EDITORIAL

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The connection between oral pathology and systemic diseases.

Laura Ștef

Lucian Blaga University of Sibiu, Romania.

If the eyes are the "mirror of the soul", then oral cavity often reflects the state of health of the whole body. Oral pathology is the specialization at the border of dentistry and different medical specialties, which analyze diseases that occur at the level of the oral cavity without a dental or surgical cause. This connection is demonstrated by a two-way mechanism: (A) any change in the homesostasis of the tissues in the oral cavity may induce changes in the rest of the body, and (B) any systemic disease may influence the development and reactivity of the tissues in the oral cavity.

(A) Change in the homeostasis of the tissues in the oral cavity may induce changes in the rest of the human body

Studies show that there is an ecosystem of different microbial species that maintain oral health as long as it is in balance. Joshua Lederberg, used the term "microorganisms" to describe an ecological system of commensal, symbiotic, and perhaps pathogenic microorganisms that reside in the human body [1].

The oral microbiome has a special role in metabolic, immunological and endocrine homeostasis. The balance of the different bacterial species ensures health status. The basic pathogens co-exist with many cultivable germs, their interactions determine dysbiosis [1,2].

While immune evasion is one of the major ways that leads to dysbiosis, new processes and new virulence factors of bacteria have been shown to be involved in this important process that determines a disease or health state [2]. The transformation of these comensal species into an opportunistic flora, capable of producing the parodontal disease, is more of a host organism than of the bacterial species. Key pathogens interact with other bacteria and their interactions cause dysbiosis [3].

Periodontal degradation creates a suitable medium for the multiplication of specific microbes. Deep periodontal pockets provide an oxygen-free environment that creates an environment favorable to anaerobic bacteria. This theory concentrates on such dysbiotic congregations, their reciprocations and their virulence coefficients that predispose hosts to others systemic involvements [2,4]. Periodontal diseases, influenced by age, gender, smoking, oral hygiene, patient genomics, daily stress, are related to bacteremia and endotoxemia, arteriosclerosis, myocardial infarction, pregnancy complications, insulin resistance, obesity, type 2 diabetes, oral cancer, pancreatic cancer, liver disease, respiratory infections, rheumatoid arthritis, osteoporosis [5-7].

A1. The link between chronic periodontitis (CP) and cardiovascular diseases (CD)

In the larger context and given the evident high prevalence of chronic oral infections, early associations were sought between the presence of oral infections and cardiovascular events. Existence of systemic predisposition to periodontitis and relationship between local periodontal disease and systemic inflammatory and immune changes was observed. In principle two types of mechanisms are involved: bacteria from the periodontal disease may enter circulation and directly contribute to the development of atheroma plates (or thrombosis) and/or systemic inflammation, resulting from periodontitis, may contribute to

atherosclerotic cardiovascular disease. A biological mechanism suggest that bacteria or their toxic products can easily gain access to the circulatory system. Bacterial episodes were detected after normal activity, such as chewing or brushing of teeth. Similar to bacterial release, excessive local production of pro-inflammatory cytokines can gain access to blood and trigger an acute systemic response. So, patients with periodontal damage have higher levels of CRP and interleukin 6, compared to a healthy control group. For example, Prevortella gingivalis, aterogenic bacteria, uses the Trojan horse method. The bacteria flow freely through the blood and induces HDL oxidation, damaging the atheroprotective function of HDL [8]. Chronic inflammatory processes that may amplify vascular inflammation in atherosclerosis [9].

A2. The correlation between periodontal disease and pregnancy problems

Several studies have assumed that periodonal diseases can trigger premature birth, and are the cause of reduced fetal weight at birth, so, consideration was given to the possible hematogenic invasion of the hourly pathogens and their metabolites, the circulation of inflammatory products through blood flow, as well as immune responses of the mother/fetus from pathogens [10,11].

A3. The correlation between periodontal diseases and cancer

Clinical studies have observed higher risks of oral, gastro-intestinal, lung and pancreatic cancer in subjects with periodontal disease [12,13]. WHO recognizes that there is an obvious relationship between the oral microbiome and carcinogenicity through the existence of Human Papilloma Virus (which cause oral cancer) and Ebstein Barr Virus (who is involved in nazo-pharingeal cancer) [14,15].

A4. Correlation between oral microbiota and rheumatoid polyarthritis

The presence of chronic inflammation in rheumatoid arthritis alters the symbiosis in the oral cavity leading to a decrease in 'good' bacteria and an increase in the number of pathogenic bacteria (Prevotella spp., Selenomonas spp.) [16]. In rheumatoid arthritis, the history of infections and oral microbes play an important role in the pathogenicity of this disease, along with genetic predisposition, gender, immunological context [17]. The presence of inflammation of the host increase the pathogenicity of microbes in the oral cavity. The success of treatment with anti-inflammatory medication also partially solves oral dysbiosis [18].

(B) Systemic disease may influence the dislotion and reactivity of the tissues of the dental system

The oral cavity is considered the "indicator barometer"/"primary alarm signal"/"primary diagnostic key" of multiple general conditions [19]. Mostly, the oral mucosa can be the place of self-manifestations, easy to diagnose, determined by local factors. Systemic factors may also be involved in the appearance of these lesions, so that the effects of lesions appearance may be the first signs of systemic diseases, or manifestation of diseases, or side effect of drug administraton.

Oral cavity is frequently involved in systemic disorders (haematological, rheumatismic, digestive, endocrine diseases). Sometimes it is the dentist who provides an early diagnosis and management, which can often reduce the morbidity associated with systemic disease, improve the quality of life and reduce the costs of treatment [20].

B1. Oral manifestations in haematological diseases

Among the many conditions which may be encountered in the oral cavity, those in the sphere of haematological disorders should be an area of extreme responsibility for the dentist in the way any treatment is dealt with.

Most of the times, a patient with diagnosed leukemia goes to his dentist for the treatment of oral lesions, without suspecting that their

nature is more than local. Leukemia is a disease characterized by progressive overproduction of white corpuscles usually occurring in circulatory blood. This proliferation of white corpuscles or their precursors occurs in such an unorderly and independent manner that leukemia is generally considered a true malignant tumor, especially as the disease is so often fatal. Typical oral manifestations of acute leukemia include gingival swelling, spontaneous gingival bleeding oral ulceration, petechiae, mucosal pallor, oral candidosis and herpetic infections. Other symptoms include fever, fatigue, pallor, mucosal bleeding, petechiae and local infections leukemic gingival enlargement [21]. Anemia and thrombocytopenia are characteristic of acute leukemia. Gingival hyperplasia, which is one of the most constant characteristics of the disease is usually generalized and varies in severity. The gingiva is edematous and of a bright red, and bleed slightly. Gingival edema is due to leukemia infiltration in areas with chronic mild irritation. Purple lesions of the buccal mucosa similar to skin ecchymosis may also be observed [22,23]. Spontaneous gingival hemorrhage is due to ulceration of the sulcular epithelium and the necrosis of the underlying tissue, and serious ulceration of the nomadic oral mucosa may occur. Thrombosis of gingival vessels seems to contribute to this phenomenon. The mobility of teeth has been observed due to the impairment of the periodontal ligament, and in some cases bone resorbtions also occurs. In early diagnosis and treatment of leukemia it is important to improve the opportunity to resubmit patients' condition. The dentist can play an important role in identifying oral events in this disease and ordering appropriate haematological tests to confirm the diagnosis of leukemia [22,24]. Other hematologic conditions eg. anemia can enclose mucosal pallor, atrophic glossitis, and candidosis. In thrombocytopenia, severe periodontal inflammation or bleeding or ecchymosis can be the first signs [25]. Cyclic neutropenia is a rare acquired disease caused by gene mutation for neutrophil elastase. Patients usually have a fluctuating number of neutrophils and severe neutropenia that occurs every 3 weeks and lasts 3-5 days. During these periods, patients may report recurrent fever, lymphatic nodules, foot-and-mouth ulcers, malaise and pharyngitis. Other oral manifestations may include gingivitis, and gingival ulceration [26,27].

B2. Oral manifestations as first signs in the dermatological diseases

In lupus erythematosus, the reported incidence of oral lesions is between 8-45% in the patients with systemic lupus erythematosus, and 4-25% in the patients with discoid lupus erythematosus [28,29]. The oral lesions vary very much, from the classic presentation of an oral discoid lesion with a very well delimited area of erythema, and atrophy, to ulceration enclosed by white, and radiating striae. All these lesions arise to be like those which exist in the patients suffering by erosive lichen planus [30,31]. In pemphigus vulgaris, the oral lesions appears as an initial manifestation in 50-80% of the patients affected by pemphigus vulgaris, and the disease can be preceded by skin lesions one or more years prior. The patients typically endure painful, diffuse oral ulceration [32-33].

B3. Oral manifestations in inflammatory bowel diseases and autoimmunne diseases

Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis often lead to oral ulcers. Patients experience abdominal pain, diarrhea, fever, fatigue, weight loss, anemia, and all can be detected by a careful history, although oral signs may precede general symptoms. Crohn's disease is a granulomatous inflammatory condition of unknown etiology, although genetic, immunological, environmental, microbial, dietary, and vascular factors have been implicated. It alters the ileum and the large intestine in more than 90% of the patients [34]. It is frequently associated with foot-and-mouth disease. The patients with Crohn disease can present diffuse swelling and oedema of the oral

mucosa, with cracks heaving "cobblestone mucosa" aspect, respectively localised mucogingivitis/cheilitis. In addition, patients may also have pustular and ulcerative lesions in the oral cavity (pyostomatitis vegetans). The pustules usually fuse and then break, leaving superficial erosions [35].

Gluten enteropathy (celiac disease, an autoimmune disease), is caused by a reaction to gliadin. Foot-and-mouth ulcerations are found in 3% to 61% of patients with defects of the enamel. If there is suspicion of this disease, haematological tests for anti-gliadin, anti-endomysial and tissue anti-transglutaminase antibodies should be carried out. Signs and symptoms can be removed by a gluten-free diet, and vitamin B12 [36,37].

B4. Oral manifestation in Covid 19

SARS-CoV-2 infection is the direct cause or is predisposing factor in oral lesions. The new coronavirus possibly has the capability to modify the equilibrium of the oral microbiota, which added to a low responding immune system permits the colonization of the opportunistic microorganisms. SARS-CoV-2 may induce an immune response similar to that observed in other viral disorders in the oral cavity [38]. The oral cavity is an ideal habitat for SARS-CoV-2, due to their particular affinity for the cells with receptors for the converted angiotensin enzyme (ACE2), existent in the respiratory tract, in the mucosa of the oral cavity, and in salivary glands [39]. It is capable to alter the integrity and functionality of the oral mucosa and of the salivary glands, including dysfunctionalities in the sensations of taste and smell [40]. Salivary glands may be the target of SARS-CoV-2 because AEC2 receptors are present in the glandular channel epithelium. This explains why SARS-CoV2 could be detected in human patient saliva [41]. Oral manifestations associated with Covid 19 are agusia, oral ulcerations, occurring in patients who have not had in the past episodes of recurrent ulcerations, saburral tongue, dry mouth, candidosis.

For intubated patients, poor hygiene, disturbances of the balance of the oral microbiocenosis are the result of systemic therapies, and changes in the intra-oral environment may lead to additional respiratory problems [42].

In conclusion, knowledge and connections in the patient's medical history, respectively early highlighting of the oral mucosa lesions are extremely important in establishing the correct diagnosis and prognosis of affections.

Conflict of interest: None to declare.

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Corresponding author:
Laura Ștef
Lucian Blaga University of Sibiu, Faculty of Medicine, 2A Lucian Blaga Str., Sibiu, 550169, Romania
Email: laura.stef@ulbsibiu.ro

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