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INDICATIVE FEATURES OF TISSUE AND MICROBIAL SENSITIZATION IN THE PATHOGENESIS OF GENERALIZED PARODONTITIS ASSOCIATED WITH RHEUMATOID ARTHRITIS

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Ключові слова: *ревматоїдний артрит, генералізований пародонтит, реакція гальмування мігруючих лімфоцитів, тканинна алергія, стрептококовий антиген, стафілококовий антиген, синовіальний антиген*

Abstract. Indicative features of tissue and microbial sensitization in the pathogenesis of generalized parodontitis associated with rheumatoid arthritis. Proschenko A.M., Proschenko N.S., Reshetnyk L.L., Zelinskaya N.A., Chervonna N.V., Melnychyk T.A. *In the literature, there are not enough studies that reflect the role and place of tissue and microbial sensitization in patients with generalized parodontitis (GP) associated with rheumatoid arthritis (RA). In our opinion, the research of these components will help to better understand the etiopathogenetic mechanisms of development of GP against the background of RA, which will improve the formation of preventive and therapeutic measures for this disease treatment. The purpose of the research was to determine the location and integration features of tissue and microbial sensitization in the pathogenesis of generalized parodontitis associated with rheumatoid arthritis. Immunological studies were carried out in 335 people, who were divided into 4 groups: Group 1 – the main – consisted of 136 patients with GP on the background of RA; Group 2 – control – 71 people with GP without signs of RA; Group 3 – comparison – 128 people without GP, but with diseases of the musculoskeletal system not related to RA and Group 4 – 30 practically healthy people. To determine microbial and tissue sensitization, we used inhibition reaction of migrating lymphocytes with microbial antigens of streptococci and staphylococci, tissue antigens (bone and synovial). A high frequency of microbial sensitization to streptococcal and staphylococcal antigens was established in patients with GP on the background of RA and in patients with GP without signs of RA. The parodontal focus turned out to be an active focus of microbial sensitization in patients with GP associated with RA and in patients with GP without signs of RA. Established sensitization to bone antigen in a small number of patients (27-33%) with GP, which was significantly more frequent (61-80%) in patients with GP associated with RA, indicates that in the latter, allergy is to a greater extent due to tissue systemic damage to connective tissue than GP. However, a certain allergy to bone tissue in GP may indicate the inclusion of an immune component in the pathogenesis of GP. The presence of microbial and tissue sensitization in patients with GP and RA indicates that similar and cross antigens of streptococcal and staphylococcal microorganisms with connective tissue are a potential trigger for the development of both GP and RA, which is a reason to consider GP and RA comorbid diseases with similar pathogenetic mechanisms of development.*

Реферат. Індикативні особливості тканинної та мікробної сенсибілізації в патогенезі генералізованого пародонтиту, асоційованого з ревматоїдним артритом. Прощенко А.М., Прощенко Н.С., Решетник Л.Л., Зелінська Н.А., Червонна Н.В., Мельничук Т.А. *У літературі недостатньо досліджень, які відображають роль і місце тканинної та мікробної сенсибілізації у хворих на генералізований пародонтит (ГП), асоційований з ревматоїдним артритом (РА). Вивчення цих компонентів допоможе краще зрозуміти етіопатогенетичні механізми розвитку ГП на тлі РА, що покращить формування профілактичних та лікувальних заходів щодо захворювання. Метою дослідження було визначення місця та інтеграційних особливостей тканинної та мікробної сенсибілізації в патогенезі генералізованого пародонтиту, асоційованого з ревматоїдним артритом. Імунологічні дослідження були проведені в 335 осіб, які були розподілені на 4 групи: 1 група – основна – 136 хворих з ГП на тлі РА; 2 група – контрольна – 71 особа з ГП без ознак РА; 3 група – порівняльна – 128 осіб без захворювань пародонта, які мали захворювання опорно-рухового апарату не пов'язані з РА, та 4 група – 30 практично здорових людей. Для визначення мікробної та тканинної сенсибілізації використовували реакцію гальмування міграції лейкоцитів (РГМЛ) з*

мікробними антигенами стрепто- та стафілококів, тканинними антигенами (кістковим та синовіальним). Установлена висока частота мікробної сенсибілізації до антигенів стрепто- та стафілокока у хворих з ГП на тлі РА та в осіб з ГП без ознак РА. Пародонтальний осередок виявився активним вогнищем мікробної сенсибілізації у хворих на ГП, асоційований з РА, та у хворих на ГП без ознак РА. Установлена сенсибілізація до кісткового антигену в невеликої кількості хворих (27-33%) з ГП, яка значно частіше (61-80%) зустрічалась у хворих на ГП, асоційований з РА, свідчить про те, що в останніх тканинна алергія більшою мірою зумовлена системним ураженням сполучної тканини, ніж наявністю ГП. Визначена алергія до кісткової тканини при ГП може вказувати на включення імунного компонента в патогенезі ГП. Наявність мікробної та тканинної сенсибілізації у хворих на ГП при РА свідчить про те, що подібні та перехресні антигени мікроорганізмів стрепто- та стафілокока зі сполучною тканиною є потенційним тригером для розвитку як ГП, так і РА, що дає право вважати ГП та РА коморбідними захворюваннями зі схожими патогенетичними механізмами розвитку.

Diseases of parodontal tissues, including generalized parodontitis (GP) in recent years occupy one of the first places in the structure of dental diseases [1]. Thus, according to the latest epidemiological studies, the prevalence of GP is 80-100% with a steady tendency to increase in frequency of GP in young and working-age people with a stable gender and population advantage [2]. This circumstance causes serious concern of state, social, medical, scientific institutions [3]. The unaesthetic condition of the soft tissues of the parodontal complex, disturbed functional capacity of the chewing apparatus, which is due to early tooth loss, as well as the duration of the treatment of the disease, often with an unstable result, short periods of remission, as well as significant material and time costs, exert a cardinal influence on the psycho- emotional state of patients, distracting them from active work and personal life, creating deterioration of the patient's quality of life.

Often, the low effectiveness of the results of treatment of GP is largely explained by the lack of clear ideas about the cause-and-effect relationships of the occurrence and course of the disease. Despite the lack of fundamental ideas about the etiology and pathogenesis of GP, most researchers agree that qualitative and quantitative changes in the oral microbiome are a key paradigm of antigenic microbial attack on periodontal tissues [4, 5, 6, 7, 8]. Long-term expansion under the influence of changes in the microbiofilm activates osteoclastic processes, disrupting the coordination of remodeling towards the predominance of osteoresorption over osteosynthesis [9, 10, 11, 12, 13, 14]. The changed microbial biotope potentially provokes not only a high degree of microbial sensitization and endogenous intoxication of the body, but also forms a target for playing out the pathological process in GP [15, 16, 17, 18].

That is, in the paradigm of the quantitative and qualitative composition of microorganisms in the pathogenesis of GP, many studies have been devoted to it, but it is very often overlooked by researchers that GP often occurs against the background of internal diseases of the body, which cause not only special manifestations of the course of GP, but can also affect the results of prevention and its treatment. In this sense, RA, which is accompanied by chronic systemic damage to connective tissue, attracts attention. In general, more than one hundred million people in the world suffer from RA, and this pathology takes one of the leading places in terms of the severity of damage to the musculoskeletal system. After 3 years of the disease, more than 50% of patients lose their ability to work, and one third become disabled persons of group 1. An important role in the development of this disease is played by the antigenic load of microorganisms and a special and distorted immunological response to them. Some researchers find many related etiopathogenetic links in patients with GP and RA. In our opinion, this is very appropriate, because the target of both diseases is connective tissue, and the microbial load is one of the main triggers of the development of both diseases.

In the literature, there are not enough studies that reflect the role and place of tissue and microbial sensitization in patients with GP associated with RA. In our opinion, the study of these components will help to better understand the etiopathogenetic mechanisms of the development of GP against the background of RA, which will improve the development of preventive and therapeutic measures for the disease.

The purpose of the research was to determine the location and integration features of tissue and microbial sensitization in the pathogenesis of generalized parodontitis associated with rheumatoid arthritis.

MATERIALS AND METHODS OF RESEARCH

Immunological studies were carried out in 335 people, who were divided into 4 groups:

Group 1 – the main one – consisted of 136 patients with GP on the background of RA;

Group 2 – control – 71 people with GP diseases without signs of RA;

Group 3 – comparison – included 128 people without GP disease, with had diseases of the musculoskeletal system not related to RA;

Group 4 – 30 practically healthy people.

It is worth noting that the groups were homogeneous in terms of age, gender and social characteristics.

To determine microbial and tissue sensitization, the reaction of inhibition of migrating leukocytes –

(RIML) with microbial antigens of streptococci and staphylococci, tissue antigens (bone and synovial) was used. We used RIML due to its high specificity and informativeness. It is included in the WHO list for level 1 screening researches. Taking into account that the reaction was carried out outside the body (*in vitro*), conditions were created for multiple examination of the patient and use of tissue antigens.

The choice of tissue antigens was determined by the intervention in the pathological process in GP and RA of the connective tissue. In this connection, sensitization to connective tissue antigens of bone and synovial was studied.

The choice of RIML to antigens of streptococci and staphylococci was determined by their important role in the occurrence of delayed-type hypersensitivity, the existence of similar and cross antigens in these microorganisms and antigens of connective tissue – (Streptolysin-O and staphylococcus toxin were used in this reaction).

As tissue antigens, water-salt extract of bone tissue of group O/I D and synovial membrane of patients with RA O/I D – after synovectomy obtained in the laboratory of immunology of the Kyiv Institute of Orthopedics and Traumatology were used.

The correlation coefficient was calculated according to the formula:

$$r = \frac{\sum dx \cdot dy}{\sqrt{\sum d^2x \cdot \sum d^2y}};$$

where dx and dy - are deviations from the average x and from the average y.

The association coefficient was determined by the formula:

$$Q=(ad-bc)/(ad+bc),$$

The formula was used to calculate the reliability of the obtained data:

$$t= (x_1-x_2) / \sqrt{m_1^2+ m_2^2}, \text{ де } m= \sqrt{P(100-P) / n}, \text{ де } P= n_1/n_1+ n_2 =n_1/n$$

The migration index was calculated according to the formula:

$$\textbf{migration index (MI)} = \frac{\textbf{area of migration with antigen}}{\textbf{area of migration without antigen}};$$

where MI equals 0.1-0.5 corresponded to a high degree of sensitization.

Also clinical and radiological methods of parodontal assessment were used to verify the diagnosis (according to the systematics of parodontal diseases after M.F. Danilevsky, 1994).

All studies were conducted after the patients had read and signed the informed consent for permission to participate in research in compliance with the basic requirements of the Council of Europe Convention on Human Rights (1997) and the Declaration of the World Medical Association on Ethical Principles in the Conduct of Scientific Medical Research Involving Humans (2000, Helsinki).

The examination of the materials was conducted by the Commission for Bioethical Examination and Ethics of Scientific Research at Bogomolets National Medical University, Kyiv, Ukraine (protocol No. 2, August 28, 2023).

The study was carried out as part of the research work of the Department of Dentistry at Bogomolets National Medical University "Scientific substantiation of early diagnosis of generalized chronic and acute periodontal diseases" (state registry No. 0118U100471).

The analysis of the obtained results was performed using the methods of variation statistics with the calculation of frequency characteristics of indicators (P), averages (arithmetic mean – X) and assessment of their variability (standard deviation – σ). The statistical value of the results was estimated at a given marginal level of error of the first kind (α) not higher than 5% ($p<0.05$). All mathematical calculations were automated using the computer software package for statistical processing of data analysis SPSS version 11.5 for Windows. Statistical calculations

were performed using special programs for statistical analysis (STATISTICA 6.0, Microsoft Excel), (license number K9366093I 2016) [19].

RESULTS AND DISCUSSION

The results of immunological studies to determine the level of sensitization to the streptococcal antigen are presented in Table 1. As can be seen from the above data, the majority of patients with GP associated with RA had a pronounced sensitization to the streptococcal antigen, which in the chronic course of GP amounted to 70.3±4.3%. The acute course in this group was accompanied by a high level of sensitization in a slightly smaller percentage of patients in this group and amounted to 62.5±7.0%. In the control group, the frequency of sensitized individuals to the streptococcal antigen was significantly lower, 37.5±8.9% in the chronic course and 44.0±6.1% in the acute course. In practically healthy people without pathology of internal organs, locomotor apparatus and without GP, this indicator was only 26.0±8.0%. We obtained slightly different indicators when studying microbial sensitization to the staphylococcus antigen (Table 2).

Table 1

Frequency of microbial allergy to streptococcus antigen (M±m)

Group of examined	Diagnosis	Course of GP	Microbial allergy to streptococcus	
			number of examined	RIML
Main GP+RA	Generalized parodontitis	Chronic course	108	70,3±4,8, p<0.01
		Aggravation	48	62,5±7,0 p<0.01
Control GP without RA		Chronic course	29	37,5±8,9 p>0.05
		Aggravation	42	44,0±6,1 p>0.05
Comparable without GP: with damage to the musculoskeletal system		Absence of GP	93	47,0±5,1 p>0.05
Practically healthy people			30	26,0±8,0

Note. p – significance of differences in indicators between groups of patients with RA, GP, and without.

Table 2

Frequency of microbial sensitization to staphylococcus antigen (M±m)

Group of examined	Diagnosis	Course of GP	Microbial allergy to streptococcus	
			number of examined	RIML
Main GP+RA	Generalized parodontitis	Chronic course	82	60,9±5,4, p<0.01
		Aggravation	57	73,65±5,7 p<0.01
Control GP without RA		Chronic course	29	60,0±9,1 p<0.01
		Aggravation	42	53,1±7,7 p<0.01
Comparable without GP: with damage to the musculoskeletal system		Absence of GP	84	56,0±5,4 p<0.01
Practically healthy people			30	0

Note. p – significance of differences in indicators between groups of patients with RA, GP, and without.

Thus, we determined an increase in microbial sensitization to staphylococcus during an acute course in a group of patients with GP on the background of RA. We noted that in the main group there were always high levels of microbial sensitization – both to streptococcus and staphylococcus (62.5±7.0%-73.6±5.7%). It should be noted that allergy to streptococcal and staphylococcal antigens was noted only in patients with GP associated with RA.

The reaction of inhibiting the migration of leukocytes with bone antigen in GP of a chronic course established the degree of tissue sensitization in 32.3±4.0% of people of the main group, that is, in GP on the background of RA. The acute course of GP was accompanied by a significant increase in number of patients with a pronounced degree of sensitization and reached 60.6±6.0%. Sensitization to synovial antigen revealed a high level of sensitization in the main group compared to the control group (Table 3). So, if in the group of patients with GP on the background of RA, sensitization to synovial antigen was 70.3±4.8% in the chronic course of GP, and in the acute course it was slightly less – 62.5±7.0%, and in the control group, that is, in the group of patients with GP without signs of RA, both in chronic and acute course, it was absent. The same regularity was determined in the comparison group (Table 3).

Table 3

Frequency of tissue allergy to bone and synovial antigen (M±m)

Group of examined	Diagnosis	Course of GP	Microbial allergy to streptococcus			
			number of examined	bone antigen, RIML	number of examined	synovial antigen, RIML
Main: GP+RA	**Generalized parodontitis**	**Chronic course**	**72**	**32,3±4,0 p<0.01**	**72**	**70,3±4,8 p<0.01**
		Aggravation	**60**	**60,6±6,0 p<0.01**	**54**	**62,5±7,0 p<0.01**
Control: GP without RA		**Chronic course**	**29**	**81,2±7,2 p<0.01**	**29**	**0**
		Aggravation	**42**	**81,2±6,0 p<0.01**	**42**	**0**
Comparable without GP: with damage to the musculoskeletal system		**Absence of GP**	**73**	**38,0±4,9 p<0.01**	**73**	**0**
Practically healthy people			**30**	**0**	**30**	**0**

Note. p – significance of differences in indicators between groups of patients with RA, GP, and without.

Thus, the presence of tissue sensitization to bone antigen in patients with both RA and GP is a pathognomonic symptom for these two diseases, because these pathological processes have the same type of lesions. The presence of tissue sensitization to synovial antigen in patients with RA is a pathognomonic symptom of this disease, but it is not a pathognomonic symptom of GP, because the structure of synovial antigen is significantly different from the structure of the connective tissue of the alveolar process.

We believe that the presence of similar and cross antigens of the connective tissue with the antigen of streptococcus, which is present in periodontal pockets and is a key component of the microbiome of the oral cavity, can be a key trigger for a disturbed immune recognition of "self"-"foreign" with the subsequent inclusion of a persistent autoimmune reaction, which determines the peculiarity of the course of the disease and the result of its treatment.

Thus, the data of the conducted study indicate sensitization to bone and synovial antigen only in patients with GP, associated with RA.

CONCLUSIONS

1. A high frequency of microbial sensitization to streptococcal and staphylococcal antigens was established in patients with generalized parodontitis on the background of rheumatoid arthritis and in patients with generalized parodontitis without signs of rheumatoid arthritis.
2. The parodontal focus turned out to be an active focus of microbial sensitization in patients with generalized parodontitis associated with rheumatoid arthritis and in patients with generalized parodontitis without signs of rheumatoid arthritis.
3. Established sensitization to bone antigen in a small number of patients (27-33%) with generalized parodontitis, which was significantly more frequent

(61-80%) in patients with generalized parodontitis associated with rheumatoid arthritis, indicates that in the latter, allergy is to a greater extent is due to systemic damage is to connective tissue than generalized parodontitis. However, a certain allergy to bone tissue in generalized parodontitis may indicate the inclusion of an immune component in the pathogenesis of generalized parodontitis.

4. The presence of microbial and tissue sensitization in patients with generalized parodontitis and rheumatoid arthritis indicates that similar and cross antigens of streptococcal and staphylococcal microorganisms with connective tissue are a potential trigger for the development of both generalized parodontitis and rheumatoid arthritis, which is a reason to consider generalized parodontitis and rheumatoid arthritis as comorbid diseases with similar pathogenetic mechanisms of development.

Contributors:

Proschenko A.M. – conceptualization, methodology, verification, formal analysis, research, data curation, writing – the initial project, editing, visualization, management, project administration;

Proschenko N.S. – methodology, verification, formal analysis;

Reshetnyk L.L. – formal analysis, research, reviewing, verification;

Zelinskaya N.A. – formal analysis, research, writing – initial design, editing, visualization;

Chervonna N.V. – the formal analysis, research, editing;

Melnychyk T.A. – methodology, visualization, management.

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