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Precancerous gastric lesions: pathophysiology and symptomatology

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Abstract

Background: Independent risk factors for chronic atrophic gastritis, gastric intestinal metaplasia and gastric cancer are: *Helicobacter pylori* infection (especially virulent CagA strains), genetic factors (advanced age, reflecting the duration of *Helicobacter pylori* infection, male gender, family history of gastric cancer in first-degree relatives), gastric ulcer, biliary reflux, acute or chronic gastric inflammation, smoking, alcohol consumption, prolonged use of proton pump inhibitors or non-steroidal anti-inflammatory drugs, diet low in fruits, vegetables and vitamin C, excessive salt intake and consumption of canned foods with salt). *Helicobacter pylori* infection and inflammatory cells induce the expression of inducible nitric oxide synthase in the gastroduodenal mucosa, which causes various clinical lesions (duodenal ulcer, gastric ulcer and chronic gastritis without ulcer). Another important condition associated with *Helicobacter pylori* infection is gastric cancer. Overproduction of nitric oxide, through inducible nitric oxide synthase and oxidative stress, is a genotoxic and mutagenic metabolism which plays a crucial role in the process of gastric carcinogenesis.
Conclusions: Chronic atrophic gastritis is considered a multifaceted condition because it can manifest itself through a variable spectrum of nonspecific gastric and extra-gastric symptoms, with an overlap of the clinical features of the two entities of chronic atrophic gastritis – autoimmune and associated with *Helicobacter pylori* infection. Thus, in contrast to the classic perception of a silent condition, patients with chronic atrophic gastritis report a wide range of gastrointestinal symptoms, ranging from dyspeptic symptoms to those of gastroesophageal reflux.
Key words: gastric intestinal metaplasia, epithelial dysplasia, gastric cancer, *Helicobacter pylori*.

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Introduction

In many cases, the development of intestinal gastric adenocarcinoma is the final stage of the inflammation-atrophy-metaplasia-dysplasia-carcinoma sequence, also called Correa's multi-stage cascade of gastric oncogenesis, a model confirmed by a considerable number of longitudinal clinical-pathological and epidemiological studies [1-5]. According to this well-defined cascade of premalignant conditions or lesions, gastric cancer (GC) develops as a result of a gradual progression. The first real step in the precancerous cascade is from the normal gastric mucosa to a chronic active inflammation associated with *Helicobacter pylori* (HP) infection, which may persist (chronic non-atrophic gastritis without loss of glands) or may progress to chronic atrophic gastritis (CAG) – mild, moderate and severe. The next steps are: gastric intestinal metaplasia (IM), initially "complete" and then "incomplete", and dysplasia of the gastric mucosal epithelium (DGME), initially low-grade and then high-grade. GC is the last step in this multi-stage cascade, triggered by long-term inflammatory conditions (especially HP infection) [3-7]. According to estimates, Correa Waterfall is involved in about 50% of cases of GC, especially intestinal type [8].

Material and methods

The aim of the paper is to develop a narrative synthesis of contemporary studies on the pathophysiology and clinical picture of precancerous gastric lesions and their role in the development of GC. The publications were selected from the PubMed, Hinari and SpringerLink databases by keywords: chronic atrophic gastritis, gastric intestinal metaplasia, gastric mucosal epithelial dysplasia, gastric cancer, *Helicobacter pylori*. After processing the information from the databases, we selected all publications in English starting from January 1990. After a preliminary analysis of the titles, the final bibliography included original articles, editorials, articles of narrative synthesis, systematic and meta-analysis that contained information on the pathophysiology and clinical picture of gastric precancerous lesions. Additionally, the bibliography of the selected articles was studied in order to find other relevant articles on this topic. According to the search criteria, 563 complete articles were found. The final bibliography contains 46 relevant sources, which were considered representative for the materials published on the topic of this synthesis article.

***Helicobacter pylori* infection.** HP is located in the mucous layer along the surface of the gastric epithelium and in

the luminal portion of the gastric fovea, being rarely present in the deeper glands. The infection is usually contracted in childhood and progresses throughout life in the absence of proper treatment. The host responds to the presence of the bacterium by activating B and T lymphocytes, followed by infiltration of the *lamina propria* and gastric epithelium with polymorphonuclear and mononuclear inflammatory cells, which phagocytose the bacterium. The release of toxic bacterial and inflammatory products causes damage to gastric epithelial cells, which progress to atrophy. Some glandular units develop an intestinal-type epithelium. MIG subsequently occurs in several areas of the atrophied gastric mucosa. Other glands are replaced by fibrous tissue from the expansion of the *lamina propria.* The loss of the glands of the gastric body produces functional changes with the loss of the ability to secrete acid, pepsin and intrinsic factor and the increase of gastric pH. There is a good, but not complete, correlation between the severity of gastric mucosal atrophy (GMA) and depression of gastric function [9,10].

Most HP strains can be classified into 3 major types: type 1 – highly infectious, have the gene encoding CagA antigen and VacA antigen, type 2 – transitional, expressing CagA antigen independent of VacA antigen or vice versa and type 3 – with low resistance, which does not express any antigen [11].

Gastritis associated with HP infection progresses on two topographic models that have different clinico-pathological consequences. The first model, most common in Western countries, is antral CAG, characterized by inflammation located predominantly in the gastric antrum. Peptic ulcer usually overlaps with this type of lesion [9, 10]. The second model is the multifocal CAG. The special virulence of HP CagA-positive strains, with a predominant role in CAG and the evolution towards GC, is widely accepted. GMA involves the body, fundus and antral regions, with the progressive evolution of CAG and the gradual replacement of the gastric glands with intestinal-type epithelium (IM). This pattern is more common in developing countries and in Asia [9, 10].

Multiple studies and meta-analyses have highlighted the very strong association between HP infection and CAG. CAG develops late in the course of chronic non-atrophic gastritis associated with HP infection, even in HP-negative patients. On average, about 50% of people infected with HP will develop CAG of some degree or type during their lifetime. In addition, HP is also the leading cause of GC [12].

HP is the most important and significant risk factor in establishing CAG and IM, often associated with GCA, but there are other clinical, environmental, and genetic conditions that are important risk factors (RF) for the progression of IM to GC. CAG is not a normal aging process, but it is the result of HP infection, and IM is caused by both the aging process and HP infection. A low risk of IM among HP-negative women may partially explain the lower prevalence of GC in women compared to men [13, 14, 15, 16]. It is well documented that long-term exposure to HP infection is a RF for the development, worsening and progression of precancerous lesions (CAG and IM). HP CagA-positive strains are associated with increased prevalence and severity of CAG and IM [14-18].

It was found that bacterial factors are important RF for CAG, and environmental and host factors are more important for IM [14-18]. These include age, male gender, gastric ulcer, biliary reflux, severe acute and chronic gastric inflammation, smoking, alcohol consumption, diet low in fruits, vegetables and vitamin C diet, and a high salt intake [14, 19]. Therefore, independent RFs for CAG, IM and GC are considered: HP infection (especially CagA virulent strains), severe CAG, autoimmune CAG, certain rheumatic diseases (Sjögren's syndrome), genetic factors (advanced age, which reflects the duration of infection with HP, male gender, family history of GC in first-degree relatives), gastric ulcer, biliary reflux, severe acute and chronic gastric inflammation, smoking, alcohol consumption, prolonged use of proton pump inhibitors or non-steroidal anti-inflammatory drugs, alimentation (diet low in fruits, vegetables and vitamin C, excessive salt intake and consumption of canned foods with salt) [11, 18].

A key RF of chronic inflammation is the release of large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are associated with DNA damage and increased rates of mutations. Previous studies have shown that ROS and RNS, secreted by inflammatory and epithelial cells, can cause oxidative and nitrative damage to DNA, including the production of nitric oxide (NO) – a known mutagenic substance derived from inducible nitric oxide synthase (iNOS). Deterioration of cellular components results in increased mutations, disorders of the functions of important enzymes and proteins in premalignant tissues, thus contributing to the process of multistage and multifactorial carcinogenesis [13, 20].

NO is an important intracellular and intercellular signaling molecule involved in the regulation of various physiological and pathophysiological mechanisms in the cardiovascular, nervous and immune systems. According to experimental data, NO is normally involved in the physiological regulation of gastric microcirculation and its integrity. NO is also a SRA that acts as a cytotoxic agent in pathological processes, especially in inflammatory disorders, not only for the microorganism, but also for cells and tissues. When the generation of ROS and RNS exceeds the antioxidant capacity of the cell, they play an important role in cell damage and carcinogenesis of HP-infected gastric mucosa. Simultaneously with oxidative damage (ROS and RNS) of tissue and DNA with modification of target proteins, NO overproduction during chronic inflammation, including HP infection, increases histamine secretion and the formation of carcinogenic compounds with increased risk of carcinogenesis (initiation and progression of carcinogenesis to GC). Thus, long-term inflammation of the gastric mucosa generates significant amounts of NO, which contributes not only to the deterioration of basic nucleotides in DNA and proteins, but, by hypermethylation of promoter sequences, leads to epigenetic changes in gene expression and suppression of gene activity [1, 20-24].

Recent advances in basic research on HP-associated carcinogenesis have explained that iNOS-derived NO plays a crucial role in the process of gastric carcinogenesis. iNOS expression has been reported to be absent in the normal gastric mucosa, increases significantly in HP-negative patients with chronic gastritis, and increases significantly in HP-positive patients with chronic gastritis. This expression is closely related to the infiltration of inflammatory cells in the gastric mucosa, modulates inflammation and epithelial changes. In HP-positive patients, high levels of RNS in the gastric mucosa contribute to neoplastic transformation. A number of activities may contribute to the tumor-modifying effects of NO, including damage to DNA and DNA-repairing proteins, endogenous mutagenesis, increased angiogenesis and increased blood flow, inhibition of apoptosis with genetically modified cell survival, enzyme activation cyclooxygenase-2 and suppression of the immune system [14, 20].

Increased expression of iNOS has been observed in inflamed human gastric mucosa (in inflammatory cells – olymorphonuclear, plasma, lymphocytes and macrophages), as well as in some gastrointestinal, gynecological and central nervous system tumors. It is known that inflammatory cell infiltrate is generated in the gastric epithelium and *lamina propria* during the development of chronic gastritis, including chronic gastritis associated with HP. The results of the studies support the hypothesis that HP infection, especially HP CagA-positive strains and certain VacA-positive alleles, induces iNOS expression and activity and causes NO overproduction in the gastro-duodenal mucosa in order to regulate the inflammatory process. NO is a factor in the oxygen-dependent system for antiviral and antibacterial protection. Thus, NO has an essential role in inflammatory processes, but the excessive accumulation of this metabolite in tissues causes toxic effect on cells, severe destructive changes and dysregenerative disorders. As a result, significant destructive changes of the gastric mucosa, erosions and regenerative disorders, including IM, occur. However, the latest studies have shown that eradication of HP causes a significant reduction in iNOS expression [20-25]. In the gastrointestinal tract, excess NO aggravates mucosal lesions. Prolonged oxidative and nitrosative stress in severe CAG contributes to the development of IM and DGME and subsequently to intestinal GC. In atrophic gastric mucosa, associated with HP infection, a significant increase in iNOS expression and NO-modified proteins has been found, and hypergastrinemia is a feature of iNOS-producing gastritis, which has an increased risk for carcinogenesis [20-25].

Evaluation of the relationship between oxidative stress and early onset of GC, especially poorly differentiated intramucosal adenocarcinoma in young people, revealed a significant reduction in iNOS expression in cancer cells compared to non-cancer cells, which may play an important role in CAG-associated carcinogenesis induced by HP [25].

In addition, research has detected an increased expression of iNOS in the gastric mucosa adjacent to HP-infected sites and in the non-cancerous gastric mucosa adjacent to intestinal cancer tissue. After successful eradication of HP, iNOS expression decreases. Persistence of IM, a precancerous lesion, is probably a source of continuous induction of iNOS even after eradication of HP infection [21, 22].

Therefore, HP infection induces iNOS expression in the gastroduodenal mucosa, an important element in lesions associated with HP infection. The expression of iNOS, stimulated by HP and inflammatory cells, contributes to the mechanisms by which HP causes various clinical lesions (duodenal ulcer, gastric ulcer and chronic gastritis without ulcer). Another important condition associated with HP infection is GC. NO is genotoxic and mutagenic, suggesting that NO overproduction via iNOS and ROS, derived from polymorphoneutrophils in HP-infected gastric mucosa, is involved in carcinogenesis.

Chronic atrophic gastritis. CAG is a prevalent condition, the final consequence of an inflammatory process that eventually leads to the loss of the corresponding mucous glands with reduced gastric secretory function. This histological change is the result of an autoimmune-mediated reaction directed to parietal cells or may be associated with HP infection [26, 27].

In the last two decades there has been a wide shift in the paradigm of understanding GC and its premalignant states from histological models to increasingly accurate molecular descriptions. Despite recent advances in the molecular and cellular understanding of the events involved in GC, little is known about how premalignant gastric lesions contribute to carcinogenesis [13]. Intestinal type GC carcinogenesis is an example of a malignant disease with a well-described cascade of precancerous lesions (Correa cascade). GMA and IM pose a high risk for the development of GC, a risk that increases with the severity of precancerous lesions, as it is the background in which DGME and intestinal gastric adenocarcinoma may develop, although the molecular mechanisms responsible for this progression are not yet well understood. For this reason, CAG and IM are considered the main histological precursors, which exponentially increase the risk of intestinal GC. However, only a minor proportion of lesions (except DGME) progress to cancer [3, 6, 13, 17, 28, 29]. The extent and topographic distribution of GMA are parallel to the risk of developing GC, which theoretically allows the application of either non-invasive (serological) or invasive (endoscopic / histological) methods to quantify GMA in order to assess the risk of CG [30 , 31].

Gastric intestinal metaplasia. Numerous studies, systematic reviews and meta-analyses have evaluated the association between IM and GC risk. Patients with incomplete IM, compared to complete IM, have a higher risk of DGME and GC [17, 19, 29, 32-34]. Several studies have shown that IM is associated with a higher risk of cancer in the gastric body than in the gastric antrum alone, which suggests that IM progresses concomitantly with GMA and predicts the risk of GC [19, 33]. Therefore, patients with IM, especially incomplete IM and in the gastric body, have a higher risk of GC [33].

Dysplasia of the epithelium of the gastric mucosa. IM is a precursor to low-grade DGME, which can culminate in high-grade DGME and gastric carcinoma. DGME is the penultimate stage in the succession of gastric carcinogenesis. This lesion is a combination of three basic morphological abnormalities: epithelial atypia without evidence of tissue invasion (variation in size, shape, and orientation of epithelial cells), loss of native epithelial engagement, and disorganized glandular architecture. Thus, DGME is considered a direct precancerous lesion [2, 3, 6, 28, 32, 34].

Gastric cancer. The high prevalence of GC in HP-positive subjects probably occurs because HP infection contributes to the progression of CAG to IM and DGME with a significant increase in the risk of GC [7, 12, 35]. For the development of GC, especially intestinal type, the end result of chronic inflammation caused by bacterial colonization, is more important than HP infection itself [35]. The risk of developing CG depends on the degree of GMA at the time of eradication: it is 0.31-0.62% per year for successful eradication of HP in cases of severe CAG (cases of unintentional eradication in the treatment of other infections and cases of unreported eradication) and 0.53-0.87% annually for cases with severe CAG and spontaneous regression of HP due to CAG progression. The prevalence of GC in HP-negative people is extremely low – 0.66% [12]. Among people with IM, the cumulative rate of progression to DGME was 15% at 3 and 5 years, and the cumulative rates of 3, 5 and 10 years incidence of GC were 0.4%, 1.1% and 1.6–2.0%, respectively [32, 35]. In general, among people with IM the annual rate of progression in GC exceeds 0.5-1% [35].

Among 98000 patients with premalignant gastric lesions in the Netherlands, the average risk of GC was 2-3% over 10 years. This risk varied concomitantly with the baseline stage of premalignant lesions: 0.8%, 1.8%, 3.9% and 32.7% for patients with CAG, IM, mild-to-moderate DGME and severe DGME, respectively [36].

All the above data suggest that there are other factors than GMA and IM, which have a role in gastric carcinogenesis. In addition to infection with HP, CAG, and IM, there are several RFs for GC – sex, age, blood type, HP infection, family history of GC, smoking, alcohol consumption, and eating habits [2, 28].

Chronic atrophic gastritis symptoms. Gastritis is an inflammation of the gastric mucosa, most often accompanied by structural changes. The term gastritis most often refers to dyspeptic symptoms, defined as disorders of the upper gastrointestinal tract. Dyspepsia is the most common gastrointestinal problem in general practice with prevalence rates between 5.3% and 20.2% [37], and 20-40% of the population report these symptoms at least once in a lifetime [38]. About 80-90% of people with HP remain asymptomatic throughout their lives. Chronic HP infection contributes to the development of CAG, which has also traditionally been considered asymptomatic or with nonspecific symptoms and diagnosed incidentally, especially autoimmune CAG [27, 39, 40, 41]. However, due to the marked decrease in gastric functional activity, dyspeptic syndrome (anorexia, belching, nausea, postprandial fullness and early satiety), bacterial overcrowding syndrome (noise and flatulence in the abdomen, belching, unstable stool, with frequent diarrhea, weight loss and anemia may occur), anemic syndrome, pain syndrome, dystrophic syndrome. Gastrointestinal manifestations are associated with non-acid reflux and are not specific [27, 40].

Typical symptoms of reflux (heartburn and / or acid regurgitation), epigastric pain syndrome (epigastric pain and / or epigastric heartburn) and postprandial distress syndrome (postprandial fullness and / or early satiety) were present at 10.5% of patients with non-atrophic gastritis or mild CAG, in 19.8% of patients with predominantly antral CAG and in 16.2% of patients with CAG predominantly in the gastric body. Symptoms of epigastric pain syndrome and postprandial distress syndrome were significantly more common in male patients with predominantly CAG in the gastric body and in female patients with predominantly antral CAG. Thus, the extent and severity of CAG affect the generation of specific dyspeptic symptoms and this influence was different depending on gender. The reason why there is a gender difference in the results cannot be clearly explained [42].

At least one typical symptom of gastroesophageal reflux was reported in 24.1% of patients with CAG in the gastric body, including 9.2% reported epigastric heartburn and 18.5% – regurgitation. These data showed that gastroesophageal reflux disease is present in about ¼ of these patients, which suggests that hypochlorhydria does not exclude, in itself, the occurrence of esophageal symptoms [43]. However, there is no correlation or overlap between symptoms and endoscopic or morphopathological data [44].

CAG is considered a multifaceted condition because it can manifest through a variable spectrum of gastric and extra-gastric symptoms. The clinical spectrum of CAG is not clearly defined and is often nonspecific, with an overlap of clinical features between the two CAG entities. Studies have been conducted mainly on autoimmune CAG, while data on the clinical presentation of CAG associated with HP infection are limited [27, 45]. Thus, in contrast to the classic perception of a silent condition, patients with CAG report a wide range of gastrointestinal symptoms, ranging from dyspeptic symptoms to symptoms of gastroesophageal reflux [46].

Conclusions

1. Independent risk factors for chronic atrophic gastritis, gastric intestinal metaplasia and gastric cancer are: *Helicobacter pylori* infection (especially CagA virulent strains), genetic factors (advanced age, reflecting the duration of *Helicobacter pylori* infection, male history, gastric cancer in first-degree relatives), gastric ulcer, biliary reflux, acute or chronic gastric inflammation, smoking, alcohol consumption, prolonged use of proton pump inhibitors or non-steroidal anti-inflammatory drugs, diet low in fruits,

vegetables and vitamin C, excessive salt intake and consumption of canned foods with salt).

2. *Helicobacter pylori* infection and inflammatory cells induce the expression of inducible nitric oxide synthase in the gastroduodenal mucosa, which causes various clinical lesions (duodenal ulcer, gastric ulcer and chronic gastritis without ulcer). Another important condition associated with *Helicobacter pylori* infection is gastric cancer. Nitric oxide overproduction, through inducible nitric oxide synthase and oxidative stress, is a genotoxic and mutagenic metabolism with direct involvement in carcinogenesis.

3. Chronic atrophic gastritis is considered a multifaceted condition, because it can manifest itself through a variable spectrum of nonspecific gastric and extra-gastric symptoms, with an overlap of the clinical features of the two entities of chronic atrophic gastritis – autoimmune and associated with infection with *Helicobacter pylori*. Thus, in contrast to the classic perception of a silent condition, patients with chronic atrophic gastritis report a wide range of gastrointestinal symptoms, ranging from dyspeptic symptoms to symptoms of gastroesophageal reflux.

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AB designed the trial and drafted the first manuscript; NB and VI interpreted the data and revised the manuscript critically.
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