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Research Article

COVID-19 AND CLINICAL AND IMMUNOLOGICAL ASPECTS OF THE ORAL CAVITY IN WOMEN

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ABSTRACT

The study included 254 Covid-19 positive patients, from which 105 eligible patients were selected. The aim of the study was to determine the damage to the oral cavity in various degrees of severity of coronovirus infection, for early prediction of the clinical course of COVID-19 by using modern methods for studying local immune and inflammatory responses of the oral mucosa. During the study, the state of the oral cavity, laboratory data, including the determination of the level of IgA and IL-17, were studied, as well as bacteriological culture was carried out. During the study, an oral manifest was determined, indicating a high expression of ACE-2 receptors in the oral cavity, an inverse correlation with the clinical course of the disease and the state of the oral cavity, a complete blood count is less informative compared to determining the level of IgA and IL-17.

KEYWORDS

Covid-19, ACE-2 receptor expression, IgA level, IL-17 level, bacterial culture, C-reactive protein (CRP), SARS-CoV-2.

INTRODUCTION

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Despite the fact that the current coronavirus epidemic is receding into the background, post-Covid conditions are increasingly attracting the interest of researchers in various fields of medicine. As we know, coronavirus infection (COVID-19) is caused by an RNA virus belonging to the beta-corona subfamily, and currently has many strains.

According to the WHO, "as of February 6, 2022, more than 392 million people worldwide have been diagnosed with COVID-19, and more than 5.7 million deaths have occurred." Complex treatment of this disease with a full understanding of the complex pathophysiological mechanisms of penetration of COVID-19 into a human cell and the study of complex, both systemic and local immuno-inflammatory reactions is one of the most complex, global sections in modern virology and today the problem is far from your permission. Currently, there are a number of approved global and national strategies and certified vaccines for the diagnosis and treatment of COVID-19, however, "given the clinical manifestation in the form of changes in the oral mucosa, the question of studying the ability of COVID-19 to directly infect the oral cavity and multiply in the salivary glands or oral mucosa remains unresolved."

The question of the progression of COVID-19 related to the development and role of the local immune response of the oral mucosa against SARS-CoV-2 still remains a controversial issue. It is known that SARS-CoV-2 affects the upper respiratory tract, penetrating both through the nasal epithelium and through the tonsils and adenoids, which contributes to the immune-inflammatory response of the mucous membranes and lymphoid tissue of the nasopharynx (Brandtzaeg P., 2015). It is reported that in a SARS-CoV-2 patient with periodontal disease, the general condition may worsen due to the downregulation of ACE-2 and the increase in ACE and angiotensin II, leading to the involvement of several pro-inflammatory factors. At the same time, there is little mention in the literature about the role of the oral mucosa in the development of a local inflammatory response during SARS-CoV-2 (Czerkinsky C., 2011). It has long been known that secretory immunoglobulin A (sIgA) of the mucous membrane is crucial in the fight against viruses that enter the body through mucous membranes, which is confirmed much more often by the determination of anti-SARS-CoV-2 sIgA in the oral cavity in asymptomatic or low-symptomatic COVID patients -19 patients (p=0.02) (Caselli E., 2020). It is reported that microbiome composition such as Prevotella, Lactobacillus, Capnocytophaga, Porphyromonas, Abiotrophia, Aggregatibacter and Atopobium interacts with and influences the IgA response in different anatomical structures (Salk H., 2016; Grosserichter-Wagener C., 2019; Pabst O., 2020).

During the observation period of patients, one of the common symptoms was a change in the sense of taste,

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the formation of plaques on the tongue and swelling of the palate, tongue and gums [9]. To date, according to the results of a study by Chinese scientists, the most commonly described oral manifestation associated with COVID-19 is dysgeusia (complete or partial loss of the sense of taste of food), the frequency of which varies from 5.6% [14] to 88.8% [15].

Cases of new-onset bad breath in a patient with COVID-19 have been described. Using a halimeter, the team found that patients had elevated sulfur levels during the active phase of SARS-CoV-2 disease and normal sulfur levels after the active phase [17], which is most likely due to a primary, virus-mediated change in the oral mucosa or secondary changes associated with dry mouth and decreased salivation.

Histological analysis of oral lesions from SARS-CoV-2 revealed vascular changes in the oral mucosa [18] and the association of the pathogenesis of COVID-19 oral mucosal lesions with the accumulation of lymphocytes and Langerhans cells in the vasculature of the subcutaneous junction. The virus causes the synthesis of cytotoxic lymphocytes, under the influence of which keratinocytes are destroyed [19]. Histological examination of biopsies from patients with COVID-19 who also had cutaneous manifestations confirmed vascular ectasia with dilated capillaries and a perivascular lymphocytic infiltrate with eosinophilia [18].

Studies have shown the presence of viral particles in the gingival crevice, which is believed to create favorable conditions for the replication and persistence of the virus [12]. Moreover, SARS-CoV-2 infection of the salivary glands can produce large amounts of viruses in the tissues of the salivary glands and release them into oral secretions [20]. Studies conducted in rhesus monkeys have shown that there is rapid infection of salivary gland epithelial cells by SARS-CoV-2, suggesting that the salivary glands are the primary sites of coronavirus proliferation [11].

In COVID-19, salivary gland secretion is often disrupted due to xerostomia and loss of taste [13]. Xerostomia is a subjective complaint of dry mouth due to hypofunction of the salivary glands. In SARS-CoV infections, xerostomia may be aggravated by increased oral breathing due to difficulty in nasal breathing, which is caused by nasal congestion and rhinorrhea [9]. Also, psychosocial factors caused by the pandemic have a negative impact on the function of the salivary glands and salivary secretion [9, 16].

Saliva-based diagnosis of COVID-19 is receiving increasing attention for several important reasons. First, obtaining a saliva sample is an easy and non-invasive procedure and minimizes the likelihood of healthcare workers becoming infected with the highly virulent SARS-CoV-2 virus. Secondly, this diagnostic method is suitable for screening and for patients of special groups - elderly people, pediatric patients [14].

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According to the literature, compared with nasopharyngeal aspirate, saliva testing is 92% positive for SARS-CoV-2. Also, live virus can be successfully cultured through saliva samples, highlighting the value of saliva in the diagnosis of COVID-19 [15], in both symptomatic and asymptomatic patients [16].

Also of interest are the results of the study by Huang et al. [17], who indicate two potential sources of SARS-CoV-2 in saliva: a cell-free fraction from infected glands that produces virus de novo, and a cellular fraction from infected oral mucosa. To study the infectivity of both cell-free and cellular fractions of saliva and the cytopathic effect of the virus, saliva samples with high viral loads from COVID-19 patients were incubated with Vero cells. After confirming the presence of SARS-CoV-2 RNA in the saliva of asymptomatic individuals, samples were processed to extract cell-free salivary fluid from epithelial cells. It has become known that cell-free saliva induces a cytopathic effect of the virus starting from the 2nd day and this effect becomes more pronounced on the 6th day. The cell fraction induced a cytopathic effect only on the 6th day. These results demonstrate that saliva is contagious in both asymptomatic and symptomatic patients with COVID-19.

According to the above, early detection of SARS-CoV-2 in saliva can be important in diagnosing patients with COVID-19 before the onset of respiratory symptoms in asymptomatic patients, which greatly helps to control infection in society, especially in quarantine areas [11, 20, 22].

Purpose of work determination of damage to the oral cavity in various degrees of severity of coronavirus infection, for early prediction of the clinical course of COVID-19 by using modern methods of studying the local immune and inflammatory responses of the oral mucosa.

METHODS

The scope of work was 254 patients with COVID-19 who were treated at the SamSMU multidisciplinary clinic from June 2021 to October 2021, of which 105 women, taking into account the inclusion criteria, were included in the study. All patients had a positive PCR test result for COVID-19. Laboratory confirmation was carried out using the AmpliSens® Cov-Bat-FL test system.

Exclusion criteria from the study were:

- history of chronic smoking;
- severe obesity with body mass index ≥35kg/m2;
- concomitant diseases (diabetes mellitus, cardiovascular diseases, arterial hypertension, chronic renal failure, chronic obstructive bronchitis, diseases controlled by immunosuppressive therapy).

The questionnaire was created and approved by an expert committee consisting of dentists and general

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practitioners of our institute. Written consent was obtained from all patients for questionnaire data collection using a telephone interview, as well as for examination. All patients underwent a daily visual examination of the oral cavity, registration and assessment of the features of the clinical course of the disease, the severity of temperature, and symptoms of intoxication. In order to assess the impact of initial oral health as a primary endpoint on the severity of COVID-19, oral health was interpreted in accordance with the scoring system. The questionnaire consisted of 18 questions. Total scores ranged from 0 to 37, with a higher score indicating good baseline oral health.

Based on the total score of the oral oral health survey, patients were classified as follows:

- poor oral health with a threshold of 0–14;
- satisfactory oral health with a threshold of 15–23;
- good oral health with a threshold of 24–37.

Patients also underwent laboratory tests - a complete blood count, determination of the level of C-reactive protein, analysis of immunoglobulin A, analysis of cytokine concentrations. Microbiological research was carried out by inoculation on solid nutrient media using a WASP device, Copan, Italy. Identification of microorganisms was carried out by mass spectrometry using a Microflex Brucker MALDI Biotyper, Brucker, Germany.

RESULTS

During the examination, the following changes were identified: Plaque of the mucous membrane of the tongue in 86.6%, parageusia in 60.9%, Pigmentation in the area of attachment of the gums to the upper and lower jaw in 42.8%, angular cheilitis in 24.7%, U- shaped papillitis in 14.3%, hemorrhagic manifestations on the buccal mucosa in 12.4%, lentigo in 12.4%, aphthous stomatitis in 10.5%, glossalgia in 8.5%, swelling of the tongue 7.6%, cavity candidiasis mouth in 6.6%, mucositis in 5.7%, pigmentation of the hard palate and glossitis with focal depapilation in 4.7%. Also, dysfunction of the sense of smell was noted in 81% in the form of parosmia and in 10.5% in the form of anosmia.

According to the survey, 80% of patients had signs of severe COVID-19, and 20% had mild symptoms. The initial oral health status was poor in 73.8% of patients with severe disease and in one patient with mild disease. 20.2% of patients with severe Covid and 80.9% with mild Covid had satisfactory oral health. The oral cavity condition was assessed as good in only 5.9% of patients with severe disease and 14.2% with mild disease.

According to the results, it could be observed that the initial good oral condition in 79.4%, satisfactory condition in 17.4% and poor condition in 3.2% were determined in the first week. In the second week, it

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was possible to notice an increase in the mild degree of the disease and, accordingly, good oral health. But in severe cases, a negative trend of 8.6% was observed with an increase in poor oral health.

The study noted a negative correlation between the initial state of the oral cavity and the period of clinical recovery of patients with COVID-19 ($p < 0.001$, $r = -0.614$). Since at the 4th and 6th weeks of observation, clinical recovery was on average in 44.8% of patients with poor oral health, and only 7.1% with good one.

In terms of recovery time, patients with good oral health were ahead (85.8%), followed by patients with satisfactory oral health (56.8%).

Accordingly, clinical recovery as soon as possible (second week of observation) was 7 times more likely to be observed in the group with a clinically mild course (71.2%) compared to the group with a severe course (8.3%) ($p < 0.001$), but in the fourth week observation there was a crossover of indicators: in patients with a mild course, clinical recovery was in 19.0% of cases, and in the group with a severe course - 41.6% ($p < 0.001$).

According to laboratory studies, the level of eosinophils was reduced in 54.3% of patients. An increase in the value of leukocytes occurred in 9.5% of patients, while there was no increase in leukocytes during hospitalization, while a decrease in the number of leukocytes was noted in 15 (14.3%) patients. There was also a decrease in the concentration of lymphocytes in 15.2%. An increase in fibrinogen was found in 68 people (average 5.96±1.6 g/l). The average C-reactive protein (CRP) level was 38.1±24.7 mg/dL; it is noteworthy that the patients had no concomitant pathologies with such C-reactive protein values.

It is worth noting that the incidence of elevated CRP values (>18 mg/dL) was significantly observed in 73.8% of patients with severe clinical course of COVID-19 ($p < 0.001$), while lower CRP values (5-18 mg/dL) were significantly were observed in mild cases of COVID-19 in 85.7% of patients ($p < 0.025$; $r = -0.478$).

According to the results of a bacteriological study of culture for microflora from the oral cavity, the microflora profile in patients with COVID-19 changed statistically significantly compared to the control group. Specifically, the relative abundance of the bacterial species Streptococcus oralis (20% vs. 8%), Veillonella parvula (25% vs. 19%), Neisseria mucosa (11% vs. 8%), Lactobacillus fermentum (6% vs. 4%) was determined in patients with COVID-19 compared to controls, while Haemophilus parainfluenzae (13% vs. 20%), Fusobacterium (8% vs. 20%), Neisseria subflava (3% vs. 11%), Gemella sanguinis (3% vs. 10%) fewer came to light. Notably, the genera Enterococcus faecalis (11% vs. 0%) were present exclusively in COVID-19 patients and were not detected in control subjects ($p < 0.001$).

A statistically significant increase in IgA in the oral mucosa was detected in 73/105 (69.5%) patients with

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COVID-19 compared with this indicator in the control group (p=0.004). According to the data obtained, 21 of 105 patients (20.0%) had a very high concentration of sIgA (> 2.0), 22 of 105 patients (21.0%) had intermediate sIgA values (0.8-2 .0), while 62 of 105 patients (59.0%) had a threshold sIgA value (<0.8) or no sIgA (p=0.004).

The value of IL-6 (p=0.004) was significantly higher in patients with COVID-19 compared with that value in the control group. Also, a statistically significant higher level of IL-17 was found in patients with COVID-19 compared to this indicator in the control group (p = 0.025).

Summarizing the study data, it can be noted that a high level of damage to the oral mucosa occurred in 91 patients (86.6%). Damage to the oral cavity had an inverse correlation with the clinical course of the disease, although the dynamics of recovery were consistent with the literature data. Despite this, greater rates of clinical recovery were observed in patients with poor initial oral health.

Laboratory data showed an inflammatory response in the body with a slight increase in white blood cells (9.5%), a decrease in eosinophils (54.3%) and lymphocytes (15.2%), an increase in fibrinogen (64.7%) and CRP (73.8%).). Bacteriological culture indicates an increase in various microflora, both pathogenic and conditionally pathogenic.

A statistically significant increase in IgA in the oral mucosa was detected in 69.5% of patients with COVID-19; a high level of IL-17 was found in patients with COVID-19 in comparison with this indicator in the control group (p = 0.025).

CONCLUSION

Based on the data, we can conclude that a high level of oral manifestation indicates a high expression of ACE-2 receptors in the oral cavity; this undoubtedly requires special attention in organizing dental treatment and preventive consultations for patients, since in this case the indicators of a general blood test have minor changes from the norm. Also, during diagnosis, it is necessary to use determination of the level of IgA in the oral mucosa and IL-17, which have diagnostic value for the early detection of patients with COVID-19.

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