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ORAL HYGIENE LEVEL AND COMPOSITION OF ORAL MICROBIOTA IN PATENTS WITH PEMPHIGUS VULGARIS DURING THE PERIODS OF EXACERBATION AND REMISSION

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Abstract

Vulgar pemphigus is a rare autoimmune disease characterized by the development of blisters and erosions on visually unchanged skin and mucous membranes due to acantholysis. It is the most common type of pemphigus, accounting for 70% of all pemphigus cases in the world. The main therapeutic goal is to decrease the inflammatory response and production of autoantibodies. No specific treatment for vulgar pemphigus is currently developed, and corticosteroids and immunosuppressants are widely used for the treatment. Long-term intake of corticosteroids leads to the alterations in protein and mineral metabolism which may manifest as the decrease of both systemic and local host response and the progression of dental diseases such as caries, gingivitis, and periodontitis.

Thirty consent patients aged 18-75 years were recruited for the study, 16 females (53 %) and 14 males (47%). The main age was 50±14 years, 49±17 years and 51±9 years for female and male patients, respectively. The diagnosis of pemphigus vulgaris (ICD-10: L.10.0) was confirmed by primary and secondary immunofluorescence. The level of individual oral hygiene (plaque index, PI, Russel A., 1956) and the composition of oral microbiota (real-time PCR) were compared during the remission and exacerbation phases.

The level of individual oral hygiene was significanly higher in remission ($p<0.001$, effect size = 0.20). The log bacterial counts of P.intermedia, T.denticola, T.forsythensis, and P.gingivalis determined by PCR were significantly lower during the period of exacerbation compared with the period of remission ($p = 0.028$, 0,047, 0.026, and 0.022, respectively). In contrast, the log viral counts of Epstein-Bar virus were significantly greater in exacerbation period ($p = 0.007$).

Keywords: *pemphigus vulgaris, polymerase chain reaction, exacerbation, remission, chronic periodontitis.*

Introduction

Pemphigus refers to a group of autoimmune, mucocutaneous blistering diseases, in which the keratinocyte antigens are the target of the autoantibodies, leading to acantholysis and blister formation. In more than 60% of patients with pemphigus vulgaris, the disease manifests with the development of intraepidermal blisters on the oral mucosa, which disrupt soon with the formation of painful ulcers and erosions. And as a rule, a dentist is one of the first to encounter this disease. For a long time, the intraoral lesions may remain the only manifestation of pemphigus vulgaris, leading to the inappropriate diagnosis and therapy, and further spread and progression of the disease [*Kuriachan D. et al., 2015; Bulgakov A. I.et al., 2016; Khamaganova I. V. et al., 2017; Kiran K. C.et al., 2018*].

The role of microorganisms in the development of dental pathologies in patients with pemphigus vulgaris is diverse. Microorganisms organized in

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biofilms break down food carbohydrates to form aggressive acids, which, when exposed for a long time, destroy tooth enamel and dentin. Therefore, without regular removal of plaque from the surface of the teeth, caries develops. Thus, violation of oral hygiene, high carbohydrate intake, mucosal damage, and hypofunction of the salivary glands increase the risk of its occurrence and progression [*Gao L. et al., 2018*; *Dikopova N.Zh.et al., 2020*].

The main objective in the treatment of pemphigus vulgaris is to control the disease progression and prevent exacerbations. Systemic corticosteroids remain the gold standard treatment for pemphigus vulgaris. However, prolonged use of steroids entails a large number of side effects [*Sinha A. A. et al., 2015; Harman K. E. et al., 2017; Pollmann R. et al., 2018*]. Long-term intake of corticosteroids leads to the alterations in protein and mineral metabolism which may manifest as the decrease of both systemic and local host response and the progression of dental diseases such as caries, gingivitis, and periodontitis [*Markitziu A. et al., 1990; Van Dyke T. E., Sheilesh D. 2005; Beeraka S. S. et al.,2013*].

Therefore, patients need to be monitored by a dentist even during remission. Oral blistering and dental diseases complicate individual oral hygiene of the patients increasing plaque accumulation and causing changes in the oral microbiota. Flabby blisters with serous contents appear on the unchanged mucous membranes, and they can be located on any site. Over time, their number increases. Bubbles quickly open, forming wet erosions (Fig.1a, 1b).

The appearance of painful erosions makes it difficult to eat, speak, swallow saliva and oral hygiene. There is deterioration in the dental status: there is an increase in soft and hard plaque, the presence of gingivitis, damage to hard tooth tissues. All that leads to a decrease in the quality and criterion of life. In addition, a secondary infection is added, which causes a deterioration in the

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

FIGURE 1. *Oral lesions of pemphigus vulgaris:* ***(a)*** *located to free gingiva with the aspect of marginal gingivitis* ***(b)*** *widespread erosions.*

General condition of patients: weakness and subfebrile temperature appear [*Rath S.K. et al.,2014; Fine D. H. et al., 2017; Khamaganova I. V.et al., 2018; Arzukanyan A.V. et al., 2020*]. These changes may in turn contribute to the progression of oral diseases [Socransky S. S., Haffajee A. D, 2002].

Diagnosis of true pemphigus is based on the totality of the results of clinical, cytological, histological and immunological examinations. Laboratory data (anemia, leukocytosis, increased ESR, proteinuria, hypoalbuminemia, decreased urinary sodium excretion, etc.) play a certain auxiliary role, allowing to assess the severity of the process [*Pollmann R. et al., 2018; Porro A. M. et al., 2019*].

However, the literature is scarce on the changes of oral microbiota in patient with pemphigus vulgaris during the exacerbation and remission phases. The aim of the present study was to compare the level of individual oral hygiene and the composition of gingival fluid microbiota during the remission and exacerbation phases in patients with confirmed pemphigus vulgaris.

Materials and methods

The present research is observation longitudinal study. The study was performed at the Department of Therapeutic Dentistry, Institute of Dentistry named after EV Borovsky, and AV Rakhmanov Clinic of Skin and Venereal diseases, I.M. Sechenov First Moscow State Medical University, Moscow, Russia from 15.04.2019 to 31.10.2020.

The study was approved by the Local Ethics Committee of I.M. Sechenov First Moscow State Medical University rotocol No. 05-19 (10.04.2019). Thirty patients aged 18-75 years, who underwent inpatient and outpatient treatment at VA Rakhmanov Clinic of Skin and Venereal diseases (Sechenov University, Moscow, Russia), were recruited for the study. All patients signed informed consent at the initial examination.

Inclusion criteria:

- written informed consent of the patient to participate in the research
- male and female patients aged 18-75 years
- the diagnosis of pemphigus vulgaris (ICD-10 (International Classification of Diseases-10): L.10.0) confirmed by the clinical examination and primary and secondary immunofluorescence [*Giurdanella F.et al., 2016*]

Non-inclusion criteria:

- age under 18 years
- pregnancy/breastfeeding
- severe somatic, neurological and mental disorders and concomitant diseases.

Exclusion criteria:

- refusal to further participate in the research
- refusal to comply with oral hygiene recommendations
- emergency conditions.

Dental examination of the patients was performed at the Department of Therapeutic Dentistry, Institute of Dentistry named after EV Borovsky (Sechenov University, Moscow, Russia). At the initial appointment, full dental examination was performed. The periodontal status of patients was assessed, based on clinical and x-ray assessment. Patients with gingivitis, and mild to moderate periodontitis were prescribed chlorhexidine-containing products (mouthwashes based on chlorhexidine 0.12 % 3-6*X/day*, gentle teeth brushing 3X/day after each meal using toothpaste for children or chlorhexidine gel at 0.12%) [*Mezzour M. et al.,2018*]. Oral debridement was performed, if indicated. Patients were given recommendations for improving their oral hygiene level with individual selection of oral hygiene products. The patients were referred to the Depatment of Dental Surgery (Sechenov University, Moscow, Russia) if indicated.

The level of individual oral hygiene plaque index (PI) [*Russel A., 1957*] and the composition of gingival fluid microbiota (real-time PCR) were compared during the remission and exacerbation phases.

Periodontal status was assessed using the periodontal index (PI) [*Russel A., 1957; Arduino P. G et al., 2011*] for each tooth from 0 to 8 points. The degree of inflammation, depth of the periodontal pocket and the mobility of the tooth were assessed. Evaluation criteriawere as follows: 0–no changes; 1–gingivitis is mild (inflammation does not cover the gums throughout the tooth); 2–inflammation engulfs the gums around the entire tooth, the gingival junction is preserved; 4–the same, but the x–ray shows bone resorption, the tooth is stable; 6-gingivitis with the formation of a periodontal pocket (epithelial attachment is damaged, there is a pathological dentition pocket, the chewing function of the tooth is impaired, the tooth is immobile); 8–pronounced destruction of periodontal tissues with loss of chewing function, the tooth is easily mobile, can be displaced.

To determine the qualitative and quantitative content of periodontal pathogens, viruses and fungi in the oral cavity, the polymerase chain reaction real-time (PCR) method was used [*Trofimov D. Yu., et al., 2008; Volkov A. N. 2014*]. Microbiological analysis was performed in the Laboratory RPC Research and production firm"Genlab" (Moscow, Russia). As a biological material for molecular genetic studies we used the gingival fluid and in the epithelial scrapings of the oral mucosa. Epithelial scrapings were collected using disposable brushes, which were then placed in an Eppendorf tube with saline solution. Then, the Eppendorf tubes were transported to the laboratory. To identify infectious agents and determine the patient's DNA (as a normalizing indicator), DNA extraction from biologi-

cal material was performed (DNA extraction kit "Sample-GS", "Replication protein A (RPA) DNA-technology", Russia). Diagnostic system Multident-5 ("RPC "Genlab" Russian Federation) was used to assess six periodontal pathoges (Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tanerella forsythensis, Treponema denticola, Candida albicans). Diagnostic system Multident-3 ("RPC "Genlab" RF) was used to assess three viruses (Epstein-Barr virus, Cytomegalovirus, Herpes simplex virus). Diagnostic kit Multican-2 was used to assess the presence of Candida spp.

The results of PCR were presented as the log of the amount of target DNA (i.e. log of the number of bacteria in the sample). The data were imported into statistical software (RStudio version 1.2.1335 2009-2019, RStudio Inc., Boston, MA). The normality of distribution was checked using Shapiro-Wilk test. Greenhouse-Geisser sphericity correction was automatically applied to factors violating the sphericity assumption. The differences between bacterial counts and PI values in remission and exacerbation phases were analysed using repeated measures ANOVA with the significance level set at 0.05.

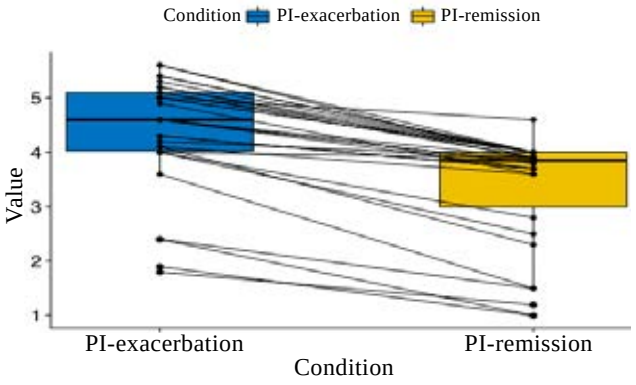

FIGURE 2. *The dynamics of PI in the study group in the periods of exacerbation and remission of pemphigus.*

RESULTS

Thirty patients aged 18-75 years were recruited for the study, 16 females (53 %) and 14 males (47%). The main age was 50±14 years, 49±17 years and 51±9 years for female and male patients, respectively.

The assessment of oral hygiene.

Mean plaque index values were significantly lower in the period of exacerbation compared with the period of remission, and comprised 4.4±1.1 and 3.3±1.0, respectively ($p<0.001$, effect size = 0.20) (Fig. 2).

The results of real-time PCR-analysis.

Bacteria

P.intermedia was found in 12 (40%) and 5 (17%) patients in remission and exacerbation, respectively. In 6 patients (20%) these bacteria were found in remission, but not in exacerbation; in 2 patients (7%) P.intermedia was present only in exacerbation. The bacterial counts of P.intermedia in

TABLE 1.

Mean microorganisms' counts (Log) in patents with pemphigus vulgaris during the periods of exacerbation and remission.

Microorganism	Mean numbers of microorganisms (Log)		ANOVA results		
	Exacerbation	Remission	F-value	P-value	Effect size
P.intermedia	0.9±2.1	2.2±2.8	5.3	0.028*	0.065
T.denticola	1.2±1.9	2.1±2.4	3.7	0.062*	0.047
T.forsythensis	2.4±2.8	4.0±2.6	5.5	0.026*	0.083
P.gingivalis	0.7±1.9	2.5±3.1	5.8	0.022*	0.104
A.actinomycetemcomitans	1.2±1.9	2.2±2.6	3.7	0.065	0.049
C.albicans	0.5±1.6	2.3±2.8	3.3	0.08	0.047
Cytomegalovirus	0.1±0.7	0.1±0.7	-	-	-
Epstein-Bar virus	3.7±3.2	1.8±2.3	8.5	0.007*	0.102
Herpes simplex virus	2.1±2.5	1.4±2.4	1.1	0.31	0.018

NOTES: ** - statistically significant result*

exacerbation were significantly lower than in remission (p = 0.028). T.denticola was found in 14 (47%) and 9 (30%) patients in remission and exacerbation, respectively. In 8 patients (27%) these bacteria were found in remission, but not in exacerbation; in 3 patients (10%) T.denticola was present only in exacerbation. The bacterial counts of T.denticola in exacerbation were significantly lower than in remission (p = 0.047). T.forsythensis was found in 22 (73%) and 14 (47%) patients in remission and exacerbation, respectively. In 11 patients (33%) these bacteria were found in remission, but not in exacerbation; in 3 patients (10%) T.forsythensis was present only in exacerbation. The bacterial counts of T.forsythensis in exacerbation were significantly lower than in remission (p = 0.026). P.gingivalis was found in 12 (40%) and 4 (13%) patients in remission and exacerbation, respectively. In 11 patients (33%) these bacteria were found in remission, but not in exacerbation; in 3 patients (10%) P.gingivalis was present only in exacerbation. The bacterial counts of P.gingivalis in exacerbation were significantly greater than in remission (p = 0.022). A.actinomycetemcomitans was found in 13 (43%) and 4 (13%) patients in remission and exacerbation, respectively. In 8 patients (27%) these bacteria were found in remission, but not in exacerbation; in 3 patients (10%) A.actinomycetemcomitans was present only in exacerbation. The differences between bacterial counts of A.actinomycetemcomitans in exacerbation and remission were insignificant (p = 0.065).

Fungi

C.albicans was found in 13 (44%) and 3 (10%) patients in remission and exacerbation, respectively. In 12 patients (40%) these fungi were found in remission, but not in exacerbation; in 2 patients (7%) C.albicans was present only in exacerbation. The counts of C.albicans in exacerbation were significantly lower than in remission (p = 0.047).

Viruses

Epstein-Bar virus was identified in 12 (40%) and 18 (60%) patients in remission and exacerbation, respectively. In 10 patients (33%) viral DNA was present in exacerbation, but not in remission; in 4 patients (13%) it was present only in remission. The viral counts in exacerbation were significantly greater, than in remission (p = 0.007).

Herpes simplex virus was detected in 8 (27%) and 13 (44%) patients in remission and exacerbation, respectively. In 9 patients (33%) this virus was present in exacerbation, but not in remission; in 4 patients (13%) Herpes simplex virus was present only in remission. The differences between the log viral counts in exacerbation and remission were insignificant (p = 0.31). Cytomegalovirus was detected only in 1 patient, and its counts didn't change in exacerbation and remission.

Discussion

We assessed the individual oral hygiene and the composition of periodontal pathogens in patients with confirmed pemphigus vulgaris using PCR at the stages of exacerbation and remission, as the development of periodontitis is affected by the presence of these bacteria *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* и *Tannerella forsythensis* [*Gao L. et al., 2018*]. According to the results of the present study, the bacterial counts of P.intermedia, T.denticola, T.forsythensis, and P.gingivalis were lower in exacerbation compared with the remission. This may be due to the frequent use of chlorhexidine-containing product in exacerbation. In contrast, the viral counts of Epstein-Bar virus were significantly greater in exacerbation period, probably due to the decrease of a host response during the exacerbation phase caused by the increased doses of corticosteroids.

Current literature presents a small number of large-scale studies on the problem of oral diseases in patients with vulgar pemphigus. The main focus of these studies is to assess the association of pemphigus vulgaris with periodontal diseases. Most of these studies have confirmed that pemphigus vulgaris contributed to the development of periodontal diseases. Patients with pemphigus vulgaris showed an increase in the incidence of periodontitis, had worse periodontal parameters [*Akman A, et al., 2008; Thorat MS et al., 2010*].

Long-term use of corticosteroids, inability to perform meticulous oral hygiene, and the presence of multiple periodontal pathogens increase the progression of periodontal diseases in patients di-

agnosed with vulgar pemphigus [Markitziu A. et al., 1990; Beeraka S. S. et al.,2013]. Thus, a comprehensive interdisciplinary approach to the treatment of patients with vulgar pemphigus is necessary. Also, the patients need a thorough timely diagnosis and prevention of dental diseases to improve their oral status and quality of life.

CONCLUSION

The level of individual oral hygiene (determined by PI) was significanly higher in remission ($p<0.001$, effect size = 0.20). The log bacterial counts of P.intermedia, T.denticola, T.forsythensis, and P.gingivalis determined by PCR were significantly lower during the period of exacerbation compared with the period of remission ($p = 0.028$, 0,047, 0.026, and 0.022, respectively). In contrast, the log viral counts of Epstein-Bar virus were significantly greater in exacerbation period ($p = 0.007$).

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