Pathogenesis of esogastric junction cancer

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ABSTRACT

Introduction: Adenocarcinomas of esogastric junction are divided in three subgroups according to their relation with proximal extremity and gastric folds: AEG I – cancers of distal oesophagus; AEG II – cancers of true cardio; AEG III – sub-cardiac cancers. AEG I and AEG II are considered the same descriptive entity, being similar from the point of view of the patients’characteristics (fatness, medium-aged white men suffering from reflux illness without gastritis with Helicobacter Pylori), of the incidental tendencies and of molecular profile. Predisposing factors: genetic predisposition for the development of carcinomas on the bottom of Barrett oesophagus is supported by the fact that these ones affect almost exclusively the white men. There are familiar forms of the illness, where there were indentified polymorphisms and genetic alterations associated to adenocarcinomas of esogastric junction. As risky factors, there have been incriminated: gastro-oesophageal reflux illness, fatness, hiatal hernia, prematurity, smoking, alcohol consumption. Pathogenesis of esogastric junction cancers developed on the bottom of Barrett oesophagus which represents a premalignant condition that arises on the bottom of the long term gastro-oesophageal reflux illness, its formation implying at least three different phases. The progression towards malignity inside Barrett oesophagus is a multistep process, implying the transition from metaplasia to low degree dysplasia, to high degree dysplasia and invasive carcinoma. Conclusions: as the formation of the adenocarcinoma on the bottom of Barrett oesophagus represents a multiphase process, implying the transition from metaplasia to low degree dysplasia, to high degree dysplasia and invasive carcinoma, it is important that the patients with Barrett oesophagus should be carefully supervised, in order to diagnose the carcinoma from an early phase.

KEY WORDS esogastric junction, Barrett oesophagus, adenocarcinoma

Introduction

The cancers of esogastric junction still represent a problem of high medical importance as it might be impossible to establish their origins at the level of the gastric cardia or distal oesophagus. In both situations, cancers are associated with a gastro-oesophageal reflux illness (BRGE) and Barrett oesophagus (BE). Cardiac cancer presents the same secular tendencies, epidemiological funds and molecular profiles as well as the adenocarcinoma associated to Barrett oesophagus and differs from this point of you from noncardiac gastric cancers (6,7).

Adenocarcinomas rises in the distal oesophagus from Barrett oesophagus. The cancers associated to the Barrett oesophagus are responsible with over 90% of oesophageal adenocarcinomas. The rest of them appear from the heterologue remains or sub mucous glands. Not all the esogastric junction cancers are of oesophageal origin; some of them have their origin in the gastric cardia or affect the oesophagus through the proximal extension of the noncardiac gastric cancers.

The presence of dysplasia in the Barrett oesophagus helps identifying a cancer originated in the oesophagus, but it might appear problems in case of advanced adenocarcinomas which replace the pre-existent Barrett oesophagus.

The former definition of Barrett oesophagus includes any columnar epithelium which covers the distal oesophagus.

The present definition affirms that it has to be accomplished both histological and endoscopic criteria. The endoscopic component supposes the presence of the columnar mucous, recognized by its rosy colour, extending proximally from the level of the esogastric junction in the tubular oesophagus; the histological component requires that the biopsies removed from the level of the columnar pink mucous, endoscopically identified, should include the columnar epithelium of intestinal type or metaplastic with calceiform cells.

Generally, Barrett oesophagus is divided in:

Barrett oesophagus – long segment – the columnar mucous extends 3 centimetres or more over the esogastric junction;

Barrett oesophagus – short segment – the specialized columnar epithelium is restricted to less than 2 centimetres over the esogastric junction

Siewert and colab. (1987) separate the esogastric junction cancers in three subgroups, depending on their relation with proximal extremity and gastric folds:

Esogastric junction adenocarcinoma
- AEG I – cancers of distal oesophagus;
- AEG II – cancers of real cardia
- AEG III – sub-cardiac cancers (19).

It is believed that AEG I and AEG II are so similar from the point of view of patients (fatness, middle-aged white men with reflux illness, without Helicobacter Pylori gastritis), of the secular incidental tendencies and molecular profile, that they are in fact the same cancer.

**Predisposing factors for developing the esogastic junction cancer**

It seems that there is a genetic predisposition in developing the carcinoma which appear on the bottom of Barrett oesophagus. The fact that these cancers develop almost exclusively at white men suggests the implication of a genetic factor, still unknown in the development of illness. In addition, there are familiar forms of the illness which seem to have a dominant autosomal transmission (8, 10). The genetic polymorphism might play an important role in determining the risk of development of these tumours. There is an association between glutathione-S– transferase P1 (GSTP 1) polymorphisms and the adenocarcinoma associated to Barrett oesophagus where GSTP 1 is responsible with the detoxification of various carcinogenesis (21). There is also an association between the MTHFR 677 C-T mutation (a predictor of early-onset coronary artery disease risk) variant and oesophageal adenocarcinoma. Among the earliest and most frequent genetic alterations specific to neoplasia we can mention the alterations of the oncoproteins p54 and p16 (1, 16).

Another risky factor of carcinomas that might appear on the bottom of Barrett is the degree of the gastro-oesophageal reflux illness which is more severe in case of patients with cancer of Barrett oesophagus that in case of those without cancer, where the anti-reflux therapy does not decrease the risk of cancer. The risk of cancer increases at the same time with the duration of the gastro-oesophageal reflux illness (18). This could explain the increased risk of developing the cancer in case of adults whose birth weight was below 2000g, as long as the gastro-oesophageal reflux is more frequent at premature ones (11).

The presence and dimension of the hiatal hernia is directly correlated with the presence of Barrett oesophagus and junction adenocarcinoma. As well, the identification of bile acids in the refloated contents seem to be critical in generating the adenocarcinoma associated to Barrett oesophagus (17, 15).

Fatness is tightly associated to the oesophageal adenocarcinoma, maybe because of the increased risk of the gastro-oesophageal reflux illness in these cases (12). Recent studies find a positive independent association of fatness with esogastic junction cancer in case of patients with gastro-oesophageal reflux illness (5,14).

Smoking and alcohol are directly and deeply correlated to esogastic junction cancer, but the risk is not as high as the one implied in the development of squamous carcinoma and according to some studies they do not represent statistical significance (18).

Helicobacter Pylori is a well-known risky factor for distal gastric cancer; on the contrary, this latter is correlated inversely with the gastro-oesophageal reflux illness and esogastic junction cancer (4, 9). The low gastric acidity associated to the gastritis induced by Helycobacter Pylori prevents the development of the reflux illness, of metaplasia and its neoplastic consequences. The successful eradication of the infection with Helicobacter Pylori doubles the frequency of the gastro-oesophageal reflux illness comparing to the untreated patients.

Medicinal treatments which promote the gastro-oesophageal reflux illness by relaxing the oesophageal sphincter, as for example the anticholinergics, may increase the risk of esophageal adenocarcinoma, whereas the medicines that inhibit the synthesis of prostaglandins and block the imuno - suppression induced by these, may protect against cancer development associated to Barrett oesophagus (13).

**Pathogenesis of esogastic junction cancer developed on the bottom of barrett oesophagus**

Barrett oesophagus is a metaplastic modification which results from gastro-oesophageal reflux illness on long term, being the consequence of the combination of some substances of the refloated contents including acids, bile salts, lipo-phospholipids and activated pancreatic enzymes. The interaction between these substances determines various lesion degrees of repairing, transforming and maturing the clinic phenotype in forms of esophagitis, Barrett oesophagus, stricts, dysplasia and carcinoma. In this abnormal environment, immature multi-potent stem cells differentiate in various epithelial types, including the columnar epithelium which is more resistant to acid digestion and which has a faster regeneration capacity than the one of native squamous epithelium (7). Once formed, Barrett oesophagus is a highly proliferate mucous.

The formation of Barrett oesophagus goes through at least three different phases. During the
initiation phase, the genetically susceptible patients suffering from gastro-oesophageal reflux illness develop reflux esophagitis which leads to the formation of metaplastic epithelium, having the characteristics of intestinal columnar epithelium; the metaplastic columnar cells might come from three sources:

1) metaplasia of squamous epithelium, similar to vaginal mucosa
2) columnar/squamous mixed population of the transition area, as it appears in the cervical metaplasia
3) columnar cells of oesophageal glands that might be associated to ulcers healing

Stem cells recruitment from the bone marrow, as a response to the inflammation induced by the reflux may serve as another potential source in the formation of Barrett oesophagus.

During the formation phase, the metaplasied epithelium which continues to be exposed to the refluxed contents, stabilizes and occupies a variable surface of the distal oesophagus which leads to the proximal migration of the squamous-columnar junction in time.

All along the progression phase, permanent and transitory molecular alterations are accumulated at the level of the squamous cells or the cells of Barrett oesophageal epithelium, which is under the influence of different environmental factors and factors related to the host.

The high exposure to acid increases the villin expression and correlates with the aspect of microvilli. Another important factor in the intestinal differentiation is CDX2, a transcription factor which belongs to the genes family homeobox lagate caudal, and its expression in the intestinal tract is specific to the intestine (2).

Bile acids act as tumourous promoters increasing the cell proliferation. The activation of CCK2 receptors may stimulate the proliferation of gastrina cells that induce cyclooxygenase which play an important role in inhibiting the apoptosis, promoting the cell proliferation, the invasion of the malign cells and promoting the angiogenesis.

The progression to malignity in Barrett oesophagus is a multistep process, implying the transition from metaplasia to low degree dysplasia, high degree dysplasia and evasive carcinoma. In some cases, the dysplasia persists for many years without progression. The high degree of dysplasia is associated to competitive adenocarcinoma in almost a third of the cases while examining the biopsy tests; the presence of the associated invasive cancer may not be suspected until the resected piece is examined (20).

As the dysplasia often appears adjacent to the area of invasive carcinoma, its presence represents both a marker of the high risk for the development of the secondary cancer, and a potential marker for the coexistence of a invasive cancer. The level of the risk is correlated to the extension of the high degree dysplasia, although a recent study indicates that a cancer might be accompanied by high degree focal dysplasia, as well as a high degree diffuse dysplasia (3).

Dysplasia is frequent at 5-10% of the patients presenting Barrett oesophagus and it grow in frequency, insofar as the lesion is pursued in time. A cohort study, which includes the patients presenting Barrett oesophagus pursued for 20 years, finds a cancer rate of 1/274 patients in the presence of dysplasia comparing to 1/1114 patients without dysplasia (3).

The problems related to the determination of the diagnosis of dysplasia include difficulties related to removal errors, to the distinction between the reactive modifications and dysplasia, to the subjective interpretation of the dysplasia results and difficulties in differentiating the dysplasia from invasive carcinoma. The early invasive adenocarcinoma may develop everywhere at the level of the Barrett oesophagus length. The presence of the high degree dysplasia represents an indication for the surgical intervention and most of physicians recommend the re-biopsy in order to determine if there is an associated carcinoma. The surgical procedure depends on the length of Barrett oesophagus; some patients develop a post-resectional secondary carcinoma, which usually develops itself on the residual Barrett oesophagus.

Conclusions

Knowing the natural history of dysplasia in Barrett oesophagus of progression to malignity, it is important that these patients should be carefully supervised and investigated by a inter-disciplinary team (gastroenterologist, anatomopathologist and surgeon), with a view to discover the invasive cancer in an early phase, thus increasing the survival chance. As a consequence, the dysplasia diagnosis is a decisive factor in managing the patients presenting Barrett oesophagus.

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