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Esophagogastric premalignant conditions. A literature review

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ABSTRACT
Esophagogastric cancers are serious malignancies with high mortality and low overall survival for advanced tumors. Detection of premalignant lesions and early treatment of malignant lesions are of paramount importance. Precancerous esophagogastric conditions develop from interaction between environmental and genetic factors. Chronic irritation and inflammation may result in metaplasia, increased mutations, cellular atypia, and altered function (dysplasia). Helicobacter pylori (HP) infection is one of the most important risk factors for gastric carcinogenesis, but other environmental factors (e.g. alcohol, tobacco, nitrites, infection) and autoimmune disorders play a role as well. Esophageal adenocarcinoma (EAC) usually arises in the distal esophagus and is linked to obesity, gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE). Squamous cell carcinoma (ESCC) typically occurs in the presence of risk factors causing chronic inflammation (e.g. tobacco, alcohol abuse, achalasia, tylosis). High-quality endoscopic imaging is of primary importance in the diagnosis and assessment of premalignant and early malignant esophagogastric lesions. Biological markers such as aberrant p53 protein expression may be associated with increased risk of malignant transformation of precancerous lesions; however, none of those biomarkers has been validated for either diagnosis or risk stratification yet.

Keywords:
esophagogastric; cancer; premalignant; precancerous; metaplasia: dysplasia; atrophic gastritis; Barrett's esophagus; Helicobacter pylori; risk factors.

Background:

Esophagogastric cancers are serious malignancies with high mortality and an overall 5-year survival of less than 20% for advanced tumors [1-3]. To reduce this burden, prevention as well as early detection and treatment of premalignant or early malignant lesions are of paramount importance.

Precancerous esophagogastric conditions generally develop from a complex interaction between environmental and genetic factors against a background of chronic inflammation [4]. Basically, chronic irritation can result in metaplasia, the process in which one type of tissue is replaced by another that is presumably better able to resist injury from the underlying condition. However, persistent inflammatory cells can trigger a multistep, sequential process of carcinogenesis by producing cytokines and oxidant products that damage cellular DNA, RNA, and proteins, resulting in increased mutations, cellular atypia and altered function (dysplasia). Due to increased genetic alterations, this disordered proliferation of cells extends into deeper layers and determines invasive carcinoma [4-6].

This article reviews the current status of diagnosis and management of premalignant and early malignant conditions of the esophagus and stomach. The role of the most significant risk factors is also discussed, and technological advances in early cancer detection are reported.

Premalignant conditions and esophageal cancer

There are two predominant types of primary esophageal cancers, namely squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), which differ with regards to etiology, ethnic distribution, pathogenesis, location in the esophagus, and precursor lesions [1,3]. Although ESCC is the most common esophageal cancer worldwide, EAC is the most frequent form in Western countries, where it has been recorded an estimated 350% increase over the last half century, probably linked to increase in obesity and gastroesophageal reflux disease (GERD) [3,6].

As far as ESCC is concerned, this type of cancer arises from the squamous epithelial lining of the esophagus (usually in the middle third, less commonly in the lower third or upper esophagus) through progression of a disordered proliferation of cells occurring in the presence of risk factors causing chronic inflammation (e.g. tobacco, alcohol abuse, achalasia, tylosis) [3-4,6]. According to the extent of epithelial involvement by atypical cells, squamous dysplasia can be distinguished in low-grade dysplasia, when less than half of thickness of epithelium is involved, and high-grade dysplasia, when greater than half of thickness is involved. Full-thickness involvement is termed non-invasive squamous cell carcinoma, whereas invasion into lamina propria and deeper layers defines invasive ESCC, with variable histological differentiation [4,6]. However, changes in the mucosa are usually subtle in the early stages of cancer, passing unnoticed at normal endoscopic examination, thus ESCC tends to present late with dysphagia, weight loss and retrosternal pain [4-7].

As previously stated, ESCC rates in Western countries have declined over the last few decades, while EAC incidence has increased dramatically, becoming the most frequent esophageal cancer in the United States and Western Europe [1,3,6].

EAC is a carcinoma with glandular differentiation which usually arises in the distal esophagus, in the setting of Barrett's esophagus (BE). As a matter of fact, BE is the only recognized precursor of EAC and its most important etiological factor. Other risk factors include GERD, obesity, male sex, Caucasian race, and tobacco smoking, whereas HP infection seems to be inversely correlated to EAC [3,6,8-9].

BE is defined as columnar metaplasia that replaces the stratified squamous epithelium of the distal esophagus, spanning in the form of tongue-shaped metaplastic islets from the gastroesophageal junction (GEJ) into the distal esophagus. The diagnosis of BE requires both endoscopic and pathologic evaluation [3,6]. According to the most recent recommendations by the American College of Gastroenterologists (ACG), BE should be diagnosed when there is extension of salmon-colored mucosa ≥ 1 cm proximal to the GEJ on endoscopy and presence of intestinal metaplasia (IM; i.e. intestinal-type goblet cells) on biopsy evaluation [10]. However, there is international disagreement regarding whether a distal esophagus lined by cardiac mucosa, which also has intestinal features but lacks goblet cells, represents a metaplasia that qualifies for BE diagnosis [11]. Indeed, it is now widely accepted that any type of columnar mucosa located proximal to the GEJ is metaplastic in origin and has developed following chronic injury due to GERD. Thus, BE represents the end-result of this metaplastic transformation of normal squamous epithelium into columnar epithelium [12-14]. Once formed, the metaplastic epithelium can present a gastric differentiation, characterized by the formation of parietal cells within glands, or an intestinal differentiation, characterized by the formation of goblet cells within the columnar epithelium. The latter transformation is considered an unfavorable change because the mucosa is capable of further progression to epithelial dysplasia and adenocarcinoma. However, the molecular pathway by which the columnar epithelium differentiates in one way or the other remains elusive [8,10-14].

The presence of BE is associated with a 30- to 50-fold increased risk of developing EAC. However, the rate of progression from BE to EAC is only 0.1-0.3% per year and up to 80-90% of EAC patients report no previous history of BE [12]. Therefore, there is considerable interest in understanding the pathological mechanisms determining how BE develops and who will progress to EAC. As far as non-genetic factors are concerned, GERD is the strongest known factor for the development of BE and EAC [3,8]. Its prevalence is rising worldwide and medical therapy (e.g. proton pump inhibitors, H2-receptor antagonists, alginate formulations) has shown excellent results in controlling GERD symptoms (e.g. heartburn, regurgitation, hoarseness, chronic cough, chest pain, dysphagia) [8]. However, no medication seems to prevent metaplastic progression and around 10-15% of patients with GERD will eventually develop BE. This transformation may take several years to happen and is provoked by the chronic injury produced by recurrent reflux episodes. Therefore, the duration of reflux is the most important factor in determining BE

[3,8,10-12]. Recently, much work has focused also on the potential role of the upper gastrointestinal microbiome as a cofactor in BE and EAC. Although results are far from being conclusive, preliminary outcomes suggest that there is a significant alteration in the resident flora of pathological states and these changes may contribute to the pathogenesis of metaplasia and dysplasia [15].

In the context of BE, the presence and grading of dysplasia are the most important factors in predicting the development of EAC [3,8]. Indeed, annual incidence of EAC is 0.5% in patients with low-grade dysplasia compared to 7% in patients with high-grade dysplasia [8]. Therefore, considering that endoscopic therapy is highly effective for the eradication of BE and associated dysplasia, patients with high-grade dysplasia should be promptly referred for endoscopic management [3,10]. Other risk factors for dysplasia include increasing length of BE (with greater prevalence of dysplasia in BE length ≥ 3 cm), advancing age, central obesity, male sex, and smoking [3,10].

High-quality endoscopic imaging is of primary importance also in the diagnosis and assessment of premalignant and early malignant esophageal lesions. Squamous dysplasia is usually asymptomatic, and the mucosa may either appear completely normal at standard white light endoscopy (WLE) or show mucosal changes, such as erythema, erosions, friability, plaques, and nodules [6]. In order to increase the sensitivity of lesion detection, the visualization of the surface mucosa and underlying capillary pattern can be enhanced either through conventional chromoscopy (i.e. with Lugol's solution injection) or by using virtual methods like narrow band imaging with magnification endoscopy (NBI-ME), which enhance subtle mucosal changes without the risk inherent to the use of vital dye [7].

As far as molecular markers are concerned, several studies have attempted to assess the utility of biological markers to predict progression and assist with risk stratification. Specifically, aberrant p53 protein expression may be associated with increased risk of malignant transformation of BE [3,7]. However, to date none of the potential molecular biomarkers has been validated for either diagnosis or risk stratification [10-12].

Premalignant conditions and gastric cancer

According to the persistent inflammatory irritation model, the pathogenesis of gastric cancer can be explained by a sequential progression from chronic gastritis through atrophic gastritis (AG), intestinal metaplasia (IM), and dysplasia to invasive adenocarcinoma (the "Correa" cascade) [5,16]. In this context, AG and IM are considered the main precursor lesions of gastric cancer as its incidence increases in the gastric mucosa involved with AG and IM [5,16-18]. Specifically, AG is characterized by the loss of gastric glandular cells, which can be caused by either intrinsic (e.g. autoimmune disorders) or environmental factors (e.g. alcohol, tobacco, nitrites, infection) [4]. The risk of gastric cancer increases with the extent and degree of mucosal atrophy and AG is considered to be an antecedent to IM [2,4-5]. Histologically, IM can be either complete or incomplete. Complete IM resembles small intestinal glands, with loss of gastric mucins and presence of eosinophilic enterocytes with an identifiable brush border, well-defined goblet cells, and occasional Paneth cells at the base of the gland. Incomplete IM (also known as gastric IM) is characterized by a combination of gastric foveolar epithelium and intestinal goblet cells, with simultaneous expression of both gastric and intestinal mucins [18]. Although the prognostic implication of IM subtypes is currently uncertain, several studies have suggested that incomplete IM has a higher proliferative index resulting in a higher risk of progression to cancer [18-19].

Among the several factors that have been considered playing a role in gastric carcinogenesis, Helicobacter pylori (HP) infection is currently the most important risk factor for AG, IM, and gastric cancer [2,17,20]. Epidemiological studies suggest that HP strains containing the cagA gene are more virulent and its prevalence varies according to ethnicity and geographical location [2,19-22]. Therefore, eradication of HP infection is regarded as a primary chemoprevention strategy for reducing the incidence of gastric cancer. However, it has to be noted that only 1-2% of HP-positive subjects will eventually develop gastric cancer and HP is generally absent from areas with IM, suggesting that other environmental and host factors are involved in the carcinogenesis [2,5,20-22]. In this context, a Swedish study recently evaluated the role of non-HP microbiota in the development of gastric cancer through the multistep "Correa cascade" [23]. Ndagwe et al. analyzed 316 individuals from a low HP prevalence general population and appraised differences in stomach microbial composition across the healthy and disease states, with AG and non-atrophic HP gastritis presenting the lowest microbial diversity. In particular, the Swedish group found an increasing abundance of pathogenic bacteria from normal stomach to early precancerous states and postulated that some of the identified non-HP bacteria may potentially play a role in promoting inflammation and gastric carcinogenesis through N-nitroso compounds or urease production. However, the role of gastric microbiota and the molecular pathways are far from being fully disclosed.

Another factor that has been extensively examined in several observational studies is obesity, although results are mostly inconclusive [21-22]. Recently, a large cohort analysis by Kim et al. [24] showed that obesity was associated with a higher incidence of AG and IM, with risk increasing as BMI category increased. In addition, the Korean study demonstrated that the positive association between BMI and IM was more evident in individuals younger than 40 years old, suggesting that accumulative exposure to other environmental factors may play a role in the prevalence of gastric cancer and its precancerous lesions with more advancing age.

The first step into diagnosis and assessment of gastric premalignant conditions is standard WLE associated by random mucosal biopsies to stage the extent and severity of gastritis and possible IM [5,19-20]. Macroscopically, the main endoscopic features of AG are loss of gastric rugae, mucosal pallor and increased visibility of mucosal vessels, whereas IM typically appears as an irregular surface characterized by small, grey-white, elevated plaques surrounded by mixed patchy pink and pale

areas of mucosa [19-20]. However, these macroscopic findings are neither sensitive nor specific and a higher degree of diagnostic accuracy can be achieved by using NBI-ME, which can reliably identify normal gastric mucosa, HP-associated gastritis, AG, and IM, thus supporting targeted biopsies that can lead to more accurate risk assessment [19-20]. Specifically, NBI-ME with or without chromoendoscopy (i.e. methylene blue, indigo carmine, and/or acetic acid) can increase the sensitivity up to 94% for detection of IM [19].
As for the role of serologic markers, several studies have demonstrated a possible significant association with digestive enzymes levels. Specifically, a decreased pepsinogen I/II ratio appears to be associated with higher risk of IM and gastric cancer, whereas increased serum gastrin levels are associated with AG [19]. However, current evidence is still ambiguous and further studies are required to provide definite conclusions.

Conclusion

Esophagogastric cancers are serious malignancies with high mortality. Prevention as well as early detection and treatment of premalignant or early malignant lesions are of paramount importance. Esophagogastric malignancies generally develop from precancerous conditions in a setting of a complex interaction between environmental and genetic factors. Inflammation can trigger a multistep, sequential process of carcinogenesis resulting in increased mutations, cellular atypia and dysplasia, which eventually may determine carcinoma.
Since frequently asymptomatic, high-quality white light endoscopy imaging and biopsies are the first steps into diagnosis and assessment of gastric and esophageal premalignant conditions. Visualization can be enhanced either through conventional chromoscopy or by using virtual methods. Some biological markers may be associated with increased risk of malignant transformation of precancerous lesions, but to date, the utility of those markers to make diagnosis, predict progression and assist with risk stratification, is still not validated.

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