small case series of four pediatric patients with PPI-responsive esophageal eosinophilia found that these patients ultimately developed PPI-unresponsive symptoms, and were subsequently diagnosed with EoE (67).

Some have speculated that GERD may in some way predispose an individual to the development of EoE, making true separation of these two diseases impossible (68). Alternatively, EoE may induce changes in the esophageal lining predisposing to the development of GERD. This may be particularly true in adult patients. Acid peptic injury to the squamous epithelium of the esophagus may affect tight junctions making the epithelium permeable to allergens. In addition, GERD could cause recruitment of inflammatory cells into the esophageal mucosa which could contribute to the local development of allergic reactions. EoE could predispose to GERD as a result of release of eosinophil secretory products. Vasoactive intestinal peptide and platelet-activating factor, two eosinophil secretory products, have been shown to cause LES relaxation (69). EoE also induces fibrosis in the lamina propria of the esophagus (70), a factor that could result in impaired peristalsis and acid clearance, and ultimately, stricture formation.

Recent studies have shown increased intraepithelial mast cells in esophageal biopsies from patients with EoE (70-72), and some suggest that staining for mast cell tryptase may be a helpful in differentiating EoE from reflux esophagitis (73, 74). One study (73) found that when mast cell counts (cutoff of 96 mast cells/mm<sup>3</sup>) were combined with eosinophil counts (cutoff greater than 15 eosinophils/high power field), sensitivity and specificity for the diagnosis of EoE was 91% and 95 % respectively. This compares with sensitivity and specificities of 80% and

80% respectively for mast cell number alone, or 80% and 84% respectively for eosinophil counts alone.

### ***Treatment and Follow-up of Eosinophilic Esophagitis***

Therapy for EoE includes dietary avoidance of known allergens, administration of anti-inflammatory agents and physical dilation of esophageal strictures that may develop. Patients with EoE are additionally treated with anti-reflux therapy since GERD may contribute to development of eosinophilic infiltrates in the esophagus. Elimination diets, including elemental diets, are often successful in diminishing clinical symptoms and improving histologic findings (55). Dietary avoidance, however, is often difficult to implement since EoE is often associated with sensitivity to multiple food types. Glucocorticoids may be beneficial in some patients. They are generally given systemically for initial treatment followed by topical administration for long-term maintenance. Biologic therapies, for example use of anti-IL-5 antibodies, is currently under investigation in EoE (75).

## **Barrett Esophagus**

### ***Definitions***

Barrett esophagus (BE) is an acquired condition in which any extent of the normal stratified squamous epithelium of the esophagus is replaced by a metaplastic columnar epithelium that predisposes to cancer development (76). Presently intestinal metaplasia is required for the diagnosis of Barrett's esophagus because intestinal type mucosa is the only type of columnar metaplasia that clearly disposes to malignancy. The current definition of Barrett esophagus requires that both endoscopic and histologic criteria be met before the diagnosis can be established (77). The endoscopic component requires the presence of columnar mucosa identified endoscopically by its salmon pink color, extending proximally from the GEJ into the tubular esophagus. BE is generally divided into long-segment BE (LSBE), in which the columnar mucosa extends 3 cm or more above the GEJ, and short-segment BE (SSBE), in which the specialized columnar epithelium is restricted to <2 to 3 cm above the GEJ (78).

In the United States, the histologic component requires that biopsies taken from the endoscopically identified columnar pink mucosa contain metaplastic, intestinalized columnar epithelium with goblet cells (77). The reason for this approach is that many past studies showed that dysplasia and carcinoma were much more likely to arise in intestinal-type than in gastric-type metaplastic epithelium. Recently, however, this contention has been challenged. In the last several years, a number of studies have shown that cardia type epithelium within the tubular esophagus has similar molecular abnormalities to intestinal type metaplasia, and may also predispose patients to development of adenocarcinoma (79-84). This has prompted the British Society of Gastroenterology to define Barrett mucosa more broadly as a "columnar-lined oesophagus on histology" (including either cardia- or intestinal-type epithelium or both) (85). The American Gastroenterological Association, however, requires the presence of intestinal metaplasia for the diagnosis of Barrett esophagus since the magnitude of risk for dysplasia or adenocarcinoma in cardia-type metaplastic epithelium has not yet been defined (86). In addition, the likelihood of histologically identifying intestinal type epithelium increases with the length of the Barrett segment, and therefore, cardia-type mucosa alone is essentially only found in individuals with short segment Barrett esophagus. The risk for esophageal adenocarcinoma in patients with SSBE is likely different from those with LSBE, and the risk for neoplastic

transformation has yet to be determined in patients with ultra short segments of columnar epithelium.

### ***Prevalence/Incidence***

Barrett esophagus is thought to occur secondary to gastroesophageal reflux. Therefore, like GERD, BE demonstrates geographic, temporal, and ethnic incidence differences. Overall, BE affects approximately 1.6% of the general population (87). It is more common in older patients. For example, BE was found in 25% of asymptomatic male veterans over the age of 50 who underwent an upper endoscopy at the same time that they had a screening sigmoidoscopy (88). The prevalence of BE in the asymptomatic population is probably much higher than might be expected from data based on endoscopic examinations of symptomatic patients. An autopsy study in Olmstead County, Minnesota, found BE in 7 of 733 (1%) cases. When adjusted for age and sex to correspond to the U.S. population, the true prevalence was 376 per 100,000 population, or 17 times that of the 27 cases per 100,000 diagnosed endoscopically during the study period (89). Among patients undergoing colonoscopy, the prevalence of BE overall was 6.8%; 1.2% had long segment BE and the remainder had SSBE. Long segment BE was uncommon in patients without a history of heartburn, but SSBE was common among patients over 40 years of age, and those without a clinical history of previous endoscopy or complaints of heartburn (90).

Most patients who seek medical treatment usually have underlying symptomatic GERD. BE develops in up to 44% of patients with reflux esophagitis (91, 92). It demonstrates a bimodal age distribution with one peak at 0 to 15 years and another at 40 to 80 years (89,93,94). BE preferentially affects white males. The male:female ratio is 4:1 (91). Patients with complications of BE are usually older. BE may also complicate other forms of esophageal injury beside GERD, including chemotherapeutic drug injury (95) or lye ingestion (96).

The significance of establishing a diagnosis of Barrett's esophagus lies in the fact that patients with BE are at increased risk for the development of esophageal adenocarcinoma. Recent studies suggest that the risk for development of esophageal cancer in patients with BE is approximately 0.5% per year. In other words, one in 200 BE patients will develop esophageal adenocarcinoma each year. Some studies suggest a higher cancer risk in individuals with long segment BE, and among males compared with females (97).

### ***Pathogenesis***

BE is an acquired metaplastic change that results from longstanding GERD. It results from a combination of substances in the refluxate including acid, bile salts, lysophospholipids, and activated pancreatic enzymes. In this abnormal milieu, multipotential immature stem cells differentiate into various epithelial types, including columnar epithelium, which is more resistant to acidic digestion and which is able to regenerate more rapidly than the native squamous epithelium (98,99). Once established, BE is a highly proliferative mucosa (100).

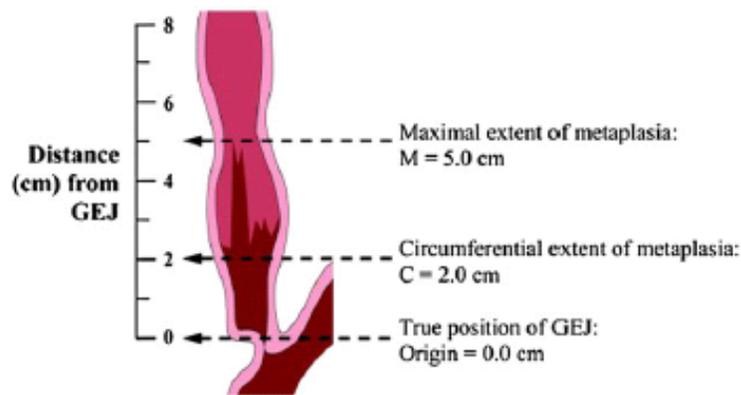
The development of BE is a multistep process with at least three distinct phases. During the *initiation phase*, genetically predisposed individuals (mostly white men) suffering from GERD develop reflux esophagitis. This leads to the formation of a metaplastic epithelium with features of intestinal columnar epithelium. The metaplastic columnar cells of BE could derive from three sources (101): (a) metaplasia of squamous epithelium; (b) from the mixed squamous/columnar cell population at the transitional zone; or (c) from the columnar cells of the esophageal glands, such as may be associated with ulcer repair. Circulating bone marrow–

derived stem cells (BDSCs) recruited in response to reflux-induced inflammation might serve as another potential source of BE (102).

During the *formation stage*, the metaplastic epithelium, which continues to be exposed to the refluxate, establishes its presence and occupies a variable surface area of the distal esophagus. This results in the oral migration of the SCJ over time (103). A long and multifaceted *progression phase* follows, during which the metaplastic epithelium either remains dormant and clinically insignificant or progresses to dysplasia and eventually invasive adenocarcinoma. Unfortunately, distinguishing which patients will progress to develop dysplasia is not possible at the present time, so all patients with BE undergo routine endoscopic surveillance.

### ***Gross and Endoscopic Features***

Barrett mucosa appears salmon pink or red and velvety, contrasting with the lighter tan colored, smooth squamous epithelium. Grossly, there are several distinct patterns of BE: Circumferential, islands, and fingerlike projections or tongues. The island type accompanies less severe epithelial injury than the circumferential type and probably represents an earlier stage, which then progresses to the circumferential lesion (104). Sometimes it is difficult to distinguish the distal border of the metaplastic epithelium from the adjacent gastric mucosa with which it may appear to merge. Locating the proximal extent of gastric folds or the distal most extent of the esophageal longitudinal vessels delineates the gastroesophageal junction. Patients with SSBE have short tongues or patches of red mucosa lying <3 cm above the GEJ. An endoscopic system for grading Barrett esophagus has been developed and is referred to as the Prague system (105). In the Prague system, the endoscopist determines two values; the C value represents the circumferential extent of the columnar mucosa, and the M value the maximum extent of the columnar mucosa above the GEJ measured in centimeters.



**Figure 1.** Diagrammatic representation of endoscopic Barrett's oesophagus showing an area classified as C2M5 (C: extent of circumferential metaplasia, M: maximal extent of the metaplasia, GEJ: gastro-oesophageal junction).

Typically the endoscopist biopsies the following areas: The stomach just distal to the upper end of the gastric folds, particularly along the lesser curvature; 1 to 2 cm above the GEJ; tongues of mucosa or irregular areas above the SCJ; and the SCJ and squamous epithelium of the

native esophagus. Biopsies at the upper end of the gastric folds may allow one to determine whether there is gastritis, particularly *HP*-induced gastritis and possibly intestinal metaplasia.

### ***Histology of Barrett Esophagus***

There are two major problems in the pathologic evaluation of patients with BE: Overdiagnosis of BE and overdiagnosis of dysplasia in the setting of BE. The diagnosis of BE is covered here. The diagnosis of dysplasia and its mimics is discussed in Chapter 3. The histology of the columnar-lined esophagus displays heterogeneous histologic features with respect to the surface architecture and the types of glandular mucosa that are present. As noted earlier, the definition of BE requires histologic confirmation of intestinal metaplasia in biopsies taken from the columnar regions of the esophagus (106). Examination of multiple biopsies and multiple levels is necessary since goblet cells may be sparsely distributed.

The pathologist often must rely on the endoscopic findings to determine that a biopsy originated from the tubular esophagus. Histologic findings that help to confirm the esophageal origin of a biopsy include the presence of esophageal glands or ducts (107), the presence of squamous islands (108, 109) and the presence of a duplicated muscularis mucosae (110). The presence of palisade vessels (veins greater than 100  $\mu$ m in size located above the muscularis mucosae) has recently also been suggested as another histologic marker of esophageal origin (111).

The columnar Barrett's epithelium commonly contains a mixture of gastric foveolar cells and intestinal cells. The latter include goblet cells, intestinal columnar cells, endocrine cells, and sometimes Paneth cells. The majority of the intestinal columnar cells are so-called intermediate, principal, or pseudoabsorptive cells that have characteristics of both absorptive and secretory cells. A villiform architecture may be present on the surface. *H. pylori* may be found associated with the gastric-type columnar epithelium of some patients with BE but only when it is also present in the stomach. It may contribute to the severity of the inflammation seen in BE.

Careful histologic attention should be paid to potential BE mimics, particularly pseudogoblet cells. These columnar cells are hyperdistended gastric foveolar cells. They contain a mucinous droplet that is larger than the typical foveolar cell but smaller than the usual goblet cell. They occur in the surface epithelium at the GEJ and distal esophagus. They may occur in the presence or absence of true goblet cells. With some hematoxylin preparations, true goblet cells have a bluish staining quality, while pseudogoblet cells appear pale pink. Pseudogoblet cells and the adjacent foveolar cells often stain positively with Alcian blue at a pH 2.5; for this reason they are sometimes referred to as the "columnar blues". However, the pseudogoblet cells stain less intensely than true goblet cells. *If only Alcian blue–positive columnar cells are present in the absence of true goblet cells, the diagnosis of BE should not be made.* Because of the lack of specificity of Alcian blue staining for true goblet cells, there has been interest in finding a more specific marker of intestinal goblet cells. Markers of interest have included stains for sulphomucins and sialomucins. Sulphomucin expression is less sensitive (sensitivity 62%) but more specific (specificity 90%) for the presence of true goblet cells. However, sialomucins or sulphomucins can also be present in the surface epithelium of a small percentage of patients without goblet cells (112), contradicting the commonly held belief that gastric-type surface epithelial cells only contain neutral-type mucins. Another marker that may represent an early indicator of BE is MUC2. MUC2 is expressed in goblet cells in BE, and is also expressed in a subpopulation of adjacent columnar cells (113).

Of note, the muscularis mucosae is hyperplastic and reduplicated in the distal esophagus of patients with BE. In some areas collagen-rich fibrous tissue replaces the muscularis mucosae. An understanding of these features is important in two situations: The first is the correct interpretation of alterations that may affect the submucosal glands, and the second is in the correct staging of invasive malignancies. The fibroblastic or muscular abnormalities may deform the ducts of the submucosal glands, causing the glands to dilate. The combination of irregular ductal compression in the presence of atypical epithelial cells lying in the fibrous tissue can cause difficulty in differentiating normal or dysplastic esophageal glands trapped in the collagen-rich fibrotic tissue from invasive cancer.

### **Pathologic Features of Short-Segment Barrett Esophagus and Intestinal Metaplasia of the Cardia**

Intestinal metaplasia at the GEJ is either SSBE, which has a cancer risk at most of 0.5% per year, or intestinal metaplasia of the proximal stomach, which appears to have a substantially smaller risk for malignancy (114). These two conditions cannot be distinguished reliably because the morphologic and histochemical features of gastric and esophageal intestinal metaplasia resemble one another and because the gross landmarks used to identify the GEJ do not have the precision necessary to localize a mucosa, whose extent may be measured only in millimeters. The significance of intestinal metaplasia in the cardia is currently unknown but it can be found in up to one third of individuals without endoscopic evidence of BE (115-117). Recent immunohistochemical data show similar phenotypes in LSBE and SSBE and intestinal metaplasia at the GEJ, and a different phenotype from gastric antral intestinal metaplasia (118), suggesting that both LSBE and SSBE are related disorders and that they differ from the intestinal metaplasia resulting from *HP* infections. Intestinal metaplasia is relatively uncommon in North America as compared to other parts of the world so that the presence of intestinal metaplasia in the area of the cardia most likely represents GERD. This may be particularly true in white men, since this is the dominant demographic group that develops BE-associated carcinomas. In addition, differences in risk for neoplastic transformation among those with ultrashort, short and long segment BE may not be related to histologic features, but to the length of the segment affected by intestinal metaplasia (119, 120). Regardless of the cause, intestinal metaplasia on either side of the GE junction is abnormal. For patients found to have intestinal metaplasia at the GEJ, a conservative approach is to assume a worst-case scenario in which the condition is SSBE and to manage the patients according to guidelines established for Barrett esophagus. One could use the term *intestinal metaplasia of the GEJ* to describe the intestinal metaplasia found at the Z line (91).

### **Multi-layered Epithelium in the Distal Esophagus**

Squamous epithelium repopulates the distal esophagus following treatment of BE. It appears as a normal-appearing neosquamous epithelium or as a multilayered epithelium. The neosquamous epithelium appears in areas previously occupied by BE, often appearing as squamous islands surrounding the Barrett epithelium.

Multilayered epithelium resembling immature squamous metaplasia that seen in the uterine cervix develops at the GEJ in patients with BE (121). The epithelium has morphologic and cytochemical characteristics of both squamous and columnar epithelium and may be a precursor of BE. It is possible that a multipotential stem cell is stimulated to differentiate toward a columnar phenotype after passing through an intermediate multiepithelial-layered phase.

Multilayered epithelium typically consists of four to eight cell layers. The basal cells contain a small round to oval nucleus with a small centrally placed nucleolus and abundant eosinophilic cytoplasm, features similar to those of normal basal or suprabasal esophageal squamous cells. Nuclear pseudostratification is common. Intercellular bridges are absent. The suprabasal and superficial layers of the multilayered epithelium show increasing degrees of columnar differentiation characterized by cells with clear or slightly bubbly cytoplasm and a basally oriented nucleus having an appearance like that of basal cells. Most cases contain rare superficial columnar cells with distended cytoplasm similar in appearance to goblet cells. The epithelium expresses cytokeratin patterns characteristic of both stratified squamous and columnar epithelium (122). The multilayered epithelium shows a high proliferative capacity as demonstrated by Ki67 immunoreactivity and the strong expression of growth factors such as TGF- $\alpha$  and EGFR. This epithelium may also serve as a potential source of multipotential cells for the development of both the multilayered epithelium and BE. Others suggest that it is a metaplastic change and that the mature form of this change may be ciliated pseudostratified epithelium with an immunophenotype that resembles that of the bronchial mucosa (123).

### **Pathology of Treated Barrett Esophagus**

The aim of therapeutic strategies for BE is to eliminate the abnormal epithelium, thereby removing the risk of neoplastic progression. Regression occurs following both surgical treatment and treatment with proton pump inhibitors and is more common in patients with SSBE than LSBE (124). Newer techniques for eradicating BE include photodynamic therapy, laser therapy, and endoscopic mucosal resection.

Biopsies are often taken after these therapies to evaluate their effectiveness. Restoration of squamous epithelium may occur if the established columnar tissue is ablated and the acid secretion is reduced while the esophageal epithelium heals. The histologic changes following treatment show partial squamous re-epithelialization of the previously metaplastic columnar epithelium. Squamous re-epithelialization results from the ingrowth of contiguous squamous epithelium, extension of epithelium from the submucosal glandular ducts, and growth of progenitor stem cells within the glandular mucosa. When regression occurs, one may see squamous epithelium overlying columnar epithelium, especially near the area of the squamocolumnar junction. The mucosa may also show evidence of scarring and mucosal hyperplasia with acanthosis. In some cases, intestinal-type epithelium underlies the squamous islands. The Barrett epithelium under squamous islands shows a significantly lower KI67 proliferative index and a lower degree of cyclin D and p53 positivity compared to adjacent areas of BE, perhaps due to decreased exposure to the luminal contents (125). This raises the question as to the subsequent risk of neoplasia in the buried metaplastic epithelium. However, low-grade and high-grade dysplasia may be present in these buried regions (125). Patients with dysplasia in the Barrett epithelium under squamous islands almost always have coexisting dysplasia in other areas of the esophagus that can be recognized endoscopically. Adenocarcinomas arising in the esophageal wall and presenting as unresectable or metastatic cancers have been reported following argon plasma coagulation (126), photodynamic therapy (127), or laser treatment (128). There is concern that any technique using chemical or thermal measures to ablate the epithelium may potentially make it difficult to detect occult carcinoma buried beneath the squamous epithelium during endoscopic surveillance. One recent multi-center study, however, found that squamous overgrowth did not obscure the most advanced neoplasia in any high grade dysplasia patient treated with photodynamic therapy (129).

## Tumor Development

Patients with BE develop hyperplastic polyps, squamous papillomas, dysplasia, and rarely adenomas in addition to adenocarcinomas. The management of patients with Barrett esophagus includes careful examination of endoscopic biopsies for evidence of dysplasia. Cytology may also have a role in assessing Barrett metaplasia in terms of monitoring it for the development of neoplasia. Cytology, however, should not be relied on without biopsy confirmation since one cannot assess either the exact location or the extent of the lesion using only cytology.

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