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ABSTRACT

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ASSESSING MUCOSAL IMMUNITY IN PATIENTS WITH ORAL DISEASES ASSOCIATED WITH RHEUMATOID ARTHRITIS

Introduction. The association between diseases of connective tissue and oral cavity are of increased interest for scientists because they can contribute to the burden of the pathological process of each other and the occurrence of recurrences. Given that autoimmune disorders in rheumatoid arthritis are the main ones, it is advisable to study the specific and non-specific immunity features of the oral cavity in associated diseases.

Methods. The research group included 19 patients with benign migratory glossitis and 16 patients with atrophic glossitis. 15 practically healthy persons made up the control group. The levels of IgA, IgG and lysozyme were determined by radial immunodiffusion according to Mancini method and with the use of biomass powder of Micrococcus lysodeicticus, respectively. Statistical analysis of the obtained results was performed using Statistica 6.1.

Results. The high levels of IgG in the oral fluid was found in both research groups ($p<0.001$). In patients with benign migratory glossitis, high levels of secretory IgA ($p>0.05$) and serum IgA ($p<0.001$) were found, while in patients with atrophic glossitis associated with rheumatoid arthritis, there was a significant decrease in the content of sIgA and lysozyme, and similar increase in mIgA content.

Conclusions. Oral mucosal diseases associated with RA are accompanied by suppression of defense mechanisms of the oral cavity and its local immunity, which is characterized by a decrease in the levels of lysozyme and secretory IgA in the oral fluid of patients.

Keywords: mucosal immunity, oral mucosa, glossitis, rheumatoid arthritis, lysozyme, Immunoglobulin A, Immunoglobulin G.

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ОЦІНКА МУКОЗАЛЬНОГО ІМУНІТЕТУ У ПАЦІЄНТІВ ЗІ СТОМАТОЛОГІЧНИМИ ЗАХВОРЮВАННЯМИ, ПОЄДНАНИМИ З РЕВМАТОЇДНИМ АРТРИТОМ

Вступ. Поєднання захворювань сполучної тканини та органів порожнини рота викликають підвищений інтерес для науковців, оскільки можуть сприяти обтяженню патологічного процесу один одного і виникненню рецидивів. Враховуючи, що аутоімунні порушення при ревматоїдному артриті є основними, доцільно вивчити особливості специфічного і неспецифічного імунітету порожнини рота при поєднаних захворюваннях.

Методи. Дослідну групу склали 19 пацієнтів з доброякісним мігруючим глоситом і 16 з атрофічним глоситом. 15 практично здорових осіб склали групу контролю. Імуноглобуліни A, IgG і лізоцим визначали методом радіальної імунодифузії в гелі за методом Mancini та з використанням сухого порошку культури Micrococcus lysodeiticus відповідно. Статистичну обробку отриманих результатів проводили за допомогою програм "Statistica 6.1".

Результати. В обох дослідних групах встановлений високий рівень IgG в ротовій рідині ($p<0,001$). У хворих з мігруючим глоситом виявлено високий рівень секреторного IgA ($p>0,05$) і сироваткового IgA ($p<0,001$), в той час як в пацієнтів із атрофічним глоситом, поєднаним з ревматоїдним артритом – достовірні зниження вмісту sIgA і лізоциму, та аналогічне підвищення mIgA.

Висновки. Захворювання слизової оболонки порожнини рота, поєднані з ревматоїдним артритом супроводжуються пригніченням захисних механізмів ротової порожнини та її місцевого імунітету, що характеризується зниженням рівня лізоциму і секреторного IgA у ротовій рідині хворих.

Ключові слова: мукозальний імунітет, слизова оболонка порожнини рота, глосит, ревматоїдний артрит, лізоцим, імуноглобулін A, імуноглобулін G.

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INTRODUCTION / ВСТУП

An actual problem of modern medicine is the study of the course of dental pathology against the background of systemic diseases and the research of their interaction and mutual influence [1, 2, 3]. The most common disease among systemic autoimmune lesions of the connective tissue is rheumatoid arthritis (RA) [4]. Patients with RA are often diagnosed with rampant caries, cervical necrosis of hard dental tissues, generalized periodontitis, and Sjogren's syndrome [5, 6, 7]. The close relationship of oral mucosa with the condition of internal organs and systems causes the occurrence of functional and structural changes in it in various systemic diseases [8]. However, not enough attention is paid to the issue of lesions of the oral mucosa associated with RA.

The study of the main components of the pathogenesis is a leading factor for the appointment of adequate treatment [9]. Among the pathogenetic factors of RA, the main importance belongs to autoimmune processes, and increased morbidity is associated with disorders in the immune system [10]. However, most studies are devoted to the analysis of systemic defense factors for RA development, and the importance of mucosal immunity in the development of oral mucosal diseases in association with RA has not been studied enough.

The state of both specific and non-specific resistance of the organism is an important link in the pathogenesis of oral mucosal diseases. It is known that local mucosal immunity plays an important role in the oral cavity defense [11].

The synthesis of antibodies is an important defense mechanism of the oral cavity against the penetration of microorganisms into the tissues. It is known that secretory IgA plays a leading role in the formation of oral mucosa immunity, as it has antiviral and antibacterial properties, and its deficiency reduces the activity of mucosal immunity, which leads to the development of oral inflammatory diseases [12]. Among the protective enzymes of saliva, lysozyme is most often the main biomarker for assessing the non-specific defense of the oral cavity [13]. A decrease in salivary lysozyme levels plays a significant role in the increased growth of pathogenic microflora and the development of dental pathology [14].

Determination of immunoglobulins and lysozyme levels in the oral fluid of patients with diseases of the oral mucosa and RA can serve as a criterion for assessing the state of immune defense of the oral cavity under the conditions of dental and systemic pathology.

The aim of the work is to evaluate the mucosal immunity in patients with diseases of the oral mucosa and RA based on parameters of specific and non-specific immunity in the oral fluid.

MATERIALS AND METHODS

To achieve the goal of the study, 35 patients with oral mucosal lesions associated with RA (M05. Seropositive RA; I-II degree of activity) were selected. Among oral mucosal diseases in 19 patients benign migratory glossitis (K14.1 BMG, geographic tongue) and in 16 patients atrophic glossitis (K14.4 Atrophy of tongue papillae) were diagnosed. The average duration of RA was 6.3 ± 0.58 years. Among the patients, 63% (22 participants) were women, 37% (13 participants) were men. The average age of the patients was 54.3 ± 1.6 years (between 30 and 64). The control group consisted of 15 practically healthy persons, comparable in age (51.1±2.9 years) and gender distribution (60% women, 40% men).

The immunological study included determination of the content of sIgA, mIgA, IgG in the oral fluid. Immunoglobulins were measured by the method of radial immunodiffusion in a gel according to Mancini in Simmons modification with the use of antiserum against sIgA, mIgA, IgG and microplates of Hyland company (USA).

Unstimulated oral fluid was collected at a fixed time in the morning, on an empty stomach. Patients were instructed to rinse the oral cavity with cooled boiled water. In 30 minutes, the saliva samples were collected by spitting 4 ml into plastic sterilized tubes that were hermetically sealed. The collected oral fluid was delivered to the laboratory, centrifuged at 1500 rpm for 10 min. The liquid phase was collected with a pipette and frozen in the fast freezing mode at a temperature of -20ºC. Frozen samples were delivered to the laboratory, where they were thawed using heat treatment in a water bath at a temperature of 37ºC. Then the concentration of immunoglobulins was determined by non-graphical method.

The analysis of salivary lysozyme was carried out by the method of radial immunodiffusion in agar containing 0.05% biomass powder of Micrococcus lysodeicticus. The intensity of the color change is measured spectrophotometrically (Osserman & Lawlor, 1966).

The clinical levels of oral hygiene were determined by Simplified Oral Hygiene Index (OHI-S) (J. G. Greene and J. R. Vermillion, 1964). OHI-S was assessed as a quantitative outcome variable.

The statistical analysis of the obtained results was carried out by parametric methods of variation statistics with the determination of Student's criteria of reliability using the computer programs "Statistica 6.1" and Microsoft® Excel 2017. Average arithmetic and relative values and errors (M ± m), (P ± m), standard deviation (t) and the significance of differences (p-value) were calculated; a probability value $p < 0.05$ were considered as statistically significant. In the case of confirmation of the normal law of distribution, when comparing quantitative indicators between groups, we used parametric methods – Student's t-test for independent variables.

The work complies with the requirements of World Medical Association Declaration of Helsinki (1994, 2000, 2008), the research protocol was approved by the Bioethics Committee of National Pirogov Memorial Medical University, Vinnytsya (protocol No. 7 dated November 1, 2023); voluntary informed consent of the patients was obtained.

RESULTS

Considering the fact that oral mucosal lesions in RA are the most frequent manifestation of chronic autoimmune connective tissue diseases [5, 15], a study of the state of mucosal immunity in this category of patients was performed.

The results of the study of mucosal immunity of patients with oral mucosal involvement in RA are presented in Table 1. The given data indicate

ambiguous changes in the local humoral immunity of the oral cavity in patients with various lesions of the oral mucosa in RA, compared to practically healthy patients of the control group. At the same time, in all patients with BMG and AG, a steady tendency to a significant increase in the number of IgG antibodies in the oral fluid was found in comparison with the control group ($p < 0.001$), which is probably related to the pronounced influence of systemic pathology.

Table 1 – Immunological parameters examination of the oral fluid in patients with oral mucosal diseases associated with rheumatoid arthritis

Immunological research parameters	Control group (n=15)	Patients with BMG (n=19)	Patients with AG (n=16)
sIgA, g/l	1.27 ± 0.13	1.36 ± 0.16 p > 0.05	0.86 ± 0.08 p < 0.01
mIgA, g/l	0.13 ± 0.05	0.39 ± 0.06 p < 0.001	0.45 ± 0.08 p < 0.001
IgG, g/l	0.01 ± 0.003	0.12 ± 0.01 p < 0.001	0.08 ± 0.007 p < 0.001
Lysozyme, μg/ml	3.41 ± 0.25	3.82 ± 0.18 p > 0.05	1.53 ± 0.09 p < 0.001

Note: p – the significance of the difference between the parameters of patients with different types of glossitis and the control group

The local immune status of oral mucosa in patients with BMG was characterized by high levels of serum IgA ($p < 0.001$) in the oral fluid compared to the control group (Table 1). The increased concentration of secretory IgA in this group of patients probably indicates the activation of the colonization resistance system of oral mucosa, although it did not have a significant difference with the control group ($p > 0.05$).

The analysis of parameters of local humoral immunity of oral mucosa in the examined patients with AG revealed a significant reduction of sIgA concentration compared to practically healthy patients of the control group. Even so sIgA levels in mixed saliva of the main patient group was 0.86 ± 0.08 g/l ($p < 0.01$). This indicated the insufficiency of oral mucosa immunity in this group of examined patients, its specific defense barrier that protects the macroorganism from the harmful effects of various pathogenic and opportunistic microorganisms.

At the same time, serum mIgA content in the unstimulated mixed saliva of patients with AG and RA exceeded the same parameter in healthy persons by 3.5 times and was 0.45 ± 0.08 g/l, which differed with a high degree of probability value ($p < 0.001$) from a similar value of the control group.

When determining the state of local non-specific immunity, it was found that lysozyme levels in the oral fluid of patients with AG was almost 2 times lower than in the control group ($p < 0.001$). At the same time, in patients with BMG and RA, no significant difference in results was revealed with the group of healthy persons ($p > 0.05$).

Oral hygiene plays an important role in maintaining mucosal immunity. During the dental examination, in patients with concomitant pathology of oral mucosa and RA were observed poor oral hygiene, the presence of dental plaque and calculus. The assessment of the OHI-S index showed that the level of oral hygiene in patients with BMG and AG was unsatisfactory, and the quantitative values of the index were 2.32 ± 0.16 and 1.98 ± 0.11 scores, respectively (Fig. 1). A high degree of probability value compared to the control group was noted ($p < 0.001$).

The obtained results probably are caused by the unpleasant and painful sensations that accompany glossitis, which hinder thorough oral hygiene. In addition, the effect of RA is possible, which is accompanied by dryness of oral mucosa and a decrease in salivation rate.

DISCUSSION

Maintenance of oral homeostasis is provided by local immunity, which includes the humoral link, which forms lines of defense with specific antibodies [11, 16]. Taking into account the genetically determined imperfection of immune system regulation processes in autoimmune diseases [17], the content of sIgA, mIgA, IgG in the oral fluid of patients with oral mucosa lesions associated with RA

was studied. The results of the study of the humoral link of defence mechanisms of the oral cavity indicate ambiguous changes in mucosal immunity in patients with various lesions of oral mucosa. However, in all patients, the highest level of the main antibody of the secondary immune response, IgG, was revealed, which confirms the influence of concomitant RA on the condition of the oral mucosa.

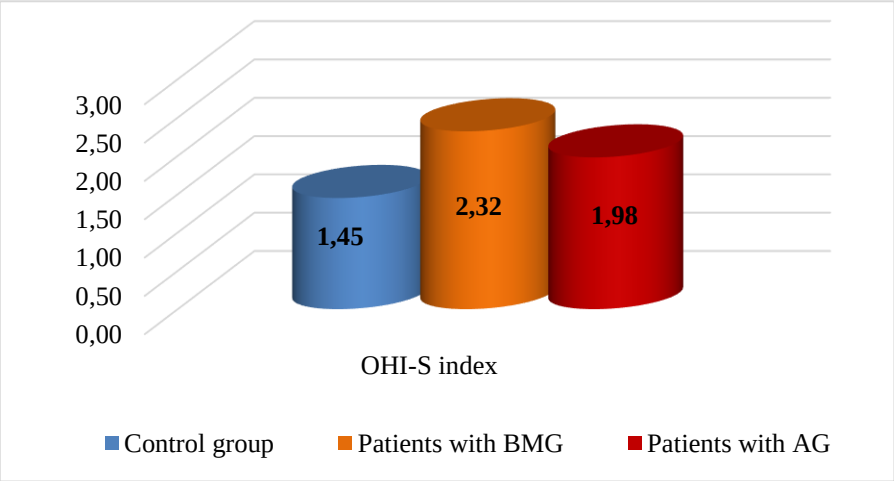

Figure 1 – Oral hygiene status according to the OHI-S index in patients with oral mucosal diseases and RA

IgG levels in oral fluid increased significantly from 8 to 12 times, compared to the control, that indicates a state of hyperreactivity of oral mucosa, mainly a humoral response by a systemic type instead of a secretory one. At the same time, IgG has an anti-inflammatory orientation, ensuring the retention and elimination of foreign antigens by inflammatory mechanisms within the proper oral mucosa [18].

Considering the infectious nature of the cross-immune reaction and the formation of superantigens in autoimmune diseases development [16], it is possible to assume a significant decrease in the "first line" of the humoral defense of oral mucosa at the level of sIgA, which suppresses the colonization of the epithelium by microorganisms and prevents the penetration of foreign antigens into the internal environment of the body. Their interaction with the immune system is limited at oral mucosal surface [19]. According to Nazaryan R. (2019), the decrease in this immunoglobulin is due to the long course of the pathological process and the possible cleavage of the sIgA dimeric molecule by the enzymes of microorganisms, the activity of which increases in oral mucosa lesions. This is confirmed by a persistent tendency to increase its monomeric form (mIgA) in the oral fluid of the examined patients.

It should be noted that the increased concentration of this immune protein is formed as a result of certain disorders in the oral mucosa [14, 18]. Presumably, part of the monomeric IgA has a vascular origin, and the other part is formed due to the splitting of the secretory IgA structure into separate fragments that are not able to agglutinate microorganisms and prevent bacterial adhesion to epithelial cells.

The determined significant reduction in the content of sIgA and lysozyme, and a similar increase of mIgA and IgG in patients with AG and RA may be due to the exhaustion of the immune system during the prolonged course of the disease [20], a decrease in the body's reactivity and the negative impact of an unsatisfactory oral condition (poor oral hygiene, hyposalivation), revealed during the clinical examination of this group of patients. A simultaneous reduction in the levels of sIgA and lysozyme probably indicates a certain compensatory increase of one of these parameters when the level of the other decreases. A certain increase in the concentration of class A immunoglobulins and lysozyme in patients with BMG can be considered as a compensatory reaction in response to antigenic load.

Therefore, BMG is accompanied by an increase of sIgA content, presumably due to increased antigenic stimulation of secretory immunity by the microflora of the oral cavity (acid-producing), which is usually combined with high indices of carious process intensity. AG develops against the background of a decrease in this protective component of the oral fluid, and a high microbial load (urease-producing microflora) is accompanied by a decrease in sIgA content, possibly due to the depletion of this protective link.

CONCLUSIONS / ВИСНОВКИ

1. The development of oral mucosal diseases in the association with RA is accompanied mainly by a humoral response of systemic type instead of a secretory one, that confirms the influence of the accompanying pathology.

2. A significant decrease of sIgA content in the oral fluid of patients with AG indicated the exhaustion of the secretory link of defense, and the increase of this protective component in patients with BMG indicated a slight increase in antigenic stimulation of secretory immunity.

3. Oral mucosal diseases associated with RA are accompanied by suppression of defense mechanisms of the oral cavity and its local immunity, which is characterized by a decrease in the levels of lysozyme and secretory IgA in the oral fluid of patients.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Identified significant violations of the main links of immune system of the oral cavity have a negative effect on the course of oral mucosal diseases and require appropriate correction and development of pathogenetic therapeutic and preventive measures.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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