Neoplastic precursor lesions of the upper gastrointestinal tract

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Abstract

Carcinomas of the esophagus and stomach are major causes of morbidity and mortality, especially in high prevalence regions, such as eastern Asia. The incidence rate of adenocarcinoma of the gastroesophageal junction is also increasing in the United States. Most carcinomas of the upper gastrointestinal (GI) tract develop in association with dysplasia and occur in patients with long-standing mucosal injury, although some are derived from benign polyps on a background of normal mucosa. Not surprisingly, increased utilization of endoscopy and mucosal biopsy has led to the frequent detection of mucosal atrophy, intestinal metaplasia, and glandular dysplasia, as well as asymptomatic polyps of the duodenum, stomach, and gastroesophageal junction. Although appropriate classification of these lesions is straightforward in most cases, inflammation-induced epithelial changes may closely simulate, or mask, dysplasia, resulting in diagnostic confusion, or precluding definitive diagnosis in some cases. Emerging evidence also suggests that specific molecular changes in non-dysplastic esophageal and gastric mucosa herald development of dysplasia and/or carcinoma, indicating that ancillary molecular analyses may play a role in the future management of high-risk patients. The purpose of this review is to discuss the clinical, pathologic, and molecular features of pre-cancerous lesions of the upper GI tract, as well as the potential pitfalls in their recognition and classification.

Keywords adenoma; Barrett esophagus; duodenum; esophageal carcinoma; gastritis

Introduction

Carcinomas of the upper gastrointestinal (GI) tract develop via heterogeneous mechanisms depending on the location and setting in which they occur. Most adenocarcinomas of the proximal small bowel arise from pre-existing adenomas, similar to their colonic counterparts; duodenal tumors that develop in association with chronic inflammatory conditions, such as Crohn disease and celiac disease, are much less common. In contrast, esophageal and gastric carcinomas usually develop in the setting of prolonged mucosal injury and epithelial dysplasia, whereas tumors derived from pre-existing adenomas are much less common. Most cases of glandular dysplasia of the esophagus and stomach are preceded by intestinal metaplasia, which denotes an early morphologically identifiable precursor to adenocarcinoma. Improved endoscopic techniques (*e.g.* narrow band imaging, chromoendoscopy, and magnifying endoscopy) have made it easier for clinicians to identify and evaluate foci of intestinal metaplasia and dysplasia, affording gastroenterologists an opportunity to resect cancer precursors and intervene in the natural history of carcinogenesis. As a result, pathologists are often provided with mucosal biopsy samples to exclude the possibility of dysplasia or early cancer, or to classify incidentally discovered polyps of the upper GI tract. The purpose of this review is to discuss the clinical, pathologic and molecular features of pre-cancerous lesions of the upper GI tract, as well as potential pitfalls in their recognition and classification.

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Squamous dysplasia of the esophagus

General comments

Squamous cell carcinoma is the most common malignant tumor of the esophagus worldwide, and shows marked geographic, racial, and ethnic variation in incidence. Patients are usually older adult males, and the disease occurs more frequently in black individuals compared to whites. Esophageal squamous cell carcinoma is most prevalent in China, Iran, South America, and South Africa, where it is associated with lower socioeconomic status, diets rich in nitrates and nitrosamines, and vitamin deficiencies. The incidence in western countries has been decreasing in recent decades, possibly reflecting different risk factors, such as alcohol use, smoking, and ionizing radiation. Other predisposing conditions include achalasia, Plummer–Vinson syndrome, chronic esophagitis, chronic strictures, and tylosis palmaris et plantaris, a hereditary disorder resulting from a defect in *RHBDF2*, which encodes a serine protease important to epithelial integrity. Although human papillomavirus (HPV) was implicated as a causal agent in development of esophageal squamous cell carcinoma at one point, this hypothesis has since been disproven. Recent studies utilizing stringent conditions have failed to demonstrate a relationship between oncogenic HPV infection and either squamous cell carcinoma or squamous dysplasia of the esophagus.[1] There is no relationship between esophageal squamous cell carcinoma and sexual behavior, immunosuppression, and other HPV-related malignancies. Epidemiologic features of squamous dysplasia are similar to those of esophageal squamous cell carcinoma.[2]

Clinical features

Squamous dysplasia and early invasive squamous cell carcinomas are clinically asymptomatic, and endoscopic manifestations are often subtle when viewed by white light examination. Dysplasias and early cancers may appear as erosions, friability or erythema, nodules or plaques, vague areas of mucosal irregularity, or white patches that reflect abnormal keratinization (Figure 1). Enhancing techniques exploit properties unique to squamous neoplasia and improve detection. A lack of iodine uptake in glycogen-depleted dysplastic mucosa is a highly sensitive (>90%) and specific (>9%) marker of high-grade dysplasia.[3,4] Confocal laser endomicroscopy employs magnifying endoscopy in combination with a fluorescein dye to

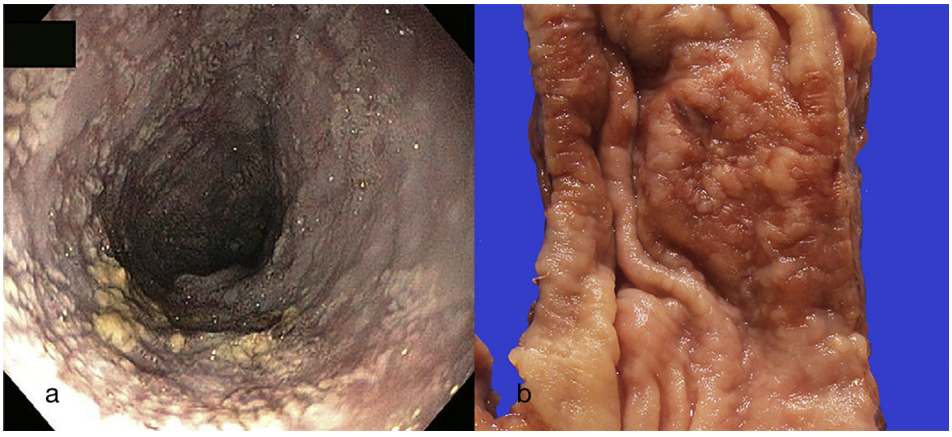

Figure 1 Endoscopically apparent plaques reflect the presence of abnormal keratinization and squamous dysplasia in the esophagus (**a**). Squamous dysplasia in a resection specimen appears as an ill-defined area of irregularity with a nodular, erythematous appearance (**b**).

facilitate visualization of the altered microvasculature in neoplastic mucosa.[5] Narrow band imaging combined with magnifying endoscopy is a widely available technique that can be used to detect early squamous neoplasia without use of vital dyes.[6] Although these diagnostic modalities aid clinicians in detecting and excising precursor lesions, pathologic evaluation of biopsy material ultimately remains the gold standard for diagnosis.

Pathologic features

Most examples of squamous dysplasia show characteristic architectural and cytologic changes. Disorganization of cells (loss of polarity, overlapping nuclei), decreased surface maturation, and cellular crowding is most prominent in the deep mucosa, but can be present near the luminal surface in cases of severe dysplasia. Neoplastic squamous cells reveal nuclear enlargement and irregularity, hyperchromasia, and increased typical, and atypical, mitotic figures. Severity of squamous dysplasia is assessed using a two-tiered grading system. Low-grade dysplasia displays neoplastic cells that occupy less than 50% of the thickness of the squamous epithelium, and includes lesions previously considered to show mild or moderate dysplasia (Figure 2a). High-grade dysplasia is defined by the presence of neoplastic cells in more than 50% of the mucosal thickness and encompasses both severe dysplasia and carcinoma *in situ* (Figure 2b). Although the World Health Organization (WHO) advocates replacement of the terms "low-grade dysplasia" and "high-grade dysplasia" with "low-grade intraepithelial neoplasia" and "high-grade intraepithelial neoplasia", respectively, this terminology has not yet been universally embraced.[7]

Some cases of esophageal squamous dysplasia do not show the classic features enumerated above. Rather, they appear to show maturation with minimal cellular crowding and cytologic atypia, similar to verrucous lesions of the head and neck and female genital tract.[8] The mucosa is expanded by proliferative squamous epithelial cells surfaced by a variable amount of hyperkeratosis or parakeratosis (Figure 2c). The basal cell layer shows minimal deviation from a normal distribution of keratinocytes. Nuclei are slightly enlarged with open chromatin, but cells generally contain abundant eosinophilic cytoplasm and mitotic figures are inconspicuous. Broad projections of squamous epithelium show an irregular, pushing interface with the lamina propria; dyskeratotic cells and keratinization in the deep mucosa are helpful clues to the diagnosis of dysplasia (Figure 2d). Assignment of dysplasia grade can be problematic when maturation is present, as criteria for assessment are not well established (Figure 2e).

Epidermoid metaplasia is a recently described harbinger of squamous cell carcinoma in the esophagus likened to leukoplakia of the oral mucosa.[9] It is characterized by squamous hyperplasia, expansion of the basal zone, acanthosis, prominence of the granular cell layer, and hyperorthokeratosis. Although its prognostic significance is not clear, epidermoid metaplasia is commonly observed in esophagi of patients with invasive squamous cell carcinoma and may represent an extremely mature-appearing variant of dysplasia in some cases (Figure 2f).[10]

Molecular features

Squamous cell carcinomas frequently show increased expression of epidermal growth factor receptor (EGFR), abnormal expression of cell cycle regulatory proteins, and loss of *TP53*, *Rb*, and *INK4/CDKNA*.[11] Molecular alterations of squamous dysplasia include altered telomerase activity, loss of heterozygosity (LOH), increased cyclin D1 expression, and hypermethylation of *INK4/CDKNA* (p16); *TP53* mutations accompany onset of high-grade dysplasia.[12,13] Other biomarkers have been implicated as important players in the evolution of esophageal squamous cell carcinoma, but none have proven to be clinically useful for diagnostic or therapeutic purposes.

Natural history and treatment

Squamous dysplasia is associated with development of invasive squamous cell carcinoma; the strength of this relationship increases with progressive degrees of dysplasia. In the most comprehensive study to date, Wang et al. followed a high-risk group of 682 patients for a 13.5-year period and found that cancer risk increased with dysplasia severity. In that study, the authors utilized a three-tiered, rather than a two-tiered, dysplasia grading system and found that the relative risk for mild, moderate, and severe dysplasia was 2.9, 9.8, and 28.3, respectively, but was highest for squamous cell carcinoma *in situ* (34.4).[14] Based on their experience, these authors suggested that low-

