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MODERN PRESENTATION OF IMMUNOPATHOGENESIS OF CHRONIC GASTRITIS AND ITS SIGNIFICANCE IN CARCINOGENESIS

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✓ ***Resume***

In the review risk factors which transformations chronic atrophic a gastritis in a stomach cancer promote are analyzed. The characteristic of precancer conditions as increase in risk of development of a cancer of a stomach is given. Processes of a chronic inflammation, an atrophy, intestinal metaplasia, displasia and risk of formation adenocarcinoma of stomach are estimated. The role of a genetic susceptibility of an organism to infected H pylori, the factors of its pathogenicity promoting metaplasia epithelium is analyzed. It is proved that the combination virulence a microorganism and a genetic susceptibility of the owner conducts to heavier chronic inflammation and faster progressing of a cancer of a stomach, at least, for intestinal type the role of genetic polymorphism interleukins in pathogenesis gastric carcinogenesis is revealed. Also role Toll-like of receptors 4 types (TLR4), participating in recognition H. pylori is established. Development of the superfluous immune answer of the owner is connected with receptors of this type, leading to damage of a mucous membrane at H. pylori-infected persons. In particular, carriers TLR4+896A>G polymorphism have heavier atrophy of a stomach and inflammation degree, and also the raised risk a stomach cancer

Key words: chronic gastritis, stomach mucous membrane, stomach cancer, intestinal metaplasia, an atrophy, Helicobacter pylori, gastrin, pepsinogen, interleukin.

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЕ ИММУНОПАТОГЕНЕЗА ХРОНИЧЕСКОГО ГАСТРИТА И ЕГО ЗНАЧЕНИЕ В КАНЦЕРОГЕНЕЗЕ

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✓ ***Резюме***

Проанализированы факторы риска, способствующие трансформации хронического атрофического гастрита в рак желудка. Дана характеристика предраковых состояний в порядке увеличения риска развития рака желудка. Оценены процессы хронического воспаления, атрофии, кишечной метаплазии, дисплазии и риск формирования аденокарциномы желудка. Проанализирована роль генетической восприимчивости организма к инфицированности H. pylori, факторы его патогенности, способствующие метаплазии эпителия. Доказано, что сочетание вирулентности микроорганизма и генетической восприимчивости хозяина ведет к более тяжелому хроническому воспалению и более быстрому прогрессированию рака желудка, по крайней мере, для кишечного типа. Выявлена роль генетического полиморфизма интерлейкинов в патогенезе желудочного канцерогенеза. Также установлена роль Toll-like рецепторов 4 типа (TLR4), участвующих в распознавании H. pylori. Именно с рецепторами этого типа связано развитие избыточного иммунного ответа хозяина, приводящее к повреждению слизистой оболочки у H. pylori-инфицированных лиц. В частности, носители TLR4+896A>G полиморфизма имеют более тяжелую атрофию желудка и степень воспаления, а также повышенный риск некардиального рака желудка.

Ключевые слова: хронический гастрит, слизистая оболочка желудка, рак желудка, кишечная метаплазия, атрофия, хеликобактер пилори, гастрин, пепсиноген, интерлейкин.

SURUNKALI GASTRIT IMMUNOPATOGENEZI HAQIDA ZAMONAVIY QARASHLAR VA UNING KANTSEROGENEZDAGI AHAMIYATI

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Surunkali atrofik gastritni oshqozon saratoni kasalligiga aylantiradigan xavf omillari tahlil qilingan. Oshqozon saratoni rivojlanish xavfini oshirish uchun rak oldi shartlarning xarakteristikasi berilgan. Surunkali yallig'lanish, atrofik, ichak metaplasiyasi, displaziya va oshqozon adenokarsinomasi xavfi baholangan. H. pylori infektsiyasiga genetik ta'sirga ega bo'lgan organizmning roli, uning epiteliya metaplazasiga yordam beruvchi patogenezi omillari tahlil qilingan. Mikroorganizmlarning virusli kasalligi va xo'jayin genetik sezuvchanligining kombinatsiyasi shubhali surunkali yallig'lanish va oshqozon-ichak saratoni tez rivojlanishi, hech bo'lmasa ichak tipi uchun olib keladi. Oshqozon kantserogenezining patogenezida interleykinlarning genetik polimorfizmining roli aniqlandi. Shuningdek, H. pylori tan olinishida ishtirok etgan Toll-like 4 retseptorlari (TLR4) ning roli ham aniqlandi. Haddan tashqari xo'jayin immunitetining rivojlanishi ushbu turdagi retseptorlari bilan bog'liq bo'lib, natijada H. pylori bilan kasallangan odamlarda shilliq qavat zararglanishiga olib keladi. Qisman, TLR4 + 896A> G polimorfizmining tashuvchilari oshqozon atrofiyasi va yallig'lanish darajasi, shuningdek, kardial bo'lmagan oshqozon saratoni xavfini oshiradi.

Kalit so'zlar: surunkali gastrit, oshqozon shilliq qavati, oshqozon saratoni, ichak metaplasiyasi, atrofiya, Helicobacter pylori, gastrin, pepsinogen, interleykin.

Relevance

Over the course of a number of years of our own research, the issues of immunopathogenesis of acute and chronic gastritis (CG), peptic ulcer disease have been studied based on literature data. However, the issues of the relationship between chronic atrophic gastritis (CAH) and the risk of developing adenocarcinoma of the stomach remained untouched, and, moreover, insufficient attention is paid to this in clinical practice. It was found that the risk of developing stomach cancer increases exponentially depending on the stage and severity of atrophic gastritis. At the same time, in patients with severe atrophy, it increases approximately 9-16 times compared to the risk in people with healthy gastric mucosa (GAS). HCG is the most common (50-80%) disease of the gastrointestinal tract among the adult population of the world. CG suggests the presence of a chronic pathological process, which is morphologically characterized by inflammatory and dystrophic changes in the coolant with symptoms of impaired cellular renewal, progressive atrophy, functional and structural rearrangement with various clinical signs.

Self-diagnosis of chronic hepatitis is of no great direct clinical significance. According to the classification concept, a purely morphological approach is embedded in the concept of HG, and none of the four modern classifications ("Sydney" 1990; "Houston" 1994, modified Sydney system of 1990; classification OLGA-2008 and classification OLGIM-2010) does not contain a section concerning assessment of clinical manifestations. This is partly due to the often asymptomatic course of chronic hepatitis, and if any clinical manifestations do occur, they are usually associated with concomitant functional, primarily dyskinetic gastroduodenal disorders.

The conceptual view of chronic hepatitis in foreign gastroenterology from a purely morphological standpoint is explained by the need for early screening of dysregenerative-dystrophic processes and the severity of the progression of structural changes in the mucous membrane, which have a certain unfavorable prognosis. In particular, atrophy and intestinal metaplasia, common pathological changes, constitute the background against which epithelial dysplasia and intestinal adenocarcinoma of the stomach develop [1, 2, 4].

Today there is no doubt about the association between H. pylori and stomach cancer. Back in 1994, the International Agency for Research on Cancer (IARC) recognized this infection as a 1st order carcinogen due to its epidemiological connection with gastric adenocarcinoma and gastric MALT lymphoma [3, 9].

Of particular interest is the cancer "gastritis phenotype", chronic atrophic multifocal gastritis, which occurs in countries with a high incidence of gastric cancer and is a morphological phenotype and the result (with a few exceptions) of

prolonged H. pylori infection in more than half of infected individuals [4, 8]. Only less than 5-10% of cases of CAH are autoimmune (type A, diffuse gastric body) associated with B12-deficiency anemia. Taking into account the fact that coolant atrophy can occur in 1-5% of cases in persons under 30 years of age [5, 7], CAH is currently an important medical and social problem. In Finland, moderate to severe chronic atrophic gastritis is diagnosed in almost 10% of asymptomatic individuals or in patients with dyspepsia over 50 years of age [20]. At the same time, despite the general trend 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 towards an increase in the incidence of gastric cancer (intestinal form) in young people [10-12]. Thus, detection and monitoring of patients with previous precancerous conditions / lesions (precancerous changes), timely screening of H. pylori can lead to early diagnosis of gastric cancer. However, there are no clear recommendations for a uniform approach to the management of these patients. At the same time, the standardization of the management of patients with precancerous conditions will identify those at greatest risk. In addition, it is necessary to analyze both the main sections of the European clinical guidelines for the management of patients with precancerous conditions and lesions in the stomach (MAPS 2012) and new data on the immunopathogenesis of acute and chronic hepatitis.

Precancerous conditions. It is generally accepted that gastric adenocarcinoma develops in the pathologically altered mucous membrane. In this case, HG is always considered as a mandatory initial link. Japanese experts and a committee of the World Health Organization proposed to distinguish between precancerous conditions and precancerous changes in the cutting fluid [13, 15]. The first concept is clinical, associated with an increased risk of stomach cancer, the second is microscopic pathology (morphological changes in tissues) - areas where cancer develops more often than in normal tissues. Thus, precancerous conditions are diseases that can lead to the development of cancer.

If you arrange all precancerous conditions in order of increasing risk of cancer, then adenomatous polyps of the stomach (polyps that are benign glandular tumors - adenomas) should be put in first place. Such polyps become malignant in 60-70% of cases. Another variant of stomach polyps, the so-called hyperplastic polyps, on the contrary, turn into cancer extremely rarely - the probability of malignancy of these polyps is small and is found in 0.5% of cases; the second place should be given to HAG. Due to the wide prevalence of this disease, hCG occupies one of the leading places in the structure of precancerous conditions. Subsequent precancerous conditions include:

- cancer of the operated stomach (in persons who have previously undergone surgery on the stomach, the incidence of stomach cancer increases by 3-4 times);

- Menetrie's disease (hypertrophic gastropathy) (transformation into stomach cancer is observed in 15% of cases); - B12-deficiency anemia (malignancy in 1-10% of cases); - stomach 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, tk. cases of morphological verification of cancer in epithelialized (healed) "ulcers" have become more frequent. There are no obvious endoscopic signs of malignancy (malignancy). At the site of such an ulcer, normal granulation tissue and a mucous membrane can form, into which a tumor grows again, which will create an imitation of an exacerbation of a peptic ulcer. In fact, we are talking about primary ulcerative cancer and a tendency in the early stages to epithelialization (healing).

Precancerous changes are histologically proven dysplastic changes in the coolant, indicating the progression of the process towards malignant growth, but not sufficient to establish cancer at the moment.

Currently, the development of stomach cancer (primarily of the "intestinal type" is considered as a multi-stage process, including a sequence of changes in the mucous membrane: chronic inflammation, atrophy, intestinal metaplasia, dysplasia and adenocarcinoma. According to the R. Sorrea cascade, within 30 years, 50% of those infected with H. pylori develop atrophy of the coolant, 40% have intestinal metaplasia, 8% have dysplasia, and 12% have gastric adenocarcinoma.

Atrophy is the loss of gastric glands and their replacement by metaplastic epithelium or fibrous tissue. It is known that 25-75% of all types of stomach cancer occur on the background of CAH, which occupies one of the leading places in the structure of precancerous conditions. Approximately 10% of patients with CAH develop stomach cancer within 15 years. The risk of developing stomach cancer is increased by 18 times in patients with severe atrophic gastritis of the antrum. As a risk factor for gastric cancer, atrophic gastritis of the antrum and body is independent in multifocal atrophic gastritis (atrophic gastritis of both departments). The

overall risk increases to an extreme degree [10, 16]. Among patients with gastric cancer, normal mucosa is extremely rare. The steady progression of mucosal atrophy in persons suffering from chronic hepatitis does not in itself lead to a deterioration in the general condition of the patient, but it may be a background for the development of other more serious diseases. The development of intestinal metaplasia and subsequent dysplasia is a key moment in the development of cancer and lymphoproliferative processes in the stomach.

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

As a risk factor for gastric cancer, it is proposed to define the subtypes of intestinal metaplasia, dividing into complete and incomplete. When complete ("small intestine" or type I) goblet and absorbing cells are detected, there is a decrease in the expression of gastric mucins MUC1, MUC5AC and MUC6. When incomplete ("small intestine" or type IIA / II, and "colonic" 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 used classifications also take into account the presence of Paneth cells (complete metaplasia) or crescent-shaped architectural changes, dedifferentiation, and the absence of Paneth cells (incomplete metaplasia), as well as the nature and type of mucin produced. Another picture of metaplasia has been described, called "metaplasia with the expression of an antispasmodic peptide" - MESP. It is characterized by the impression of the antispasmodic polypeptide TFF2, which is associated with atrophy of the acid-producing zone. MESP is naturally formed in the body and fundus of the stomach. And it probably has some common characteristics with pseudopyloric metaplasia, and a strong association with chronic H. pylori infection and gastric adenocarcinoma [20].

Gastric dysplasia is the penultimate stage in the sequence of gastric carcinogenesis / non-progressive changes and is defined as histologically unambiguous tumor epithelium without signs of invasion, and, thus, is directly precancerous tumor lesion [14]. The correct diagnosis and degree of dysplasia are critical as they determine both the risk of malignant transformation and the risk of metachronous gastric cancer. The indicated rates of progression of gastric cancer from dysplasia vary from 0 to 73% per year [13-15].

"Intestinal" adenocarcinoma of the stomach is the culmination of the sequence "inflammation - atrophy - metaplasia - dysplasia - cancer". This multistage cascade of gastric carcinogenesis may be a process that develops from a normal mucous membrane through chronic non-atrophic gastritis, atrophic gastritis and intestinal metaplasia to dysplasia and gastric cancer [20].

Pathophysiology of the stomach and secretion of hydrochloric acid in chronic atrophic gastritis. Atrophy naturally implies a violation of the secretory function and physiology of the gastric mucosa. Atrophy of the mucous membrane of the body of the stomach leads to a decrease in the secretion of hydrochloric acid, while atrophic changes in the antrum of the stomach lead to disturbances in the secretion of gastrin-17 by G-cells (G-17). In CAH, dysregulation of acid and pepsinogen (PG) secretion, and hence the feedback mechanism, leads to varying degrees of hypochlorhydria or even achlorhydria, and hypo- or hypergastrinemia, depending on whether there is atrophy in the antrum of the stomach or not. The degree of histological changes in CAH 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. With severe atrophic gastritis of the gastric body and normal mucous membrane of the antrum, intragastric acidity decreases, the secretion of G-cells of the antrum is not suppressed by the feedback mechanism, which leads to hypergastrinemia, while the level of G-17 in serum in some individuals can increase to several hundred pmol / l.

Atrophy is accompanied by the appearance of metaplasia of the glands in the atrophically altered mucosa (i.e., pseudopyloric metaplasia with / without intestinal metaplasia). Metaplastic glands do not secrete hydrochloric acid or G-17, but to varying degrees acquire the properties of glands of the mucous membrane of the small or large intestine. As atrophy progresses, the metaplastic

glands and epithelium may become increasingly immature, reflecting the transition from complete intestinal metaplasia (small intestinal type) to intestinal metaplasia of immature or incomplete type (large intestinal type). This transition is believed to reflect the increased risk of gastric cancer in CAH. The states of hypochlorhydria or achlorhydria in the stomach create conditions for the colonization of bacteria other than Helicobacter pylori, some of which can produce mutagenic and carcinogenic substances.

In addition to a decrease in the release of hydrochloric acid, CAH from the body of the stomach leads to a violation of the secretion of an internal factor by acid-forming cells, which is necessary for the normal absorption of vitamin B12 in the small intestine. Subsequently, all persons suffering from moderate to moderate CAH of the gastric corpus fall into the risk group for vitamin B12 deficiency, which is often associated with hyperhomocysteinemia. Vitamin B12 is an essential co-factor in the synthesis of methionine, which in turn plays a key role in the methylation of homocysteine to methionine in all cells, especially in the brain.

The role of the organism's genetic susceptibility to H. pylori infection. Differences in the carcinogenic potential of H. pylori strains are now considered proven. It is believed that the combination of the virulence of the microorganism and the genetic susceptibility of the host leads to more severe chronic inflammation and faster progression of gastric cancer, at least for the intestinal type [12, 16]. However, there are no studies of the clinical significance of genotyping of H. pylori strains in terms of diagnosis and monitoring of precancerous conditions / gastric lesions. The issue of genes and genetic changes, as well as their consequences for gastric carcinogenesis, has been repeatedly considered, although their role was not always clear. With 50% of the world's population infected with H. pylori, only a small part - less than 2% - develop stomach cancer [20]. With trophic H. pylori-associated gastritis, hyperplastic polyps often appear in 25% of cases, however, their malignant transformation is rarely observed - in less than 3% of cases [16].

Chronic H. pylori-induced inflammation over time leads to a loss of the normal architectonics of the mucous membrane, with the destruction of the gastric glands, replacing them with 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 developing 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 patients with gastric ulcer, in contrast to patients with duodenal ulcer, exhibit decreased secretion of hydrochloric acid, pangastritis, progressive CAH and intestinal metaplasia. The number of areas with loss of gastric glands and intestinal metaplasia increases over time and, although they do not develop into the development of clinical symptoms (in 90% of cases, it is asymptomatic), significantly increases the risk of developing stomach cancer.

The main determinant of the expressed degree of inflammation is the content of the virulence factor CagA. 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 increased the risk of stomach cancer by 1.64 times [15]. Bacterial virulence factors such as CagA-forms with multiple EPIYA-C segments and strains with harbor VacA signaling region type s1 and mid-region m1 are also associated with an increased risk of gastric cancer [13].

Other cytotoxin-associated genes (Cag) pathogenicity islands (PAIs) are virulence factors that also include vacuolating toxin (VacA), blood group antigen-binding adhesin (BabA), and external inflammatory protein (OipA). These proteins are encoded in a 40 kb DNA segment that contains a group of about 30 genes, including components of a type IV secretion system. Carcinogenesis is caused not only by genetic abnormalities (changes in the DNA sequence), but also by epigenetic changes (violation of DNA methylation is often observed in gastric epithelial cells in chronic atrophic gastritis).

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 widely studied. First of all, IL-β, an antagonist of the IL-1 receptor (IL1RA), IL8, IL10, and TNF-α, are described, which play an important role in the inflammatory response to H. pylori infection and inflammation of the mucous membrane, which leads to mucosal atrophy and the progression of gastric cancer. Confirmed 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 , 7 for the development of gastric cancer in homozygous carriers of these alleles compared with non-carriers [18]. A relationship between IL-1β and IL-1RN * 2 with the risk of gastric cancer in Caucasians, but not in Asians, has been found [10, 13, 15]. L. Gutierrez-Gonzalez, N.A. 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 and distal cancer. In the Asian population, a reduction in risk was observed in carriers of IL-1β-31C. Caucasian people who carry TNF-α-308A have an increased risk of developing stomach cancer [5].

It has also been proven that functional polymorphisms of Toll-like type 4 receptors (TLR4) involved in the recognition of H. pylori underlie the excessive immune response of the host and is associated with damage to the mucous membrane in H. pylori-infected individuals. In particular, carriers of the TLR4 + 896A> G polymorphism have a more severe gastric atrophy and degree of inflammation, as well as an increased risk of noncardial gastric cancer [11].

Conclusion

It is necessary to take into account the role of the organism's genetic susceptibility to H. pylori infection, the factors of its pathogenicity, which contribute to epithelial metaplasia. It has been proven more than once that the combination of the virulence of the microorganism and the genetic susceptibility of the host leads to more severe chronic inflammation and faster progression of gastric cancer, at least for the intestinal type. According to recent studies, the role of genetic polymorphism of interleukins in the pathogenesis of gastric carcinogenesis has been revealed**.** The role of type 4 Toll-like receptors (TLR4) involved in the recognition of H. pylori has also been established. It is with receptors of this type that the development of an excessive immune response of the host is associated, leading to damage to the mucous membrane in H. pylori-infected individuals. In particular, carriers of the TLR4 + 896A> G polymorphism have a more severe gastric atrophy and degree of inflammation, as well as an increased risk of noncardial gastric cancer. These conclusions are the basis of our further scientific research in this direction.

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