Available online at www.sciencedirect.com
ScienceDirect
Annals of Diagnostic Pathology 13 (2009) 212–221
Annals of DIAGNOSTIC PATHOLOGY

Review Article

Barrett's esophagus: diagnostic challenges and recent developments

Dipen M. Maru, MD*

Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Abstract Inclusion of histologic classification into the risk assessment of adenocarcinoma arising from Barrett's esophagus (BE) has placed surgical pathologist in the center of clinical care and research endeavors. Recent advances in endoscopic diagnostic and therapeutic modalities demand additional proficiency in diagnosis and grading of dysplasia. The objectives of this study are as follows: (1) Discuss the definition of BE and features differentiating BE vs intestinal metaplasia involving cardia. (2) Describe the morphological approach of diagnosing and grading of dysplasia and differentiation of high-grade dysplasia from intramucosal carcinoma. (3) Role of special stains in diagnosis of BE and dysplasia. (4) Brief review the literature on histologic and endoscopic factors associated with progression of BE to adenocarcinoma. (5) Discuss the biomarkers in progression of BE to adenocarcinoma. The following conclusions from this review are important and should be applied in routine practice. Because of the controversy in defining BE, the histologic type of columnar mucosa and presence or absence of intestinal metaplasia should be specified in pathology report. The major limitations of appropriately diagnosing and grading dysplasia include technical problems related to biopsy processing and staining, presence of acute inflammation, and high interobserver variations among pathologists. The extent of high-grade dysplasia, high-grade dysplasia with certain endoscopic abnormalities, and low-grade dysplasia, when diagnosed with consensus by 2 or 3 gastrointestinal pathologists, has higher risk of progression to adenocarcinoma. All nonhistologic markers are still in the investigational phase and have not yet been validated in phase 3/4 prospective trials.

Keywords: Barrett's esophagus; Intestinal metaplasia; Dysplasia; Review; Recent developments

1. History

In 1906, Tileston [1], a Boston surgeon, described cases of esophageal ulcers at autopsy and suggested that the ulcers were due to esophageal reflux and weak muscle at the cardia. He did not describe columnar mucosa. In 1950, Nunan Barrett [2], a British surgeon, published an article titled "Chronic peptic ulcer of the oesophagus and oesophagitis," which described columnar epithelium surrounding ulcers. He suggested that these ulcers with columnar epithelium are due to congenitally short esophagus. However, a subsequent article from Allison and Johnstone [3] described a series of 7 patients with reflux esophagitis with gastric mucous membrane in the esophagus, which further clarified the characteristics of these esophageal ulcers. Barrett [4] subsequently published another article in 1957 titled "The lower esophagus lined by columnar epithelium," which accepted the view of Allison and Johnstone. In 1970, Trier [5] expanded earlier observations by demonstrating that the epithelium in Barrett's esophagus (BE) resembled that of the intestine. The first case of esophageal adenocarcinoma associated with columnar epithelium had been described by Morson and Belcher [6] in 1952. This association was strengthened by Naef and Savary [7] who described 7 patients with esophageal adenocarcinoma among 62 patients with BE. Cameron et al [8] published the first data on cancer incidence based on longitudinal follow-up of patients with BE who were without cancer when first seen. The increasing incidence of distal esophageal cancer in the past 20 years and inclusion of the histologic classification of precancerous dysplastic lesions in risk assessment for BE has put surgical pathologists at the center of clinical care and research on BE and esophageal adenocarcinoma.

* Tel.: +1 713 792 2678; fax: +1 713 745 1105.
E-mail address: dmaru@mdanderson.org.

1092-9134/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.anndiagpath.2009.02.004

2. Definition

Currently, the American College of Gastroenterology [9] defines BE as columnar mucosa in the tubular esophagus, with intestinal metaplasia (goblet cell metaplasia) demonstrated on histologic testing. However, 3 types of columnar epithelium—cardiac-type mucosa, fundic-type mucosa, and intestinal metaplasia—can be detected in columnar lined esophagus [10]. The requirement of intestinal metaplasia in the definition of BE is based on results showing that most of the esophageal adenocarcinoma is accompanied by intestinal metaplasia [11-13]. However, the yield of intestinal metaplasia in an endoscopic biopsy depends on the length of columnar lined mucosa, the number of biopsy samples procured, and the presence or absence of esophagitis. A recent retrospective study [14] showed that at least 8 biopsy specimens are required to adequately assess intestinal metaplasia. In addition, the yield of intestinal metaplasia is lower in the presence of either short-segment BE or esophagitis. Repeat endoscopy and biopsy are often necessary in these patients to document intestinal metaplasia.

The requirement of intestinal metaplasia as a necessary criteria for the diagnosis of BE is not universally accepted. The American College of Gastroenterology, German Society of Pathology, Amsterdam Working Group, and French Society of Digestive Disease include the histologic evidence of intestinal metaplasia in their definition of BE. However, the British Society of Gastroenterology [15] has excluded the need for intestinal metaplasia from the diagnosis of BE. To date, there has been no data available documenting the risk of esophageal adenocarcinoma in columnar lined epithelium lacking intestinal metaplasia [16]. Because of this and the potential difficulty in obtaining heath insurance and increased cost of life insurance for patients with BE, it has been recommended that intestinal metaplasia be listed as one of the requirements of diagnosis of BE [16].

3. Cardia intestinal metaplasia vs ultrashort BE

The present definition of BE does not include intestinal metaplasia involving the cardia. It has been shown that intestinal metaplasia is present in the gastroesophageal (GE) junction in up to one third of patients without clear endoscopic evidence of BE [17,18]. There is disagreement among gastrointestinal pathologists about the normal histologic features of the GE junction. Data from the University of Southern California Group [19-21] suggest that the gastric cardia is not a normal structure but is instead a metaplastic phenomenon. In a study of 30 pediatric autopsies, Kilgore et al [22] found cardia-type mucosa on the gastric side of the GE junction in all patients. These results support the view that cardia is a normal structure but do not exclude the possibility that cardia is a metaplastic phenomenon in adult patients with GE reflux disease. Regardless of this controversy, the presence of intestinal metaplasia is an abnormal feature and should be noted in the pathology report.

Endoscopic appearance is helpful in determining whether intestinal metaplasia represents ultrashort-segment BE or cardia intestinal metaplasia. Two landmarks of importance are the GE junction and the squamocolumnar junction (the “Z line”). There is consensus among gastroenterologists in the Western world that the GE junction is identified by the most proximal extent of the gastric folds. The presence of a short tongue of columnar mucosa extending from the GE junction proximally or of an irregular Z line will favor a diagnosis of BE over one of the cardia intestinal metaplasia.

Srivastava et al [23] evaluated various histologic features on esophageal biopsy specimens in an attempt to differentiate ultrashort BE from cardia intestinal metaplasia, and the authors suggest that the presence of intestinal metaplasia associated with hybrid glands, squamous mucosa overlying intestinal metaplasia, and intestinal metaplasia associated with esophageal glands or ducts are exclusively associated with BE. The distinction between BE and cardia intestinal metaplasia is important because of their differing etiology (*Helicobacter pylori* infection vs GE reflux disease) and natural history, as indicated in some studies [24-26]. The issue is unresolved for regular clinical practice, and we recommend specifying the histologic type of columnar mucosa seen in the biopsy and indication of the presence or absence of intestinal metaplasia.

4. Role of special stains in the diagnosis of BE

Mucin histochemistry has long been suggested to be helpful in identifying true goblet cells [27,28]. The pure neutral mucin of gastric foveolar epithelium stains red and a mixture of neutral/acidic mucin stains magenta in the Alcian blue/periodic acid-Schiff (PAS) stain. Goblet cells have an acidic mucin that stains blue with Alcian blue/PAS stain. The Alcian blue/PAS stain can be useful in some cases to differentiate pseudogoblet cells (swollen foveolar epithelial cells) from true goblet cells. The High Iron Diamine-Alcian blue stain differentiates sialomucin from sulfomucin by showing blue color for sialomucin and black for sulfomucin. In BE, goblet cells contain both sulfomucin and sialomucin, so it is unclear whether High Iron Diamine-Alcian blue can be useful in the diagnosis of intestinal metaplasia. In addition, Younes et al [29] described goblet cell mimickers in esophageal biopsies that are weakly positive for Alcian blue stain and are not associated with increased risk of dysplasia. The American Gastroenterology Association (AGA) Chicago workshop (2004) [9] concluded that, in most cases, the intestinal metaplasia can be easily identified in sections stained with hematoxylin-eosin; thus, Alcian blue/PAS stain is not required for histologic diagnosis. Only in selected cases, when goblet cells are rare or prominent pseudogoblet cells