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A.L. Loskutov, I.V. Loskutova
Luhansk State Medical University, Rubizhne

INNATE IMMUNITY IN OSTEOARTHRITIS IN COMORBIDITY WITH NON-ALCOHOLIC STEATOHEPATITIS IN PATIENTS WITH HELICOBACTER PYLORI INFECTION

e-mail: loskutov115@gmail.com; loskutovai115@gmail.com

The pathogenesis of comorbid pathology of joints and liver in patients infected with *Helicobacter pylori* is considered in the study. We examined 57 patients with osteoarthritis in comorbidity with non-alcoholic steatohepatitis, of whom 23 showed specific antibodies to *Helicobacter pylori* without clinical and instrumental manifestations of gastric and duodenal mucosa. The study revealed a decrease in phagocytic activity of monocytes, the number of populations of NK lymphocytes, which can be characterized as a lack of nonspecific reactivity in the examined patients. There was a significant decrease in phagocytic activity of monocytes with activation of nonspecific reactivity of the body (increase in the number of NK lymphocytes), growth of serum proinflammatory (IL-8, IL-12) cytokines, against the background of *Helicobacter pylori* infection in osteoarthritis in comorbidity with non-alcoholic steatohepatitis, indicating the presence of chronic systemic inflammation. The study of the level of cytokines and innate immune factors in the comorbid course of osteoarthritis and non-alcoholic steatohepatitis on the background of Helicobacter pylori infection can be used to predict the further progression of the inflammatory reaction in the liver, the intensity of immunopathological reactions in the joints and the development of pathogenetic therapy methods of the specified category of patients.

Key words: osteoarthritis, non-alcoholic steatohepatitis, Helicobacter pylori, innate immunity, phagocytic activity of monocytes, cytokines.

А.Л. Лоскутов, І.В. Лоскутова

СТАН ВРОДЖЕНОГО ІМУНІТЕТУ ПРИ ОСТЕОАРТРОЗІ В КОМОРБІДНОСТІ З НЕАЛКОГОЛЬНИМ СТЕАТОГЕПАТИТОМ У ХВОРИХ НА ХЕЛІКОБАКТЕРІОЗ

В статті розглянуто питання патогенезу коморбідної патології суглобів та печінки у хворих, інфікованих *Helicobacter pylori*. Обстежено 57 хворих на остеоартроз в коморбідності з неалкогольним стеатогепатитом, з яких у 23 осіб виявлено специфічні антитіла до *Helicobacter pylori* без клініко-інструментальних проявів ураження слизової оболонки шлунка та дванадцятипалої кишки. В результаті дослідження встановлено зменшення показників фагоцитарної активності моноцитів, кількості популяції NK-лімфоцитів, що можна характеризувати як недостатність неспецифічної реактивності організму в обстежених хворих. На фоні інфікування *Helicobacter pylori* при остеоартрозі в коморбідності з неалкогольним стеатогепатитом відмічалось суттєве зменшення показників фагоцитарної активності моноцитів з активацією неспецифічної реактивності організму (збільшення кількості NK-лімфоцитів), зростання сироваткових прозапальних (IL-8, IL-12) цитокінів, що свідчить про наявність хронічного системного запалення. Дослідження рівня цитокінів і факторів вродженого імунітету при коморбідному перебігу остеоартрозу та неалкогольного стеатогепатиту на фоні хелікобактеріозу можна використовувати для прогнозування подальшого прогресування запальної реакції в печінці, інтенсивності імунопатологічних реакцій у суглобах та розробки методів патогенетичної терапії означеної категорії хворих.

Ключові слова: остеоартроз, неалкогольний стеатогепатит, Helicobacter pylori, вроджений імунітет, фагоцитарна активність моноцитів, цитокіни.

The work is a fragment of the research project "Features of pathogenesis and optimization of treatment of patients with comorbid pathology on the background of Helicobacter pylori infection", state registration No. 0118U000822.

Despite the urgency of the problem, there is still no consensus on the pathogenesis of osteoarthritis (OA). For a long time, OA was considered a non-inflammatory disease that is associated with degeneration of cartilage tissue, without its regeneration. Chronicity of the pathological process in the joint leads to the progression of the secondary alteration of hyaline cartilage, and the decay products of cartilage (fragments of collagen and proteoglycans) enter the synovial fluid, developing and intensifying the inflammatory response in the joint, which leads to a predominance of catabolic processes in the cartilage [9, 14]. The content of cytokines in the serum depends on the involvement of systemic immune responses to the

inflammatory response. It is believed that determining the level of interleukin-8 (IL-8) is more informative than studying the level of C-reactive protein to predict the severity of the disease, because the peak of its concentration occurs earlier than C-reactive protein [2, 15]. At the same time, innate immunity is an important component of the immune response in any process, but in OA this aspect is poorly understood.

The pathogenetic role of Helicobacter pylori infection (H. pylori) in the development of extra-gastroduodenal diseases and conditions is currently being actively studied. Using various diagnostic methods, the microorganism was detected in the tissues of the liver, gallbladder, colon, skin, arteries, etc. [11]. It has been proven that H. pylori infection promotes the activation of both local and systemic inflammatory processes and can be considered as a possible additional risk factor for the formation and/or exacerbation of somatic pathology. H.pylori has been shown to inhibit phagocytosis. Moreover, the insufficiency of the phagocytic link is not so much in reducing the antibacterial activity of macrophages, as in disrupting the process of presentation of H.pylori antigens by dendritic cells. This is a key factor for the inclusion of adaptive immunity to protection and the corresponding outcome of the infectious process [4]. Therefore, Helicobacter pylori infection becomes chronic, and inflammatory activity may increase under the influence of adverse factors (stress, alcohol, the presence of chronic diseases, etc.) [5]. Activation of macrophages and increase in their formation of proinflammatory cytokines contributes to further invasion of H. pylori, and the microorganism, in turn, causes Th1-type changes in the immune status [4].

In recent years, the role of stimulation of innate immune receptors (Toll-like receptors) and the associated increase in cytokine secretion as a key pathogenetic mechanism for the development of non-alcoholic steatohepatitis (NASH) has been discussed [8, 13]. Cytokines are able to cause all the classic histological characteristics of NASH, including hepatic necrosis, neutrophil chemotaxis, and also participate in the regulation of the development of inflammatory reactions of liver tissue with the development of cholestasis and fibrosis [1].

The purpose of the study was to establish the features of innate immunity, the level of pro-inflammatory cytokines in the blood of patients with osteoarthritis in comorbidity with non-alcoholic steatohepatitis and to compare the obtained data with immune disorders in the comorbidity of the degenerative and dystrophic process in the joints with non-alcoholic steatohepatitis on the background of Helicobacter pylori infection.

Materials and methods. 57 patients with idiopathic OA (according to the International Classification of Diseases (ICD10 – M15-M19)) in the comorbid course with NASH (according to ICD-10 – K75.8) were examined for the study. All patients were aged 37 to 59 years (mean age 46.1±2.4 years), of which there were 23 men (40.4 %) and 34 women (59.6 %).

The examined patients were more likely to have lesions of the distal interphalangeal joints of the hands (36 people), knee joints (28 people), less often – hip joints (16 people) and elbow joints lesions (8 people). There were 14 patients with monoarthritis, 27 patients with oligoarthritis and 7 patients with polyarthritis. Radiological signs of degenerative and dystrophic process in the joints of degrees I and II were found in all the examined patients who were under observation: degree I – 21 patients, degree II – 32 patients (according to Kellgren-Lawrence Classification of Osteoarthritis) [12]. Physical and ultrasound examination of the abdominal cavity, according to the results of biochemical parameters characterizing the functional state of the liver, revealed chronic pathology of the liver and biliary system (LBS) in the stage of unstable or persistent remission in all examined patients. In the 23 patients included in the observation, the presence of total specific IgA and IgG antibodies to H.pylori in the blood was detected in diagnostic titers. However, these patients showed no signs of damage to the gastric and/or duodenal mucosa during esophagogastroduodenoscopy (EGD).

Exclusion criteria were severe infections (tuberculosis, viral hepatitis B and C), toxic hepatitis (alcoholic, opioid), acute and chronic renal failure, erosive and ulcerative diseases of the stomach or duodenum, autoimmune diseases of the joints, diseases of the cardiovascular system, diabetes mellitus and obesity (Body Mass Index did not exceed 28 kg/m^2).

In examining patients, we studied the results of clinical blood test with the count of leukocytes and their varieties in percentage terms (leukocyte formula) using the method of capillary photometry on the Auto Hematology Analyzer "MicroCC–20Plus" (USA).

Confirmation of Helicobacter pylori presence was performed by examining the total titers of antibodies of IgA and IgG classes to the complex of H.pylori antigens using a quantitative method of enzyme-linked immunosorbent assay (ELISA) using the "ImmunoComb® II Helicobacter pylori IgG" kit manufactured by ORGENICS LTD (Israel).

Studies of phagocytic activity of monocytes (PAM) were performed by the cup plate method [3] using the museum culture of daily S.aureus (strain 505). PAM indices were calculated: phagocytic number

(PN) – the number of absorbed bacterial cells per 1 monocyte, phagocytic index (PI) – the percentage of phagocytic monocytes, attraction index (AI) – the number of microbial cells fixed per 100 monocytes and digestion index (DI) – the percentage of digested microbial cells from their total number absorbed by 100 monocytes.

Serum IL-8 and IL-12 content were determined by quantitative ELISA on an Immunochem-2100 microplate analyzer (HTI, USA) using Bender MedSystems kits (Austria). Blood was taken in vacutainer on an empty stomach from the ulnar vein. Quantitative evaluation of the results was carried out by constructing a calibration curve that reflects the dependence of the optical density on the concentration for a standard antigen and allows comparing the studied samples with it. The research was carried out according to the manufacturer's method.

Statistical processing of the obtained results was performed by the method of variation statistics for unrelated observations using the software package Statistica 6.0; the distribution of almost all variation series was subject to the criteria of normality, so Student's t-test was used to determine the significance of differences. The difference was considered significant at $p<0.05$.

Results of the study and their discussion. The conducted studies have shown that the examined patients have no changes in the indicators in the clinical blood test. The number of white blood cells did not exceed the reference norm and averaged 7.4±0.6 g/L (with a norm of 5.6±0.8 g/l; p=0.08); the content of monocytes was on average 7.0±0.5 % (with a norm of 5.9±0.7 %; p=0.21), and their number was 0.48±0.09 g/L (with a norm of 0.33±0.09 g/l; p=0.24). The content of white blood cells in OA in combination with NASH on the background of Helicobacter pylori infection was 8.3±0.5 g/L, and in patients without contamination H.pylori – 6.4±0.8 g/L, that is, the number of white blood cells in both groups of examined patients did not exceed the physiological norm (p=0.02 and p=0.48, respectively) and statistically did not differ (p=0.08). The relative level of monocytes in the peripheral blood in comorbid pathology of LBS and OA without Helicobacter pylori infection was 6.6±0.7 % (p=0.48), and in patients with the presence of antibodies to H.pylori – 7.3±0.5 % (p=0.11), that is, it remained within the reference norm. However, the content of monocytic cells in OA in comorbidity with NASH was insignificantly higher in patients without Helicobacter pylori (1.11 times; p=0.42). The number of monocytic-phagocytic cells averaged 0.47±0.11 g/L in both groups of subjects. Moreover, their number in the degenerative-dystrophic process in the joints in comorbidity with NASH, regardless of the presence or absence of H.pylori contamination, unreliably exceeded the limits of the physiological norm (by 1.42 times; p=0.36–0.33). The content of white blood cells and the value of the components of the white blood cell formula did not change statistically in patients with OA with comorbid pathology of LBS and joints on the background of Helicobacter pylori infection in comparison with patients without H.pylori contamination (table 1).

Table 1

Innate immunity indices in the peripheral blood of patients with OA in comorbidity with NASH (M±m)

Indices	Norm	Examined patients with OA in comorbidity with NASH (n=57)		p
		without antibodies to H.pylori (n=36)	with antibodies to H.pylori (n=23)	
White blood cells, g/L	5.6±0.8	6.4±0.8	7.3±0.7	=0.40
Monocytes, % g/L	5.9±0.7	7.3±0.5	6.6±0.7	=0.42
	0.33±0.09	0.47±0.12	0.47±0.11	=1.0
NK cells, % g/L	12.3±1.1	11.6±1.2	14.0±0.9	=0.08
	0.34±0.08	0.23±0.09	0.37±0.05	=0.18
PAM				
PI, %	28.6±0.8	21.8±1.1***	24.5±1.2***	=0,10
PN	4.0±0.15	3.0±0.08***	3.4±0.09***	<0.001
AI, %	12.0±0.6	9.8±0.5**	14.2±0.7**	<0.001
DI, %	26.5±0.9	22.7±0.6***	18.7±0.9***	<0.001

Note: the probability of results is calculated between the indicators in the group and the norm at: p<0.01 – ** and p<0.001 – ***; p – the probability of results between the indicator in the groups of subjects.

In our studies, it was found that 51 subjects (89.5 %) had a violation of the macrophage-phagocytic system, which was manifested by a decrease in 40 patients (78.4 %) and an increase in 11 patients (35.3 %). In the examined patients with degenerative-dystrophic processes in the joints in the comorbidity with NASH, the value of AI tended to decrease (11.0±0.5 % with a norm of 12.0±0.6 %; p=0.20). At the same time, some patients (7 people – 12.3 %) showed an increase in the AI index (1.38 times; p<0.001), while most patients (30 people – 52.6 %) showed a decrease in the studied index. Individual analysis of the rate of attraction of microbial bodies on monocytes in the comorbid process in the joints and LBS in patients without Helicobacter pylori infection indicated a decrease in AI by 1.22 times (p<0.01), which was 9.8±0.5 %, while in the presence of antibodies to H.pylori on the contrary, there was a tendency to increase

(1.18 times; p<0.01). OA in comorbidity with NASH revealed a decrease in active phagocytes, which averaged 23.2±0.9 % (with a norm of 28.6±0.8 %; p<0.001), and the absorption coefficient – up to 3.2±0.07 (with a norm of 4.0±0.15; p<0.001). That is, both parameters were 1.23 times and 1.25 times less than the norm, respectively. In patients with chronic joint pathology and LBS without Helicobacter pylori infection, the PI was 21.8±1.1 %, which is 1.31 times lower than normal (p<0.001), and the PN value was 3.0±0.2, i.e. the multiplicity of decrease was 1.33 times (p<0.001). The presence of H.pylori contamination showed a less pronounced decrease in PI and PN (1.17 times; p<0.001). Large changes in PAM indicators occurred during the digestion phase in terms of DI values. In patients with degenerative-dystrophic process in the joints in comorbidity with NASH, the DI value decreased by 1.34 times (with a norm of 26.5±0.9 %; p<0.001), which averaged 19.8±0.7 %. Evaluating the changes in the last phase of PAM depending on the presence of antibodies to H.pylori, we found a more significant decrease in DI in patients with H.pylori contamination (1.42 times; p<0.001), whereas in the absence of an infectious agent, this index decreased in 1.17 (p<0.001). Comparing the PAM between the groups of examined patients with comorbid pathology of the joints and liver on the background of H. pylori infection and in the absence of contamination, it can be noted that in the presence of Helicobacter pylori the value of DI was lower by 1.21 times (p<0.001), while PI PN and AI increased by 1.12 times (p=0.10), 1.13 times (p<0.001) and 1.45 times (p<0.001), respectively.

The level of cells with the CD16+ phenotype in the examined patients with OA in comorbidity with NASH averaged 12.5±0.8 % (with a norm of 12.3±1.1 %; p=0.88), while the number of these cells tended to decrease (by 1.13 times) with a norm of 0.34±0.08 g/L (p=0.66). The content of NK-lymphocytes in the peripheral blood in OA in comorbidity with NASH in both groups of patients (regardless of H.pylori infection) did not exceed the reference norm: against the background of H.pylori infection – 14.0±1.0 % and in its absence – 11.6±0.9 %. However, in the presence of antibodies to H.pylori there was a tendency to increase the level of CD16+lymphocytes (by 1.14 times; p=0.26), while in patients without contamination with an infectious agent – a tendency to decrease (by 1.06 times; p=0.62). The number of NK cells in the blood of patients with antibodies to H.pylori averaged 0.37±0.09 g/L, that is, it remained normal (p=0.75). In patients with combined liver and joint pathology in the absence of Helicobacter pylori, the number of CD16+lymphocytes tended to decrease (by 1.48 times; p=0.37) and amounted to 0.23±0.09 g/L. Comparative group analysis of the obtained data did not reveal significant differences in NK lymphocytes, neither in percentage (p=0.08) nor in absolute quantity (p=0.18).

In patients with degenerative-dystrophic process in the joints in comorbidity with NASH (total number of examined patients), the content of serum IL-8 was 43.5±6.2 pg/ml (at a rate of 19.4±3.7 pg/ml, p<0.001), which was 2.24 times higher than the reference norm. The maximum content of IL-8 in the blood serum of patients with NASH in comorbidity with OA against the background of H.pylori infection was established (52.2±8.7 pg/mL), that is, the multiplicity of increase was 2.69 times (p<0.001). In patients in whom no antibodies to H.pylori were detected, the serum chemokine level increased more slowly (1.79 times; p<0.01) and averaged 34.8±6.1 pg/ml. Comparison of the level of IL-8 in the blood serum of patients between the groups showed an unlikely difference (1.5 times; p=0.11) (table 2).

Table 2

Serum cytokine values in patients with OA in comorbidity with NASH (M±m)

Indices	Norm	Examined patients with OA in comorbidity with NASH (n=57)		p
		without antibodies to H.pylor (n=36)	with antibodies to H.pylori (n=23)	
IL-8, pg/ml	19.4±3.7	34.8±6.1**	52.2±8.7***	=0.11
IL-12, pg/ml	70.2±3.3	115.8±9.8***	163.5±10.2***	<0.001

Note: the probability of results is calculated between the indicators in the group and the norm at: p<0.01 – ** and p<0.001 – ***; p – the probability of results between the indicator in the groups of subjects.

The level of IL-12 in the serum of the examined patients with OA in comorbidity with NASH averaged 139.6±9.7 pg/mL (at a rate of 70.2±3.3 pg/mL; p<0.001), which is almost twice the reference rate (table 2). Thus, in patients with comorbid pathology of the joints and LBS on the background of Helicobacter pylori infection, the content of IL-12 in the serum was 163.5±10.2 pg/mL, that is, the growth rate was 2.33 times (p<0.001). Moreover, it should be noted that 9 patients out of 23 (39.1 %) had hyperproduction of IL-12 (above 170 pg/mL). In patients without H.pylori infection, the concentration of IL-12 in the blood serum was 115.8±9.8 pg / mL, which is 1.65 times higher than the reference norm (p<0.001) and by 1.41 times (p<0.001) lower than in infected patients.

The presence of H.pylori in the patient's body as a stimulating infectious agent, in the comorbid course of OA and NASH, contributed to the activation of some chains of the process of phagocytosis (AI), which was regarded as the development of an inflammatory process in which activated phagocytes increase

their cytotoxic and phagocytic activity [4, 6, 10]. In a chronic pathological process in the joints and LBS, the activity of PAM (especially DI) decreases, which indicates a decrease in the functional reserve of phagocytes and characterizes the intensity of metabolic processes of cellular elements of the phagocytic link. Evaluation of phagocytic cell function is of great diagnostic importance in inflammation, given that the main phagocytes that are most important in anti-infective immunity are monocytes/macrophages [7]. Low levels of NK cells do not inhibit the infectious-inflammatory process and provoke the progression of the pathological process, both in the liver and in the joints [4, 6]. There was a high content of serum IL-8 in all patients, which increased the production of proinflammatory cytokines by mononuclear cells, hepatocytes, synovial cells with the formation of inflammation [6, 10]. It is known from the literature [4] that H.pylori, unlike other extracellular pathogens, is able to induce the synthesis of IL-12. The data obtained confirmed this thesis. Hyperproduction of IL-12 (above 170 pg/ml) in H.pylori contamination was regarded as excessive activation of the cell-mediated immune response with the possibility of developing autoimmune pathology.

Conclusions

1. In osteoarthritis in combination with non-alcoholic steatohepatitis during Helicobacter pylori contamination, the clinical blood test did not reveal quantitative changes in white blood cells and cells with phagocytic activity (monocytes).

2. In patients with a comorbid course of degenerative-dystrophic process in the joints and NASH, there are violations of non-specific reactivity of the body (according to PAM and the number of NK cells), which are most pronounced in the presence of an infectious agent (H.pylori), which indicates a decrease in the ability of hepatic macrophages to eliminate by phagocytosis metabolic products, toxins and pathogens.

3. In patients with OA in comorbidity with NASH on the background of Helicobacter pylori, the level of proinflammatory (IL-8 and IL-12) cytokines is significantly higher than in patients without H. pylori infection, which indicates the formation of an inflammatory process in the joints with accelerated destruction of the joint surface.

4. In further studies, it is planned to analyze the dynamics of indicators of non-specific reactivity of the body and serum cytokines because of the use of immunostimulants.

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