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CLINICAL AND MOLECULAR FEATURES OF STOMATITIS IN PATIENTS WITH ACUTE AND CHRONIC LEUKEMIA

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Introduction:there is an increase in such oncohematological diseases as leukemia, the incidence of which is 150-200 cases per year per 1 million people [1, 2], and among the causes of death from malignant neoplasms, they occupy 4th-5th place [3]. These are clonal neoplastic processes originating from hematopoietic cells, accompanied by their uncontrolled proliferation and disruption of the process of reproduction of mature cell populations. It is known that the balance between the processes of proliferation and cell death in the process of homeostasis is subject to regulation by a multilevel enzymatic system [4], in which the role of an apoptosis marker actually belongs to transglutaminase, accompanied by its increased expression [5]. In addition, in the process of apoptosis, individual cells undergo self-destruction, therefore, this enzyme can be considered as the main indicator of cellular renewal. Among the intensively renewed cells are epithelial cells lining the oral mucosa. In all hemoblastoses, regardless of their form, 19–89% of patients develop necrotic lesions of the oral mucosa due to tumor growth [6], and 98% of patients with acute leukemia have periodontal diseases [7, 8], which occur against the background of a decrease in the immunobiological reactivity of the body, being the reason for the insufficient effectiveness of the therapy used. In this regard, the search for new molecular indicators of the development of inflammatory-destructive changes in the oral mucosa associated with the enzyme transglutaminase will help to provide valuable information on the severity of oral lesions and ensure long-term remission of dental, and therefore somatic health of patients with leukemia.

The aim of the work: to consider the clinical and molecular features of lesions of the oral mucosa in patients with acute and chronic leukemia by determining specific indicators in the oral fluid - antibodies to transglutaminase and gliadin of immunoglobulin classes A and G.

Materials and methods A total of 125 patients were examined, formed into three groups: the first - 45 patients with acute leukemia (men - 45%, women - 55%), average age - 45 ± 0.5 years, including 31 patients with acute myeloblastic leukemia (M1 and M2 according to the FAB classification) and 14 with acute lymphoblastic leukemia, the second group - 45 patients with chronic leukemia (men - 47%, women - 53%), average age 62 ± 0.3 years, including 15 patients with chronic myeloid leukemia (Ph-positive or bcrabl-positive) and 30 with chronic lymphocytic leukemia (B-cell); the third group - 35 practically healthy individuals, of which 36% were men, 64% were women, the average age was 45±1.06 years. The diagnosis of leukemia was verified morphologically by microscopic examination of bone marrow puncture (Zeiss microscope), immunologically by flow laser cytofluorometry (Facs Calibur flow cytometer, Becton Dickinson)

and genotypically. Clinical methods of dental examination included identifying patient complaints; collecting anamnesis; visual examination of the oral cavity with assessment of the condition of the oral mucosa and the severity of stomatitis according to the classification of L. S. Lyubimova [9]; index assessment: bleeding index according to Müllemann as modified by Cowell, determination of the hygiene index according to Fedorov-Volodkina, and the KPU index. The material for the study was oral fluid, in which the relative content of immunoglobulins of classes A and G to transglutaminase and gliadin was determined by the enzyme immunoassay method using an enzyme immunoassay complex consisting of a Proplan washer and a Uniplan spectrophotometer (Picon, Russia), and an Elmi Sky Line shaker (Estonia). The following reagent kits were used as diagnostic test systems: IgA-transglutaminase-IFA-Best, IgG-transglutaminase-IFA-Best, IgA-Gliadin-IFA-Best, and IgG-Gliadin-IFA-Best (Russia). The forms of distribution of the studied parameters of the oral fluid of the examined patients were studied. We used a visual assessment of the distribution histograms, assessed the skewness and steepness indicators reflecting the asymmetry of the distribution, and tested for normality using the Kolmogorov–Smirnov test with the Liliefors and Shapiro–Wilk corrections [10]. Spearman's rank correlation analysis was used to study the relationships between the metabolic parameters of oral fluid [11].

Results and discussion The design of the present study was based on the objective and involved several stages. The first stage included examination of the oral cavity, which showed that among patients with acute myeloid leukemia, 72% had grade I stomatitis, 63% had acute lymphocytic leukemia, 22% had chronic lymphocytic leukemia, and 26% had chronic myeloid leukemia. With grade II stomatitis, 13% of patients with acute myeloid leukemia, 23% had acute lymphocytic leukemia, 8% had chronic lymphocytic leukemia, and 10% had chronic myeloid leukemia. Grade III stomatitis was observed in 14% of patients with acute myeloid leukemia, 10% with acute lymphocytic leukemia, 5% with chronic lymphocytic leukemia, and 9% with chronic myeloid leukemia. Assessment of the dental status showed that patients with acute leukemia have more pronounced changes in dental indices: KPU (in acute lymphocytic leukemia 16.62±1.72, in acute myeloid leukemia - 12.54±1.68), hygiene index according to Green-Vermillion (in acute myeloid leukemia 3.07±0.34 ($p<0.05$) in acute lymphocytic leukemia 2.52±0.28), bleeding index according to Müllemann ($p<0.05$) (in acute myeloid leukemia 2.43±0.26, in acute lymphocytic leukemia 1.73±0.17), which is significantly lower than in the control group - 6.77±1.01 ($p<0.05$). The listed facts indicate a high intensity of caries, a decrease in the antibacterial and antiviral protection of the body, which in combination with a low level of oral hygiene contributes to the progression of inflammatory-destructive changes in stomatitis. Thus, ulcerative-necrotic lesions of the mucous membrane were noted in 62% of patients with acute myeloid leukemia, in 37% of patients with acute lymphocytic leukemia, in 23% of patients with chronic myeloid leukemia and in 15% of patients with chronic lymphocytic leukemia. In this regard, at the second stage of the study, the question of "molecular" confirmation of the identified structural disorders of the connective tissue of the oral cavity turned out to be natural. The tissue enzyme transglutaminase, an indicator of the formation of fibronectin-collagen three-dimensional structures at the early stages of collagen formation, was taken as such "molecular receptors" [12, 13]. The relationship between this polymer and local mechanisms of local resistance was traced through protein-protein interactions - by studying the content of antibodies to transglutaminase in oral fluid as a biological environment reflecting the state of the oral cavity. It turned out that in the oral fluid of patients with acute leukemia there are antibodies of the immunoglobulin A class to transglutaminase, and the highest level was observed in patients with grade II stomatitis: 1.90 ± 0.9 U / ml. As for antibodies to transglutaminase class Ig G, their

highest number was detected in patients with grade I stomatitis - 9.98 ± 1.50 U / ml, and the maximum level of antibodies in this group - 23.00 U / ml - significantly exceeds the reference threshold (10.0 U / ml). Since transglutaminase plays an important role in providing the strength and continuity of connective tissue molecules by forming a covalent bond between the residue of glutamine, lysine and two molecules of fibronectin with collagen and other proteins of the extracellular matrix, an increase in the content of antibodies to this polyfunctional enzyme can act as a factor destabilizing connective tissue. As a result of such molecular disorders, hemorrhagic syndrome was diagnosed in such patients, and 77% of them were patients with acute lymphocytic leukemia with II and III degrees of stomatitis. Bleeding of the gums was observed when eating, brushing teeth, and in 20% of patients with acute myeloid leukemia and in 14% of patients with acute lymphocytic leukemia it was spontaneous. Along with this, it was noted that with an increase in the degree of damage, a decrease in the number of IgG antibodies to transglutaminase was observed down to a reliably lowest value of 1.27±0.32 (1.15; $p<0.05$) U/ml in grade III stomatitis. In addition, acute forms of hemoblastoses are characterized by hyperplastic syndrome with the development of hypertrophic gingivitis and hypertrophy of the tonsils, which has a symmetrical lesion, as well as hyperplasia of the lymph nodes, while in 78% of cases mainly in one area. In patients with acute myelogenous leukemia, this syndrome was observed in 59% of patients with grade I, in 50% with grade II and in 40% with grade III stomatitis, and in patients with acute lymphocytic leukemia in 52% of patients with grade I, 54% with grade II and 60% with grade III stomatitis. As for chronic forms of leukemia, hyperplastic syndrome was diagnosed in 34% of patients with chronic lymphocytic leukemia with grade I stomatitis, in 30% with grade II and in 25% with grade III stomatitis; in 34% of patients with chronic myelogenous leukemia with grade I, in 35% of patients with grade II and in 24% with grade III stomatitis. Along with such clinical features, the following “molecular picture” was observed in patients with chronic leukemia: the content of IgA antibodies to transglutaminase increased in parallel with the severity of stomatitis, reaching a maximum at grade III – 1.76±0.53 (2.5) U/ml. In contrast, the highest content of antibodies to transglutaminase class IgG was found in the presence of grade I stomatitis (2.44±0.44 U/ml), and in the rest of the examined subjects the values of this indicator are minimal and reach the lowest level at grade III stomatitis – 0.35±0.01 U/ml. Apparently, in grade II–III stomatitis accompanying both acute and chronic leukemia, the molecular manifestations of damage are smoother, indicating depression of immune processes in the oral cavity, aggravating the course of stomatitis and contributing to a decrease in the quality of life in general. Another pathway of the body's immune response to tissue transglutaminase is associated with the formation of its complex with the protein gliadin. It has been established that the gliadin molecule has a region responsible for its toxic effect, the recognition of which as an immunologically active component occurs by T-lymphocytes with genetic features in the form of the DQ2 heterodimer, present in people with HLA DR5, 7 and 17. Activation of such T-lymphocytes is accompanied by the induction of cellular immune reactions with the implementation of cytokines that have both a direct and indirect cytotoxic effect. In addition, the transglutaminase-gliadin complex activates the proliferation and differentiation of plasma cells, which synthesize specific antigliadin antibodies [14]. However, the appearance of antigliadin antibodies is currently explained by a normal immune reaction, which indicates the insufficient specificity of antigliadin antibodies and their frequent detection in individuals with a history of celiac disease [15], as well as many connective tissue diseases [16]. They are also found not only in the blood, but also in oral fluid, in particular, in chronic generalized periodontitis [17]. In this regard, at the next stage of the work, the content of antibodies to gliadin in the oral fluid of patients with leukemia was studied. It was revealed that the highest

content of IgA antibodies to gliadin was found in patients with severe stomatitis: 3.25±0.86 U/ml (median 2.80 U/ml), and the reliably lowest – with grade I stomatitis: 1.44±0.19 U/ml (median 1.42 U/ml; $p<0.01$) (Table 2). Among patients with chronic leukemia, the lowest content of Ig A antibodies to gliadin was found in the development of grade I stomatitis – 0.15±0.04 (median 0.50) U/ml, and with grade II severity, the content of these antibodies increases to 2.48±0.34 (0.70) U/ml. Immunoglobulin A is a regulator of immunological processes, interacting with immune system cells, as well as with humoral factors of non-specific protection (complement, lysozyme), and an increase in its content in the blood can be regarded as a positive shift, ensuring an increase in the body's resistance. However, with an aggravation of the severity of clinical signs of stomatitis, a tendency for a drop in the content of these antibodies to 0.15 ± 0.01 (0.80) U/ml is noted. Anti-gliadin antibodies of class IgG were detected in the oral fluid of patients with acute leukemia in lower concentrations compared to IgA antibodies: the highest concentration was significantly higher in individuals with grade II stomatitis: 1.96±0.27 U/ml (median 1.93 U/ml; $p<0.05$), and the lowest concentration was found in those examined with grade I stomatitis: 1.55±0.10 (1.56) U/ml. Effector functions of IgG immunoglobulins determine their cytotropic properties and the ability to fix complement, which enables antibody complexes with antigens and the antibodies themselves to be fixed in tissues and, by combining with macrophages, to influence target cells. . In patients with chronic leukemia, a different dynamics of the content of IgG antibodies to gliadin was observed: the highest amount was observed in grade II stomatitis (3.40±0.20 U/ml), and the lowest was observed in grade III stomatitis (1.10±0.30 U/ml). Apparently, the structure of the Fab fragment of IgG immunoglobulins allows them to serve as mediators of inflammation, which significantly reduces their specificity; therefore, any immunological shifts of a nonspecific nature can be reflected in a change in the concentration of these immunoglobulins in the oral fluid. At the final stage of the work, an analysis of the correlation interdependencies between the studied indicators was carried out, which showed that in acute leukemia their content is 4 times higher than in chronic ones: between antibodies A and G, both to gliadin and to transglutaminase ($R = 0.81$; $p <0.05$), as well as between the same antibodies: A - to gliadin and transglutaminase ($R = 0.81$; $p <0.05$), G - to gliadin and transglutaminase. Systematization of the obtained data on the metabolic profile of oral fluid in combination with the specific features of the dental status of patients made it possible to develop a method for predicting the manifestations of stomatitis in patients with acute leukemia by changing the content of antibodies to transglutaminase of immunoglobulin classes A and G in oral fluid [18]. Conclusion The results of the study indicate that antibodies to transglutaminase and gliadin of classes A and G are present in the oral fluid of all patients with leukemia, being the molecular basis for the occurrence of clinical manifestations of damage to the oral mucosa in the form of hemorrhagic, ulcerative-necrotic, hyperplastic syndromes, but their number depends on the type of hemoblastosis. Thus, in acute leukemia, saliva diagnostics revealed the highest content of IgA antibodies to transglutaminase and gliadin in stomatitis of II-III severity and IgG antibodies to transglutaminase in the presence of stomatitis of severity I. Patients with chronic leukemia had the highest level of antibodies to gliadin of both classes in severity of stomatitis II along with differently directed content of antibodies to transglutaminase: Ig G - in grade I stomatitis, Ig A - on the contrary, in severe damage to the oral mucosa. Thus, the determination of the listed metabolic parameters in oral fluid allows us to consider the clinical features of stomatitis in patients with leukemia in direct connection with molecular indicators of their development, which is relevant in relation to the search for early markers of targeted diagnostics and timely correction of impaired metabolism.

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