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Histopathology of Barrett's esophagus: A review for the practicing gastroenterologist

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Barrett's esophagus (BE) is the replacement of the normal squamous lining of the distal esophagus by columnar mucosa. It is the recognized precursor of esophageal adenocarcinoma, with tumors arising through an inflammation–metaplasia–dysplasia–carcinoma sequence. Effective communication between the gastroenterologist and pathologist is crucial to the diagnosis, risk assessment, and management of BE. This review will focus on the histopathologic aspects of BE especially relevant to the practicing gastroenterologist, including discussion of normal anatomy and histology of the distal esophagus and gastroesophageal junction, varying definitions of BE used around the world, histology of nondysplastic BE, significance of goblet cells, grading of Barrett neoplasia, natural history of BE, biomarkers of progression, and pathology of postablation BE and endoscopic mucosal resection.

Normal anatomy and histology

The esophagus is normally lined by stratified squamous epithelium. Scattered compact submucosal glands and their associated squamous-lined ducts are also characteristic features of this organ. Historically, it was believed that the distal 1-2 cm of the "normal" esophagus was lined by columnar mucosa. However, contemporary evidence points to the contrary. In fact, it is now widely believed that most, if not all, columnar mucosa proximal to the anatomic gastroesophageal junction (GEJ) is abnormal (metaplastic) and is attributable to chronic gastroesophageal reflux.[1-4]

The most proximal portion of the stomach is often referred to as the gastric "cardia."[5-7] This narrow region of mucosa is typically composed of surface foveolar cells and either pure mucous glands or glands with mixed mucous and parietal cells. The origin of this type of mucosa is a subject of debate. Some authorities believe it to be always esophageal and, thus, metaplastic, whereas others believe it is normally present at birth. Regardless, it is accepted that the length of "cardia-type" mucosa increases (extends proximally) with age, probably as a reflection of physiological reflux. Because the "cardia" is an ill-defined structure of questionable etiology, the authors of this review prefer to abandon this confusing term in favor of the term "proximal stomach." The "proximal stomach" transitions to the body of the stomach, which is composed of pure oxyntic-type glands (ie, mixture of parietal and chief cells).

Accurate detection of abnormal (metaplastic) columnar mucosa in the distal esophagus is incumbent on precise localization of the anatomic GEJ. Unfortunately, identification of this critical landmark is fraught with difficulty and controversy. For instance, various definitions of the GEJ exist, two of which are used most commonly in clinical practice. In Japan, the GEJ is defined by the distal-most limit of the palisading longitudinal blood vessels, which correspond to veins in the lamina propria of the distal esophagus in histologic tissue sections.[8-11] Palisading vessels may be confused for other types of vascular patterns in the proximal stomach, and they are frequently difficult to identify in patients with esophagitis. In contrast, in the United States and in many other parts of the world, the GEJ is defined by the most proximal extent of the gastric folds.[10,12-14] Unfortunately, identification of this landmark is also difficult because it may vary with respirations and procedure-related air insufflation. Nevertheless, use of the proximal limit of the gastric folds as the "definition" of the

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GEJ has been incorporated into the Prague C & M Criteria, an international effort to develop and validate an endoscopic grading system for Barrett's esophagus (BE). In this scheme, recognition of the GEJ was accomplished with "almost perfect reliability."[10]

Definition of Barrett's esophagus

Fundamentally, BE represents replacement of normal squamous epithelium of the distal esophagus by metaplastic columnar epithelium. Unfortunately, the definition of BE varies worldwide. The main difference concerns the requirement for histologic confirmation of columnar mucosa with goblet cells. In Japan, columnar-lined esophagus (CLE) is diagnosed when columnar mucosa (salmon-colored, velvety mucosa distinct from the normal pearlescent squamous mucosa) is identified endoscopically in the distal esophagus; histologic confirmation is not required.[8,9,11] According to the British Society of Gastroenterology, BE represents an endoscopically apparent area of columnar mucosa proximal to the GEJ, proven on histologic examination; the most recent guideline has dropped the requirement for the demonstration of intestinal metaplasia (IM) (ie, goblet cells).[15] Biopsies allow distinction of metaplastic columnar mucosa from endoscopic mimics, such as esophagitis. In contrast, in the United States, a diagnosis of BE is dependent on the finding of endoscopic evidence of columnar mucosa proximal to the anatomic GEJ and histologic confirmation of IM (ie, goblet cells).[13,14] Evidence for and against this definition is presented later in this review.

Historically, BE has been divided into long-segment (>3 cm), short-segment (1-3 cm), and ultrashort-segment (<1 cm) categories. However, these are no longer recognized as distinct entities. For instance, the American Gastroenterological Association refers to the distinction of long- from short-segment BE as "arbitrary and not clinically valid."[13]

Histology of Barrett's esophagus

Barrett epithelium contains a mosaic of cell types, including those normally seen in the stomach (ie, surface and glandular mucinous cells and parietal cells), intestine (ie, goblet cells and less frequently enterocytes, endocrine cells, and Paneth cells), and even the pancreas (ie, acinar cells). In addition, a variety of cells with features intermediate between gastric and intestinal phenotype, such as "multilayered epithelium," are present as well.[16,17] In fact, goblet cells are often not the predominant cell type and may be difficult to identify. These must be distinguished from "pseudogoblet" cells, which superficially resemble goblet cells due to the presence of apical mucous, but in contrast to the latter, tend to occur in concentrated rows within surface epithelium, are barrel-shaped, and contain pale, neutral mucin. Unfortunately, pathologists often have trouble distinguishing these cell types, and histochemical stains are not useful in this distinction. Representative images of BE are presented in Figure 1.

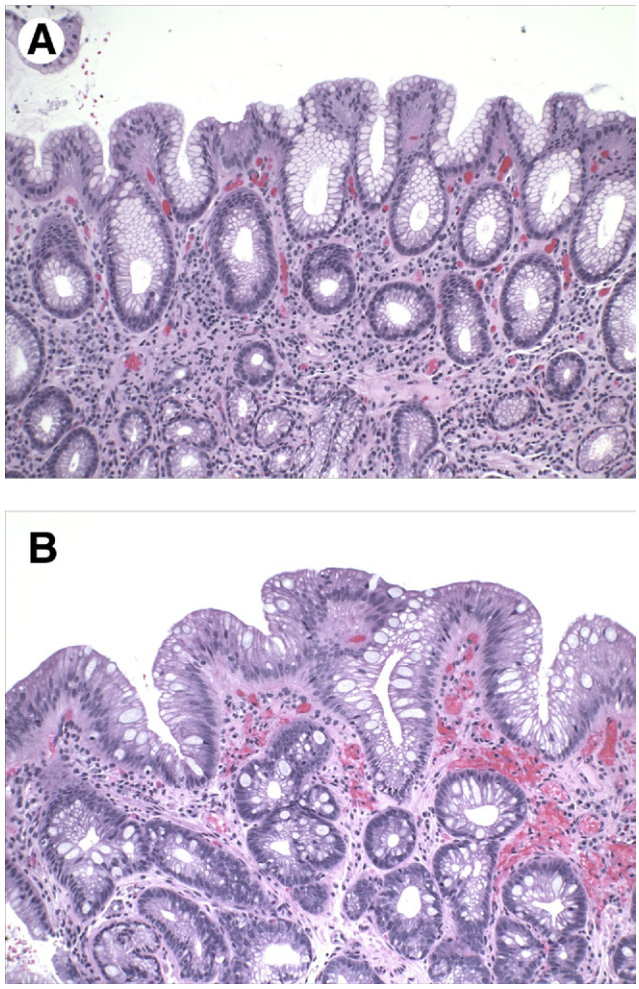

Figure 1 (A) BE, characterized by columnar epithelium with mucous cells and pseudogoblet cells. Mucous glands, and one gland with an isolated goblet cell, are identified in the deep lamina propria. There is increased inflammation in the lamina propria as well. (B) BE, characterized by columnar epithelium with numerous goblet cells. In this example of nondysplastic BE, the bases of the crypts, and the glands, show architectural distortion, branching, and a slight back-to-back configuration. Nuclear atypia is present in the bases of the crypts, with increased mitotic figures, but these changes do not reach the threshold for dysplasia. (Color version of figure is available online at www.techgiendoscopy.com.)

Although BE is generally thought of as an epithelial disorder, most cases also exhibit stromal alterations.[18-21] These alterations include duplication and fragmentation of the muscularis mucosae (MM), increase in the number of blood vessels and lymphatics, and changes in the constituent inflammatory cells. Duplication of the MM results in two layers, one being newly formed and superficial, and the other being deep (original MM). Thus, the new, superficial MM, which forms at the base of metaplastic crypts, divides the mucosa into essentially four compartments: (1) inner (native) lamina propria, (2) inner (neo) MM, (3) outer (neo)