Barrett’s Esophagus and Barrett’s-Associated Neoplasia: Etiology and Pathologic Features

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Enhancement of molecular markers and cytology may improve outcomes for Barrett’s esophagus

Background: The incidence of Barrett’s esophagus (BE) has been increasing in recent years. Patients with BE have 30- to 125-fold increased risk of developing adenocarcinoma. New techniques allowing early diagnosis, in addition to the identification of markers capable of predicting tumor progression, are needed.

Methods: The authors discuss the diagnostic features of BE and BE-associated neoplasia.

Results: BE can exhibit different types of metaplastic mucosa, but only the specialized (intestinal) mucosa has the potential to progress to dysplasia and carcinoma. The problems associated with diagnosing BE and with predicting the behavior of this condition are outlined.

Conclusions: Studies are underway to identify molecular markers capable of predicting which BE patient will progress to carcinoma. Brush cytology and flow cytometry may become useful tools in the early detection of this disease.

Introduction

Barrett’s esophagus (BE) is defined as the replacement of the normal stratified squamous epithelium of the lower esophagus with metaplastic columnar epithelium of various types. This condition predisposes to the development of adenocarcinoma of the esophagus, which has dramatically increased in frequency over the past years.

Etiology and Pathogenesis

In general, the patients with BE acquire the columnar metaplasia in the lower esophagus as a consequence of gastroesophageal reflux. Therefore, any condition increasing the reflux of acid from the stomach to the esophagus represents a risk factor. These conditions include a hiatal hernia, the presence of duodenogastric reflux, delayed esophageal acid clearance time, and decreased resting pressure of the lower esophageal sphincter. In a minority of cases, other etiologic factors may be involved such as bile reflux following gastrectomy, esophageal injury (lye ingestion), and possibly congenital rest of gastric epithelium (especially in cases of infantile BE). The last possibility is plausible since during the fetal life, the esophagus is lined by mucin-secreting cells.

The exact mechanism by which the squamous epithelium is replaced by the metaplastic mucosa is not certain. However, it seems that initially, following erosion of the squamous mucosa by the acid-peptic action of the gastric content, undifferentiated progenitor cells migrate into the denuded areas. These cells are multipotent stem cells that, in the presence of persistent gastroesophageal reflux, selectively differentiate into columnar mucin-secreting epithelium. Alternatively, metaplasia could occur simply by upward migration of the columnar epithelium from the stomach to reepithelialize the ulcerated mucosa.

Cancer Risk in Barrett’s Esophagus

BE predisposes to the development of adenocarcinoma. It is estimated that of the patients with symptomatic gastroesophageal reflux who seek medical attention and undergo endoscopy, approximately 10% to 20% will have BE. Of these, 7% to 15% already will have adenocarcinoma at the time of their first endoscopy. It has also been shown that 18% of all the patients undergoing upper gastrointestinal endoscopy for any reason are found to have BE. The incidence of BE has been increasing in recent years and, consequently, adenocarcinoma arising in BE is the most rapidly increasing cancer in the last two decades. It is estimated that patients with BE have a 30- to 125-fold increased risk of developing adenocarcinoma. Patients who develop adenocarcinoma are usually elderly white men with metaplastic or dysplastic epithelium. This is also true for patients with very short segment BE, which suggests that even small areas of metaplastic epithelium increase the cancer risk. It has been speculated that cancer in BE arises through a multistep sequence of events initiated by gastroesophageal reflux that induces metaplasia and eventually progresses to dysplasia and carcinoma.

Diagnostic Features

Grossly, Barrett’s mucosa is usually represented by a well-defined area of salmon-pink, velvety mucosa similar to the adjacent gastric mucosa. It has irregular margins and may contain islands of residual squamous, pearly white esophageal mucosa, or it may be ulcerated (Fig 1). It is usually limited to the lower third of the esophagus, but in severe cases, it may extend to the middle and upper esophagus (Fig 2). The endoscopic diagnosis of BE may be challenging, especially if the gastroesophageal junction is difficult to identify.

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Ten Thousand Islands, Florida, Silver gelatin fiber photograph.
Histologically, problems in diagnosing BE may arise if the precise site of the biopsy is not known or if one does not realize that the metaplasia in BE can exhibit different patterns. Barrett’s epithelium may be of the gastric fundic type (Fig 3), gastric cardiac type (Fig 4), or specialized (intestinal type) (Figs 5A–B). The first two types of epithelium are histologically indistinguishable from their normal counterpart in the stomach and could represent hiatal hernia. However, this is not a diagnostic problem since it is now accepted that dysplasia and carcinoma arise almost exclusively from the specialized (intestinal type) Barrett’s metaplasia. Therefore, it is believed that a diagnosis of BE should be made only if goblet cells are present. These are barrel-shaped cells with a distended, acidic mucin-filled cytoplasm, which can be easily identified using either an Alcian blue pH 2.5 stain or an Alcian blue PAS stain. If this rule is followed, then knowing the exact landmark of the biopsy is not so critical since any intestinalized epithelium carries an increased risk of cancer regardless of its precise location.
Grading Dysplasia

If gastroesophageal reflux persists in patients with BE, dysplasia can develop. Dysplasia is the development of neoplastic epithelium, which is confined within the superficial layer of epithelium by an intact basement membrane. When neoplastic cells bridge the basement membrane, a carcinoma is born. Dysplasia in BE has been graded following criteria similar to those used by the Inflammatory Dysplasia Morphology Study Group. Barrett’s metaplasia can be negative, indeterminate, or positive for dysplasia. It is indeterminate if features of dysplasia are present but do not reach the surface epithelium or if these changes are associated with severe inflammation, thus raising the possibility of reactive atypia.

Low-grade dysplasia (Fig 6) is characterized by preservation of the glandular architecture, stratified cigar-shaped nuclei (which do not reach the cell surface), nuclear hyperchromasia, a moderate increase in mitotic activity, a decrease in goblet cells, and the presence of dystrophic goblet cells (mucin lies on the basal side of the nucleus). These changes are extending to the surface epithelium. High-grade dysplasia (Fig 7) is characterized by marked distortion of the crypt architecture with cribriform pattern (back-to-back glands). The nuclear stratification involves the cellular surface, there is nuclear anisocytosis and pleomorphism, prominent nucleoli and loss of nuclear polarity. The mitotic figures are numerous. Areas of intestinal metaplasia are often intermingled with areas of dysplasia and adenocarcinoma that may not be endoscopically or grossly visible; therefore, small areas of dysplasia or carcinoma may be missed. In most institutions, four-quadrant biopsies are performed, beginning at the top of the gastric folds and proceeding every 2 cm throughout the entire length of the columnar lined esophagus, in addition to biopsies of any
Three additional problems are associated with the application of this grading system: (1) the assessment of degree of dysplasia, which is subjective, (2) the lack of correlation between the degree of dysplasia and subsequent biologic behavior of the lesion, and (3) inter- and intra-observer variation, especially when assessing intermediate grades of dysplasia (indefinite or low grade).

Cytology and Barrett’s-Associated Neoplasia

Some studies have reported the application of cytologic methods in the diagnosis of BE. Studies using brushing cytology have shown good correlation with routine histologic examination in identifying the metaplastic epithelium and carcinoma.27

Balloon cytology has been used to evaluate the degree of dysplasia in BE. This technique was found to have 66% sensitivity and 100% specificity when using histology as the “gold standard.” However, balloon cytology has poor sensitivity in detecting low-grade dysplasia.28 Prospective studies are underway in several institutions, including our institute, to further assess the value of this technique that has a potential cost advantage.

In Search of Predictors of Neoplastic Progression

Not all patients with BE will progress to adenocarcinoma. Some live for years without developing dysplasia, and they eventually die of unrelated disease. Others demonstrate a rapid progression to dysplasia and carcinoma and will die of esophageal adenocarcinoma if it is not diagnosed early and treated appropriately. Several recent attempts have been made to identify molecular markers that can predict which patients with BE will progress to carcinoma. Utilizing such markers would allow closer follow-up and earlier intervention for these patients; therefore, late diagnosis of Barrett’s-associated adenocarcinoma, when disease is already disseminated, would be avoided.

To date, the most reliable marker of tumor progression in Barrett’s-associated neoplasia has been DNA ploidy. It has been reported that dysplasia arising in BE is commonly associated with aneuploidy.26,29 Reid et al.26 observed that 9 of 13 patients with aneuploidy and increased G2/tetraploid cell population developed high-grade dysplasia or carcinoma within 34 months. Forty-nine patients without these abnormalities did not progress to dysplasia. However, these results have not been confirmed.30 This perhaps reflects the difficulty in endoscopically differentiating between metaplastic and dysplastic mucosa, rendering appropriate correlation and reproducible sampling for flow cytometry problematic.

In recent years, the expression of proto-oncogenes, tumor suppressor genes, and death-inducing signaling molecules has been reported in patients with Barrett’s-associated neoplasia. In a report by al-Kassponoles et al.,31 31% of 13 human esophageal adenocarcinomas had epidermal growth factor receptor (EGF-R) gene amplification and had overexpressed EGF-R. Alterations have also been described for Src-specific activity, which is 3- to 4-fold higher in BE and 6-fold higher in adenocarcinomas compared to the control tissues,32 and for E-cadherin, which is significantly lower in patients with BE compared to those with normal esophageal epithelium.33 Fibroblast growth factor sequentially accumulates during the progression from metaplasia to neoplasia,34 and CDKN2/p16 gene becomes mutated and is detected early, in association to allelic loss of 9p21 chromosome, in diploid cells, just before turning to aneuploid during the neoplastic progression.35 Rab 11 is a small GTP-binding protein that increases in low-grade dysplasia.36 Similarly, Bcl-2 protein is highly expressed in low-grade dysplasia, protecting the cells from apoptosis, but it decreases in high-grade dysplasia and adenocarcinoma.37 Fas/APO-1, a cell receptor that induces apoptosis when activated, is reduced on the cell surface of...
esophageal adenocarcinoma cells, but it is retained within their cytoplasm as a mechanism to evade Fas-mediated apoptosis. In a study of 56 patients with adenocarcinoma arising in BE, we found progressive loss of Rb protein expression as the metaplasia progressed to dysplasia and carcinoma. Finally, nuclear accumulation of abnormal p53 tumor suppressor protein has been described in approximately 33% to 50% of adenocarcinomas arising in BE. When genetic sequencing is performed, p53 abnormalities in Barrett’s cancer are found in up to 90% of cases. Independent investigators have detected increased frequency of p53 mutations that parallel increasing degree of dysplasia. However, mutated p53 has also been reported in BE without dysplasia. Recent data seem to support the value of p53 as a predictor of BE progression to dysplasia or carcinoma.

Conclusions

To overcome the limitations of the pathologic criteria for detecting and evaluating BE-associated neoplasia, attempts have been made to identify molecular markers that can predict neoplastic progression in BE. It is possible that the future routine use of brush cytology in the diagnosis of BE will allow sampling of larger areas of diseased mucosa, thus increasing sensitivity and specificity in detecting dysplasia and/or carcinoma. The use of flow cytometry is promising, especially considering that it could be applied to the cytologic specimens, with consequent improvement of the sampling limitation associated with this procedure.

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References


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