# CHANGES IN THE ORAL MICROFLORA OF PATIENTS WITH CHRONIC LEUKEMIA

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**Abstract:** Chronic Lymphocytic Leukemia (CLL) is one of the most common neoplastic diseases in clinical practice that belongs to the immunohaematological spectrum and is distinguished by its high degree of heterogeneity. According to research results, not only the clinical course but also the prognosis and mechanisms of response to treatment differ significantly across patients with this disease.The oral cavity microflora is an important biomarker reflecting the internal state of the body; when immunity decreases or against the background of oncohematological diseases, particularly leukemia, the balance of this microflora is disturbed (dysbiosis). This dysbiosis weakens the protective function of the mucosa and increases the susceptibility to the development of inflammation and infection.

**Key words:** petechiae,local immune,candida,pathogenic microorganism,oral microflora.

Leukemias (leukoses) are clonal neoplasias of the blood-forming tissues, characterized by impaired hematopoiesis, immune dysfunction, and numerous clinical complications. Chronic Lymphocytic Leukemia (CLL) is the most common form among adults in developed countries, and its clinical outcomes are closely linked to complex changes in the immune system.

Although the clinical signs of leukemias vary, patients often experience anemia, thrombocytopenia, and the associated hemorrhagic syndrome. This syndrome manifests as petechiae, ecchymoses, mucosal bleeding, and large hematomas. Such changes significantly affect not only the general clinical course but also the problems encountered in dental practice. The oral cavity mucosa is often prone to bleeding, and the gums may bleed or profuse bleeding may occur even from minor injuries. Furthermore, against the background of immune deficiency, the ulcerative-necrotic syndrome rapidly develops, and severe secondary infections are observed.

Impairment of hematopoiesis and immune dysfunction in leukemias are clearly manifested not only through general clinical signs but also through changes in the oral cavity. Stomatological symptoms often appear in the initial stages of the disease, prompting the patient to seek medical attention. Therefore, they hold diagnostic and prognostic significance and occupy a special place in clinical practice.

The general and local immune disorders observed in leukemias are often closely related to the specific characteristics of the disease pathogenesis and the treatment methods applied. Cytostatic, antimicrobial, and hormonal therapy not only suppresses hematopoiesis but also significantly reduces the functional activity of immunocompetent cells. As a result, favorable conditions for the active growth of exogenous and endogenous microflora emerge in the patient's body, leading to the development of various pathological processes in the oral cavity mucosa.

Among the observed clinical signs, mucosal erosions and ulcerative lesions, candidomycosis, necrotic processes, and gingival hypertrophy hold leading positions. Interestingly, these stomatological signs often appear long before the systemic clinical symptoms of leukemia. Therefore, early detection of such changes in dental practice holds important diagnostic significance in referring the patient for a hematological examination (Shah et al., 2022; Woo & Kerr, 2020).

Mucosal injury poses a high risk of infection in leukemia patients. Infectious and inflammatory processes, especially those that develop against the background of neutropenia and thrombocytopenia, aggravate the general clinical picture of the disease, reduce treatment effectiveness, and worsen the prognosis. Therefore, stomatological observation, oral hygiene prophylaxis, and timely therapeutic measures are an integral part of the comprehensive management strategy for leukemia patients.

Among the most common signs in the oral cavity are gum bleeding, ulcerative-necrotic processes, and infectious complications. Gum bleeding is mainly explained by thrombocytopenia and coagulopathy, manifesting as bleeding gums from simple mechanical effects, petechiae, and prolonged hemorrhages. This condition poses a high risk during dental interventions, particularly tooth extraction or simple scaling. Ulcerative-necrotic processes occur against the background of leukopenia and decreased phagocytic activity. They manifest as necrotic gingivitis or stomatitis, are resistant to standard conservative treatment, and can sometimes lead to severe consequences such as sepsis.

Secondary infectious processes are also common in the oral cavity due to weakened immunity. Candidiasis caused by Candida albicans is the most frequently recorded fungal infection; it is particularly severe in patients treated with BTK-inhibitors or antibiotic therapy. Viral infections such as Herpes simplex and cytomegalovirus cause recurrent mucosal lesions, while bacterial infections present as necrotic gingivitis and periodontitis. These processes are distinguished by their rapid spread, tendency to recur, and resistance to treatment. Gingival hyperplasia is also observed in some patients; it develops as a result of blast cell infiltration or the prolonged use of certain drugs, such as cyclosporine. In this condition, the gums thicken, become inflamed, and their tendency to bleed increases.

These processes in the oral cavity drastically reduce the patients' quality of life. Ulcers and necrotic foci increase pain, making it difficult for patients to eat, which further exacerbates general cachexia and immune deficiency. Therefore, stomatological signs should not be viewed only as local problems but as a part of the entire disease pathogenesis.

From a practical standpoint, a special approach is necessary in dental interventions due to the high risk of bleeding and infection. Sometimes, transfusion of platelet mass, antibiotic prophylaxis, and enhanced antiseptic care measures are required before extraction or other surgical manipulations. Furthermore, the cooperation between the dentist, hematologist, and immunologist determines the effectiveness of treatment.

Changes in the composition of the oral microflora in patients with leukemia are considered an important pathogenetic factor in the development of stomatitis. In such patients, the natural defense of the oral mucosa is weakened due to immunosuppression, the toxic effects of

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chemotherapy agents, and the long-term use of antibiotics. Consequently, a disbalance (dysbiosis) occurs in the microbiocenosis—the number of beneficial bacteria decreases, and conditionally-pathogenic and pathogenic microorganisms become active. Therefore, determining the qualitative and quantitative composition of the microflora is essential for assessing the causes and severity of stomatitis.

Among the most common microorganisms in leukemia patients are fungi belonging to the Candida genus, as well as bacteria from the Staphylococcus, Streptococcus, and Enterobacteriaceae families. Studies have identified Candida albicans as the most dominant species, with its share noted to reach 40-50\% in some sources (Lu et al., 2021). Against the background of immunosuppression, these fungi activate from an endogenous source; that is, they are typically normal residents of the oral mucosa but become pathogenic when the body's defense system is weakened. Dryness of the mouth, mucosal erosion, and the appearance of painful inflammatory foci after chemotherapy courses are clinical signs of Candida proliferation. From a diagnostic perspective, identifying blastospores, pseudomycelia, and hyphal forms is straightforward using cytological methods (Gram stain, PAS-reaction). Molecular methods (PCR, MALDI-TOF mass spectrometry) show high sensitivity in the differential identification of Candida species. Therefore, cytological "express-analyses" are the most effective method for the early diagnosis of candidal stomatitis.

Bacteria of the Staphylococcus genus, particularly Staphylococcus aureus, S. epidermidis, and S. haemolyticus, are detected as secondary infections in leukemia patients. They typically intensify ulcerative-necrotic processes, form purulent discharge, and slow down mucosal healing. Along with classical bacteriological methods, biochemical tests—catalase and coagulase reactions, mannitol fermentation, and novobiocin susceptibility analyses—are used to identify these bacteria. In particular, S. aureus is differentially identified as a coagulase-positive, mannitol-fermenting species that forms golden-colored colonies. S. aureus colonization in leukemia patients is generally associated with decreased immunity, and its detection increases the risk of infectious complications.

Overall, the change in oral microflora in leukemia patients is polymicrobial in nature. The simultaneous involvement of Candida, staphylococci, and enterobacteria leads to the severe course of stomatitis. Early detection of Candida fungi using cytological methods, differential diagnosis of bacterial species through biochemical tests, and assessment of the overall structure of the microflora using molecular analyses constitute the most appropriate direction for complex diagnostics. Determining the ratio of microorganism species and their interaction provides important prognostic information about the severity of stomatitis, the clinical stage of leukemia, and the degree of immunosuppression.

Thus, the diagnostic analysis of the oral microbiota in patients with leukemia is of crucial importance in determining the etiology of stomatitis, selecting the treatment strategy, and preventing infectious complications. For this purpose, it is necessary to use cytological, cultural, and molecular methods in an integrated manner, regularly monitor the species composition of the microflora, and individually select antibiotic and antifungal therapy.

Analysis of scientific sources indicates that the condition of the oral cavity mucosa in patients with leukemia is closely related to the immunobiological reactivity of the organism. The

development of stomatitis in these patients often has a complex etiology, proceeding based on the interaction of bacterial and mycotic factors. Consequently, the clinical presentation of stomatitis in most cases shows similarity with ulcerative-necrotic or candidal forms, which requires precision during the diagnostic process.

The immunosuppression observed in leukemia, the long-term use of chemotherapy agents, and the extensive use of antibiotics lead to a significant disbalance in the oral cavity microbiota. As a result, components of the normal microflora decrease, while the colonization by conditionally-pathogenic bacteria and fungi of the Candida genus intensifies. This increases the risk of stomatitis progressing not only to local but also to systemic infectious-inflammatory processes.

Modern microbiological and molecular studies show that changes in the species composition of the oral microbiota are reflected not only at the level of the oral mucosa but also in the entire organism's immune-metabolic response. Candida albicans and related species are detected in around half of the patients and are considered the main etiological factor in the severe course of stomatitis. Simultaneously, bacterial components – Staphylococcus aureus, Streptococcus viridans, and representatives of Enterobacteriaceae – also contribute to the activation of the inflammatory process.

Numerous studies note that regular monitoring of the oral microflora and the use of cytological and molecular diagnostic methods provide high accuracy in assessing the patient's condition. In particular, cytological express-analyses allow for the early detection of Candida fungi and the rapid initiation of therapy. This, in turn, reduces the severe course of infectious complications.

Overall, the existing scientific literature confirms that changes in the oral microflora have significant diagnostic and prognostic importance in patients with leukemia. Therefore, an individual approach to treating stomatitis, based on microbiological analyses, is necessary. When selecting antibacterial and antifungal therapy, the composition of the microflora, the patient's immune status, and pharmacological interactions must be systematically analyzed.

Furthermore, it is advisable that future research focuses on exploring ways to modulate the oral cavity microbiota, including modern approaches such as probiotic agents, prebiotics, and microbiota transplantation. These directions are considered promising for increasing the effectiveness of preventing and treating stomatitis in patients with leukemia.

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