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MICROFLORA CHANGES OF ORAL CAVITY IN PATIENTS WITH SYSTEMIC SCLERODERMA AND SJOGREN'S SYNDROME

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Abstract

Oral microflora plays an important role in maintaining the patient's health and protecting the body from pathogenic microflora, which is an etiological factor in many dental diseases, and can also lead to various pathological conditions, including immuno-inflammatory rheumatic diseases. One example is systemic scleroderma. Systemic scleroderma is a progressive polysyndromic immuno-inflammatory rheumatic disease with characteristic changes in the skin, musculoskeletal system, various internal organs and common vasospastic disorders, including Raynaud's syndrome.

The aim of our study was to reveal the changes of oral microflora in patients with systemic scleroderma and Sjogren's syndrome.

The study included 30 patients with systemic scleroderma and 25 patients with Sjogren's syndrome. Bacteriological investigations of oral microflora were performed. The control group included 30 patients without rheumatologic pathology. To assess the intensity of caries and the level of oral hygiene, the caries intensity index and Oral Hygiene Indices-Simplified were determined.

The average caries intensity index in the systemic scleroderma group was 17.8±7.08 (very high caries intensity), the average Oral Hygiene Indices-Simplified was 2.27±0.7 (satisfactory hygiene); in the control group the average caries intensity index was 15.25±5.06 (high caries intensity), the average value of the Oral Hygiene Indices-Simplified - 2.01±0.6 (satisfactory hygiene). According to the results of a microbiological study in patients with systemic scleroderma, in 21.95% of cases pathogenic Staphylococcus aureus was detected in an etiologically significant amount $>10^6$ CFU/ml, in the Sjogren's syndrome group it was detected in 28.36% of cases, in the control group – in 7.81% of cases. Candida albicans in an etiologically significant amount $>10^6$ CFU/ml was detected in 20.73% of cases in the systemic scleroderma group, in 20.9% of the Sjogren's syndrome group and in 9.38% of cases in the control group. Conclusions: high level of caries intensity and an unsatisfactory level of oral hygiene were detected. Dysbiotic shift of 3 degrees in patients with systemic scleroderma and Sjogren's syndrome was observed.

Keywords: *systemic scleroderma, Sjogren's syndrome, dysbiosis.*

Introduction

The oral cavity is a complex ecosystem that includes a wide range of microorganisms with a high density of microbial contamination, quantitatively only to the large intestine microflora. The composition of the microbial flora of the oral cavity is heterogeneous. In different areas, different quantitative and qualitative composition of organisms is determined [*Aznauryan A et al., 2017*]. Bacteria occupy a dominant position both in terms of the variety of species living in the oral cavity and in terms of the number. The number of bacteria in the oral cavity in terms of the number of species and content per unit of material competes with the gastrointestinal tract. The concentration of oral microflora normally has a relative constancy and is characterized by the following indicators: streptococci $10^{6\text{-}7}$ *CFU/ml*, lactobacilli - 10^3 *CFU/ml*, staphylococci - 10^3 *CFU/ml*, fungi of the genus Candida - 10^2 *CFU/ml*, saprophytic neiseria – 10^5 *CFU/ml* while Escherichia coli bacteria are absent [*Guseva N, 2011*]. The species composition

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of the oral microflora is characterized by a certain level of balance between the available strains, despite the environmental situation, hygienic status, features of immune protection, daily changes in the amount and composition of saliva, etc. [*Lamont R et al., 2010*]. This balance is achieved by microbial antagonism with normal bacterial flora, which competes with pathogenic bacteria and fungi for nutrients, and also inhibits their growth. Oral microflora plays an important role in maintaining the patient's health and protecting the body from pathogenic microflora, which is an etiological factor in many dental diseases, and can also contribute to reducing immunity and increasing the risk of developing various pathological conditions, including immuno-inflammatory rheumatic diseases [*Martynova E et al., 2008a; Mineoka T et al., 2008b; Gordeev A et al., 2018*]. Oral cavity microorganisms secrete various endotoxins, primarily lipopolysaccharides and structural antigens of gram-negative bacteria, which are able to induce and maintain inflammation. Normally, the qualitative and quantitative composition of the oral microflora is quite stable, and various microorganisms are in a harmonious balance [*Chapple I, Matthews J, 2007; Arzukanyan A et al., 2020*]. However, there are many factors that can lead to changes in the oral microflora: age, smoking, chronic somatic diseases, consumption of various medications [*Tokmakova S et al., 2001*].

Systemic scleroderma is a progressive polysyndromic immuno-inflammatory rheumatic disease with characteristic changes in the skin, musculoskeletal system, various internal organs (lungs, heart, digestive tract, kidneys) and common vasospastic disorders, including Raynaud's syndrome. The disease is based on connective tissue damage with a predominance of fibrosis and vascular pathological changes in the form of obliterating microangiopathy. The etiology of systemic scleroderma is complex and insufficiently studied. A multifactorial genesis of the disease is assumed, due to the interaction of different factors with a genetic predisposition to the disease. Despite a large amount of date about systemic scleroderma the main idea of the etiology and pathogenesis of the disease remains unclear. Among the various views on the nature of the fibrotic process and microvascular damage, great importance is currently attached to T-cell immune disorders [*Vincent C et al., 2009; Guseva N, 2011*]. Immune cell mediators, cytokines, are considered as the main factors in the pathophysiology of sclerodermic fibrosis. Systemic scleroderma can lead to a wide range of pathological changes in the maxillofacial region, in particular, to narrowing of the oral aperture due to compaction of the surrounding tissues. These changes have a negative effect on the patient's quality of life and significantly complicate oral hygiene, which can contribute to violations of the oral microbiocenosis with a predominance of pathogenic microflora [*Poole J et al., 2005; Thombs B et al., 2009*].

The diagnosis and treatment of dental disorders in patients with systemic scleroderma is an important interdisciplinary problem that unites dentistry and rheumatology.

Microbiological examination is a simple and non-invasive method for determining the qualitative and quantitative composition of the oral microflora that makes possible to diagnose disorders and adapt dental care methods for a specific patient [*Peterson J et al., 2009; Selifanova E, Simonova M, 2009*]. In some cases systemic scleroderma was accompanied by Sjogren's syndrome.

The aim of the study was to study the composition of the oral microflora in patients with systemic scleroderma and Sjogren's syndrome.

MATERIAL AND METHODS

The prospective study included 30 patients with an systemic scleroderma and 25 patients with systemic scleroderma + Sjogren's syndrome who were observed at the V.A. Nasonova Research Institute of Rheumatology. The study was approved by the local ethics committee. All patients signed an informed consent to participate in the study.

The diagnosis of systemic scleroderma responded to the classification criteria of the American College of Rheumatology and the European League Against Rheumatism. Inclusion criteria were age over 18 years, diagnosis systemic scleroderma (diffuse and limited

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

form), diagnosis Sjogren's syndrome. Exclusion criteria were the chronic virus infections (HIV, hepatitis B, C), cancer, pregnancy, smoking. The median age of patients was 61.2 years in the systemic scleroderma group and 63.2 years in the systemic scleroderma + Sjogren's syndrome group. All patients received immunosuppressive treatment including glucocorticoids (100%), cytostatics (60%), and the genetically engineered biological drug rituximab (20%). The control group included 30 patients without rheumatological pathology, but with some general diseases (arterial hypertension, chronic gastritis). The median age in control group was 58.3 years.

The caries intensity index (DMF) and the Oral Hygiene Indices-Simplified (OHI-S) were used for dental assessment [*Molokov V, Dorzhieva Z, 2008*]. The DMF index (decay, missing, filled) is considered as very low with a total index of less than 1.5; low - up to 6.2; moderate - up to 12.7; high - up to 16.2 and very high - more than 16.3. The Green-Vermillion hygiene index (OHI-S) allows an objective assessment of the state of individual oral hygiene and separately assesses the amount of plaque and dental calculus. To determine it, the vestibular surfaces 16, 11, 26, 31 and lingual surfaces 36, 46 were examined using plaque indicators. Good hygiene (0-1.2 points) was considered as a low hygiene index; satisfactory hygiene (1.3 - 3.0 points) as an average hygiene index and unsatisfactory hygiene (3.1-6.0 points) as a high hygiene index [*Molokov V, Dorzhieva Z, 2008*].

All patients underwent a microbiological study. Scrapings were taken in the morning on an empty stomach using disposable sterile probes in places of the greatest accumulation of plaque, as well as from the mucous membrane of the tongue, palate and cheek. For storage and transportation, the probe shank was cut off with sterile scissors and placed in a disposable test tube with a nutrient medium. All the obtained biomaterials were transported to the laboratory in special thermal containers at a temperature of 4ºC.

In the laboratory the material was examined using standard microbiological media. Identification of isolated microorganisms was performed based on morphological, cultural, biochemical, and antigenic characteristics in accordance with the Bergey classification (1980) [*Lamont R et al., 2010*]. In the isolation of pathogenic and facultative bacteria we used 5% blood and chocolate agars, for the selection of Streptococcus and Candida - nutrient medium Saburo, to isolate gram-negative and gram-positive bacteria – tripcase soy agar. The cultivation time under anaerobic conditions was up to seven days. The results of a quantitative study of microflora were calculated in colony-forming units (*CFU/ml*). Based on morphological, tinctorial, and biochemical characteristics and the study of the antigenic structure, identification was performed using a binary nomenclature with the determination of the amount of the isolated strain in the material.

Statistical data processing was performed in SPSS Statistica version 23.0.0.0 (USA). Equality of variances between the groups of control group (n=30), systemic scleroderma (n=30) and systemic scleroderma + Sjogren's syndrome (n=25) by non-parametric one-factor analysis of variance by Kruskal-Wallis. The differences were considered significant at $p<0.05$.

RESULTS

According to dental examination data (Table, Fig. 1) in the systemic scleroderma group the DMF index was 17.8±7.08 on average, the OHI-S index was 2.3±0.7 on average; in the systemic scleroderma + Sjogren's syndrome group the DMF index was 21.7±7.4. on average, the OHI-S index was 2.7±0.7. on average, the DMF and OHI-S index values were lower in the control group 15.3±5.06 and 2.01±0.6, respectively, but the differences were not statistically significant (p 0.21 – 0.24). Examination of the orofacial area in patients with systemic scleroderma is shown in figures 1, 2.

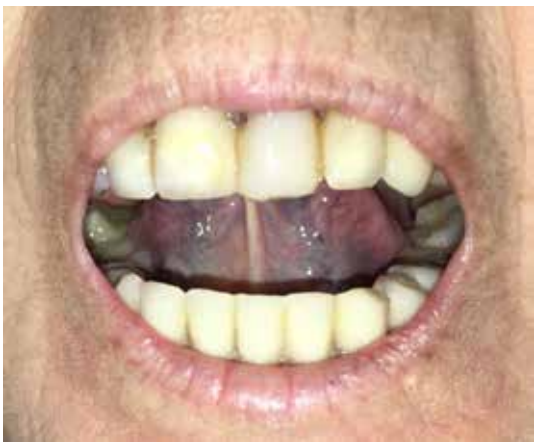

FIGURE 1. *Microstomia in patient with systemic scleroderma*

Table 1.

Results of microbiological investigation.

Bacteria	Groups n(%)			p value Kruskal Wallis Test	p_1	p_2	p_3
	C n=30	SSc n=30	SSc+SS n=25				
Candida albicans	6 (9.38 %)	17 (20.73 %)	14 (20.9 %)	0.006	0.013	0.023	1.000
Enterobacter cloacae	1 (1.56 %)	2 (2.44 %)	1 (1.49 %)	0.816	—	—	—
Enterococcus faecalis	0 (0 %)	3 (3.66 %)	3 (4.48 %)	0.168	—	—	—
Escherichia coli	1 (1.56 %)	1 (1.22 %)	4 (5.97 %)	0.119	—	—	—
Klebsiella pneumoniae	1 (1.56 %)	5 (6.1 %)	4 (5.97 %)	0.208	—	—	—
Lactobaccilus acidophilus	7 (10.94 %)	0 (0 %)	0 (0 %)	0.001	0.003	0.006	1.000
Lactobaccilus brevis	5 (7.81 %)	0 (0 %)	0 (0 %)	0.008	0.019	0.028	1.000
Staphylococcus aureus	5 (7.81 %)	18(21.95 %)	19 (28.36 %)	0.000	0.003	0.000	0.720
Streptococcus salivarius	10 (15.63 %)	2 (2.44 %)	2 (2.99 %)	0.009	0.017	0.037	1.000
Streptococcus oralis	7 (10.94 %)	3 (3.66 %)	2 (2.99 %)	0.197	—	—	—
Streptococcus viridans	10 (15.63 %)	9 (10.98 %)	9 (13.43 %)	0.895	—	—	—

Notes: *C – control group, SSc – Systemic scleroderma group, (SSc+SS) - systemic scleroderma + Sjogren's syndrome group,* p_1 *- SSc vs C,* p_2 *- (SSc+SS) vs C ,* p_3 *- (SSc+SS) vs SSc*

Results of microbiological investigation are shown in table. Staphylococcus aureus in an amount $>10^6$ *CFU/ml* were detected in 21.95% of patients with systemic scleroderma and 28.36% of patients with systemic scleroderma + Sjogren's syndrome, in the control group it was present in 7.81% of cases. Candida albicans in the amount of $>10^6$ *CFU/ml* was detected in 20.73% of patients with systemic scleroderma, 20.9% with systemic scleroderma + Sjogren's syndrome and 9.38% in the control group. There were no statistically significant differences in the composition of the oral microflora between patients with systemic scleroderma and systemic scleroderma + Sjogren's syndrome. Streptococcus salivarius was significantly more common in patients of the control group (15.63%), p=0.009. The absence of such representatives of normal microflora as Lactobaccilus acidophilus, Lactobaccilus brevis, a significant decrease in Streptococcus salivarius, as well as the presence of pathogenic bacteria, including Klebsiella pneumonia , Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, allows us to diagnose a shift of three degrees in 90% of cases of patients with systemic scleroderma and systemic scleroderma + Sjogren's syndrome dysbiotic.

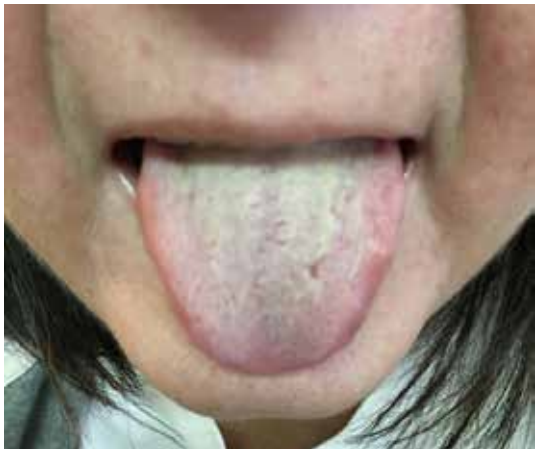

Figure 2. *Candidiasis of oral cavity in patient with systemic scleroderma.*

Discussion

The composition of the microbial flora of the oral cavity is heterogeneous. In different areas, a different quantitative and qualitative composition of organisms is determined [*Kodola H, Prudnikova A, 1988*]. Bacteria occupy a dominant position both in terms of the variety of species living in the oral cavity and in terms of the number. The number of bacteria in the oral cavity in terms of the number of species and the content per unit of material competes with the gastrointestinal tract [*Komarovskaya T, 1984*]. The following picture is seen in several biotopes: the oral mucosa has a variable composition of microflora. However, it can be determined that its surface contains mainly gram-negative anaerobic and facultative anaerobic flora,

as well as streptococci. In the sublingual area, in the folds and crypts of the mucosa, obligate-anaerobic species predominate.

The gingival groove is a second biotope with the gingival fluid located in it. Due to the isolation of this zone from the oral cavity as a whole, the composition of the microflora here differs significantly from other parts of the oral cavity. Filamentous obligate-anaerobic bacterial species predominate here. It is also home to bacteroids, porphyromonads, protozoa and mycoplasmas [*Orehova L et al., 2013*]. Oral fluid is a third, important biotope. Through it, the relationship between all other biotopes of the oral cavity is carried out [*Ushakov R, Tsarev V, 1999*]. It is localized on the surface of the tooth, and almost all the microorganisms mentioned above are detected in it.

Results of our study showed that patients with systemic scleroderma and systemic scleroderma + Sjogren's syndrome have severe dysboisis of the oral cavity. Dysbacteriosis of the oral cavity was accompanied by a very high level of caries intensity in systemic scleroderma - 7.8±7.08, which may be associated with a low level of oral hygiene observed in the examined patients with systemic scleroderma (OHI-S 2.3±0.7)). Thinning of the lips, subcutaneous fibrosis in the mouth area, with the formation of a so-called pouch, and damage to the temporomandibular joints lead to a decrease in the oral aperture with a significant restriction of opening and closing the mouth, which prevents adequate oral hygiene. In addition, patients with systemic scleroderma receive immunosuppressive therapy, which in turn contributes to pathological changes. Thus, in the study of the oral microflora, the presence of Candida albicans in patients with systemic scleroderma was detected much more often than in the control group.

From our point of view the lesion of the oral mucosa in patients with systemic scleroderma consists of two main components: a decrease in the hydrophilization of the mucosa due to sclerotic changes in the salivary gland ducts and the multiplication of secondary infection, which occurs under conditions of changes in the quantity and quality of saliva and a decrease in its protective properties [*Selifanova E, Simonova M, 2009*]. Dysbiotic shift in the microflora can cause local inflammation that can influence on somatic pathology [*Mineoka T et al., 2008*]. However, for example, Staphylococcus aureus is known to play an important role in the initiation and recurrence of the granulomatosis with polyangiitis [*Popa E et al., 2007*]. Streptococcus viridans and staphylococci are the leading etiological agents of infectious endocarditis. The virulent species that can support the inflammatory process in the oral cavity, skin, and lungs should also include yeast-like fungi of the genus Candida. In addition, lactobacilli that support normal microbiocenosis and prevent the growth of pathogenic microflora are not detected in the oral cavity in patients with systemic scleroderma and systemic scleroderma + Sjogren's syndrome. Successful treatment of the dysbiotic changes in the oral cavity as part of complex therapy can improve the results of treatment of the patients with systemic scleroderma.

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THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021). No 1

CONTENTS

4. ***Esayan M.S., Selifanova E.I., Margaryan E.G., Makeeva I.M.***
MICROFLORA CHANGES OF ORAL CAVITY IN PATIENTS WITH SYSTEMIC SCLERODERMA AND SJOGREN'S SYNDROME

10. ***Sitdikova O.F., Kabirova M.F, Gerasimova L.P., Kudashkina N.V, Gubina O.F.***
INTERCONNECTION BETWEEN THE PECULIARITIES OF CHRONIC GINGIVITIS AND THE DENTAL PLAQUE BIOFILM COMPOSITION UNDER CONDITIONS OF PSYCHOEMOTIONAL STRESS

19. ***Romanenko I.G.,Golubinskaya E.P., Zyablitskaya E.Yu., Arakelyan K.A., Makalish T.P.***
MUCOUS MEMBRANE OF THE ORAL MUCOSA ON THE MODEL OF COMPLICATIONS OF HIGH-DOSE RADIATION AND CYTOSTATIC CANCER THERAPY OF THE OROPHARYNGEAL REGION

27. ***Gireeva A.I., Polyakova M.A., Lalaev K.V., Babina K.S., Sokhova I.A., Doroshina V.Yu., Selifanova E.I., Eshtieva A.A., Kadzhoyan A.G., Podkhvatilina A.S., Pianzina A.V., Novozhilova N.E.***
ORAL HYGIENE LEVEL AND COMPOSITION OF ORAL MICROBIOTA IN PATENTS WITH PEMPHIGUS VULGARIS DURING THE PERIODS OF EXACERBATION AND REMISSION

34. ***Apresyan S.V., Stepanov A.G.***
THE DIGITAL PROTOCOL DEVELOPMENT AND EFFECTIVENESS EVALUATION FOR COMPLEX DENTAL TREATMENT

44. ***Alfarraj M. ,Karabit Z.***
EVALUATION OF THE EFFICACY OF PLATELET RICH FIBRIN ON THE FOLLOWING COMPLICATIONS AFTER SURGICAL EXTRACTION OF THE LOWER THIRD MOLAR IN SMOKER PATIENTS (RANDOMIZED CLINICAL TRIAL)

53. ***Shhada J, Abou Nassar J, Almodalal M.A***
INFLUENCE OF CASTING ON MARGINAL FIT OF METAL COPINGS FABRICATED FROM WAX OR LIGHT-CURED RESIN (IN VITRO STUDY)

59. ***Volkov A.G., Dikopova N.Zh., Arzukanyan A.V., Kondratiev S.A., Paramonov Yu.O., Budina T.V., Tan Huiping***
DISTRIBUTION OF METAL COMPOUNDS IN THE TISSUES OF THE ROOT OF THE TOOTH WITH APEX-FORESES (IONTOPHORESIS OF COPPER AND SILVER)

67. ***Margaryan E. G, Daurova F.Yu., Atanesyan A. V.***
THE IMPACT OF PROFESSIONAL ACTIVITIES ON PERSONAL LIFE AND HEALTH OF DENTISTS

72. ***Kharazian A.E.' Gevorkyan A.A.***
3D PRINTED MID-FACE NON-DELAYED PROSTHETIC RECONSTRUCTION AFTER CANCER SURGERY OF ORBIT (EXENTERATION)

77. ***Dikopova N.Zh., Volkov A.G., Kopecky I.S., Nikolskaya I.A., Margaryan E.G., Budina T.V., Samokhlib Ya.V., Kondratiev S.A., Paramonov Yu.O., Arakelyan M.G.***
CLINICAL AND EXPERIMENTAL VALIDATION OF THE OZONE THERAPY EFFECTIVENESS IN CASE OF ACCIDENTAL EXPOSURE OF THE DENTAL PULP

85. ***Kolesnik K.A, Romanenko I.G.***
CHANGES IN TOOTH HARD TISSUES AND PERIODONTAL TISSUES DURING ORTHODONTIC TOOTH MOVEMENTS IN RATS WITH EXPERIMENTAL GASTRITIS

91. ***Gizhlaryan M. S., Mesrobian A.A., Tamamyan G. N, Anastasiadi M. G., Sahakyan L. S., Krmoyan L.M., Petrosyan M. T., Melnichenko I. V., Danelyan H. S., Danielyan S. H., Vagharshakyan L. H.***
CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA: A SINGLE-INSTITUTION REPORT

95. ***Chebysheva S.N., Zholobova E.S., Geppe N.A., Aleksanyan K.V., Meleshkina A.V., Nikolaeva M.N., Khachatryan L.G., Farber I.M.***
FEATURES OF PSORIATIC SKIN LESIONS IN CHILDREN WITH JUVENILE PSORIATIC ARTHRITIS

100. ***Gelezhe K.A., Kudravtseva A.V., Ryzhii E., Khachatryan L.G., Bogdanova E.A. , Svitich O.A.***
THE ROLE OF THE SKIN MICROBIOME IN THE DEVELOPMENT OF ALLERGIC INFLAMMATION IN ATOPIC DERMATITIS

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