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Review Article

Some observations on Barrett esophagus and associated dysplasia

Elizabeth Montgomery[a,*], Christina A. Arnold[b], Dora Lam-Himlin[c], Kevan Salimian[a], Kevin Waters[d]

[a] Department of Pathology, Johns Hopkins University, United States of America
[b] Department of Pathology, Ohio State University, United States of America
[c] Department of Pathology, Mayo Clinic Scottsdale, United States of America
[d] Department of Pathology, Cedars Sinai Health System, United States of America

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ABSTRACT

Biopsy samples from esophageal columnar metaplasia and dysplasia are commonly encountered in Western pathology practice and knowing a few pitfalls can save both pathologists and patients a great deal of anxiety. Herein we discuss criteria for Barrett esophagus, evaluation of dysplasia, and some pitfalls in reviewing endoscopic mucosal resections. Also included is a summary of suggested follow-up for patients with Barrett esophagus.

Barrett esophagus is not defined uniformly worldwide. In the United Kingdom and Japan, the definition differs from that in the United States (US). The British [1], American Gastroenterological Association (AGA) [2], and American College of Gastroenterologists (ACG) [3] criteria appear in Table 1. The key difference between the US and British guidelines is that goblet cells are part of the US definition whereas they are not required in the British definition.

However, the 2016 definition from the American College of Gastroenterologists - columnar epithelium with goblet cells extending ≥1 cm above the top of the gastric folds [3] - makes the life of the pathologist challenging. Whereas we frequently have a good idea about the length of a segment of columnar epithelium in question, in other instances, the only information that we receive for a sample is that it is labeled "esophagus". Of course, if we receive a sample labeled "esophagus, 40 cm" and there is intestinal metaplasia and we have a second sample that is labeled "esophagus, 34 cm" and there is intestinal metaplasia, it is clear that the affected segment of lesion measures at least 1 cm. In fact, the gastroenterology colleagues who prepared the recommendations even went so far as to ask that our endoscopy colleagues refrain from taking biopsies of the gastroesophageal junction in the absence of visible alterations. However, there seems to be very little compliance with the latter suggestion. The American College of Gastroenterology applied the term "specialized intestinal metaplasia of the esophagogastric junction" for lesions with goblet cells that do not meet the 1 cm length requirement [3].

To address the length issue, prepared notes can be useful for situations for which 1) intestinal metaplasia is present without knowledge of the segment length or 2) samples labeled "gastroesophageal junction"/GEJ with intestinal metaplasia.

1. Sample notes: Barrett mucosa

Situation 1. Barrett mucosa, negative for dysplasia. See note.

Note: The above diagnosis of Barrett esophagus is made due to presence of goblet cells (intestinal metaplasia) with the assumption that the biopsies were obtained from columnar mucosa in the distal esophagus and the mucosal irregularity extends at least 1 cm above the top of the gastric folds as per 2016 American College of Gastroenterology (ACG) guidelines.

Reference: Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016 Jan;111(1):30–50.

Situation 2. Cardiac mucosa with intestinal metaplasia. See note.

Note: This biopsy shows gastric-type mucosa with scattered goblet cells. The diagnosis in this case depends on the location of this biopsy. If this biopsy was taken from the tubular esophagus and the mucosal irregularity extends at least 1 cm above the top of the gastric folds, it shows Barrett mucosa of the distinctive type. If this biopsy was taken from the gastric cardia, it shows intestinal metaplasia of the gastric cardia.

Reference: Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and

* Corresponding author at: 410 North Broadway, Weinberg Building Room 2242, Baltimore, MD 21231, United States of America.
E-mail address: emontgom@jhmi.edu (E. Montgomery).

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Table 1
Definition of Barrett esophagus.

Society	Definition
British (and Japanese) definition of Barrett mucosa 2014	- Columnar epithelium with or without goblet cells extending ≥1 cm above the gastric folds [1]
American Gastroenterological Association definition of Barrett mucosa 2011	- Columnar epithelium in the esophagus that contains goblet cells – no length requirement [2]
American College of Gastroenterologists' definition of Barrett mucosa 2016	- Columnar epithelium with goblet cells extending ≥1 cm above the top of the gastric folds [3]

Management of Barrett's Esophagus. Am J Gastroenterol. 2016 Jan;111(1):30–50.

There are some observers in the US who have suggested eliminating the requirement for goblet cells in diagnosing Barrett mucosa since some esophageal adenocarcinomas arise in the absence of intestinal metaplasia. As an example, in one study, the authors reviewed endoscopic mucosal resection samples from a cohort of German patients and found adjoining intestinal metaplasia in association with less than half with early cancers [4]. However, these authors made no attempt to learn if the patients had separate samples with intestinal metaplasia. In two subsequent studies from the US West Coast, high grade columnar epithelial dysplasia and carcinomas were essentially always accompanied by intestinal metaplasia [5,6]. Similar results were found in an East Coast study [7] such that we would endorse retaining the requirement for goblet cells, a view not shared by all [8]. Indeed, there are some examples of esophageal adenocarcinomas that are unassociated with intestinal metaplasia but these are not numerous in our Western population. Eliminating the requirement for goblet cells would even further reduce an already unfavorable cost effectiveness of surveillance for esophageal adenocarcinoma.

Endoscopically, Barrett mucosa consists of velvety “salmon colored” epithelium that can as extend as “tongues” above the gastric folds (Fig. 1). When an area of Barrett mucosa is surrounded by squamous mucosa, the appearance is referred to as an “island”.

Our endoscopy colleagues use the Prague system to describe the extent of Barrett mucosa. In this system, the distance of the circumferential length of Barrett mucosa is recorded (“C”) and the maximum length is recorded as well (“M”) [9]. This method allows standardization of endoscopy reports and when these data are provided to pathologists, they afford some confidence in our diagnoses.

In general, no special stains are needed to confirm the presence of goblet cells in esophageal biopsies. This topic was comprehensively reviewed by Panarelli and Yantiss, who concluded that neither histochemical nor immunohistochemical stains add value over H&E stains since they produce false positives [10]. In the past, the concept of using CK7/CK20 stains to separate esophageal intestinal metaplasia from gastric cardiac intestinal metaplasia was introduced by Ormsby et al. [11,12]. These authors studied long-segment Barrett esophagus cases (> 3 cm) and noted superficial and deep CK7 immunoreactivity in the intestinalized mucosa, with only superficial CK20 staining in the intestinalized zones. In contrast, distal gastric intestinal metaplasia showed patchy, superficial, and deep CK20 staining in areas of incomplete intestinal metaplasia; strong, superficial, and deep CK20 staining in areas of complete intestinal metaplasia; and patchy or absent CK7 staining in either type of gastric intestinal metaplasia. Other studies have not confirmed these findings and CK7/20 immunolabeling has fallen out of favor. Other immunostains that have been studied include mucin core (MUC) polypeptides, which seem to be of little practical value. However, the key markers are MUC5 (gastric foveolar mucin), MUC6 (cardiac glands, antral glands, Brunner glands), and MUC2 (goblet cells). CDX2 staining has also been used to label areas of intestinal metaplasia [13] and some have noted that cases lacking goblet cells express these markers and believe that this supports the need to eliminate the requirement for goblet cells [14]. Hepatocyte antigen (Hepar-1, Carbamoyl Phosphate Synthetase 1) also marks intestinalization in the absence of goblet cells [15]. However, in daily practice it is more practical to simply search for goblet cells. None of the immunostains offers added value over H&E stains in detecting goblet cells [10].

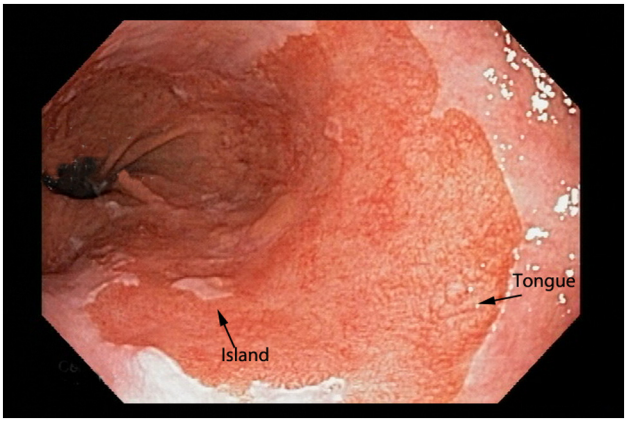

Fig. 1. This is an endocropic image from a patient with Barrett esophagus. The gastric folds are seen at the left of the image and a tongue of metaplastic epithelium is present. Note that the squamous epithelium at the right has a greyish pearly appearance.

2. Grading Barrett dysplasia

The categories that are used to interpret biopsies [16]:

Negative for dysplasia
Indefinite for dysplasia
Low grade dysplasia
High grade dysplasia
Adenocarcinoma

Assessing Barrett biopsies is usually straightforward since most cases are nondysplastic but it is well known that observer variation can be an issue [17]. We have tightened our criteria in the last few years using a novel but very simple method to assess cell polarity (the relationship of cells one to another). We have also suggested that the combined number of cases diagnosed as indefinite for dysplasia, low grade dysplasia, and high grade dysplasia should not exceed 10% [18]. Of course, those clinics specializing in dysplasia would be expected to have a higher percentage of dysplasia cases.

In evaluating Barrett mucosa, essentially the sample should be assessed for surface maturation and glandular crowding, its cytologic features, and whether inflammation is an obscuring factor before making a diagnosis.

2.1. Barrett esophagus, negative for dysplasia

Nondysplastic Barrett mucosa should show surface maturation, which can be a challenge to confirm in suboptimally embedded samples. Minor nuclear alterations in the bases of the metaplastic pits are acceptable. However, noting the polarity of the epithelial cells and how they are arranged with respect to one another makes assessment of Barrett mucosa relatively easy. We have assessed Barrett mucosa easily in most cases by paying attention to “the four lines” [18]. Finding “the four lines” indicates preserved polarity of epithelial cells in both gastric

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