Research Article

Barrett's Esophagus: An update

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Abstract

Barrett's esophagus is premalignant condition in which the stratified squamous epithelium is replaced by metaplastic intestinal epithelium. The cause is usually long-standing gastro-esophageal reflux. Infection with *Helicobacter pylori* is also believed to play a role in this. The most significant complication is development of dysplasia with an increase in relative risk for development of adenocarcinoma 40–120 times.

Keywords: Barrett's esophagus, Metaplasia, Adenocarcinoma

Introduction

In Barrett's esophagus, the normal stratified squamous lining of lower esophagus is replaced by columnar mucosa that may contain area of intestinal metaplasia.[1] It is an adaptive response to chronic gastro-esophageal reflux and is found in 10% of patients undergoing gastroscopy for reflux symptoms. Intestinal metaplasia also occurs commonly in the stomach as a consequence of chronic gastritis caused by infection with *Helicobacter pylori.*[2]

The frequency of infection with *H. pylori* has declined dramatically over the last century in many countries. *H. pylori* is a well-established carcinogen for adenocarcinoma of the stomach, but this infection has not been identified as a positive risk factor for esophageal adenocarcinoma. Indeed, some studies suggest just the opposite – infection with *H. pylori*, particularly with the more virulent cagA+ strains, may protect against the development and neoplastic progression of Barrett's esophagus.[3-7]

Epidemiology of Barrett's Esophagus

Long-segment Barrett's esophagus is strongly associated with chronic heartburn, hiatal hernia and severe reflux esophagitis.[8] Barrett's esophagus typically is discovered in middle-aged and older adults, usually during endoscopic examinations performed for the evaluation of chronic GERD symptoms such as heartburn, regurgitation, and dysphagia.

Barrett's esophagus is rare in children of any age, and virtually non-existent in children younger than age five.[9] In a retrospective study of 6731 children who had upper gastrointestinal endoscopy in 12 pediatric facilities, only 17 (0.25%) had suspected Barrett's esophagus, and only nine of those had intestinal metaplasia confirmed by esophageal biopsy.[10] Barrett's esophagus is two to three times more common in men than in women. The condition has a predilection for white people, and appears to be uncommon in black and Asian people.[11,12]

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How to cite this article: Haldwani S, Garg R, Yadav AK. Barrett's Esophagus: An update. *Rec Adv Path Lab Med 2017;* 3(2): 1-5

ISSN: 2454-8642

Obesity is associated with Barrett's esophagus, especially obesity with a predominantly intraabdominal distribution of fat.[13] Cigarette smoking is also a risk factor.[14] Community-based epidemiological studies suggest that true prevalence may be up to 5% of population, as the condition is often asymptomatic until discovered when the patient presents with esophageal cancer.[15]

Epidemiology of Esophageal Adenocarcinoma

There are two major histological types of esophageal cancer – squamous cell carcinoma and adenocarcinoma. In the 1960s, squamous cell carcinoma comprised well over 90% of all esophageal tumors, whereas adenocarcinoma of the esophagus was considered so uncommon that some authorities questioned its very existence. Since then, the frequency of adenocarcinoma of the esophagus has increased dramatically, to the point that adenocarcinoma surpassed squamous cell carcinoma in frequency in the 1990s.[16-18]

The cause of this dramatic rise in the frequency of adenocarcinoma is not clear. GERD and Barrett's esophagus are the major risk factors for this tumor. Almost all esophageal adenocarcinomas arise from previously existing Barrett's but the vice versa is not true. Less than 3% cases with Barrett's develop adenocarcinoma.[19]

Pathogenesis of Metaplasia in the Esophagus

Metaplasia, the process in which one adult cell type replaces another, is a response to chronic inflammation in a number of organs. Since the metaplastic cells may be more resistant to the factors inducing the inflammation than the native cells, metaplasia can be viewed as a protective mechanism. Unfortunately, for reasons that are not clear, metaplasia also can predispose to malignancy

A number of physiological abnormalities that predispose to severe GERD have been described in patients with long-segment Barrett's esophagus. For example, gastric acid hypersecretion and duodenogastric reflux have been described in some patients with long-segment Barrett's esophagus,[20-22] and extreme hypotension of the lower esophageal sphincter is common.[23]

The distal esophagus frequently is exposed to noxious agents that might play a role in the development of Barrett's esophagus. Even in normal individuals, the intraluminal environment of the GEJ appears to be especially hostile to the lining mucosa.

After meals, there is a pocket of acid at the GEJ that escapes the buffering effects of ingested food.[24] This postprandial acid pocket often extends above the squamocolumnar junction to affect the distal esophagus. Studies have shown that the very distal esophagus (5–10 mm above the squamocolumnar junction) of healthy volunteers can be exposed to acid for more than 10% of the day.[25,26]

This can result in acid-peptic injury of the distal esophagus, and also in exposure to high concentrations of nitric oxide (NO) generated from dietary nitrate (NO_3^-). Most dietary nitrate comes from green leafy vegetables. The ingested nitrate is absorbed by the small intestine concentrated by salivary glands and secreted into the mouth where bacteria on the tongue reduce the recycled nitrate to nitrite (NO_2^-). When swallowed nitrite encounters acidic gastric juice at the GEJ, the nitrite is converted rapidly to NO. After nitrate ingestion, high levels of NO can be found at the GEJ.[27] Those high concentrations of NO can damage DNA and are potentially carcinogenic. Thus, the GEJ is exposed repeatedly to acid, pepsin, NO, and other noxious agents in gastric juice. Chronic exposure to those agents may induce the injury and inflammation that result in intestinal metaplasia.[28] The pathogenesis of Barrett's esophagus is depicted in Fig. 1.

Morphology

Barrett's esophagus can be recognized as one or several tongues or patches of red velvety mucosa extending upward from gastro-esophageal junction (Fig. 2). This metaplastic mucosa alternates with residual smooth, pale squamous esophageal mucosa and interfaces with light brown columnar mucosa distally.[29]

Microscopy

Patients were found to have one or combination of three types of columnar epithelia:

1. Gastric fundus type with parietal cells
2. Junctional or gastric cardiac type with mucous cells
3. Intestinal type with goblet cells (Fig. 3)

Metaplastic epithelium may show dysplasia. This may progress to carcinoma as shown in the following sequence:

Normal stratified squamous epithelium→Metaplasia →Dysplasia→Carcinoma in situ which finally progresses to adenocarcinoma.[30]

Diagnosis

Endoscopic examination is required to diagnose Barrett's esophagus, and two diagnostic criteria must be fulfilled: (1) the endoscopist must document that columnar epithelium extends proximal to the gastroesophageal junction (GEJ) to line the distal esophagus, and (2) biopsy specimens of the esophageal columnar epithelium must reveal the specialized intestinal metaplasia (with goblet cells) that is characteristic of Barrett's esophagus.

To document that columnar epithelium lines the esophagus, the endoscopist must identify both the squamocolumnar junction (SCJ) and the GEJ (Fig. 4). Columnar epithelium has a reddish color and coarse texture on endoscopic examination, whereas squamous epithelium has a pale, glossy appearance. The juxtaposition of those epithelia at the SCJ forms a visible, typically zig-zag line called the Z-line. The GEJ is the imaginary line at which the esophagus ends and the stomach begins.

In Western countries like the United States, the GEJ is recognized endoscopically as the level of the most proximal extent of the gastric folds.[31,32] In some Asian countries, endoscopists identify the GEJ as the distal extent of the esophageal palisade vessels, which are fine, longitudinal veins located in the lamina propria of the distal esophagus.[33] When the SCJ is located proximal to the GEJ, there is a columnar-lined segment of esophagus. When the SCJ and GEJ coincide, the entire esophagus is lined by squamous epithelium. If biopsy specimens from the columnar-lined esophagus show specialized intestinal metaplasia, the patient has Barrett's esophagus. When the SCJ is located proximal to the GEJ, there is a columnar-lined segment of esophagus. When the SCJ and GEJ coincide, the entire esophagus is lined by squamous epithelium.

The description by Spechler and colleagues of Barrett's esophagus has categorized it as "long-segment" if the distance between the Z-line and the GEJ is ≥3 cm, and "short-segment" if that distance is <3 cm.[34]

Management

This requires multiple systematic biopsies to maximize the chance of detecting intestinal metaplasia and/or dysplasia. Neither potent acid suppression nor anti-reflux surgery will stop progression or induce regression of Barrett's and treatment is only indicated for symptoms of reflux or complications such as stricture.

Endoscopic therapies such as argon plasma coagulation, radiofrequency ablation or photodynamic therapy can induce regression but remain experimental. Regular endoscopic surveillance can detect dysplasia and malignancy at an early stage and may improve survival but because most CLO (columnar lined esophagus) is undetected until cancer develops, surveillance strategies are unlikely to influence the overall mortality rate of esophageal cancer. Surveillance is expensive and cost-effectiveness studies have been conflicting, but currently it is recommended that patients with CLO without dysplasia should undergo endoscopy every 2–3 years and those with low-grade dysplasia at 6–12-monthly intervals. Esophagectomy is widely recommended for those with high-grade dysplasia.[35]

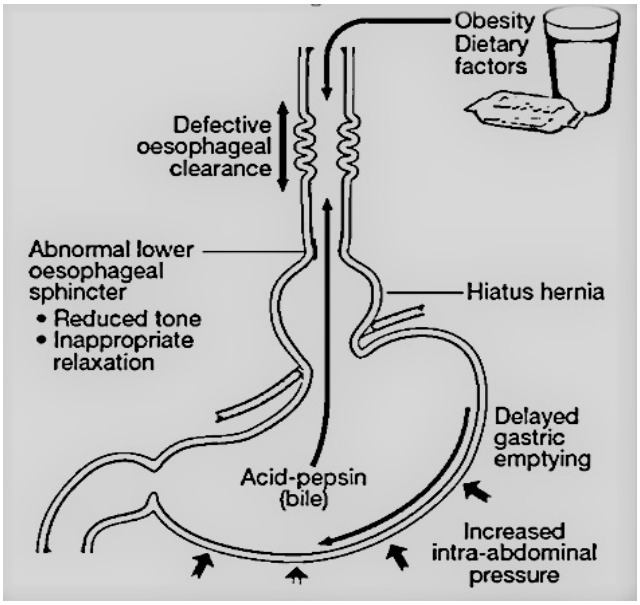

Figure 1.

ISSN: 2454-8642

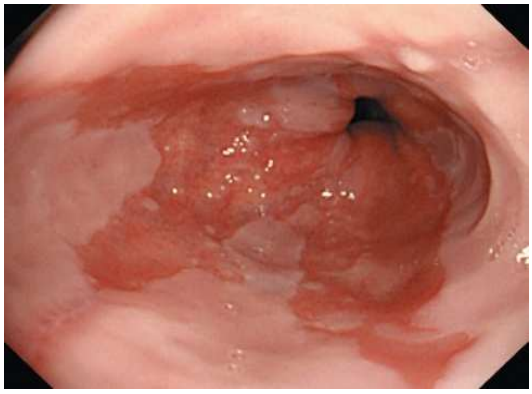

Figure 2.

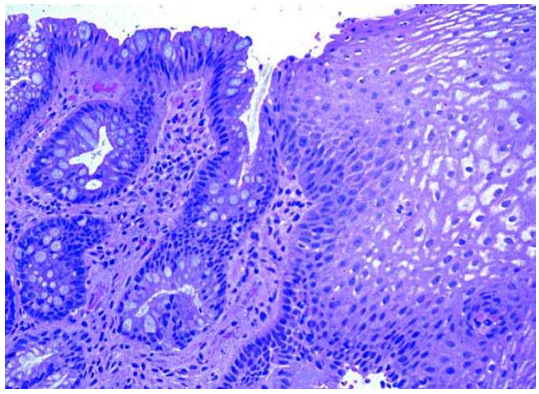

Figure 3.

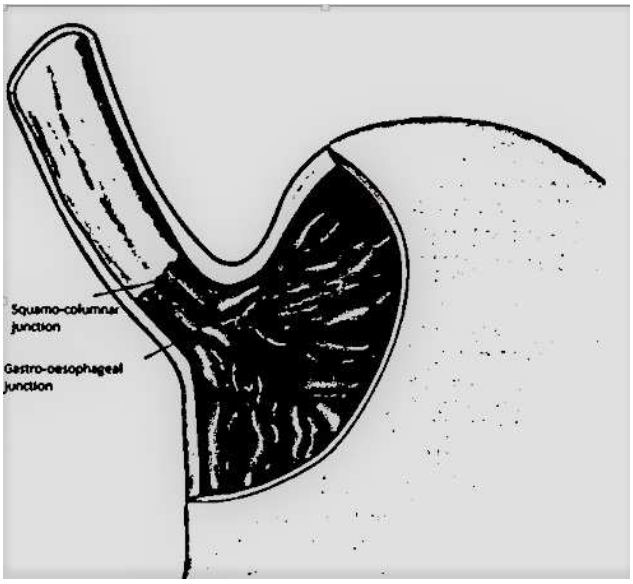

Figure 4.

Conflict of Interest: None

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Date of Submission: 25th May 2017

Date of Acceptance: 23rd Jun. 2017