Chronic gastritis and carcinogenesis issues

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Key words: chronic gastritis, gastric mucosa, gastric cancer, intestinal metaplasia, atrophy, H. pylori, gastrin, pepsinogen, interleukin

Chronic gastritis (CG) and peptic ulcer are widespread among non-cancerous diseases of the stomach [3]. CG indicates the presence of a chronic pathological process that is morphologically characterized by inflammatory and dystrophic changes in the gastric mucosa (GM) with symptoms of impaired cell renewal, progressive atrophy, functional and structural changes with various clinical signs.

An independent diagnosis of chronic hepatitis does not have much direct clinical significance. According to the classification concept, the CG concept includes a purely morphological approach, and none of the four modern classifications (Sydney 1990; Houston 1994, modified Sydney system 1990; OLGA-2008 classification and OLGIM-2010 classification) does not contain a section on the assessment of clinical manifestations. This is partly due to the often asymptomatic course of chronic hepatitis C, and if any clinical manifestations do occur, they are usually associated with concomitant functional, primarily dyskinetic and gastroduodenal disorders.

The morphological point of view of the conceptual view in foreign gastroenterology on chronic hepatitis C is due to the need for early screening of dysregenerative-dystrophic processes and the severity of the progression of structural changes in the gastric mucosa with a certain unfavorable prognosis. In particular, atrophy and intestinal metaplasia, common pathological changes, make up the background against which epithelial dysplasia and gastric adenocarcinoma of the intestinal type develop [1, 2, 3]. Thus, CG, especially with the development
of intestinal metaplasia [11, 12], is considered a precancerous condition correlating with the degree and topography of trophic/metaplastic changes.

Many new ideas about the pathogenesis of chronic hepatitis C, as well as its relationship with the development of peptic ulcer of the duodenum/stomach and non-cardiac cancer of the stomach, were caused in 1982 by H. pylori bacteria. Today, there is no doubt about the relationship between H. pylori and gastric cancer. Back in 1994, the International Agency for Research on Cancer (IARC) recognized this infection as a first-order carcinogen because of its epidemiological connection with gastric adenocarcinoma and gastric MALT lymphoma [1, 10]. The so-called phenotypes of chronic hepatitis associated with H. pylori [5].

Of particular interest is the chronic “gastritis phenotype”, a multifocal CG that occurs in countries with a high incidence of gastric cancer and is a morphological phenotype and leads (with some exceptions) to long-term H. pylori infection in more than half of cases [1, 8]. Only less than 5–10% of CG cases occur in an autoimmune disease (type A, diffuse stomach) associated with B12-deficient anemia. Considering the fact that gastric mucosa atrophy can occur in 1–5% of cases in people under 30 years of age [5, 7], CG is currently an important medical and social problem. In Finland, chronic and severe atrophic gastritis is diagnosed in almost 10% of people without clinical symptoms or in patients with dyspepsia over 50 years old [22]. At the same time, despite the general tendency towards a decrease in morbidity and mortality from this pathology, especially in economically developed countries, in the last 15–20 years there has been a tendency toward an increase in the incidence of gastric cancer (intestinal form) in young people [9, 11, 12].

Thus, the identification and monitoring of patients with previous precancerous conditions/lesions (precancerous lesions), timely screening of H. pylori can lead to an early diagnosis of gastric cancer. However, there are no clear recommendations for a unified approach to managing patient data. At the same time, standardization of management of patients with precancerous conditions will allow identifying patients with the greatest risk. In addition, it is necessary to
analyze both the main sections of European clinical guidelines for the management of patients with precancerous conditions and stomach injuries (MAPS 2012), as well as new data on the immunopathogenesis of acute and chronic gastritis.

Precancerous conditions. It is believed that gastric adenocarcinoma develops in a pathologically altered gastric mucosa. In this case, CG is always considered as a mandatory initial prerequisite. Japanese experts and the World Health Organization committee suggested distinguishing between precancerous conditions and precancerous changes in the gastric mucosa [13, 15]. The first is a clinical concept associated with an increased risk of developing gastric cancer, the second is a microscopic pathology (morphological changes in tissues) of the area where cancer develops more often than in normal tissues. Thus, precancerous conditions are diseases that can lead to cancer.

If all precancerous conditions are arranged in order of increasing risk of developing cancer, then in the first place should be placed adenomatous polyps of the stomach (polyps, which are benign tumors of the glands — adenomas). Such polyps become malignant in 60–70% of cases. Another variant of gastric polyps, the so-called hyperplastic polyps, on the contrary, rarely turn into cancer — the probability of malignancy of these polyps is small (0.5% of cases); CG should take the second place. Due to the widespread prevalence of this disease, chronic hepatitis C occupies one of the leading places in the structure of precancerous conditions.

Subsequent precancerous conditions include:
- cancer of the operated stomach (in patients who have previously undergone surgery on the stomach, the frequency of stomach cancer increases 3-4 times);
- Menetria disease (hypertrophic gastropathy) (transformation into gastric cancer is observed in 15% of cases);
- B12-deficient anemia (malignant tumor in 1-10% of cases);
- gastric ulcer (malignancy of chronic ulcers is observed only in 0.6–1% of cases).
Particular attention should be paid to the group of patients with "healed ulcers" of the stomach, since cases of increased morphological verification of cancer with enlarged (healed) "ulcers". Obvious endoscopic signs of malignancy are not defined. In place of such an ulcer, normal granulation tissue and gastric mucosa can form, into which the tumor will grow again, which will create an imitation of an exacerbation of peptic ulcer. In fact, we are talking about primary ulcer cancer and a tendency in the early stages of epithelization (healing).

Precancerous changes are histologically proven dysplastic changes in the gastric mucosa, indicating the progression of the process towards malignant growth, but insufficient to establish cancer at the moment.

Currently, the development of gastric cancer (mainly "intestinal type") is considered as a multi-stage process that includes a sequence of gastric mucosa changes: chronic inflammation, atrophy, intestinal metaplasia, dysplasia and adenocarcinoma. According to R. Corréa, over the course of 30 years, 50% of H. pylori infected patients develop atrophy of the gastric mucosa, 40% have intestinal metaplasia, 8% have dysplasia, and 12% have stomach adenocarcinoma.

Atrophy is the loss of the gastric glands with their replacement by metaplastic epithelium or fibrous tissue. It is known that 25–75% of all types of stomach cancer occur against the background of CG, which occupies one of the leading places in the structure of precancerous conditions. About 10% of patients with CG have developed gastric cancer within 15 years. The risk of developing gastric cancer is 18 times higher in patients with severe atrophic gastritis of the antrum.

As a risk factor for the development of gastric cancer, atrophic gastritis of the antrum and body is independent in multifocal atrophic gastritis (atrophic gastritis in both departments). The overall risk increases to an extreme degree [9, 16]. Among patients with gastric cancer, normal gastric mucosa is extremely rare. The steady progression of gastric mucosa atrophy in patients with chronic hepatitis C does not in itself lead to a deterioration in the general condition of the patient, but may be a background for the development of other more serious diseases. The
development of intestinal metaplasia and subsequent dysplasia is a key point in the development of cancer and lymphoproliferative processes in the stomach.

Metaplasia is a non-tumor change in the cellular phenotype of gastric mucosa tissues. In general, metaplasia means the transformation of one type of tissue into another, morphologically and functionally different from the first, while maintaining its main types. Currently, the intragastric distribution and degree of intestinal metaplasia are also identified as risk factors for gastric cancer. If atrophic gastritis is usually diffuse, then intestinal metaplasia is usually multifocal [17, 18]. At the same time, the risk of developing stomach cancer increases in patients with extensive stomach lesions. The presence of intestinal metaplasia increases the risk of gastric cancer by an average of 10 times [19].

As a risk factor for gastric cancer, it is proposed to determine the subtypes of intestinal metaplasia, dividing into full and incomplete. With full ("small intestine" or type I) goblet and absorbing cells are detected, a decrease in the expression of gastric mucins MUC1, MUC5AC and MUC6 is noted. In case of incomplete ("small-colon" or type IIA/II, and "large-intestinal" or type IIB/III), goblet and cylindrical non-absorbing cells are detected in which gastric mucins (MUC1, MUC5AC and MUC6) are expressed simultaneously with MUC2.

Currently, the classifications used also take into account the presence of Paneth cells (complete metaplasia) or changes in architecture in the form of a crescent, dedifferentiation and the absence of Paneth cells (incomplete metaplasia), as well as the nature and type of mucins. A different picture of metaplasia is described, called "metaplasia with the expression of an antispasmodic peptide" — MESP. It is characterized by the expression of the antispasmodic TFF2 polypeptide, which is associated with atrophy of the acid-forming zone. MESP is formed naturally in the body and lower part of the stomach. And it probably has some common characteristics with pseudopiloric metaplasia and a strong association with chronic H. pylori infection and gastric adenocarcinoma [20, 21].

Gastric dysplasia, the penultimate stage of the sequence of gastric carcinogenesis/non-progressive changes, is defined as a histologically unequivocal
tumor epithelium without signs of invasion, and, therefore, is a direct precancerous tumor lesion [14, 26]. The correct diagnosis and degree of dysplasia is crucial because they determine both the risk of malignant transformation and the risk of metachron cancer of the stomach. These indicators of the progression of gastric cancer from dysplasia vary from 0 to 73% per year [22, 23, 25].

"Intestinal" gastric adenocarcinoma is the culmination of the sequence "inflammation — atrophy — metaplasia — dysplasia — cancer." This multi-stage cascade of gastric carcinogenesis can be a process that develops from normal gastric mucosa through chronic non-atrophic gastritis, atrophic gastritis and intestinal metaplasia to dysplasia and gastric cancer [24].

**Pathophysiology of the stomach and secretion of hydrochloric acid in CG.** Atrophy, of course, involves a violation of the secretory function and physiology of the gastric mucosa. It leads to a decrease in the secretion of hydrochloric acid, while atrophic changes in the antrum of the stomach lead to impaired secretion of G-cells of gastrin-17 (G-17). In CG, dysregulation of the secretion of acid and pepsinogen (PG) and, consequently, the feedback mechanism, leads to different degrees of hypochlorhydria or even achlorhydria and hypo- or hypergastrinemia, depending on whether there is atrophy in the antrum or not. The degree of histological changes in CG has a pronounced negative correlation with the release of hydrochloric acid, as well as with the level of PG-1 or PG-1/PG-2 in serum/plasma. In severe atrophic gastritis of the body of the stomach and the normal mucous membrane of the antrum, intragastric acidity decreases, secretion of the antrum G-cells is not inhibited by the feedback mechanism, which leads to hypergastrinemia and the level of G in the blood serum (in some cases, it can rise to several hundred pmol/l).

Atrophy is accompanied by the appearance of gland metaplasia in an atrophically altered gastric mucosa (i.e., pseudopiloric metaplasia with or without intestinal metaplasia). Metaplastic glands do not secrete hydrochloric acid or G-17, but to one degree or another acquire the properties of the glands of the mucous membrane of the small or large intestine. As atrophy progresses, the metaplastic
glands and epithelium can become more and more immature, which reflects the transition from full-type intestinal metaplasia (small intestinal type) to immature or incomplete intestinal metaplasia (large intestine). This transition is believed to reflect an increased risk of developing stomach cancer with CG. The states of hypochlorhydria or achlorhydria in the stomach create conditions for the colonization of bacteria other than H. pylori, some of which can produce mutagenic and carcinogenic substances.

In addition to reducing the release of hydrochloric acid, CG in the body of the stomach leads to a violation of the secretion by acid-forming cells of the intrinsic factor necessary for normal absorption of vitamin B12 in the small intestine. Subsequently, all people with moderate CG or CG in the stomach are at risk of vitamin B12 deficiency, which is often associated with hyperhomocysteinemia. Vitamin B12 is a necessary co-factor for the synthesis of methionine, which, in turn, plays a key role in the methylation of homocysteine to methionine in all cells, especially in brain cells.

**Role of the organism's genetic susceptibility to H. pylori infection.** Differences in the carcinogenic potential of H. pylori strains are currently considered proven. The combination of the virulence of the microorganism and the genetic susceptibility of the host leads to more severe chronic inflammation and more rapid progression of gastric cancer, at least for the intestinal type [24, 26]. However, there are no studies of the clinical significance of genotyping of H. pylori strains in terms of diagnosis and monitoring of precancerous conditions/lesions of the stomach. The issue of genes and genetic changes, as well as their consequences for carcinogenesis of the stomach, has been repeatedly considered, although their role was not always clear. Due to the fact that 50% of the world's population is infected with H. pylori, only a small fraction, less than 2%, develop gastric cancer [20]. With trophic gastritis associated with H. pylori, hyperplastic polyps are often found in 25% of cases, however, their malignant transformation is rarely observed — in less than 3% of cases [24].
Chronic inflammation caused by H. pylori over time leads to the loss of the normal architectonics of the gastric mucosa, the destruction of the gastric glands, their replacement by fibrous tissue and intestinal epithelium. These processes are observed in half of H. pylori-positive patients and are localized in the areas of greatest inflammation. The risk of atrophy depends on the activity and prevalence of chronic inflammation. In patients with reduced acid production (hypochlorhydria), rapid colonization of the entire surface of the stomach is observed.

An outstanding observation was the detection of gastric cancer in patients with a history of gastric ulcer, in contrast to patients with a history of duodenal ulcer. The hypothesis was confirmed that in patients with a stomach ulcer, in contrast to patients with a duodenal ulcer, a decrease in the secretion of hydrochloric acid, pangastritis, intestinal metaplasia was found. The number of sites with loss of gastric glands and intestinal metaplasia increases over time and, although they are not realized with the development of clinical symptoms (asymptomatic in 90% of cases), they significantly increase the risk of developing stomach cancer.

The main determinant of the pronounced degree of inflammation is the content of CagA virulence factor. In particular, a significant part of H. pylori strains contains the CagA gene, which is a marker of cytotoxicity and is responsible for the production of the so-called CagA protein. A meta-analysis of 16 case-control studies showed that among H. pylori-infected patients, infection with CagA-positive (CagA +) strains increases by 1.64 times the risk of stomach cancer [25]. Bacterial virulence factors such as CagA forms with multiple EPIYA-C segments and strains with harbor VacA s1 and mid-region m1 signaling regions are also associated with an increased risk of gastric cancer [25].

The remaining pathogenetic islets (PAIs) of the cytotoxin (Cag) -based genes are virulence factors that also include vacuolization toxin (VacA), blood group antigen binding adhesin (BbA) and external inflammatory protein (OipA). These proteins are encoded by a 40 kilobase DNA segment, which includes a
group of about 30 genes, including Type IV secretion system components. Carcinogenesis is caused not only by genetic abnormalities (changes in the DNA sequence), but also by epigenetic changes (a violation of DNA methylation is often observed in gastric epithelial cells with CG).

The role of genetic polymorphism of interleukins. In recent years, the role of genetic polymorphism of interleukins (IL) in the pathogenesis of gastric carcinogenesis has been extensively studied. First of all, IL-β, an IL-1 receptor antagonist (IL1RA), IL8, IL10 and TNF-α, which play an important role in the inflammatory response to H. pylori infection and inflammation of the gastric mucosa, which leads to atrophy of the mucous membrane and progression of gastric cancer, are described. The association of the risk of developing gastric cancer with the IL-1 genotypes (IL-1B-511 T, IL-1B-31 T, and the genotype *2/*2 of the IL-1 receptor antagonist with an odds ratio of 2.5; 2.6 and 3 was confirmed, 7 for the development of gastric cancer in homozygous carriers of these alleles compared to non-carriers [18, 24]. A relationship was found between IL-1β and IL-1RN * 2 with a risk of gastric cancer in white people, but not in Asian people [10, 13, 15]. L. Gutierrez-Gonzalez, NA Wright [12] showed zero association in both groups. K. Nozaki, N. Shimizu, Y. Ikehara [15] found an increased risk of gastric cancer for carriers of IL-RN * 2 specific to non-Asian populations cancer and distal cancer: For the Asian population, a reduction in risk was observed in carriers of IL-1β-31C. People of the white race who are carriers of TNF-α-308A have an increased risk of developing stomach cancer [5].

Functional polymorphisms of Toll-like type 4 receptors (TLR4), which are involved in the recognition of H. pylori, have also been shown to underlie the host immune response and are associated with gastric mucosa damage in people infected with H. pylori. In particular, carriers of TLR4 + 896A> G polymorphism have a more pronounced gastric atrophy and degree of inflammation, as well as an increased risk of developing non-cardiac gastric cancer [11].
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Risk factors contributing to the transformation of chronic atrophic gastritis into gastric cancer are analyzed. Detection and monitoring of patients with precancerous conditions/lesions (precancerous changes), proper screening of H. pylori make early diagnosis of gastric cancer real. Features of precancerous conditions are given in order of increasing risk of developing gastric cancer. Adenomatous polyps of the stomach take the first place. Subsequent precancerous conditions include: cancer of the operated stomach, Menetria disease (hypertrophic gastropathy), B₁₂-deficient anemia, and gastric ulcer. A definition of intestinal metaplasia subtypes is proposed as a risk factor for gastric cancer, dividing into complete and incomplete one, taking into account reduction in the expression of gastric mucins MUC1, MUC5AC and MUC6. Currently, the development of gastric cancer (mainly of the “intestinal type”) is considered as a multistage process involving the sequence of mucosal change, such as chronic inflammation, atrophy, intestinal metaplasia, dysplasia and adenocarcinoma. Role of the organism’s genetic susceptibility to H. pylori infection, factors of pathogenicity contributing to epithelial metaplasia, are analyzed. Role of Toll-like type 4 receptors (TLR4) involved in the recognition of H. pylori is clarified. It is with this type of receptors that the development of an excessive immune response of the host is associated, resulting in damage to the mucous membrane in H. pylori-infected individuals. In particular, carriers of TLR4+896A> G polymorphism have a more severe atrophy of the stomach and degree of inflammation, as well as an increased risk of non-cardiac gastric cancer.