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The Oral Cavity: Oral Lesions as Manifestations of Systemic Disease

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RESUMEN

Introducción:

La cavidad oral puede presentar manifestaciones de enfermedades sistémicas subyacentes, como trastornos hematológicos, endocrinos, neoplásicos y cada vez más autoinmunes, que a menudo se asocian con manifestaciones extraorales. Es significativo que, el papel de la microbiota oral en la patogenia de las enfermedades autoinmunes está aumentando.

Objetivos:

Esta monografía tiene como objetivo proporcionar una descripción clínica sintética de las principales enfermedades sistémicas que dan lugar a lesiones bucales, con especial atención a las enfermedades autoinmunes. Además, este trabajo tiene como objetivo proporcionar los resultados de estudios importantes que investigan el papel de la microbiota oral en el desarrollo y / o mantenimiento de trastornos inmunitarios sistémicos.

Metodología:

La investigación bibliográfica se ha realizado principalmente a través de bases de datos y buscadores especializados como PubMed.

Resultados:

Los resultados de la investigación básica y clínica han sugerido o demostrado una relación entre la microbiota oral y el desarrollo, mantenimiento y gravedad de enfermedades sistémicas, incluidos trastornos autoinmunitarios por ejemplo el lupus eritematoso sistémico, el síndrome

de Sjogren y la artritis reumatoide. También se ha demostrado que una mala higiene bucal es responsable de un mayor riesgo de desarrollar enfermedades autoinmunes. Además, se ha encontrado una correlación entre los cambios disbióticos del microbiota oral presentes en las enfermedades periodontales y la inflamación sistémica de bajo grado, la actividad acondicionadora y la gravedad de la enfermedad sistémica.

Discusión:

Los cambios en la composición de la microbiota oral e intestinal, permiten el predominio de patobiontes que dañan los tejidos locales, difundiéndose sistémicamente y desencadenando las respuestas inmunes. Aunque actualmente se reconoce la participación de la microbiota en la patogénesis de la autoinmunidad, se necesitan más estudios para una comprensión más completa de la relación entre la microbiota oral y la respuesta inmune.

Conclusiones:

La inspección precisa de la cavidad bucal y la intervención en la higiene bucal y las lesiones son cruciales para mejorar la salud general de los pacientes. De hecho, las manifestaciones orales, como la periodontitis o la placa dental, pueden inducir cambios en la microbiota oral, que a la larga producen una inflamación sistémica sistémica de bajo grado y desencadenan procesos autoinmunes.

ABSTRACT

Introduction:

The oral cavity can provide signs of ongoing systemic diseases, such as hematologic, endocrine, neoplastic and increasingly autoimmune disorders, that often are associated with extra-oral manifestations. Interestingly, the role of oral microbiota in the pathogenesis of autoimmune diseases is growing.

Objectives:

This monograph aims at providing a synthetic clinical overview of the main systemic diseases resulting in oral lesions, with special focus on autoimmune diseases. In addition, this paper aims to provide findings from significant studies investigating the role of oral microbiota in development and/or maintenance of systemic immune disorders.

Methodology:

Bibliographical research has been carried out principally through specialised databases and search engines such as PubMed.

Results:

Findings from basic and clinical research have suggested or demonstrated a relationship between oral microbiota and development, maintenance and severity of systemic diseases, including autoimmune diseases such as Sjogren's Syndrome, Systemic Lupus Erythematosus,

and Rheumatoid arthritis. It has also been shown that poor oral hygiene is responsible for an increased risk to develop autoimmune diseases. Moreover, an association between oral dysbiotic variations in periodontal diseases was identified and the low-grade systemic inflammation, conditioning activity and extent of the systemic disease.

Discussion:

Modifications in the composition of oral and intestinal microbiota, allows the dominance of pathobionts that injures local tissues, thus diffusing systemically and triggering the immune responses. Even though the microbiota involvement in the pathogenesis of autoimmunity is presently recognized, further studies are needed for a more complete comprehension of the relationship between oral microbiota and immune response.

Conclusions:

Accurate inspection of the oral cavity and intervention on the oral hygiene and lesions, are crucial for improving patients general health. Indeed oral manifestations such us periodontitis or dental plaque, may induce changes in the oral microbiota, that at length produce a systemic low-grade systemic inflammation and trigger autoimmune processes.

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1. INTRODUCTION

A careful inspection of oral cavity may provide reliable information on patient's general health status: indeed oral lesions often are the only sign of underlying systemic diseases that are not diagnosed or even suspected yet [1-4].

Systemic disorders with oral manifestations involve autoimmune, hematologic, endocrine, and neoplastic mechanisms. As life span is increasing, the incidence of these conditions is expected to increase as well: indeed, in the last decades the occurrence of autoimmune diseases has been steadily grown [4-6].

Several oral mucosal disorders are either autoimmune in origin or are the product of immunologically-mediated activities, both in infections and may also be in some cancers (i.e. Kaposi's sarcoma).

These conditions, generally present also extra-oral manifestations, with skin, eyes, nasal, pharyngeal and genital mucosa involvement and even if sharing a similar pathogenesis, they result from different immunologic processes [7].

Recently, it has been observed that treatment of periodontitis in patients affected by rheumatoid arthritis, leads to control of their immune disease, thus suggesting an involvement of adaptative immunity in the development of periodontitis. Indeed it is recognised an association between P. gingivalis, a periodontal pathogen, and altered oral microbial community (microbiota), with early rheumatoid arthritis, mostly in patients with elevated concentrations of anticitrullinated protein antibodies [8].

Therefore, it is not surprising that the increasing role attributed to oral microbiota in the pathogenesis of oral lesions is related to immune diseases [8-10].

Moreover, low-grade systemic inflammation that influence systemic lupus erythematosus disease extent and severity, has been associated to a microbial dysbiotic alteration present in periodontal diseases [11].

Consequently, considering the impact that recognizing the systemic origin of oral lesions may have on the patient's health, this monograph aims at providing a descriptive overview of the oral disorders caused by systemic diseases. Nevertheless, as currently most of oral lesions reflect and often are the first sign of an underlying autoimmune disease, this paper particularly addresses this issue.

2. OBJECTIVES

1) Provide a synthetic clinical overview of the main categories of systemic diseases resulting in oral lesions, with special focus on autoimmune diseases.

2) Pay most attention to pathogenesis of oral lesions due to autoimmune diseases and to their reciprocal relationship.

3) Collect data from published clinical studies aimed at investigating the role played by oral microbiota on the development and/or maintenance of systemic immune disorders.

3. METHODOLOGY

Bibliographic research was carried out by consulting authentic textbooks and websites of officially recognised scientific societies, specialised databases and search engines such as PubMed. Analysis of collected papers has triggered further articles collections.

The following keywords were used:

oral lesions and systemic diseases; dentistry and systemic diseases; autoimmune diseases and aetiology; autoimmune diseases and oral disorders - microbiota and scleroderma; scleroderma and oral lesions; diabetes mellitus and oral lesions; leukaemia and oral lesions; multiple myeloma and oral lesions; diagnosis, oral and systemic diseases; oral microbiota and autoimmune; microbiota and autoimmune diseases; covid-19 and oral lesions.

Filters applied concerned abstract availability, English language, publication date, selection of type of articles (review, metanalyses, etc..). Articles were selected by taking into consideration the Journal Impact Factor, Authors relevance and date of publication, giving higher preference to more recently published papers. Based on the initially retrieved 1725 articles, 34 papers have been selected and reviewed.

4. RESULTS

A synopsis of oral lesions and relevant underlying systemic diseases is available in Annex I. Systemic disorders with oral manifestations involve autoimmune, hematologic, endocrine, and neoplastic mechanisms [4]. The associated oral lesions are numerous and may differ according to the underlying disease, but ulceration is the most frequent disorder affecting the oral cavity [12].

4.1 HEMATOLOGIC DISEASES

Oral findings of hematologic diseases can vary depending on the fundamental condition [4]. Indeed, mucosal whiteness and atrophy prevail in anaemia, while haemorrhages and gingival bleeding are usually present in hematopoietic malignancies or coagulopathies [4].

Anaemia

Atrophic tongue, mucosal whiteness and candidiasis are frequently linked to anemia, but mucosal burning, discomfort, or sensitivity and erythema may also occur [3,4].

Iron-deficiency anemia more frequently is accompanied by mucosal atrophy and pallor and atrophic glossitis, while pernicious anemia may result in focal or diffuse erythema of the tongue and atrophy (Figure 1) [4].

Burning of the lips, tongue, and oral mucosa are characteristic to all forms of anemia. Overabundance of Candida albicans could be a related phenomenon (Figure 2) [4].

Fig.1 Tongue appearance in a case with Pernicious Anemia [3].

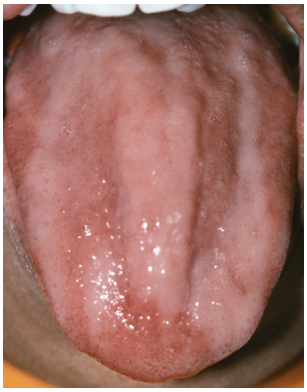
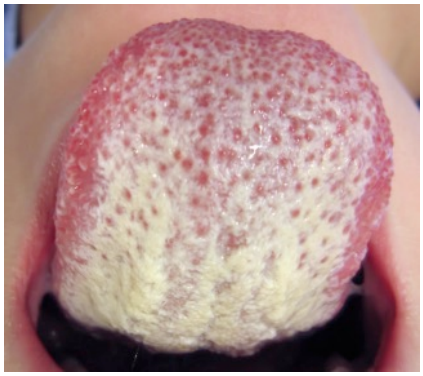


Fig.2: Tongue with candidiasis [2].



Leukemia

Leukemia is a heterogeneous group of haematological disorders arising from hematopoietic stem cells [1]. This malignancy is presented as a large number of immature leucocytes circulate [13].

Indeed the neoplastic cells undergo an uncontrolled proliferation accompanied by impaired differentiation and programmed cell death, thus causing the accumulation of newly born cells in the bone marrow and consequent suppression of normal haematopoiesis. This abnormal process leads to deficiency of mature leukocytes, erythrocytes, and platelets [1].

According to the typology of the blasts, leukemia may be classified as acute or chronic lymphoblastic or myelogenous [1, 14]. Acute lymphoblastic leukemia typically occurs in

childhood, whilst acute myeloid leukaemia is more common in adult age [1]. Monoblastic leukemia, belonging to myelogenous leukemiae, frequently involves the oral cavity [1].

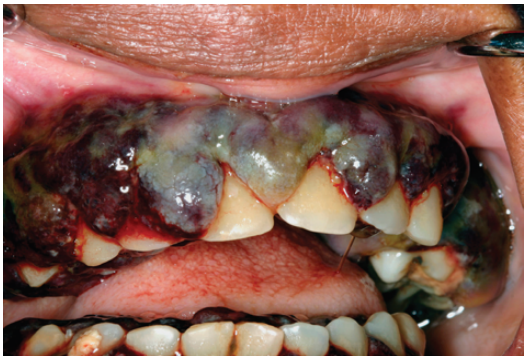
Notably, dentists are the health professionals who first discover the oral lesions and initiate the diagnostic process in 33% of patients with acute myelomonocytic leukemia [14].

Life-threatening complications of leukaemia are represented by infections, frequently recurrent, as well as severe bleeding episodes [1]. Leukemic cells can invade the gingiva (histologically detectable), besides various organs systemically [1].

Leukemia-specific oral lesions include petechiae, ulceration, mucosal bleeding, diffuse and localized gingival growth and secondary infections (i.e. periodontal bone loss, candidiasis, herpes simplex virus infection) [3, 14].

Oral lesions arise in both acute and recurrent cases of all types of leukemia, even if much more frequently in acute stages. They may be due directly to the intrusion of leukemic cells or to essential thrombocytopenia, neutropenia, or impaired granulocyte function (Figure 3) [14].

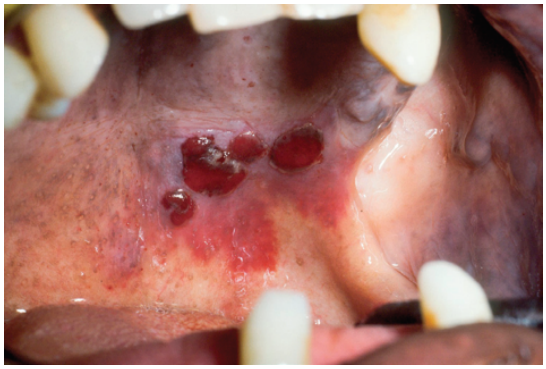
Figure 3. Oral findings with Acute Monocytic Leukemia [3] .



Thrombocytopenia

Features that include petechiae, ecchymoses, epistaxis, purpura, hemorrhagic bullae are classically associated to low platelet count thrombocytopenia and spontaneous gingival bleeding is frequent, either spontaneously or with mild trauma (Figure 4) [3, 4]. Anyway, it is worthy to note that thrombocytopenia may result also from non-neoplastic conditions [4].

Figure 4. Oral findings with Thrombocytopenia [3].



Multiple myeloma

The proliferation of malignant plasma cells and typically development of monoclonal immunoglobulin is characteristic of multiple myeloma (MM) [15].

Malignant plasma cells can associate with marrow stroma and a broad cytokine network that can contribute to osteolytic bone degradation, or in some instances, to an extra-medullar growth or soft tissue plasmacytomas [15].

Myeloma rarely produces oral lesions, but they might characterise either the sole appearance of the disease or may be part of symptoms suggestive of disease progression [15]. As patients often

report disturbs resembling common dental pathologies, delays in diagnosis and treatment may unfortunately occur [15].

The majority of the patients show complications that comprise anaemia and/or tiredness typically due to bone marrow infiltration, renal insufficiency or failure, frequent infections secondary to immunoglobulins, bony injuries, and hypercalcaemia [15].

Sometimes the disease may involve oral cavity causing mandible or teeth discomfort, paraesthesia's, bulging, soft tissue expansion, teeth mobility or migration, haemorrhage, and pathologic rupture due to cortical obliteration of bone [15].

Anyway, oral cavity is affected in the advanced multiple myeloma and results in facial asymmetry due to mandible involvement, jaw or mucosal swelling up to bony destruction and pathologic fractures [4]. Rarely, macroglossia can occur due to deposition of amyloid [4].

4.2 ENDOCRINE DISORDERS

Diabetes mellitus

Type 1 and type 2 have different pathogenesis, even if sharing a common dysmetabolic profile. Indeed, diabetes type 1 characteristically appears during infanthood and is associated to autoimmune destruction of pancreatic islet cells, while type 2 diabetes is principally related to adults and secondary to insulin resistance [4].

Intraoral appearances of both type 1 and type 2 diabetes types include several disorders of the oral cavity, that are often secondary to poor glucose control and are generally related to higher susceptibility to infections, but the relationships of some of these disorders and mellitus diabetes are still unclear [4, 16].

The pathogenesis of oral manifestations of mellitus diabetes, originates mainly from two processes:

1) The activation of the polyol pathway due to elevated glucose levels, leading to reduction of glucose into sorbitol that produces tissue destruction and several other diabetic problems

2) The creation of advanced glycosylation end materials (AGE), that originates from the link of glucose to proteins, phospholipids and nucleic acids and resulting in the shift of structures and functions. The deposition of these products in specific organs causes countless alterations. Indeed, fatty material, accumulates in the inner layer of the wall of an artery producing reduced cellular defence capability and weakened polymorphonuclear leukocyte reaction, making diabetic patients more vulnerable to infection [16].

Periodontal disease in diabetic patients: Periodontitis is the foremost oral complication linked to diabetes and can produce a negative sequence of events [16]. Indeed, in diabetic patients periodontal pathogens dissemination (occurring even thanks to simple chewing) can cause bacteraemia or endotoxemia, that are responsible for rise in serum concentrations of inflammatory mediators such as Inter-leukin6 (IL-6), fibrinogen and C reactive protein (CRP).

In this way, a vicious circle is established, and a systemic inflammation can impair insulin resistance and consequently diabetes control [16].

Periapical Pathology in diabetic patients: As a consequence of the metabolic impairment and the complications of the disease, the dental pulp of diabetic patients can develop in a limited

dental collateral flow, compromised immune reaction, and an enlarged threat of infection or pulp necrosis [16]. In addition to that, it is worthy to note that hyperglycaemia itself stimulates bone resorption, inhibits osteoblast differentiation, and reduces capacity for bone recovery [16].

Dental Caries in diabetic patients: While some reports have demonstrated no major alterations in the incidence of dental caries between diabetic and non-diabetic population, additional findings have established a greater incidence of dental caries in patients with diabetes mellitus, possibly due to the decrease of salivary secretion typically occurring in diabetics [16, 17].

Oral Mucosa in diabetic patients: Diabetic patients may suffer from mucosal conditions probably related to chronic immunosuppression, delayed recovery and salivary reduced function [16].

The more frequent disorders consist in: mycotic oral diseases such as candidiasis, fissured tongue, irritation fibroma, painful ulcers and lichen planus [16]. Nevertheless, the association between candidiasis or other oral alterations and mellitus diabetes is still question of debate [16].

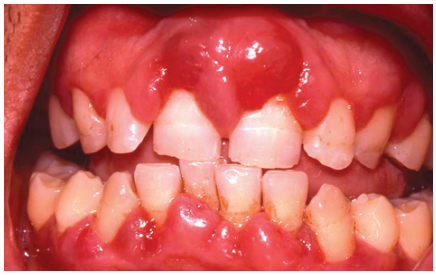
Xerostomia in diabetic patients: Some studies have shown a tendency to a reduction of salivary flow in diabetic patients with inadequately controlled type 2 diabetes, even if experimental trials on this issue present inconsistent results [16].

Nevertheless, the presence of higher salivary levels of urea and glucose levels in diabetic than healthy subjects, suggest a correlation between the onset or the grade of xerostomia and glucose concentrations in saliva, such laying the foundations for infections in the oral cavity. Indeed, it is well known that increased salivary glucose levels promote the propagation and establishment of microorganisms in the oral cavity and that glucose is the foundation for Candida development besides decreasing the action of neutrophils [16].

Taste impairment in diabetic patients: Presence of neuropathies, may promote sensory dysfunction, that in turn can inhibit appropriate nutrition, thus leading to poor glycemic control [16].

Burning Mouth Syndrome in diabetic patients: Patients with diabetes often suffer from a burning sensation in the oral mucosa, but a clear relationship with diabetes mellitus has not been identified [16].

Figure 5. Oral manifestations with Diabetes Mellitus [3] .



Thyroid disease

Thyroid dysfunctions can produce visible changes in oral cavity [4]. In hypothyroid patients, glycosaminoglycan residues that are found in the tongue and lips can lead to an associated enlargement, while hypothyroidism may affect tooth eruption in children [4]. Conversely, hyperthyroidism may lead to proptosis or exophthalmos [4].

Parathyroid disease

Hypoparathyroidism is typically produced by surgical removal of the parathyroid gland and produces hypocalcemia. Chvostek sign, that involves a trembling of the upper lip after a facial nerve stimulus located in the zygomatic apophysis, is suggestive of the disease [4].

In adolescents, hypo-parathyroidism can impede a normal dentition eruption sequence or in addition result in an enamel corrosion and hypoplasia [4].

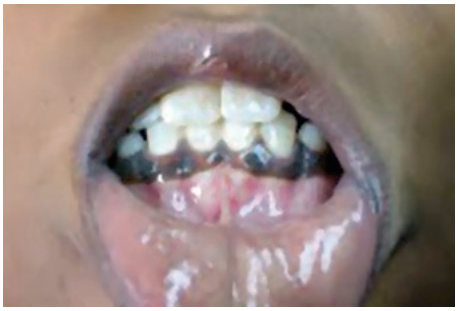
Primary hyper-parathyroidism is related to parathyroid glandular enlargement in 80% to 90% of the cases, while secondary hyper-parathyroidism is a consequence of chronic renal disease. Both conditions can produce damage of the lamina dura of teeth roots and consequently lead to a "ground glass" image on radiographs [4].

In condition of advanced disease, alleged brown tumours, frequently located on the lower jaw, can progress as a result of hemorrhage within the bone [4].

Adrenal disease

Both primary (increased endogenous hormone production by pituitary or adrenal adenomas) and secondary (consequence of chronic glucocorticoid therapy, Cushing syndrome) hypercortisolism show typical "moon" facies secondary to accumulation of adipose tissue in the face. Bone injury may be associated and distinguished on radiographs of the lower jaw [4]. Hypo-adrenocorticism (Addison disease) originates after damage from the adrenal cortex. This disorder may have different causes, but frequently recognises an autoimmune aetiology. Hyperpigmentation of the oral mucosa, though generic, can be the early sign (Figure 6) [4].

Figure 6: Addison's disease oral manifestation [2] .



4.3 NEOPLASTIC DISEASES

Oral neoplasms caused by extraoral diseases, substantially consist in metastatic tumours and Kaposi sarcoma [13].

Metastatic tumours

Metastatic tumours represent approximately 1% of oral malignant neoplasms and principally affect the jaws even if they may arise equally from the hard and soft palate (2:1 predilection) [4]. In case of soft tissues involvement, mainly the gingiva and tongue are affected at 54% and 22.5%, respectively. Discomfort, burning, or enlargement typically occur. Anesthetised chin syndrome happens when the metastatic wound implicates the mental nerve [4].

Breast cancer in females and lung cancer in men are responsible respectively for 65.3% and 53.3% of oral metastatic tumours. Breast cancer metastases mainly affect jaw, while lung cancer metastases more frequently involve the oral soft tissues [4].

Kaposi sarcoma

Kaposi sarcoma is an angioproliferative tumours affecting visceral organs or the skin [13]. This disease is the second greatest malignancy in patients that are HIV-positive and is reflected as an AIDS expressing disease [13]. Development of Kaposi sarcoma needs infection by KS herpesvirus/human herpesvirus-8 (KSHV/HHV8). Originally incidence of Kaposi sarcoma AIDS-associated was up to 80%, but currently, thanks to highly active antiretroviral therapy, it has significantly decreased and presents with an improved clinical course [13].

The disease can affect oral cavity in approximately 50% of AIDS-Kaposi patients and in up to 20% patient may be existent at the time of HIV identification [13].

Oral lesions consist in brown, blue, purple, or red spots and papules located on the hard palate, mucosa and gingiva. Initial lesions shown as uniform macules or patches on the mucosal surface, whereas over a period of time they develop into a nodular form, with a tendency to ulcerate and haemorrhage. Kaposi sarcoma may affect also the salivary glands and produce head and neck lymphadenopathy [13].

4.4 AUTOIMMUNE DISEASES

Autoimmune diseases belong to the broad family of the immune-mediated disorders, together with allergies, immunodeficiencies and autoinflammatory disorders [18].

The occurrence of autoimmune illnesses has significantly increased during the previous years and frequently oral disorders are the primary sign of their existence [5,9].

Autoimmune diseases basically arise from an anomalous immune feedback to elements of the soft tissues. These diseases are complex, heterogeneous and variable conditions affecting several organs and cell types, with a pathogenesis multifactorial and mostly unknown [19].

Currently it is recognised that immune system plays a role in the control of tissues functions and pathogens can affect this complex regulatory mechanism, thus possibly triggering an autoimmune process [19].

Infections can prompt the autoimmune process via the native or adaptive immune responses and a notable correlation occurred between viral, bacterial and autoimmunity [19].

Nevertheless, numerous elements can involve autoimmune diseases onset and clinical course, like genetics, age, gender, sex hormones pattern and lifestyle habits [19].

Clinically, autoimmune diseases may be subdivided into organ-specific diseases, obviously involving only specific organs, and systemic disorders, where conversely different organs may be attacked, like occurring in rheumatoid arthritis [19].

Autoimmune diseases, associated oral disorders and systemic inflammatory reactions, play a mutual relationship that induces a self-perpetuating vicious circle: indeed, several of the immune-mediated disorders also involve the oral mucosa and oral infections control an amount of systemic inflammatory responses which, on the downside, play a role in the advance of several systemic diseases [19].

The American Autoimmune Related Diseases Association (AARDA) has set down a list of 141 diseases, reporting both autoimmune diseases and those conditions possibly related to autoimmune diseases [19, 20].

The autoimmune diseases more frequently manifesting oral lesions comprise Systemic Lupus Erythematosus, Sjögren syndrome and Systemic sclerosis (Scleroderma) [13].

Nevertheless, oral microbiota alterations have been proven to influence the progression of other autoimmune illnesses not necessarily affecting the oral cavity, such as rheumatoid arthritis [8,10,11,19,21,22].

Autoimmune diseases involving oral cavity may present acutely and with highly painful clinical features or conversely, may be diagnosed in occasion of routine dental checks [7].

Their clinical course often is restricted to the oral cavity, but in some cases extra-oral districts may be affected as well, with special involvement of skin, ayes and reproductive apparatus [15].

The oral lesions associated to autoimmune diseases, share a similar pathogenesis consisting in an autoimmune reaction to some epithelial components. Nevertheless, they present some main differences in the clinical appearance of the autoimmune response (i.e. antibody mediated in

the bullouse diseases or cell mediated in lichen and in erythema multiforme), in the typology of cells affected and in the clinical features and duration of the disease: acute/self-limiting, acute/recurrent, chronic or chronic/recurrent [7].

Recently, the hypothesis that the autoimmune process may be linked in some way to the microbiota structure, has been notably growing [8,21].

Initially, the scientific research was focused on the intestinal microbiota, found to play an essential part in the host health status and in the modulations of both innate and adaptive immune response [21]. Therefore, special attention was spent to the relationship between intestinal microbiota and inflammatory bowel diseases. Subsequently, the significance of oral microorganisms in the pathogenesis and maintenance of some systemic autoimmune diseases has been recognized as well [8,11,21].

Indeed, there is increasing evidence that oral bacteria play a leading role in the progression and clinical course of rheumatoid arthritis [10,21]. Oral bacteria appear to influence the host systemic physiological functions and perturb the commensal microbial communities, thus paving the way to a dysbiosis [11,23].

As a matter of fact, pathogenic bacteria inhabiting the gingival sulcus and gingival crevicular liquid, may promote a local inflammatory process that affect local commensal flora, thus allowing bacteria to convert into leading organisms, comprising classes earlier grouped regarding their pathophysiology into the “Red Complex” Tannerella forsythia, Porphyromonas gingivalis, and Treponema denticola [11].

Continuous and unresolved inflammatory response may lead to injury of periodontal structures, like in periodontitis occurs, up to bone absorption, tooth damage and consequent systemic impact of the initial dysbiosis [11, 23].

In summary, first the inflammation appears and then tissue injury occurs, with the result that the originary local periodontal dysbacteriosis goes past the oral involvement [11, 23].

That is the reason why perturbation of oral microbiota negatively affects development and course of chronic diseases, like type-2 diabetes, early labour, rheumatoid arthritis, systemic lupus erythematosus (SLE), Alzheimer disease, cardiovascular illnesses and cancer [11].

Nevertheless, development and features of microbiota may be impacted by several factors: host genetics and characteristics, alimentary regimen, infections, lifestyle habits like smoking, stress or medical interventions, such as antibiotics, may produce change in the microbiota structure [21, 24].

Of particular interest is the role played by antibiotics in dysbiosis development in western countries, where the dominant culture and welfare on the one hand induce distortions in lifestyle and on the other allow a greater use of pharmacological treatments than in less developed countries [24]. It has been hypothesized that this general hygiene attitude reduces the exposition to microbial agents, thus rendering people in developed countries more prone to autoimmune diseases [24].

This predisposition to autoimmunity, may be caused by the incapacity of antibiotics to distinguish between commensals and pathogens, thus perturbing microbiota and impacting on the coevolutionary relationship between the immune system and the hosted symbionts.

Studies performed in recent years have not only documented that antibiotics commonly used in the clinical practice may produce a dysbiosis, but also that dysbiosis may influence disease progression. A dysbiosis basically may consist in harm to helpful microorganism, growth of pathological bacteria and an alteration of the general microbial variety. These three types of dysbiosis may appear concurrently [24].

A large observational cohort study was conducted in Sweden, aimed at investigating the relationship among oral health and autoimmune disorders. As reported by the Authors "this was the initial report to estimate oral conditions and the frequency of autoimmune disorders in the genealogically similar population" [19].

Generally, 1676 people between 30 and 40 years partook in the analysis of 1985. The individuals were arbitrarily chosen from Stockholm area and were evaluated during 30 years. The cohort of subjects as a mandatory condition to be born on the 20th of every month between 1945 and 1954 [19]. All patients underwent medical oral inspection and completed an organised survey. Data concerning their well-being grade as their lifestyle behaviours and employment status were collected [19].

The medical factors comprised data for plaque (PI), gingival inflammation (GI), calculus presence (CI), and records of deep pockets and/or absents of teeth [19].

CI was recorded from 0 having no calculus to 3 with abundant calculus following the Greene and Vermillion codes for tooth: Level 0= uncontaminated tooth and lack of microbial presence, Level 1= 33% of tooth by microbial organisms, Level 2= up to 50% of tooth with bacteria, Level 3= over than ½ of tooth with microorganisms [25].

Probing depth was calculated with a CP12 perio instrument and depth $\geq$ 5mm and the quantity of teeth were recorded [19].

Analyses of data showed that 50 patients presented a diagnosis of autoimmune disease [19], as follows: 1 patient was affected by ankylosing spondylitis, 6 patients were affected by Crohn's disease, 5 patients by Colitis ulcerosa, 14 patients by Diabetes mellitus Type-1, 1 patient by Graves' disease, 2 patients by Guillain-Barré syndrome, 1 patient by Henoch-Schönlein purpura, 1 patient by Lichen planus, 5 patients by Psoriasis, 15 patients by Rheumatic disease,

1 patient by Sicca condition (Sjogren), 1 patient by Lupus and 1 patient by Wegener's granulomatosis.

In addition to that, plaque presence was considerably greater in the autoimmune disorder unit. No significant dissimilarity existed amongst individuals with and without autoimmune syndrome [19].

In conclusion, according to the Authors, the results indicated that patients with an advanced degree of plaque presence, indicator of reduced hygiene, were more prone to advance into an autoimmune syndrome in the following 3 decades [19].

Nevertheless, the study presented some limitations, consisting in incomplete data of patient's daily habits, no availability of the exact time of diagnosis, the small number of subjects affected by autoimmune disease and the consequent weak statistical power. Therefore, this study, as the Authors themselves state, allows just to speculate a relationship between oral bacterial infection and systemic disease [19].

A more selective study was recently conducted in China to investigate whether pathogens of oral microbiota occurs prior to the appearance of rheumatoid arthritis symptoms [22].

For this purpose, the investigation involved 29 pre-trial patients, 27 rheumatoid arthritis subjects and 23 fit individuals underwent collection of saliva samples.

The oral saliva was assessed operating (16S) ribosomal RNA sequencing.

The α and ß variety examination was established for assessing the microbial environment, the microbiota composition and specific bacterial taxonomic characteristics between three groups, respectively.

Results of the study, show that salivary microbial diversity in pre-clinical patients was significantly lower than in patients with overt rheumatoid arthritis and in healthy subjects.

Conversely, preclinical patients, similarly to patients with overt disease but differently from healthy subjects, showed a lower amount of Defluvitaleace and Neisseria oralis, however an increase of Prevotella [6].

Surprisingly, the comparative bacteria of Porphyromonas gingivalis, described as opportunistic pathogens for rheumatoid arthritis presence, was appreciably reduced in high-risk patients.

Four species in the saliva from high-risk patients associated with serum levels of anti-citrullinated protein antibodies, and the other two genera inversely displayed.

In conclusion, the study has shown an alteration in salivary microbial composition in pre-clinical subjects, thus signifying that oral bacterial growth happens during the "pre-clinical" phase of rheumatoid arthritis and is linked with systemic autoimmune disorder [22].

Here autoimmune diseases causing oral lesions are described, focusing on the relevant injuries produced in the oral compartment.

Lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder that involves numerous organs and body compartments and its incidence is increasing worldwide. SLE affects mostly women and symptoms in most cases occur between ages of 15–44 [11].

SLE may present severe clinical manifestations and may be potentially fatal. It is described by extensive inflammation generating tissue impairment and co-morbidities involving many other organ regions [11].

Symptoms may present with significant intensity and consist in pain, weakness, alopecia, intellectual concerns, corporal deficiencies, oral and vaginal mucosa appearances, often with remarkable impact on patients' daily activities and quality of life [11].

Diagnosis of SLE requires clinical exams and positive serology. Therefore, besides presence of the classical facial butterfly rash, also the occurrence of discoid rash, arthritis and kidney disorders may be suggestive of SLE. Biochemistry may detect anaemia or leukopenia, while serology tests may show atypical antibodies [11].

Because of the involvement of different apparatus and the frequent comorbidities, diagnosis is difficult at early stages [11].

The aetiology of Lupus is partly associated to an uncontrolled inflammatory reaction to microorganisms alterations and environmental modifications [11]. Indeed, the large intestine and the oral environment, demonstrated a clear influence on Lupus individuals. Numerous reports have described relations between oral bacteria make-up in Lupus, while others have investigated the role of particular periodontal organisms and inflammatory cytokines in inflammation and development of the chronic disease.

The incidence of Systemic Lupus Erythematosus associated oral wounds can be present in 8-45% of individuals affected by Lupus and in 4-25% of subjects with discoid lupus erythematosus (DLE) and principally consist in ulcerations generally irregularly shaped, erythema, purpura, petechiae, hyperkeratosis or cheilitis [3,4]. (Figure 7-9).

Oral injuries related with DLE are characteristically ulcerated, thinning and redden. They present with burning, clear, whitened striae. These buccal injuries are present also in erosive lichen planus, but as opposed to lichen, in DLE usually manifest in conjunction with skin lesions [3,4,13]. Wounds can be medically resolved with drugs that include corticosteroidal cream, PO antimalarial medications, or PO immunosuppressive mediators, depending on the seriousness of the condition [4].

Figure 7. Oral finding with SLE [4] .

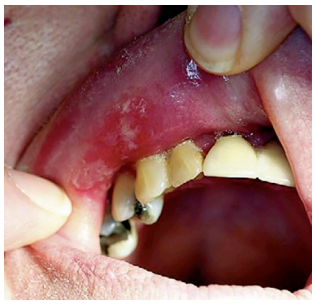


Figure 8. Oral finding with DLE [3]

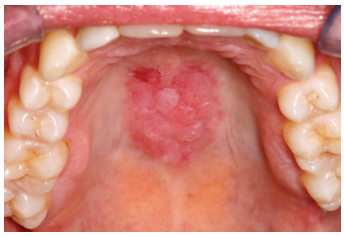
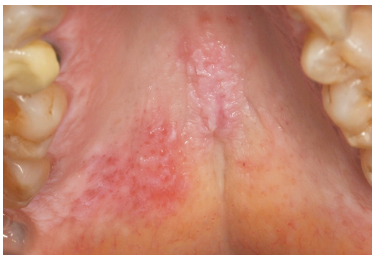


Figure 9. Oral finding with DLE [3] .



Several studies have been conducted to investigate the relationship between human oral microbiota and SLE and to better understand the role played by specific cytokines in SLE development.

Of particular interest is a recent investigation aiming to establish the mutual influence of subgingival bacteria and Lupus systemic inflammation in Brazilian individuals [11].

The subgingival microbial have been obtained from SLE and healthy controls in order to assess if particular bacteria are related to periodontitis in presenting bodywide concentrations of inflammatory cytokines.

The outcomes indicated important an increase in serum inflammatory cytokines in patients with Lupus when related to the control group.

More precisely, 10 inflammatory cytokines resulted in an increase in serum of Lupus-Inactive individuals, while in serum of Lupus-Active patients only 1 cytokine appeared increased.

The upregulated antinflammatory cytokines identified within serum of Lupus-Inactive individuals included IL4 IL-10, which were increased in Lupus-Inactive (not in Lupus-A) and were involved in controlling clinical phenotypes.

In the periodontal sites of SLE-Active patients, the most concerning oral bacteria associated to SLE (TD and TF) were more abundant than in SLE-Inactive patients and healthy controls, thus suggesting that sub-gingival pathogens related with Lupus play a role in systemic host cytokine pattern, thus impacting patient's overall health status.

In conclusion, the study shows a correlation between oral microbiota composition of patients with periodontal diseases and systemic inflammation at a lower level, that in turn conditions action and gravity of SLE diseases.

Sjögren syndrome

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disorder causing a disfunction in the normal secretion from the glands, but principally affecting lacrimal and salivary glands [(26)]. Nevertheless, the disease goes beyond the glandular compartment, thus producing systemic effects in 71% of cases [(26)].

SS can be categorised as primary or secondary, the primary form is restricted to the salivary and lacrimal glands whereas the secondary is linked with associated systemic diseases that can include RA and Lupus [4].

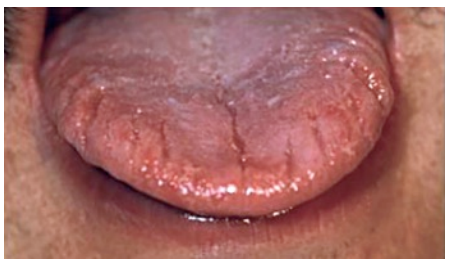
The histological features of the disease consist in inflammation of glandular tissue that results in an obliteration of the acini and a decrease in the excretion of liquids comprising antimicrobial products. With a consequent injury of the skin and the mucosal wall may promote a bacterial growth and an advanced chance of establishment by the pathobionts [26].

Oral signs of Sjögren comprise parotid expansion and a diminished saliva production, for example a higher risk for caries, diseases, and pain on swallowing [4].

Indeed, the low salivary volume decreases the dilution of the dietary sugars and consequently contributes to the growth of an optimal pabulum for the oral flora acid-producing bacteria, thus favouring caries development [2].

Thickness and scarcity of saliva are responsible for dryness of oral mucosa, that can appear red and wrinkled [4]. Also the lingua can be wounded and converted into dry and/or fissured with indentations that are accompanied with a fetid smell because of food entrapment (Figure 10) [4].

Figure 10. Fissured tongue related to Sjögren syndrome [4] .



Sjögren disease is worsened by non-Hodgkin lymphoma, with a frequency of 3.5-11% [4].

Management comprises the use of saliva replacements and stimulants, PO muscarinic agonists, including detailed instruction on oral cleanness to safeguard the mouth in its totality [4].

It has been theorized that oral bacteria alterations may trigger the immune system and effect the gravity of Sjögren.

Eventually, the impaired role of the mucosal and cutaneous membrane found in SS can facilitate the infiltration of bacterial microorganisms, which will additionally trigger an autoimmune reaction through molecular mimicry or direct association with TLRs on local dendritic cells. However, due to a lack of conclusive data, the precise involvement of the bacteria in SS still remains unknown.

It is note to worthy, that primary SS and SLE manifest similar epidemiology, clinical features, pathogenesis and etiological factors. Therefore, a recent Dutch study has investigated and compared the host microbial characteristics in pSS and SLE patients [27].

More precisely, aim of the study was to classify particular alterations in GI tract and oral bacteria compositions in these patient populations. Indeed, while the role played by genetics in development of pSS and SLE has been largely investigated and is now sufficiently known, conversely there is still poor knowledge about the involvement of environmental factors.

The determination of 16S ribosomal RNA (rRNA) sequencing has been performed in faeces and mouth swabs acquired from 39 positive Sjögren and 30 Lupus individuals. Swabs have been taken from 965 people living in the identical topographical zone, using the same procedures as the previous ill groups, being able to compare the presence of bacteria in the two patients groups. A and ß diversities and comparative presence of specific bacteria have been used as conclusive data for the evaluation of microbiota composition. These parameters are currently used in biology for the assessment of different levels of biodiversity and may be applied at different contexts: alfa indicates the number of species in a bacterial community

habiting a specific environment, while beta refers to the number of bacterial communities in a specific environment [28].

Results: alterations in intestinal microbiota presence are the same in positive Sjögren and Lupus individuals, but are different from those in the over-all population.

Conversely, oral microorganisms structure is different in pSS patients compared to SLE patients.

In conclusion, as stated by the Authors, this study highlights a crucial concept: the oral microbial composition influences the structure of the gut microbiota, strengthening the concept that the mouth will act as a source for possible bacteria implicated in intestinal inflammatory diseases. Indeed the study has documented a correlation amongst oral and intestinal comparative presence of Actinomyces and Lactobacillus.

These results contribute to clarify the chain of events leading to pSS and SLE development: increased comparative presence of Actinomyces and Lactobacillus in the mouth significantly correlates with a proliferation of these bacteria in the gut. The gut microbiota alteration induces intestinal inflammation, that in turn can consequently put at risk people to systemic inflammatory diseases.

In addition to that, while intestinal microorganisms of Sjögren and Lupus individuals are very related to each other, they differ suggestively from patients in the general population. On the contrary, oral bacteria varies between Sjögren and Lupus individuals, thus indicating a different bacterial identity at the origin of the development of the two diseases.

The study method and the relevant results, also suggest that surveys on oral status can represent a useful tool to collect notable data significant to oral microbiota investigations.

Systemic sclerosis (scleroderma)

Scleroderma affects female more commonly than males and consists in dense collagen deposition within the tissues, that may affect also oral cavity [4, 29].

Scleroderma clinically manifests ranging from a localized to a systemic disease [4, 13, 29]. As a consequence of collagen deposition in tissues, the disease leads to a progressive fibrosis in numerous apparatus [13, 29].

Limited forms of scleroderma are commonly indicated as CREST, which is the acronym for Calcinosis, Raynaud phenomenon, Esophageal involvement, Sclerodactyly, and Telangiectasias. In these conditions the oral manifestations are limited and mainly consist in intraoral and perioral telangiectasias [13]. Conversely, diffuse scleroderma may result in severe oral manifestations [13].

Diffuse scleroderma progressively induce a fibrotic process in nearly any internal organ and consequently systemic symptoms may vary depending on organs or apparatus involved [13].

Skin is markedly involved by fibrosis, resulting in movements limitation. Pigmentary changes and shiny skin occur as well [13].

Gastrointestinal manifestations frequently occur in patients with diffuse sclerodermia, even if are not incorporated in Sclerodermia classification and oral cavity is largely involved in this disease [4, 13, 30].

Indeed, as a result of oral and perioral collagen deposition, patients may present microstomia in 70 to 80% of cases, sublingual frenulum thickening, xerostomia due to progressive fibrosis of the salivary glands, telangiectasias, atrophy of the oral mucosa and secondary Sjogren's syndrome (Figure 11, 12) [4, 13, 29, 30, 31]. All these alterations can induce malnutrition due to

reduction of oral aperture and intake. Bone reabsorption may occur and affect tooth, with consequent mastication impairment [30].

Histology normally shows general fibrosis, including endothelial and capillary basal cell impairment [13]. Treatment may limit the disease progression, but frequently the damages are irreversible [4].

Fig. 11 Trismus and microstomia caused by Dense Perioral Fibrosis [31].

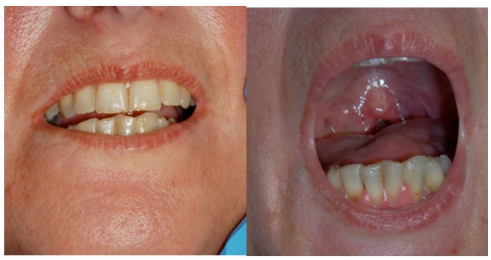
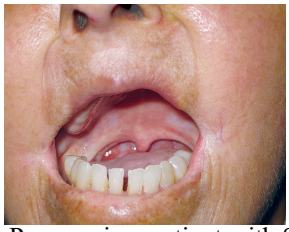
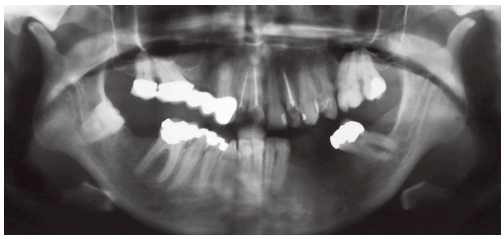


Figure 12.
Oral manifestations with Scleroderma [4].



Panorax in a patient with Scleroderma [4].

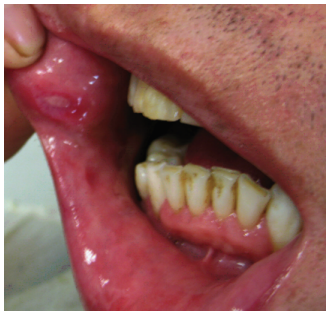


Other diseases belonging to the wide family of immune-mediated disorders and that result in oral lesions comprise pemphigus vulgaris, Wegener granulomatosis, Crohn disease, Behçet syndrome, benign mucus membrane pemphigoid, sarcoidosis, and lichen planus [3,4,].

All these conditions share painful oral ulcerations and consequently a differential diagnosis may be challenging. The following signs may guide the diagnosis: pemphigus may be suggested by a positive Nikolsky sign (displacement of the outer layer of the skin applying a pulling force); Wegener granulomatosis frequently appears as “strawberry gingival inflammation”; Crohn disease is related with an enlargement, muco-gingivitis and cobble gingiva, but may also present with nodules, tissue tags, polyps, and pyostomatitis vegetans [3,4].

Recurrent, painful aphthous-like ulcers in soft palate and oropharynx may be frequently observed in Behçet syndrome (Figure 13) [2].

Figure 13: Behcet's disease [2] .



4.5 MISCELLANEA

HIV/AIDS

Further systemic conditions presenting oral manifestations are the infection by human immunodeficiency virus (HIV) and the resulting acquired immunodeficiency syndrome (AIDS) [3].

HIV related periodontal disorder consists in gengival redness, presenting as a rectilinear group of inflammation beside the free gengival border, NUG, gengival haemorrhage and discomfort, foul smelling breath, necrotizing ulcerative periodontitis with fast loss of periodontal border attachment, oedema, discomfort, haemorrhage [3].

COVID-19

Currently, the most common manifestations by Covid-19 consists in fever, cough, pharyngeal pain, muscle pain, joint pain, headache, dyspnoea and mucus release. Nevertheless, a recent publication reports also oral expressions in a positive Covid-19 individual, such as oral ulcerative injuries, vesicular-bullous appearances and inflammation of the salivary glands. Notably, in four patients, oral expressions were the first signs of Covid-19.

Obviously, recognition of oral appearances of C-19 by practitioners is crucial for the immediate recognition of the virus and to prevent the diffusion [32].

Results from a large observational study conducted on individuals who experienced C-19 problems, suggest that periodontitis is related with an advanced risk of admission in intensive care unit, supported ventilation and death, as well as augmented levels of biomarkers associated to worse disease outcomes [33]. It has been hypothesized that this association is linked to an exacerbated inflammatory response and systemic inflammation, that characterizes periodontitis as well [33].

Anyway, further investigations on Covid-19 are necessary in order to confirm and describe the oral involvement of the disease.

5. DISCUSSION

The correlation between oral cavity conditions and general health has ancient roots, sunk in the history of medicine [34]. Indeed, evidences of dental procedures date back to the Neolithic age, while the Egyptian civilty has been proved to give much importance to dental practice. Furthermore, in the light of the contemporary findings on the relationship between oral microbiota and development of autoimmune diseases such as rheumatoid arthritis, it is undoubtedly impressive the narrative on Hippocrates, who treated joint pain with tooth extractions [34].

Indeed, recent studies conducted to investigate the influence of oral health status and oral microbial commensals on the development and maintenance of chronic diseases, have suggested, or in some cases documented, a relationship between oral microbiota and systemic autoimmune disorders comprising SLE, Sjögren and Rheumatoid arthritis.

Indeed individuals with an elevated plaque indicator, sign of a neglected oral hygiene, have been shown an increased risk to develop autoimmune diseases [19], while subjects with pre-clinical or overt rheumatoid arthritis may present an alteration in salivary microbial composition not found in healthy subjects [22]. Similarly, in women with active or inactive Systemic Lupus Erythematosus, a correlation has been found between bacterial modifications of the oral microbiota existent in periodontal diseases and the low-grade systemic inflammation, conditioning activity and gravity of the systemic disorder [11]. As a matter of fact, in the periodontal sites of patients with the active form of rheumatoid arthritis, the most serious oral microorganisms disease-associated, namely Treponema denticola and Tannerella forsythia, are more abundant than in patients with rheumatoid arthritis inactive form and in healthy controls [11].

In addition, it has been shown that the oral microbiota alteration is disease specific and consequently different bacterial families may characterize distinct diseases, as well as being reduced or expanded among different autoimmune disorders [27].

Nevertheless, even if undoubtedly all these investigations are providing new and often unexpected findings, and contribute to an increased knowledge about the pathogenesis of autoimmune diseases and relationship with the oral cavity health, it is worthy to notice that they may present some limits, as detailed in the Results Chapter above.

Basically, the novelty of the research issues impacts on the definition of the study objectives and parameters, thus potentially affecting the full significance of the results.

Accordingly, the attempt to assess the correlation between the systemic diseases and the concomitant or preceding oral lesions, leads to implement wide and long-lasting observational studies: but the larger and more detailed the observational studies, the more likely they are to

have defects in the collection of patient's data, possibly required for an exhaustive evaluation of the study results.

However, the chain of events that from the oral dysbiosis may lead to the development of an autoimmune disease is currently appearing more clear [27]. Changes in the architecture and composition of microbiota habiting the human digestive apparatus, allows the dominance of pathobionts that produce injuries to the local tissues, thus diffusing systemically. This process can produce the activation of immune responses.

Furthermore, oral and gut microbiotas appear to be linked by a mutual relationship: the dysbiosis of oral microbiota produces expansion of specific pathobionts that pour to intestine thus affecting the intestinal microbiota, whose alteration in turn is associated to the development of some chronic inflammatory mediated autoimmune disorders, including the intestinal bowel diseases.

In addition to that, many different systemic and chronic conditions may manifest with oral lesions that can occur even before the underlying disease.

All these cognitions lead to point out two basic concepts: the value of a competent inspection of the oral cavity and the importance of the dentistry intervention on the oral hygiene and lesions, such as periodontitis or dental plaque, that inducing change in the oral microbiota may at length produce a systemic low-grade systemic inflammation and trigger autoimmune processes.

This issue presently could be of particular relevant, as a study conducted in patients with Covid-19 complications, suggests that periodontitis could to be associated with higher risk of the worse disease outcomes [33]. Not surprisingly, as mentioned by the study authors "C-19 is related with an aggravated inflammatory reaction and systemic inflammation is furthermore distinctive of

periodontitis” [33]. The increasing knowledge on this disease and further investigations will clarify this finding.

6. CONCLUSIONS

The influence attributed to oral microbiota on the general health status is notably growing. Many findings from basic research and clinical studies suggest or in some cases demonstrate a relationship between oral microbiota and development, maintenance and severity of systemic diseases, including autoimmune diseases such as Systemic Lupus Erythematosus, Sjögren Syndrome and Rheumatoid arthritis.

Oral lesions may represent the first signal of an underlying systemic disease, often severe or even potentially fatal. Indeed, in some cases, autoimmune diseases involving oral cavity are diagnosed in occasion of routine dental checks. As a matter of fact, periodontitis or dental plaque, inducing change in the oral microbiota may at length produce a low-grade systemic inflammation and trigger autoimmune processes.

Therefore, particular attention should be payed to oral hygiene and mouth lesions and dentistry medical professionals may contribute dramatically to their patient's general health status, allowing in some cases an early diagnosis of potentially dangerous systemic diseases.

Further studies should be carried out in the future, either for a more complete comprehension of the complex relationship between oral microbiota and immune response or for a common definition of established criteria to assess the risk for developing autoimmune diseases.

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8. ANNEXES

Annex I. Autoimmune Disease List by The American Autoimmune Related Diseases Association (AARDA) [20].

The list includes both autoimmune disease and those conditions considered to be related to autoimmune disease.

Achalasia	Lichen sclerosus
Addison's disease	Ligneous conjunctivitis
Adult Still's disease	Linear IgA disease (LAD)
Agammaglobulinemia	Lupus
Alopecia areata	Lyme disease chronic
Amyloidosis	Meniere's disease
Ankylosing spondylitis	Microscopic polyangiitis (MPA)
Anti-GBM/Anti-TBM nephritis	Mixed connective tissue disease (MCTD)
Antiphospholipid syndrome	Mooren's ulcer
Autoimmune angioedema	Mucha-Habermann disease
Autoimmune dysautonomia	Multifocal Motor Neuropathy (MMN) or MMNCB
Autoimmune encephalomyelitis	Multiple sclerosis
Autoimmune hepatitis	Myasthenia gravis
Autoimmune inner ear disease (AIED)	Myositis
Autoimmune myocarditis	Narcolepsy
Autoimmune oophoritis	Neonatal Lupus
Autoimmune orchitis	Neuromyelitis optica
Autoimmune pancreatitis	Neutropenia
Autoimmune retinopathy	Ocular cicatricial pemphigoid
Autoimmune urticaria	Optic neuritis
Axonal & neuronal neuropathy (AMAN)	Palindromic rheumatism (PR)
Baló disease	PANDAS
Behcet's disease	Paraneoplastic cerebellar degeneration (PCD)
Benign mucosal pemphigoid	Paroxysmal nocturnal hemoglobinuria (PNH)
Bullous pemphigoid	Parry Romberg syndrome
Castleman disease (CD)	Pars planitis (peripheral uveitis)
Celiac disease	Parsonage-Turner syndrome
Chagas disease	Pemphigus
Chronic inflammatory demyelinating polyneuropathy	Peripheral neuropathy
(CIDP)	Perivenous encephalomyelitis
Chronic recurrent multifocal osteomyelitis (CRMO)	Pernicious anemia (PA)
Churg-Strauss Syndrome (CSS) or Eosinophilic	POEMS syndrome
Granulomatosis (EGPA)	Polyarteritis nodosa
Cicatricial pemphigoid	Polyglandular syndromes type I, II, III
Cogan's syndrome	Polymyalgia rheumatica
Cold agglutinin disease	Polymyositis
Congenital heart block	Postmyocardial infarction syndrome
Coxsackie myocarditis	Postpericardiotomy syndrome

CREST syndrome	Primary biliary cirrhosis
Crohn's disease	Primary sclerosing cholangitis
Dermatitis herpetiformis	Progesterone dermatitis
Dermatomyositis	Psoriasis
Devic's disease (neuromyelitis optica)	Psoriatic arthritis
Discoid lupus	Pure red cell aplasia (PRCA)
Dressler's syndrome	Pyoderma gangrenosum
Endometriosis	Raynaud's phenomenon
Eosinophilic esophagitis (EoE)	Reactive Arthritis
Eosinophilic fasciitis	Reflex sympathetic dystrophy
Erythema nodosum	Relapsing polychondritis
Essential mixed cryoglobulinemia	Restless legs syndrome (RLS)
Evans syndrome	Retroperitoneal fibrosis
Fibromyalgia	Rheumatic fever
Fibrosing alveolitis	Rheumatoid arthritis
Giant cell arteritis (temporal arteritis)	Sarcoidosis
Giant cell myocarditis	Schmidt syndrome
Glomerulonephritis	Scleritis
Goodpasture's syndrome	Scleroderma
Granulomatosis with Polyangiitis	Sjögren's syndrome
Graves' disease	Sperm & testicular autoimmunity
Guillain-Barre syndrome	Stiff person syndrome (SPS)
Hashimoto's thyroiditis	Subacute bacterial endocarditis (SBE)
Hemolytic anemia	Susac's syndrome
Henoch-Schonlein purpura (HSP)	Sympathetic ophthalmia (SO)
Herpes gestationis or pemphigoid gestationis (PG)	Takayasu's arteritis
Hidradenitis Suppurativa (HS) (Acne Inversa)	Temporal arteritis/Giant cell arteritis
Hypogammalglobulinemia	Thrombocytopenic purpura (TTP)
IgA Nephropathy	Thyroid eye disease (TED)
IgG4-related sclerosing disease	Tolosa-Hunt syndrome (THS)
Immune thrombocytopenic purpura (ITP)	Transverse myelitis
Inclusion body myositis (IBM)	Type 1 diabetes
Interstitial cystitis (IC)	Ulcerative colitis (UC)
Juvenile arthritis	Undifferentiated connective tissue disease (UCTD)
Juvenile diabetes (Type 1 diabetes)	Uveitis
Juvenile myositis (JM)	Vasculitis
Kawasaki disease	Vitiligo
Lambert-Eaton syndrome	Vogt-Koyanagi-Harada Disease
Leukocytoclastic vasculitis	
Lichen planus	
Lichen sclerosus	

Annex II. Synopsis with Oral Lesions and Relevant Underlying Systemic Diseases (A)

Systemic Disease	Oral lesions	Authors
Anaemia	Burning of the lips, tongue and buccal mucosa, angular cheilitis, oral candidiasis. In iron-deficiency anaemia prevail mucosal atrophy and pallor and atrophic glossitis. In pernicious anemia may prevail focal or diffuse erythema of the tongue and atrophy.	AC Chi et al [3], 2010; HL Gaddey et al, 2017[4]
Leukaemia	Mucosal bleeding, ulceration, petechiae, diffuse or localized gingival enlargement and secondary infections (3, ,14).	A.C. Chi et al, 2010[3]; CF Francisconi et al, 2016 [14]
Thrombocytopenia	Petechiae, purpura, ecchymosis, haemorrhagic bullae, hematomas	AC Chi et al, 2010; [3] HL Gaddey et al, 2017[4]
Multiple myeloma	Tooth pain, paresthesias, swelling, soft-tissue masses, mobility of teeth, migration of teeth, hemorrhage, pathologic fracture, facial asymmetry, macroglossia	4,15 HL Gaddey et al [4], 2017; RC Cardoso et al 2014[15]
Diabetes mellitus	Periodontal disease, periapical pathology, dental caries, oral fungal infections like oral candidiasis, fissured tongue, irritation fibroma, traumatic ulcers, lichen planus, xerostomia taste impairment, burning mouth syndrome	AC Chi et al, 2010[3]; HL Gaddey et al, 2017[4], E. Mauri-Obradors et al [16], 2017; Y Wang et al, 2019[17]
Thyroid dysfunctions	Hypothyroidism: lips and tongue swelling, tooth eruption disorders Hyperthyroidism: proptosis or exophthalmos.	HL Gaddey et al,2017[4]
Parathyroid disease	Hypoparathyroidism: Chvostek sign. In children: tooth eruption disorders or corrosion and enamel hypoplasia in children. Hyperparathyroidism: loss of the lamina dura of teeth roots and “ground glass” appearance on radiographs. In advanced conditions: brown tumours of the mandible	HL Gaddey et al, 2017[4]

SYNOPSIS WITH ORAL LESIONS AND RELEVANT UNDERLYING SYSTEMIC DISEASES (B)

Systemic Disease	Oral lesions	Authors
Adrenal disease	Hypercortisolism: "moon" facies, mandible bone loss. Hypoadrenocorticism Hyperpigmentation of the oral mucosa	HL Gaddey et al, 2017[4]
Metastatic tumours	Pain, tingling, or swelling of soft tissues, numb chin syndrome, affections of the jaw.	HL Gaddey et al, 2017, [4].
Kaposi sarcoma	Brown, blue, purple, or red patches and papules on the hard palate, mucosa, and gingiva; nodular lesions with a tendency to ulcerate and bleed; salivary glands involvement; head and neck lymphadenopathy.	HC Rosengard et al, 2016[13].
Lupus erythematosus	Ulcerated, atrophic, and erythematous lesions, usually with a central zone with radiating, fine, white striae. In DLE: erythema, purpura, petecchiae, hyperkeratosis or cheilitis.	AC Chi et al, 2010[3]; HL Gaddey et al, 2017[4]; HC Rosengard et al, 2016[13].
Sjögren syndrome	Parotid enlargement, dental caries, infections, dysphagia, xerostomia	HL Gaddey et al, 2017[4].
Systemic sclerosis	Microstomia, sublingual frenulum thickening, xerostomia, telangiectasias, atrophy of the oral mucosa	HL Gaddey et al, 2017 [4]; HC Rosengard et al 2016 [13]; A. Puzio et al, 2019 [29]; TM Frech et al, 2018[30]; HA Derbi et al, 2018[31].
Behçet syndrome	Painful oral ulcerations, recurrent painful aphthous-like ulcers in soft palate and oropharynx.	2,3,4 2 N. Geraldine et al, 2014;3 AC Chi et al, 2010 [3];4 HL Gaddey et al, 2017
Crohn disease	Painful oral ulcerations, diffuse swelling, localized mucogingivitis and cobblestoned mucosa, nodules, tissue tags, polyps, and pyostomatitis vegetans.	2,3,4 2 N. Geraldine et al, 2014;3 AC Chi et al, 2010 [3];4 HL Gaddey et al, 2017
Benign mucus membrane pemphigoid	Painful oral ulcerations, positive Nikolsky sign	3 AC Chi et al, 2010 [3]; HL Gaddey et al, 2017[4].
Wegener granulomatosis	Painful oral ulcerations, "strawberry gingivitis".	AC Chi et al, 2010[3]; HL Gaddey et al, 2017[4].
Lichen planus	Painful oral ulcerations	AC Chi et al [3], 2010; HL Gaddey et al, 2017[4].

1. Cammarata-Scalisi F, Girardi K, Strocchio L, Merli P, Bernardin AG, Galeotti A, Magliarditi F, Inserra A, Callea M. Oral Manifestations and Complications in Childhood Acute Myeloid Leukemia. Cancers (Basel). 2020 Jun 19;12(6):1634

cancers

MDPI

Review

Oral Manifestations and Complications in Childhood Acute Myeloid Leukemia

Francisco Cammarata-Scalisi [1,*], Katia Girardi [2], Luisa Strocchio [2], Pietro Merli [2], Annelyse Garret Bernardin [3], Angela Galeotti [3], Fabio Magliarditi [3], Alessandro Inserra [4] and Michele Callea [3,*]

1 Pediatrics Service, Regional Hospital of Antofagasta, Antofagasta 12440, Chile
2 Department of Hematology/Oncology, Cell and Gene Therapy, Bambino Gesù Children's Hospital, 00165 Rome, Italy; katia.girardi@opbg.net (K.G.); luisa.strocchio@opbg.net (L.S.); pietro.merli@opbg.net (P.M.)
3 Unit of Dentistry, Bambino Gesù Children's Hospital, 00165 Rome, Italy; annelyse.garret@opbg.net (A.G.B.); angela.galeotti@opbg.net (A.G.); fabio.magliarditi@opbg.net (F.M.)
4 Pediatric Surgery, Bambino Gesù Children's Hospital, 00165 Rome, Italy; alessandro.inserra@opbg.net
* Correspondence: francocammarata19@gmail.com (F.C.-S.); mcallea@gmail.com (M.C.)

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Abstract: Acute myeloid leukemia (AML) is a heterogeneous group of diseases, whose classification is based on lineage-commitment and genetics. Although rare in childhood, it is the most common type of acute leukemia in adults, accounting for 80% of all cases in this age group. The prognosis of this disease remains poor (especially in childhood, as compared to acute lymphoblastic leukemia); however, overall survival has significantly improved over the past 30 years. The health of the oral cavity is a remarkable reflection of the systemic status of an individual. Identification of the signs and symptoms of oral lesions can act as a warning sign of hidden and serious systemic involvement. Moreover, they may be the presenting feature of acute leukemia and provide important diagnostic indicators. Primary oral alterations are identified in up to 90% of cases of acute myeloid leukemia and consist of petechiae, spontaneous bleeding, mucosal ulceration, gingival enlargement with or without necrosis, infections, hemorrhagic bullae on the tongue, and cracked lips. Poor oral hygiene is a well-known risk factor for local and systemic infectious complications. Oro-dental complications due to AML treatment can affect the teeth, oral mucosa, soft and bone tissue, and contribute to opportunistic infections, dental decay, and enamel discoloration. The treatment of acute myeloid leukemia is still associated with high mortality and morbidity. The management is multimodal, involving aggressive multidrug chemotherapy and, in most cases, allogenic bone marrow transplantation. Periodontal and dental treatment for patients with leukemia should always be planned and concerted with hematologists.

Keywords: leukemia; acute myeloid leukemia; oral manifestations; treatment

1. Introduction

Leukemia is a heterogeneous group of hematological disorders arising from hematopoietic stem cells [1], resulting from the uncontrolled proliferation of neoplastic cells [2,3], characterized by impaired differentiation [1,2] and programmed cell death [2]. The failure of maturation of precursor cells results in the accumulation of blasts in the bone marrow with consequent suppression of normal hematopoiesis, leading to deficiency of mature leukocytes, erythrocytes, and platelets [4]. Life-threatening complications are represented by infections, frequently recurrent, as well as severe bleeding episodes [1–3,5]. Leukemic cells can invade various organs: Liver, spleen, central nervous system (CNS), bone, and the gingiva. Gingival infiltration can be demonstrated by biopsy [1,3].

2. Geraldine N. Urse, DO, FACOFP Systemic Disease Manifestations in the Oral Cavity. Osteopathic Family Physician, Volume 6, No. 3, May/June 2014

REVIEW ARTICLE

Systemic Disease Manifestations in the Oral Cavity

Geraldine N. Urse, DO, FACOFP
Doctors Hospital Family Practice, Grove City, Ohio

KEYWORDS:
Oral cavity
Systemic diseases
Oral mucosa
Tongue
Gingiva

The oral cavity is the window to the body and is often the area where systemic disease first presents itself. The various tissues including lips, tongue, gingiva, mucosal surfaces, dentition and bone are involved in the presentation of disease state. This review introduces an organized structure for the oral examination as well as presenting signs in various parts of the oral cavity. The review is not all inclusive however does address some of the most common, as well as a few of the more rare, disease states seen in both adults and children. A chart is included at the end of the article outlining the various disease states included as well as the area of the oral cavity in which they can be manifested.

INTRODUCTION

The oral cavity reflects the overall status of the body including hydration, and other organs.[1] Signs of systemic disease are often manifested in the oral cavity before the systemic disease itself is suspected. Some changes seen in the oral cavity are disease specific while others may simply increase the clinician's level of suspicion. A well-planned pattern for examination of the oral cavity will help ensure that no areas are unexamined. The progression utilized in this article is examination of the color and pigmentation of the mucosa, inspection of the mucosal surfaces and palate for lesions, evaluation of the tongue, the gingival surfaces and lastly the dentition. Attention must also be paid to the bony structures of mandible and maxilla when completing the physical examination.

Bacteria in the oral cavity can enter the blood stream through small abrasions or trauma due to food, brushing and flossing the teeth, self-inflicted trauma such as biting the tongue or lips or by the use of toothpicks. The bacteria may also be aspirated into the respiratory system leading to pulmonary infections such as pneumonia. The inflammatory response caused by periodontal disease can complicate already existing diseases such as diabetes, heart or kidney disease and also lead to problems with orthopedic implants such as infections or failure.

The most significant diseases indicated as having an oral systemic connection are cardiovascular disease, pulmonary disease, diabetes, orthopedic implant failure and kidney disease. Problems encountered in fetal development have also been associated with oral manifestations. Oral bacteria and periodontal disease are suspected of being contributing factors to the worsening of chronic disease states.

Address correspondence to: Geraldine N. Urse, DO, FACOFP, Doctors Hospital Family Practice, Grove City, OH
Email: gurse@ohiohealth.com

This article is not designed to be all-inclusive but rather to outline a systemic approach to identification of systemic disease as it presents within the oral cavity.

ORAL MUCOSA

The lips are the portal to the oral cavity. They reflect systemic changes through their tissue structure, color and hydration status. One of the most common viral infections of the oral mucosa is Herpes simplex virus (HSV-1) that leads to herpes labialis or primary herpetic gingivostomatitis. The virus lies dormant in the sensory ganglia and can be reactivated secondary to immunosuppression, stress or trauma. Dry, cracking lips may also be seen in patients with diabetes mellitus. Thin receding lips may be seen in patients with vitamin deficiencies that will be discussed later.

Changes in the color or pigmentation of the oral mucosa may well be the most easily identified change and is a starting point for evaluation. Mucosal pallor can be present with anemia however it can be so subtle that it is difficult to appreciate. Systemic diseases, such as Addison's disease, may change the pigmentation and may be the first indication of primary adrenal insufficiency.[2] (Figure 1) Systemic diseases such as McCune-Albright syndrome, Peutz-Jeghers syndrome and neurofibromatosis type 1 are also accompanied by changes in the melanin pigmentation of the oral cavity. Chronic liver disease can produce changes in the pigmentation of the oral cavity. Serum bilirubin levels greater than 2 – 3 times baseline will produce a yellow color in the thin mucosa of the sublingual are and the soft palate. Changes in oral pigmentation can also occur without relationship to disease such as ethnic related, tobacco-related, dietary intake related and medication-related pigmentation.

The mucosa should be inspected for hydration status as well as any lesions or growths. Ulcerated areas or aphthous lesions are commonly known as canker sores and can develop secondary

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Oral Manifestations of Systemic Disease

ANGELA C. CHI, DMD; BRAD W. NEVILLE, DDS; JOE W. KRAYER, DDS; and WANDA C. GONSALVES, MD
Medical University of South Carolina, Charleston, South Carolina

Careful examination of the oral cavity may reveal findings indicative of an underlying systemic condition, and allow for early diagnosis and treatment. Examination should include evaluation for mucosal changes, periodontal inflammation and bleeding, and general condition of the teeth. Oral findings of anemia may include mucosal pallor, atrophic glossitis, and candidiasis. Oral ulceration may be found in patients with lupus erythematosus, pemphigus vulgaris, or Crohn disease. Additional oral manifestations of lupus erythematosus may include honeycomb plaques (silvery white, scarred plaques); raised keratotic plaques (verrucous lupus erythematosus); and nonspecific erythema, purpura, petechiae, and cheilitis. Additional oral findings in patients with Crohn disease may include diffuse mucosal swelling, cobblestone mucosa, and localized mucogingivitis. Diffuse melanin pigmentation may be an early manifestation of Addison disease. Severe periodontal inflammation or bleeding should prompt investigation of conditions such as diabetes mellitus, human immunodeficiency virus infection, thrombocytopenia, and leukemia. In patients with gastroesophageal reflux disease, bulimia, or anorexia, exposure of tooth enamel to acidic gastric contents may cause irreversible dental erosion. Severe erosion may require dental restorative treatment. In patients with pemphigus vulgaris, thrombocytopenia, or Crohn disease, oral changes may be the first sign of disease. (*Am Fam Physician.* 2010;82(11):1381-1388.

In 2000, the U.S. Surgeon General's report *Oral Health in America* highlighted numerous ways in which oral and general health are linked.[1] Oral examination can reveal signs and symptoms of immunologic diseases, endocrinopathies, hematologic conditions, systemic infections, and nutritional disorders. In addition, several studies have reported associations between periodontal disease and diabetes mellitus, heart disease, stroke, and adverse pregnancy outcomes.[2-4] Identifying these oral findings may allow for early diagnosis and treatment. Family physicians should be familiar with the relationship between systemic and oral health, and be prepared to coordinate care with dental or medical subspecialists as indicated.

This article provides a guide for recognizing the oral manifestations of select systemic diseases. A number of oral manifestations of systemic disease have been covered previously[5,6]; therefore, a detailed discussion of these findings is not provided here. However, for comprehensiveness, salient features of these findings are included in *Table 1*, with a summary of the conditions and associated oral manifestations discussed in this article. For each category of oral finding, the conditions are presented in order of the frequency in which oral manifestations are encountered, from the most to least common.

Mucosal Changes

MUCOSAL PALLOR AND ATROPHY

Oral findings in patients with anemia may include mucosal pallor, atrophic glossitis, and candidiasis. Oral mucosal pallor may be difficult to appreciate.[7] Atrophic glossitis appears as complete or patchy baldness of the tongue caused by atrophy of the lingual papillae *(Figure 1)*. Atrophic glossitis is a nonspecific finding that can occur in association with iron deficiency anemia, pernicious anemia/vitamin B complex deficiencies, and various other conditions. Atrophy can be observed most easily on the dorsal tongue, although other sites may be affected. Burning, pain, tenderness, and erythema also may be present. Candidiasis may be a concurrent finding or an alternative cause of erythema, burning, and atrophy. In addition, some patients may present with angular cheilitis (a lip infection

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Oral manifestations of systemic disease

Heidi L. Gaddey, MD

On examination, the oral cavity may exhibit manifestations of underlying systemic disease and serve as an indicator of overall health. Systemic diseases with oral findings include autoimmune, hematologic, endocrine, and neoplastic processes. Autoimmune disease may manifest as oral ulcerations, changes in the salivary and parotid glands, and changes in the tongue. Patients with hematologic illnesses may present with gingival bleeding or tongue changes such as glossitis, depending on the etiology. Oral changes associated with endocrine illness are variable and depend on the underlying condition. Neoplastic changes include metastatic lesions to the bony and soft tissues of the oral cavity. Patients with chronic diseases such as gastroesophageal reflux and eating disorders may present with dental erosions that cause oral pain or halitosis. In the pediatric population, oral changes can be related to rare cancers, such as Langerhans cell histiocytosis, or infectious etiologies, such as Kawasaki disease. In both adults and pediatric patients, poor oral health has been linked to poorer health outcomes overall. Thorough history taking and physical examination by dentists may aid in determining the underlying etiology of oral changes and allow for earlier intervention by medical colleagues.

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Key words: autoimmune, endocrine, hematologic, oral manifestations

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The oral cavity can lend insight into underlying health in both adults and children. In 2000, the US Surgeon General highlighted the links between oral and general health.[1] Many systemic diseases first present as, or can be identified based on, changes within the oral cavity. This article will review select common oral cavity findings in adult and pediatric patients and the systemic diseases with which they may be associated.

Autoimmune diseases

Lupus erythematosus

Systemic lupus erythematosus (SLE) and discoid lupus erythematosus (DLE) present with oral findings in 8%-45% and 4%-25% of patients, respectively.[2] SLE is the most common vascular collagen disorder in the United States. Associated oral lesions can vary greatly in appearance, manifesting as ulcerations, erythema, or hyperkeratosis (Fig 1).[3,4] Cheilitis may also be present.[3] Oral lesions associated with DLE are typically ulcerated, atrophic, and erythematous; they usually demonstrate a central zone with radiating, fine, white striae.[3] These oral lesions are identical to erosive lichen planus; however, the absence of skin findings in patients with erosive lichen planus typically excludes the diagnosis of DLE.[4]

Lesions can be treated with topical corticosteroids, systemic antimalarial drugs, or systemic immunosuppressive agents, if needed, based on severity.

Systemic sclerosis (scleroderma)

Systemic sclerosis is characterized by dense collagen deposition within the tissues and ranges from localized to systemic disease. Females are more commonly affected.[5] Skin findings range from Raynaud phenomenon to masklike and "mouse" facies. Oral findings are variable, including changes to the lips and mouth (Fig 2). The lips appear pursed, and opening of the mouth may be limited.[6] Xerostomia is common; the tongue appears smooth, as do the palatal rugae.[5] On panoramic radiographs, mandibular resorption may be noted.[6,7]

Treatment is focused on limiting further progression, although often the changes are irreversible. Range of motion exercises may be beneficial to aid in mouth opening, and oral hygiene instruction should be provided to the patient.[6]

Sjögren syndrome

Sjögren syndrome (SS) is characterized by xerostomia and xerophthalmia and more commonly affects females. It can be classified as primary or secondary, the latter if SS is associated with another autoimmune illness. Associated autoimmune conditions include rheumatoid arthritis, SLE, and scleroderma.[8] Oral manifestations of SS include parotid enlargement and findings related to decreased saliva, such as increased risk of dental caries, infections, and dysphagia. Saliva is often thick

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Review Article

Autoimmune Diseases and Their Manifestations on Oral Cavity: Diagnosis and Clinical Management

Matteo Saccucci, Gabriele Di Carlo, Maurizio Bossù, Francesca Giovarruscio, Alessandro Salucci, and Antonella Polimeni

Department of Oral and Maxillo-Facial Sciences, Sapienza University of Rome, Viale Regina Elena 287a, 00161 Rome, Italy

Correspondence should be addressed to Matteo Saccucci; matteo.saccucci@uniroma1.it

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Oral signs are frequently the first manifestation of autoimmune diseases. For this reason, dentists play an important role in the detection of emerging autoimmune pathologies. Indeed, an early diagnosis can play a decisive role in improving the quality of treatment strategies as well as quality of life. This can be obtained thanks to specific knowledge of oral manifestations of autoimmune diseases. This review is aimed at describing oral presentations, diagnosis, and treatment strategies for systemic lupus erythematosus, Sjögren syndrome, pemphigus vulgaris, mucous membrane pemphigoid, and Behcet disease.

1. Introduction

Increasing evidence is emerging for a steady rise of autoimmune diseases in the last decades [1]. Indeed, the growth in autoimmune diseases equals the surge in allergic and cancer pathology; on the other hand, infections are shown to be less frequent in the Western societies [2]. Oral manifestations of autoimmune disease are frequently the primary sign of autoimmune diseases [3]. The dentists can therefore play a pivotal role in the detection and during the following multidisciplinary treatment. Precise and early diagnosis increases the efficiency and efficacy of treatment strategy [4–6]. Therefore, the goal of our review is to present the most common autoimmune diseases that show the first oral clinical signs and symptoms which are a manifestation of the general clinical disease. Our review is presenting details over systemic lupus erythematosus, Sjögren syndrome, pemphigus vulgaris, mucous membrane pemphigoid, and Behcet disease. Every single paragraph reviews the general conditions, and in the second part, we discuss the diagnosis and treatment strategies.

2. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a severe and chronic autoimmune inflammatory disease of unknown etiopathogenesis and various clinical presentations. SLE mainly affects women 8 times more likely than men. The worldwide prevalence of SLE ranges between 12 and 50 per 100,000, depending on location and ethnicity [7].

SLE is usually a chronic and progressive disease whose dormancy and progress are fairly regular and in sequence. There are cellular and cell-mediated processes involved in the SLE, even though it has been speculated that the primary involvement is mainly due to cell-mediated immunity and consequential humoral involvement [8]. The immune complex deposits in different organs triggering an inflammatory reaction that leads to organ functional impairment typical of the disease. In the pathogenesis of SLE, the activation of type I IFN pathways, B and T cell dysfunction, and presence of antinuclear antibodies were demonstrated [9]. Anti-DNA antibodies (deoxyribonucleic acid, antinuclear antibodies) are found in the patients' serum. The prolifer-

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Oral manifestations of systemic disease

S R Porter MD, PhD, FDS RCS, FDS RCSE, FHEA
Institute Director and Professor of Oral Medicine

Valeria Mercadante DDS PhD MJDF RCS
Research Clinician

S Fedele DDS PhD
Professor of Oral Medicine

UCL Eastman Dental Institute
256 Gray's Inn Road
London WC1X 8LD

Oral Theme
UCL NIHR Biomedical Research Centre

Tel: +44 (0) 20 3456 1038

www.ucl.ac.uk/eastman

All correspondence to:

Professor Stephen R. Porter
Institute Director and Professor of Oral Medicine
UCL Eastman Dental Institute
256 Gray's Inn Road
London WC1X 8LD

Tel: +44 (0) 20 3456 1038
Fax: +44 (0) 20 3456 1002
E-mail: S.Porter@ucl.ac.uk

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Reviews in Health Care 2011; 2(2): 113-135

DISEASES
Narrative review

Le patologie autoimmunitarie del cavo orale

Autoimmune diseases of oral cavity

Davide B. Gissi [1], Mattia Venturi [1], Andrea Gabusi [1], Annachiara De Martino [1], Lucio Montebugnoli [1]

[1] *Dipartimento di Scienze Odontostomatologiche, Università degli Studi di Bologna*

Abstract

Most diseases of oral mucosa are either autoimmune in nature or are the results of immunologically-mediated events. These include Recurrent Aphthous Stomatitis (RAS), Erythema Multiforme (EM), the bullous diseases Pemphigus Vulgaris (PV) and Mucous Membrane Pemphigoid (MMP) and Lichen Planus (LP). These conditions are characterised by lesions of the oral mucosa often associated with extra-oral manifestations that include skin, eyes, nasal and pharyngeal mucosa as well as genitals. Despite a similar pathogenesis, they are characterised by different immunologic processes that involve T-cell mediated hypersensitivity in LP, humoral-mediated immunity to cadherin intercellular adhesion molecules in PV, antibody-mediated processes giving rise to junctional separation in MMP, and other not yet completely understood processes in RAS and EM. Differences are also present in the clinical outcome, that is always acute and auto-limiting in EM, auto-limiting and often recurrent in RAS, sub-acute and often recurrent in MMP and PV and always chronic in LP. Accurate diagnosis is not always possible solely on the basis of the oral presentation, and histological and often immunofluorescence examinations are needed in order to establish a definitive diagnosis. The condition that brings together all these diseases is that thay all benefit from similar therapeutic approaches, consisting in local or systemic immunosuppressive treatments. This review provides guidance to differentiate and correctly diagnose these conditions and discusses the most appropriate management.

Keywords

Oral cavity, autoimmune diseases, erythema multiforme, aphthous stomatitis, lichen planus, pemphigus, corticosteroids

Corresponding author
Prof. Lucio Montebugnoli
lucio.montebugnoli@unibo.it

Disclosure
Gli Autori dichiarano di non avere conflitti di interesse in merito ai temi trattati nel presente articolo

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Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Oral health and plaque microbial profile in juvenile idiopathic arthritis

Sriharsha Grevich[1,2*], Peggy Lee[3], Brian Leroux[3], Sarah Ringold[1,2,4], Richard Darveau[3], Gretchen Henstorf[5], Joel Berg[3], Amy Kim[3], Elizabeth Velan[3], Joseph Kelly[3], Camille Baltuck[3], Anne Reeves[3], Hannah Leahey[5], Kyle Hager[6], Mitchell Brittnacher[6], Hillary Hayden[6], Samuel Miller[6,7,8], Jeffrey McLean[3] and Anne Stevens[1,2,5]

Abstract

Background: The oral microbiota has been implicated in the pathogenesis of rheumatoid arthritis through activation of mucosal immunity. This study tested for associations between oral health, microbial communities and juvenile idiopathic arthritis (JIA).

Methods: A cross-sectional exploratory study of subjects aged 10–18 years with oligoarticular, extended oligoarticular and polyarticular JIA was conducted. Control groups included pediatric dental clinic patients and healthy volunteers. The primary aim was to test for an association between dental health indices and JIA; the secondary aim was to characterize the microbial profile of supragingival plaque using 16S rRNA gene sequencing.

Results: The study included 85 patients with JIA, 62 dental patients and 11 healthy child controls. JIA patients overall had significantly more gingival inflammation compared to dental patients, as evidenced by bleeding on probing of the gingiva, the most specific sign of active inflammation ($p = 0.02$). Overall, however, there was a trend towards better dental hygiene in the JIA patients compared to dental patients, based on indices for plaque, decay, and periodontitis. In the JIA patients, plaque microbiota analysis revealed bacteria belonging to genera *Haemophilus* or *Kingella* elevated, and *Corynebacterium* underrepresented. In poly JIA, bacteria belonging to the *genus Porphyromonas* was overrepresented and *Prevotella* was underrepresented.

Conclusion: Increased gingival inflammation in JIA was independent of general oral health, and thus cannot be attributed to poor dental hygiene secondary to disability. The variation of microbial profile in JIA patients could indicate a possible link between gingivitis and synovial inflammation.

Keywords: Juvenile idiopathic arthritis, Oral health, Gingivitis, Microbiota

Background

Juvenile idiopathic arthritis (JIA) is a common rheumatologic disorder that can lead to significant disability. The cause is not known, precluding prevention or cure. A current hypothesis is that environmental triggers interact with specific human leukocyte antigen (HLA) and innate immunity genes associated with JIA [1].

Humans have co-evolved with microorganisms that play a pivotal role in immune development and homeostasis [2]. Crosstalk between the microbiome and the immune system has been implicated in the pathogenesis of adult-onset chronic inflammatory diseases, including rheumatoid arthritis (RA) [3, 4]. Altered oral microbial communities have been found in periodontitis, and periodontitis has been associated with RA [5, 6]. Both periodontitis and RA are characterized by innate immune activation [7]. Periodontal pathogens in the subgingival plaque, some also associated with RA, have been linked to gingival proinflammatory cytokines [8]. A causal relationship is suggested by control of RA by treating periodontitis [9, 10]. Adaptive immunity has also been implicated in the mechanism, given the association of P. gingivalis, a periodontal pathogen, with early RA, especially those patients with high levels of anticitrullinated protein antibodies ACPA [11].

* Correspondence: Sriharsha.Grevich@seattlechildrens.org
[1]Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, WA 98105, USA
[2]Department of Pediatrics, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, USA
Full list of author information is available at the end of the article

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Highlights in Autoimmunity: 2020

Elias Toubi MD and Zahava Vadasz MD PhD

Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT Innate and adaptive immune response dysregulations are equally involved in the induction of autoimmunity. Toll-like receptors play a leading role in the activation of innate immune cells, thus priming auto-reactive T cells. Th17 cells and related cytokines are widely involved in many immune-mediated diseases such as rheumatoid arthritis. Thus, the recent introduction of anti-IL-17 therapies should be further evaluated. Janus kinase inhibitors and Fc receptor-targeting drugs are some of the new therapeutic strategies that are being implemented when old classical therapies lack sufficient beneficial outcomes.

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KEY WORDS: autoimmunity, innate immunity, Th17, pregnancy

Autoimmunity is one of the fastest growing fields in medicine. During the last two decades it has turned into a vast forest of new highlights in which one can easily get lost. Planning to enter this forest, one should choose a specific direction to explore. This review focuses on innate immunity and autoimmunity, pregnancy and autoimmunity, Th17 and autoimmunity, and new therapeutic approaches in autoimmune diseases.

INNATE IMMUNITY AND AUTOIMMUNITY

The innate immune system is highly involved in the induction of adaptive immune responses against self and non-self-antigens. Toll-like receptors (TLRs) play a leading role in the activation of innate immune cells such as dendritic cells (DCs), thus inducing autoimmune responses by priming autoreactive T cells [1]. The B cell compartment is complex and comprises B cell subsets with innate-like functions, including innate response activator B cells, T-bet positive B cells, natural killer-like B cells, and human self-reactive Vh4-34-expressing B cells. The issue of the cross talk between innate-like B cells and other adaptive and innate branches is crucial for the development of autoimmune diseases and could become a therapeutic target in down-regulating immune-mediated inflammation [2]. The continuous trigger of DCs by self-antigens enhances B cell activity and autoreactive B cells to increase the production of autoantibodies and pro-inflammatory cytokines. The innate immune system is a complex network such as antigen-presenting cells, the complement cascade, C-reactive protein (CRP), C1q, and Toll-like receptors (TLRs). Among these entire molecules, there is a high expression of TLR-7 and TLR-9 in autoreactive B cells contributing to their expansion, mainly, in systemic lupus erythematosus (SLE). A subset of DCs is identified by tolerogenic properties, thus playing role in maintaining self-tolerance [3].

Natural killer cells are important players in suppressing autoimmunity

Toll-like receptors are upstream pattern recognition receptors on both innate and adaptive immune cells. By detecting pathogen associated molecular patterns, they initiate signal transduction, by which the interleukin-1 receptor-associated kinase (IRAK) family mediates activating signals from TLRs. The family includes four members, all of which have a role in either positive or negative regulation of the innate immunity and are implicated in the development of autoimmune diseases. IRAK inhibition has potential therapeutic effects [4]. Natural killer (NK) cell activity is linked to inflammasome activation, having the potential to act in driving inflammation and autoimmunity. In this case, memory-like or adaptive NK cells drive NK cell-mediated autoreactive diseases. However, NK cells, namely, CD56+ are considered important players in suppressing autoimmunity thus considered immune regulators in maintaining peripheral tolerance [5]. The over-activity of the innate immune responses is highly responsible for the evolvement of many autoimmune diseases such as rheumatoid arthritis (RA), SLE, and multiple sclerosis. This response results in damage via the production of pro-inflammatory cytokines, amplifying local inflammation and further activation of additional immune or parenchymal cells the generation of matrix degrading and proteolytic enzymes or reactive oxygen species [6]. Pro-inflammatory cytokines contributing to the development of immune-mediated inflammatory diseases, such as inflammatory bowel diseases (IBD), include interleukin-3 (IL-13). IL-13 is produced by Th2 cells, NK cells, and innate lymphoid cells. In several experimental models, IL-13 was shown to play either pathogenic or protective role in relation to the different inflammatory status. This finding suggests that targeting IL-13 should be assessed in IBD [7]. Gut microbiota appeared to affect local mucosal homeostasis contributing to the balance between the over activity of immune responses and immune tolerance. Recent evidence pointed to the relationship between gut microbiota and innate immunity, namely the role of gut microbiota, on the function of gut-associated lymphoid tissue, innate lymphoid cells, and phagocytosis. Thus a crosstalk between gut microbiota and innate immunity may contribute to the development of autoimmune diseases [8].

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The Microbiome in Systemic Autoimmune Disease – Mechanistic Insights from Recent Studies

Carina Dehner, **Rebecca Fine**, and **Martin A. Kriegel**
Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06511, USA

Summary

Complex host-microbiota interactions contribute to systemic autoimmunity outside the gut. On a molecular level, posttranslational modification of, and cross-reactivity with, autoantigens represent mechanisms of how the microbiota mediate autoimmunity. On a cellular level, translocation of live gut bacteria across a dysfunctional gut barrier allows for direct interactions with immune and tissue cells, instigating autoimmunity systemically.

Keywords

Cross-reactivity; orthologs; citrullination; gut barrier; commensal translocation; pathobionts

Introduction:

Systemic autoimmune disorders are characterized by tissue damage in anatomically diverse locations. Inflammation is mediated by innate cells, migrating autoreactive lymphocytes and circulating pathogenic autoantibodies. How these complex processes are triggered and sustained remains incompletely understood but host-microbiota interactions in the context of a genetically susceptible host are increasingly implicated (1). The adaptive immune response to gut commensal bacteria plays an integral role in maintaining homeostasis (2). Environmental factors, genetic polymorphisms and gut microbial diversity shape adaptive immune system responses (3). Furthermore, the neonatal period is critical for the development of lymphoid structures, maturation of T and B cells, and acquisition of immune tolerance to gut commensals (4, 5). Alteration in microbial communities during this critical time can result in immune dysregulation and subsequent immune-mediated diseases such as allergies or autoimmunity.

Various T cell subsets both maintain protective immunity against pathogens and prevent inflammatory immune responses against self and microbiota-derived antigens. Instructed by the environment and innate antigen-presenting cells, $CD4^+$ T helper (Th) cells differentiate into functionally diverse subsets including Th1, Th2, Th17, and regulatory T cells (Tregs).

Author of correspondence: Martin A. Kriegel, Department of Immunobiology, Yale School of Medicine, 10 Amistad Street, New Haven, CT 06519, Phone: (203) 737 2294, martin.kriegel@yale.edu.

Conflicts of interest
M.A.K. holds an international patent on the use of antibiotics and commensal vaccination to treat autoimmunity and receives salary support from Roche. The remaining authors have no conflict of interest.

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Host-Microbial Interactions in Systemic Lupus Erythematosus and Periodontitis

*Larissa Pessoa[1], Gajender Aleti[2], Saibyasachi Choudhury[2], Daniel Nguyen[3], Tina Yaskell[3], Yun Zhang[2], Weizhong Li[2], Karen E. Nelson[2,4], Leopoldo Luiz Santos Neto[5], Adriana C. P. Sant'Ana[1] and Marcelo Freire[2]**

[1] Department of Prosthodontics and Periodontics, Bauru School of Dentistry, University of São Paulo, Bauru, Brazil, [2] Department of Genomic Medicine, J. Craig Venter Institute, La Jolla, CA, United States, [3] Applied Oral Sciences, The Forsyth Institute, Cambridge, MA, United States, [4] Department of Genomic Medicine, J. Craig Venter Institute, Rockville, MD, United States, [5] Rheumatology Department, Medical Faculty, University of Brasília, Brasília, Brazil

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***Correspondence:**
Marcelo Freire
mfreire@jcvi.org

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Background: Systemic lupus erythematosus (SLE) is a potentially fatal complex autoimmune disease, that is characterized by widespread inflammation manifesting tissue damage and comorbidities across the human body including heart, blood vessels, joints, skin, liver, kidneys, and periodontal tissues. The etiology of SLE is partially attributed to a deregulated inflammatory response to microbial dysbiosis and environmental changes. In the mouth, periodontal environment provides an optimal niche for local and systemic inflammation. Our aim was to evaluate the reciprocal impact of periodontal subgingival microbiome on SLE systemic inflammation.

Methods: Ninety-one female subjects were recruited, including healthy (n = 31), SLE-inactive (n = 29), and SLE-active (n = 31). Patients were screened for probing depth, bleeding on probing, clinical attachment level, and classified according to CDC/AAP criteria with or without periodontal dysbiosis. Serum inflammatory cytokines were measured by human cytokine panel and a targeted pathogenic subgingival biofilm panel was examined by DNA-DNA checkerboard from subgingival plaque samples.

Results: The results showed significant upregulation of serum proinflammatory cytokines in individuals with SLE when compared to controls. Stratification of subject's into SLE-inactive (I) and SLE-active (A) phenotypes or periodontitis and non-periodontitis groups provided new insights into SLE pathophysiology. Ten proinflammatory cytokines were upregulated in serum of SLE-I only and one in SLE-A only. Four molecules overlapped in SLE-A and SLE-I. Anti-inflammatory cytokines included IL-4 IL-10, which were upregulated in SLE-I sera (but not SLE-A), controlling clinical phenotypes. Out of 24 significant differential oral microbial abundances found in SLE, 14 unique subgingival bacteria profiles were found to be elevated in SLE. The most severe oral pathogens (*Treponema denticola* and *Tannerella forsythia*) showed increase abundances on SLE-A periodontal sites when compared to SLE-I and healthy controls. Inflammation

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Review Article

Oral Ulcers Presentation in Systemic Diseases: An Update

Sadia Minhas[1], Aneequa Sajjad[1], Muhammad Kashif[2], Farooq Taj[3], Hamed Al Waddani[4], Zohaib Khurshid[5*]

[1]Department of Oral Pathology, Akhtar Saeed Dental College, Lahore, Pakistan; [2]Department of Oral Pathology, Bakhtawar Amin Medical & Dental College, Multan, Pakistan; [3]Department of Prosthetic, Khyber Medical University Institute of Dental Sciences, Kohat, Pakistan; [4]Department of Medicine and Surgery, College of Dentistry, King Faisal University, Hofuf, Al-Ahsa Governorate, Saudi Arabia; [5]Department of Prosthodontics and Dental Implantology, College of Dentistry, King Faisal University, Hofuf, Al-Ahsa Governorate, Saudi Arabia

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Keywords: Oral ulcer; Infections; Vesiculobullous lesion; Traumatic ulcer; Systematic disease

***Correspondence:** Zohaib Khurshid. Department of Prosthodontics and Dental Implantology, College of Dentistry, King Faisal University, Hofuf, Al-Ahsa Governorate, Saudi Arabia. E-mail: drzohaibkhurshid@gmail.com

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Abstract

BACKGROUND: Diagnosis of oral ulceration is always challenging and has been the source of difficulty because of the remarkable overlap in their clinical presentations.

AIM: The objective of this review article is to provide updated knowledge and systemic approach regarding oral ulcers diagnosis depending upon clinical picture while excluding the other causative causes.

METHODS: For this, specialised databases and search engines involving Science Direct, Medline Plus, Scopus, PubMed and authentic textbooks were used to search topics related to the keywords such as oral ulcer, oral infections, vesiculobullous lesion, traumatic ulcer, systematic disease and stomatitis. Associated articles published from 1995 to 2019 in both dental and medical journals including the case reports, case series, original articles and reviews were considered.

RESULTS: The compilation of the significant data reveals that ulcers can be classified according to (i) duration of onset, (ii) number of ulcers and (iii) etiological factors. Causation of oral ulcers varies from slight trauma to underlying systemic diseases and malignancies.

CONCLUSION: Oral manifestations must be acknowledged for precise diagnosis and appropriate treatment.

Introduction

The breach describes ulcerations in the epithelium, underlying connective tissue or both [1]. The most frequent oral mucosal lesion that comes across is oral ulceration [2], [3], [4]. Patients having ulceration of oral cavity might report primarily to a dental consultant or a general physician.

Ulcerations can be classified based on (i) duration of onset (ii) number of ulcers and (iii) etiological factors; ulcerative lesion lasts for two weeks, is considered as the chronic ulcer. Acute ulcer lasts for no longer than two weeks and is typically painful [1], [5], whereas recurrent ulcers present with a history of comparable episodes with irregular healing and chronic ulcer may last for more than two weeks [6]. The solitary ulcer is the occurrence of a single ulcerative lesion, while the term multiple explains the incidence of numerous ulcerative lesions [6].

Because of the variety of presenting features and causative factors, identification of oral ulcerative lesions may be relatively challenging. Local or systemic factors can be contributing to developing ulcers [1], [6]. Ulcers have different parts: the floor (uncovered ulcer surface), the base (ulcer rest seat), the margin (interface among the wall of ulcer and normal epithelium) and the edge (the part of the

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Oral Manifestations of Systemic Diseases

- Author: Heather C Rosengard, MPH; Chief Editor: Dirk M Elston, MD more...

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Overview

The oral cavity plays a critical role in numerous physiologic processes, including digestion, respiration, and speech. It is also unique for the presence of teeth and mucosa. The mouth is frequently involved in conditions that affect the skin, but it is also affected by many systemic diseases. Oral involvement may precede or follow the appearance of findings at other locations.

This article is intended as a general overview of conditions with oral manifestations of systemic diseases. It is not intended to provide details about the diagnosis and management of these conditions. Many of these conditions have excellent full-length Medscape Drugs & Diseases articles, which are linked herein.

Gastrointestinal Diseases

The oral cavity is the portal of entry to the GI tract and is lined with stratified squamous epithelium. The oral cavity is often involved in conditions that affect the GI tract. Both ulcerative colitis (UC) and Crohn disease are classified as inflammatory bowel disease (IBD). While Crohn disease can affect any part of the GI tract (from the oral cavity to the anus), inflammation in UC is generally restricted to the colon and is specifically limited to the mucosa and submucosa.

Ulcerative colitis

UC is characterized by periods of exacerbation and remission, and, generally, oral lesions coincide with exacerbations of the colonic disease. Lesions in the colon consist of areas of hemorrhage and ulceration, along with abscesses. Cutaneous involvement consists of similar ulcerations that may arise on the buttocks, abdomen, thighs, and face, although in rare cases patients may develop pyoderma vegetans.[1, 2] In the oral cavity, aphthous ulcers or angular stomatitis occurs in as many as 5-10% of patients, although hemorrhagic ulcers can occur.[3] Rarely, patients can develop pyostomatitis vegetans (PSV), the oral counterpart of pyoderma vegetans.

Also see Ulcerative Colitis.

Crohn disease

Crohn disease is an idiopathic inflammatory disorder that can involve the entire GI tract with transmural inflammation and noncaseating granulomas. The prevalence of Crohn disease varies significantly between populations. In North America, the incidence of Crohn disease can be as high as 20.2 cases per 100,000 population.[4] Although formerly considered a disease of Western nations, the incidence is rising in Asia. Similarly, it has long been observed that the incidence of Crohn disease is higher at northern latitudes than at southern latitudes.[4] There is a well-documental bimodal age distribution associated with the onset of Crohn disease: the peak incidence occurs in the second and third decades of life, with a second, smaller peak in the sixth and seventh decades.[4] Genetics have also been implicated in the development of the disease since certain populations (ie, Ashkenazi Jewish populations) have a much higher risk for the development of the disease; more recently, Crohn disease–associated genetic loci have been identified.[4] Changes to the gut microbiome and various environmental risk factors (including smoking, hygiene, and dietary practices) have also been implicated in the disease's onset or progression.[4]

Symptoms of Crohn disease include intermittent attacks of diarrhea, constipation, abdominal pain, and fever.[5] Patients may develop malabsorption and subsequent malnutrition.[5] Systemic features of Crohn disease include arthritis, clubbing of the fingers, and sacroiliitis.[5]

Skin findings include knifelike fissures and ulcerations, as well as fistulae. Vulvar manifestations, such as fissures, edema, tenderness to palpation, and nonspecific aphthae, have also been reported.[5] Cutaneous manifestations of Crohn disease may also be noncontiguous: metastatic Crohn disease is defined as a granulomatous inflammation of the skin that is not contiguous with the GI tract. Although well described, metastatic Crohn disease may present a diagnostic challenge since its clinical presentation is quite variable and may occur without a history of GI disease.[5] Nonspecific, reactive skin findings in patients with Crohn disease include erythema nodosum, pyoderma gangrenosum, and Sweet syndrome.[6]

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Leukemic Oral Manifestations and their Management

MINI-REVIEW

Leukemic Oral Manifestations and their Management

Carolina Favaro Francisconi[1], Rogerio Jardim Caldas[2]*, Lázara Joyce Oliveira Martins[2], Cassia Maria Fischer Rubira[2], Paulo Sergio da Silva Santos[2]

Abstract

Leukemia is the most common neoplastic disease of the white blood cells which is important as a pediatric malignancy. Oral manifestations occur frequently in leukemic patients and may present as initial evidence of the disease or its relapse. The symptoms include gingival enlargement and bleeding, oral ulceration, petechia, mucosal pallor, noma, trismus and oral infections. Oral lesions arise in both acute and chronic forms of all types of leukemia. These oral manifestations either may be the result of direct infiltration of leukemic cells (primary) or secondary to underlying thrombocytopenia, neutropenia, or impaired granulocyte function. Despite the fact that leukemia has long been known to be associated with oral lesions, the available literature on this topic consists mostly of case reports, without data summarizing the main oral changes for each type of leukemia. Therefore, the present review aimed at describing oral manifestations of all leukemia types and their dental management. This might be useful in early diagnosis, improving patient outcomes.

Keywords: Leukemia - early diagnosis - oral manifestations - dental care

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Introduction

A number of systemic diseases including hematologic disorders have manifestations in the orofacial region (Long et al., 1998). Although non-pathognomonic, these manifestations may often represent early signs of the underlying hematopoietic disease (Sklavounou-Andricopoulou et al., 2002). In this context, oral complications occur frequently in leukemia and may point out the initial evidence of the disease (Aronovich and Connolly, 2008) or of its relapse (Benson et al., 2007).

Leukemia is the most common neoplastic disease of the white blood cells with an incidence of 9 cases per 100,000 population (Cotran et al., 1999). Additionally, leukemia is an ordinary malignancy accounting for about 30% of all cancers diagnosed for children aged under 15 years (Puumala et al., 2013). The current classification of leukemia is complex and a detailed description can be found in the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, published in 2001 and updated in 2008 (Campo et al., 2011). It recognizes distinct subtypes based on the cell of origin (myeloid or lymphoid) and stage of differentiation (Valera et al., 2015). So, the classification criteria of leukemia is histological and relies on (a) the similarity between the leukemic cells and normal cells (myeloid versus lymphoid) and (b) the clinical course of the disease (acute versus chronic) (Howard and Hamilton, 2008).

The oral manifestations of leukemia include gingival enlargement and bleeding, oral ulcerations, petechia and mucosal pallor (Cooper et al., 2000; da Silva Santos et al., 2010; Reenesh et al., 2012). Oral lesions arise in both acute and chronic forms of all types of leukemia. However, they are far more frequent in acute stages (Stafford et al., 1980; Greenberg and Glick, 2003). These oral manifestations either may be the result of direct infiltration of leukemic cells (primary) or secondary to underlying thrombocytopenia, neutropenia, or impaired granulocyte function (Benson et al., 2007).

Despite the fact that leukemia has been associated with oral lesions, the available literature on this topic consists mostly of case reports, without data summarizing the main oral changes for each type of leukemia. Therefore, the present review aimed at describing oral manifestations of all leukemia types and their dental management. This might be useful in early diagnosis, improving patient outcomes.

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a relatively unusual disease, accounting for approximately 25% of all types of leukemia among adults in the western world (Deschler and Lubbert, 2006). Although the incidence of acute leukemia constitutes less than 3% of all malignancies, it is still the leading cause of death in childhood (Rubnitz et al., 2010) and represents 1.2% of cancer deaths in the United States (Jemal et al., 2002).

*Bauru School of Dentistry, University of Sao Paulo, [1]Department of Biological Sciences, [2]Department of Stomatology; Bauru, SP, Brazil *For correspondence: e-mail*

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The Multiple Oral Presentations of Multiple Myeloma

Richard C. Cardoso, DDS, MS [Assistant Professor],
Dept. of Head and Neck Surgery; Section of Oral Oncology, The University of Texas—M.D. Anderson Cancer Center

Peter J. Gerngross, DDS, MS,
Maxillofacial Prosthodontics Dental Service, Michael E. DeBakey—VA Medical Center

Theresa M. Hofstede, DDS [Assistant Professor],
Dept. of Head and Neck Surgery; Section of Oral Oncology The University of Texas—M.D. Anderson Cancer Center

Donna M. Weber, MD [Professor], and
Department of Lymphoma/Myeloma The University of Texas—M.D. Anderson Cancer Center

Mark S. Chambers, DDS, MS [Professor]
Dept. of Head and Neck Surgery; Section of Oral Oncology The University of Texas—M.D. Anderson Cancer Center

Abstract

Purpose: The purpose of this case series is to show the varied oral presentations of multiple myeloma, illustrating the importance of carefully surveying the oral cavity for suspicious lesions that could be indicative of palpable disease and/or recurrence. The diagnostic criteria and prognostic features for multiple myeloma were also reviewed.

Case Series Summary: This report focuses on 5 patients with myeloma manifestations involving the oral cavity, in which the oral presentation of multiple myeloma was an early indication of disease relapse. Although the clinical presentation may be variable, the majority of patients will develop lytic bone lesions and less commonly, extramedullary involvement during the course of their disease.

Discussion: The presentation of myeloma can be varied and the oral presentation, although rare, may be the sole manifestation, or part of a group of signs of disease progression. Clinical presentations of patients with myelomatous lesions can mimic common dental pathologies, which then, in turn, can lead to delays in diagnosis and treatment.

Conclusion: As members of an interdisciplinary oncology team, it is essential to be familiar with oral manifestations of multiple myeloma and proper diagnostic/biopsy techniques in order to avoid misdiagnosis and treatment delays.

Corresponding Author: Mark S. Chambers, DDS, MS The University of Texas MD Anderson Cancer Center Department of Head and Neck Surgery 1400 Pressler Street, Unit Number: 1445 Houston, TX 77030-4009 mchamber@mdanderson.org.

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Oral manifestations of Diabetes Mellitus. A systematic review

Elisabet Mauri-Obradors [1], Albert Estrugo-Devesa [2], Enric Jané-Salas [2], Miguel Viñas [3], José López-López [2]

[1] DDS, Department of Dentistry and Stomatology. University of Barcelona. L'Hospitalet, Barcelona, Spain
[2] DDS, MD. PhD, Department of Dentistry and Stomatology. University of Barcelona and IDIBELL. Dental Hospital Barcelona University. Spain
[3] PhD, Department Pathology & Experimental therapeutics, University of Barcelona and IDIBELL. L'Hospitalet, Barcelona, Spain

Correspondence:
University Campus of Bellvitge
Pabellón de Gobierno, 2° planta
Dept. of Dentistry
O8907 L' Hospitalet de Llobregat. Barcelona, Spain
18575jll@gmail.com

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Abstract

Background: Diabetes Mellitus has become a global epidemic and presents many complications, usually proportional to the degree and duration of hyperglycemia. The aim of this systematic review was to investigate the different oral manifestations associated with Diabetes Mellitus.

Material and Methods: A MEDLINE search for "Diabetes Mellitus and oral manifestations" was performed. A further search was conducted for "diabetes" and its individual oral manifestation. Inclusion criteria were as follows: human clinical studies with a minimum of 30 patients; studies published in relevant scientific journals between January 1998 and January 2016. Nineteen studies fulfilled the inclusion criteria and were analyzed, assessing the strength of scientific evidence according to recommendations made by the Centre for Evidence-Based Medicine, Oxford (OCEBM), which permits adequate assessment of prevalence studies.

Results: A total 3,712 patients (2,084 diabetics) were included in the studies reviewed. Of the 19 studies analyzed, 4 were longitudinal studies and 15 cross-sectional studies. Periodontal disease, periapical lesions, xerostomia and taste disturbance were more prevalent among diabetic patients. An association between diabetes and caries and mucosal lesions proved positive in 5 out of 10 studies.

Conclusions: Despite multiple oral manifestations associated with DM, awareness of the associations between diabetes, oral health, and general health is inadequate. It is necessary for doctors and dentists to be aware of the various oral manifestations of diabetes in order to make an early diagnosis.

Key words: *Diabetes Mellitus, oral manifestations, oral pathology.*

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BMC Oral Health

RESEARCH ARTICLE Open Access

Prevalence of dental caries in children and adolescents with type 1 diabetes: a systematic review and meta-analysis

Yan Wang, Lin Xing*, Hui Yu and LiJuan Zhao

Abstract

Background: Dental caries and type 1 diabetes are responsible for a large burden of global disease; however, the exact prevalence of dental caries among children and adolescents with type 1 diabetes remains controversial, and no quantitative meta-analysis exists. Thus, we performed a meta-analysis to evaluate the prevalence of dental caries among children and adolescents with type 1 diabetes.

Methods: We performed a systematic search strategy using PubMed, EMBASE and China National Knowledge Infrastructure for relevant studies investigating the prevalence of dental caries in children and adolescents with type 1 diabetes from July 1971 until December 2018. The pooled prevalence with 95% confidence intervals (95%CIs) and subgroup analyses were calculated using a random effects model.

Results: After screening 358 non-duplicated articles, a total of 10 articles involving 538 individuals were included. The overall prevalence of dental caries among children and adolescents with type 1 diabetes was 67% (95% CI: 0.56–0.77%; $I^2 = 83\%$). The prevalence was highest in South America (84%) and lowest in diabetic patients with good metabolic control (47%).

Conclusions: The prevalence of dental caries was high among children and adolescents with type 1 diabetes. Screening and preventive treatment should be included in dental clinical routines for diabetic children and adolescents, especially in those with poor metabolic control.

Keywords: Adolescent, Caries, Children, Diabetes, Meta-analysis, Prevalence

Introduction

Type 1 diabetes mellitus is a chronic autoimmune disease characterized by the destruction of pancreatic beta cells and insulin deficiency, and affects over half a million children worldwide [1]. The prevalence and incidence of type 1 diabetes is increasing, especially in European countries [2]. Numerous epidemiological studies have reported that type 1 diabetes increases the risk for cardiovascular diseases [3], kidney disease [4] and cognitive decline [5] in children and adolescents. Additionally, a growing number of studies indicate an underlying link between type 1 diabetes and oral complications, including periodontal diseases [6] and dental caries [7]. Dental caries is the most common chronic infectious disease, and has posed an international public health challenge, especially in young children [8]. Additionally, it has become a major concern as it can begin early in life, progress rapidly in those individuals who are at high risk, and often goes untreated [9]. Its consequences can lead to poor food intake, poor school performance, and mental health problems, which can affect the quality of life of the child's family, and impact significant social and economic burdens as well [10].

Clinical caries are diagnosed by the DMFT index (D = dentine caries lesion; M = missing due to caries; F = filled; T = tooth), according to World Health Organization (WHO) criteria [11]. Although dental caries have been declining, a national survey in the United States between 2001 and 2012 showed that approximately 37% of children aged 2–8 years and 60% of adolescents aged 12–19 years had experienced dental caries in their primary teeth [12]. One goal of the WHO is to reduce the DMFT index in

* Correspondence: xinglin1985@126.com
Yan Tai Stomatological Hospital, No. 142 Beida Street Zhifu District, Yantai 264008, Shandong, China

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Reumatismo, 2019; 71 (4): 177-188 REVIEW

Adult-onset systemic autoinflammatory disorders: a clinical approach

T. Borges[1], A. Barbosa[2], S. Silva[1]

[1]Department of Internal Medicine, Trofa Saúde Hospital Privado de Gaia, Vila Nova de Gaia, Portugal;
[2]Department of Internal Medicine, Centro Hospitalar de São João, Porto, Portugal

SUMMARY

Autoinflammatory disorders (AIDs) are a subgroup of immune-mediated syndromes that result from a primary dysfunction of the innate immune system. AIDs can be either monogenic or polygenic diseases. Unlike organ-specific AIDs, systemic AIDs are characterized by fever and/or elevation of acute-phase reactants. This review aims to describe the most common adult-onset systemic AIDs, focusing mostly on polygenic and mixed-pattern diseases which are expected to be more prevalent in adult patients than monogenic AIDs overall. The literature was searched in Medline database. Organ-specific or childhood-onset systemic AIDs were excluded. AIDs were divided in three distinct groups: mixed-pattern, polygenic and adult-onset monogenic AIDs. Most adult-onset AIDs are polygenic but late-onset disease is not rare among monogenic AIDs such as familial Mediterranean fever (FMF). The diagnosis of systemic AIDs in adults is often delayed due to several factors and sometimes it is only established when amyloidosis or other complications are present. Therefore, it probably makes sense to primarily exclude common AIDs in adult patients with fever of unknown origin (and probably different presentations such as polyserositis) since a high prevalence of adult-onset Still's disease or FMF is usually expected. Colchicine, nonsteroidal anti-inflammatory drugs, steroids, immunosuppressive agents, interleukin-1 inhibitors and tumor necrosis factor antagonists constitute common therapeutic options for systemic AIDs.

Key words: *Autoinflammatory disorders; innate immunity; adult.*

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INTRODUCTION

Immune-mediated disorders (IMDs) include autoimmune diseases (ADs), allergies, immunodeficiencies and autoinflammatory disorders (AIDs). IMDs usually manifest during childhood but there are several exceptions, particularly in the first two subgroups. Instead, the majority of AIDs and immunodeficiencies typically manifest during childhood. AIDs result from a primary dysfunction of the innate immune system that can be determined by genetic mechanisms and/or exogenous factors (1). After recognition of molecular patterns, inflammasomes are assembled, resulting in clinical signs and/or laboratory evidence of inflammation (2). Hereditary periodic fever syndromes, such as familial Mediterranean fever (FMF), constitute prototypes of autoinflammation and are characterized by unprovoked recurrent febrile episodes of variable duration with intercalated periods of general well-being (3, 4). Rash, serositis, arthritis, aphthosis, gastrointestinal and ocular involvement may occur (2, 5). Meanwhile, organ-specific AIDs are characterized by elevation of inflammatory cytokines without inflammatory signs and/or elevation of acute-phase reactants.

ADs such as systemic lupus erythematosus are primarily polygenic (genetically-complex) diseases involving both adaptive and innate immune systems (Table I) (6, 7). AIDs are primarily monogenic (recessive or dominant) and caused by mutations in genes involved in the activation or regulation of the inflammatory response, being expected to occur during the neonatal period or early infancy (5, 6, 8). Exceptions include gout and pseudogout, Behçet's syndrome (BS), systemic-onset juvenile idiopathic arthritis (SJIA), spondyloarthritis (SpA), Crohn's disease, Schnitzler's

Corresponding author:
Tiago Borges
Rua Fernão de Magalhães 2 Fr E,
4404-501 Vila Nova de Gaia, Portugal
E-mail: mtiagoborges@gmail.com

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Article

Autoimmune Diseases and Oral Health: 30-Year Follow-Up of a Swedish Cohort

Anna Julkunen [1], Anna Maria Heikkinen [1], Birgitta Söder [2,*], Per-Östen Söder [2], Sanna Toppila-Salmi [1] and Jukka H. Meurman [1]

[1] Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, 00014 Helsinki, Finland; anna.julkunen@helsinki.fi (A.J.); anna.m.heikkinen@helsinki.fi (A.M.H.); sanna.salmi@helsinki.fi (S.T.-S.); jukka.meurman@helsinki.fi (J.H.M.)

[2] Department of Dental Medicine, Karolinska Institutet, BOX 4064, 14104 Huddinge, Stockholm, Sweden; perosten.soder@telia.com

* Correspondence: birgitta.soder@ki.se; Tel.: +46-761-009-511

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Abstract: Oral infections up-regulate a number of systemic inflammatory reactions that, in turn, play a role in the development of systemic diseases. We investigated the association between oral health and autoimmune diseases in a cohort of Swedish adults. Hypothesis was that poor oral health associates with incidence of autoimmune diseases. Overall 1676 subjects aged 30–40 years old from Stockholm County (Sweden) participated in this study in 1985. Subjects were randomly selected from the registry file of Stockholm region and were followed-up for 30 years. Their hospital and open health care admissions (World Health Organization ICD 9 and 10 codes) were recorded from the Swedish national health registers. The association between the diagnosed autoimmune disease and the oral health variables were statistically analyzed. In all, 50 patients with autoimmune diagnoses were detected from the data. Plaque index was significantly higher in the autoimmune disease group (≥median 35 (70%) vs. <median 872 (54%), $p = 0.030$). No statistical difference was found in gingival index, calculus index, missing teeth, periodontal pockets, smoking or snuff use between patients with and without autoimmune disease. Our study hypothesis was partly confirmed. The result showed that subjects with a higher plaque index, marker of poor oral hygiene, were more likely to develop autoimmune diseases in 30 years.

Keywords: autoimmune disease; oral health; association; plaque index; follow-up study

1. Introduction

Autoimmune diseases are rare pathological states arising from an abnormal immune response to substances and tissues that are normally present in the body. These diseases are multifactorial, heterogeneous and variable conditions that may exist in several organs and cell types [1,2]. The pathomechanisms of autoimmunity are multifactorial and mostly unknown [1]. The stability and functionality of tissues is a complex and strictly regulated process where immune system plays a role [2]. Pathogens can affect the regulation and autoimmunity reactions may follow [2]. Infection can induce autoimmunity either via the innate or adaptive immune responses [3].

A strong link has indeed been shown between viral, bacterial and other microbial infections and autoimmunity [3,4]. However, there are many factors that affect autoimmune diseases, like genetics, age, gender, reproductive status, and hormones [2,5]. Smoking tobacco also associates with autoimmune diseases but this has not been observed regarding snuff use [6,7].

From a clinical perspective there are two ways to categorize autoimmune diseases; organ-specific or systemic [8]. In organ-specific autoimmune diseases the expression of autoimmunity is limited to specific organs, for example on insulin-producing β-cells in pancreas in Type-1 diabetes mellitus [8,9].

20. Available online at: http://www.aarda.org/disease-list/

Autoimmune Disease List

One of the functions of the immune system is to protect the body by responding to invading microorganisms, such as viruses or bacteria, by producing antibodies or sensitized lymphocytes (types of white blood cells). Under normal conditions, an immune response cannot be triggered against the cells of one's own body. In some cases, however, immune cells make a mistake and attack the very cells that they are meant to protect. This can lead to a variety of autoimmune diseases. They encompass a broad category of related diseases in which the person's immune system attacks his or her own tissue.

ALL | 0-9 | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

- Achalasia
- Addison's disease
- Adult Still's disease
- Agammaglobulinemia
- Alopecia areata
- Amyloidosis
- Ankylosing spondylitis
- Anti-GBM/Anti-TBM nephritis
- Antiphospholipid syndrome
- Autoimmune angioedema
- Autoimmune dysautonomia
- Autoimmune encephalomyelitis
- Autoimmune hepatitis
- Autoimmune inner ear disease (AIED)
- Autoimmune myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune pancreatitis
- Autoimmune retinopathy
- Autoimmune urticaria
- Axonal & neuronal neuropathy (AMAN)
- Baló disease
- Behcet's disease
- Benign mucosal pemphigoid
- Bullous pemphigoid
- Castleman disease (CD)
- Celiac disease
- Chagas disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA)
- Cicatricial pemphigoid
- Lichen sclerosus
- Ligneous conjunctivitis
- Linear IgA disease (LAD)
- Lupus
- Lyme disease chronic
- Meniere's disease
- Microscopic polyangiitis (MPA)
- Mixed connective tissue disease (MCTD)
- Mooren's ulcer
- Mucha-Habermann disease
- Multifocal Motor Neuropathy (MMN) or MMNCB
- Multiple sclerosis
- Myasthenia gravis
- Myelin Oligodendrocyte Glycoprotein Antibody Disorder
- Myositis
- Narcolepsy
- Neonatal Lupus
- Neuromyelitis optica
- Neutropenia
- Ocular cicatricial pemphigoid
- Optic neuritis
- Palindromic rheumatism (PR)
- PANDAS
- Paraneoplastic cerebellar degeneration (PCD)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Parry Romberg syndrome
- Pars planitis (peripheral uveitis)
- Parsonage-Turner syndrome
- Pemphigus
- Peripheral neuropathy
- Perivenous encephalomyelitis
- Pernicious anemia (PA)
- POEMS syndrome
- Polyarteritis nodosa

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REVIEW Open Access

Microbiota and chronic inflammatory arthritis: an interwoven link

Andrea Picchianti Diamanti[1,3*†], M. Manuela Rosado[2†], Bruno Laganà[1] and Raffaele D'Amelio[1]

Abstract

Background: Only recently, the scientific community gained insights on the importance of the intestinal resident flora for the host's health and disease. Gut microbiota in fact plays a crucial role in modulating innate and acquired immune responses and thus interferes with the fragile balance inflammation versus tolerance.

Main body: Correlations between gut bacteria composition and the severity of inflammation have been studied in inflammatory bowel diseases. More recently similar alterations in the gut microbiota have been reported in patients with spondyloarthritis, whereas in rheumatoid arthritis an accumulating body of evidence evokes a pathogenic role for the altered oral microbiota in disease development and course. In the context of dysbiosis it is also important to remember that different environmental factors like stress, smoke and dietary components can induce strong bacterial changes and consequent exposure of the intestinal epithelium to a variety of different metabolites, many of which have an unknown function. In this perspective, and in complex disorders like autoimmune diseases, not only the genetic makeup, sex and immunologic context of the individual but also the structure of his microbial community should be taken into account.

Conclusions: Here we provide a review of the role of the microbiota in the onset, severity and progression of chronic inflammatory arthritis as well as its impact on the therapeutic management of these patients. Furthermore we point-out the complex interwoven link between gut-joint-brain and immune system by reviewing the most recent data on the literature on the importance of environmental factors such as diet, smoke and stress.

Keywords: Microbiota, Chronic inflammatory arthritis, Immunosuppressant, Probiotic, Stress, Diet, Smoke

Background

Recent advances in sequencing technologies have allowed the deep characterization of the human microbiota, thus greatly improving our knowledge on the role of the microbiome in human health and disease. Human microbiome project consortium studies [1] demonstrated that healthy individuals have not only a high degree of bacterial diversity, dependent on their habitat (intestine, oral cavity, skin or vagina), but that there is also a remarkable inter-individual variability at the level of species. In spite of the large amount of different species found at different sites, at the level of microbial community there is evidence for a certain constancy that preserves both the function and the bacterial gene profiling associated to specific tissue sites. For example the anaerobic firmicutes/bacteroidetes spp. dominate the intestine whereas actinobacteria and proteobacteria spp. are highly abundant in the skin. Given the strong variability and abundance of microbes living in close relation with us, it becomes a difficult task to define what should be considered the "normal" microbiome. Moreover, the same microbe may behave as commensal or as pathogen depending on the dietary components, nutritional milieu, co-infection or genetic background of its host. Albeit, it is still generally accepted that commensal bacteria contribute to immune homeostasis, whereas immune reaction against intestinal flora is accepted as a pathological sign. This distinction, however, is not absolute, because

*Correspondence: andrea.picchiantidiamanti@uniroma1.it
†Andrea Picchianti Diamanti and M. Manuela Rosado contributed equally to this work
[3] Department of Clinical and Molecular Medicine, School of Medicine and Psychology, S. Andrea University Hospital, "Sapienza" University, Via di Grottarossa 1039, 00189 Rome, Italy
Full list of author information is available at the end of the article

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Oral Microbiota Perturbations Are Linked to High Risk for Rheumatoid Arthritis

Yanli Tong[1], Linlin Zheng[1], Pingying Qing[1], Hua Zhao[1], Yanhong Li[1], Linchong Su[1,2], Qiuping Zhang[1], Yi Zhao[1], Yubin Luo[1] and Yi Liu[1]*

[1] Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, China, [2] Hubei Provincial Key Laboratory of Occurrence and Intervention of Rheumatic Diseases, Enshi, China

Oral microbial dysbiosis is known to increase susceptibility of an individual to develop rheumatoid arthritis (RA). Individuals at-risk of RA may undergo different phases of disease progression. In this study, we aim to investigate whether and whereby the oral microbiome communities alter prior to symptoms of RA. Seventy-nine saliva samples were collected from 29 high-risk individuals, who were positive for anti-citrullinated protein antibodies (ACPA) and have no clinical arthritis, 27 RA patients and 23 healthy controls (HCs). The salivary microbiome was examined using 16S ribosomal RNA gene sequencing. Alpha and beta diversity analysis and the linear discriminant analysis were applied to examine the bacterial diversity, community structure and discriminatory taxa between three groups, respectively. The correlation between salivary bacteria and autoantibodies were analyzed. In the "pre-clinical" stages, salivary microbial diversity was significantly reduced comparing to RA patients and HCs. In contrast to HCs, like RA patients, individuals at high-risk for RA showed a reduction in the abundance of genus *Defluviitaleaceae_UCG-011* and the species *Neisseria oralis*, but an expansion of *Prevotella*_6. Unexpectedly, the relative abundance of *Porphyromonas gingivalis*, reported as opportunistic pathogens for RA development, was significantly decreased in high-risk individuals. Additionally, we identified four genera in the saliva from high-risk individuals positively correlated with serum ACPA titers, and the other two genera inversely displayed. In summary, we observed a characteristic compositional change of salivary microbes in individuals at high-risk for RA, suggesting that oral microbiota dysbiosis occurs in the "pre-clinical" stage of RA and are correlated with systemic autoimmune features.

Keywords: oral microbiome, rheumatoid arthritis, high risk, anti-citrullinated protein autoantibodies, dysbiosis

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****Correspondence:***
Yubin Luo
luoyubin2016@163.com

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily involves the joints. Over the past years, research focusing on the earliest stage of RA has led to the discovery of RA-related systemic inflammation and autoimmunity in the pre-clinical stage. The presence of circulating autoantibodies, elevation of cytokines and chemokines levels, and increase of acute phase reactants precede clinical arthritis (Rantapaa-Dahlqvist et al., 2003; Berglin et al., 2004; Nielen et al., 2004; Jorgensen et al., 2008; Sokolove et al., 2012). Prospective studies define

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RESEARCH ARTICLE Open Access

Oral health in children and adolescents with juvenile idiopathic arthritis – a systematic review and meta-analysis

Marit S. Skeie[1,2*], Elisabeth G. Gil[1], Lena Cetrelli[2], Annika Rosén[1,3], Johannes Fischer[1], Anne Nordrehaug Åstrøm[1], Keijo Luukko[1], Xieqi Shi[1,4], Astrid J. Feuerherm[2], Abhijit Sen[2,5], Paula Frid[6,7,8], Marite Rygg[9,10] and Athanasia Bletsa[11,1]

Abstract

Background: Observational studies examining the association between oral health and juvenile idiopathic arthritis (JIA) among children and adolescents have reported inconsistent findings. The aims of this systematic review and meta-analysis were to ascertain a potential difference in oral health and oral health-related quality of life (OHRQoL) among children and adolescents with JIA and healthy peers, and to assess the association of prevalence of oral diseases/conditions, temporomandibular disorders (TMD), including temporomandibular joint (TMJ) diseases, in relation to activity and severity of JIA.

Method: Medline Ovid, Embase, CINAHL, SweMed+ and Cochrane Library were searched up to 25 November 2018. All articles published in English, German and Scandinavian languages focusing on children and adolescents with JIA and without JIA in relation to oral health measures, were considered. Two authors independently evaluated observational studies for inclusion. The study quality was assessed using modified Newcastle Ottawa Scale. Meta-analysis was performed for studies focusing on dental caries as an outcome.

Results: Nineteen articles met the inclusion criteria, covering a range of oral diseases/conditions and OHRQoL. Eighteen studies had cross-sectional design. No mean difference of dmft/DMFT indices (decayed/missed/filled teeth) was observed between the JIA - and healthy group. None of the oral health measures including dental erosive wear, enamel defects, dental maturation and OHRQoL, indicated better oral health among children and adolescents with JIA compared to healthy group. However, periodontal conditions and TMD were more predominant among children and adolescents with JIA compared to healthy peers.

Conclusions: Based on the cross-sectional studies, periodontal diseases and TMD were found to be more frequent in children and adolescents with JIA compared to healthy peers. Furthermore, more high-quality studies with large sample size are needed before we infer any concrete conclusion regarding the association between the prevalence of oral and TMJ diseases or oral conditions in relation to activity and severity of JIA.

Keywords: Stomatognathic diseases, Temporomandibular joint disease, Arthritis juvenile rheumatoid, Juvenile idiopathic arthritis, Child, Adolescent

* Correspondence: marit.skeie@uib.no
[1]Department of Clinical Dentistry, Pediatric Dentistry, The Faculty of Medicine, University of Bergen, Norway, Årstadveien 19, N-5009 Bergen, Norway
[2]Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway
Full list of author information is available at the end of the article

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Microreview

Defining dysbiosis and its influence on host immunity and disease

Charisse Petersen and June L. Round*
Department of Pathology, Division of Microbiology and Immunology, University of Utah School of Medicine, Salt Lake City, UT 84112, USA

Summary

Mammalian immune system development depends on instruction from resident commensal microorganisms. Diseases associated with abnormal immune responses towards environmental and self antigens have been rapidly increasing over the last 50 years. These diseases include inflammatory bowel disease (IBD), multiple sclerosis (MS), type I diabetes (T1D), allergies and asthma. The observation that people with immune mediated diseases house a different microbial community when compared to healthy individuals suggests that pathogenesis arises from improper training of the immune system by the microbiota. However, with hundreds of different microorganisms on our bodies it is hard to know which of these contribute to health and more importantly how? Microbiologists studying pathogenic organisms have long adhered to Koch's postulates to directly relate a certain disease to a specific microbe, raising the question of whether this might be true of commensal–host relationships as well. Emerging evidence supports that rather than one or two dominant organisms inducing host health, the composition of the entire community of microbial residents influences a balanced immune response. Thus, perturbations to the structure of complex commensal communities (referred to as *dysbiosis*) can lead to deficient education of the host immune system and subsequent development of immune mediated diseases. Here we will overview the literature that describes the causes of dysbiosis and the mechanisms evolved by the host to prevent these changes to community structure. Building off these studies, we will categorize the different types of dysbiosis and define how collections of microorganisms can influence the host response. This research has broad implications for future therapies that go beyond the introduction of a single organism to induce health. We propose that identifying mechanisms to re-establish a healthy complex microbiota after dysbiosis has occurred, a process we will refer to as rebiosis, will be fundamental to treating complex immune diseases.

Received 21 March, 2014; revised 29 April, 2014; accepted 30 April, 2014. *For correspondence. E-mail june.round@path.utah.edu; Tel. (+1) 801 213 4164 (office) or (+1) 801587 5684 (lab).

What is dysbiosis?

Our current knowledge of the architecture of a healthy microbiota comes from multiple studies in individuals with no overt signs of disease (Huttenhower *et al.*, 2012). This structure includes *Bacteroidetes* and *Firmicutes* as the dominant bacterial phyla present in stool samples and *Proteobacteria* and *Actinobacteria* being a small but consistent presence in most people. Broadly defined, dysbiosis is any change to the composition of resident commensal communities relative to the community found in healthy individuals. In the last decade, a number of studies have documented significant changes in the structure of microbial communities in patients and mouse models of inflammatory bowel diseases (IBD) such as Crohn's and ulcerative colitis (UC) (Frank *et al.*, 2007), diabetes (Karlsson *et al.*, 2013), asthma (Abrahamsson *et al.*, 2013), allergies and even autism (Parracho *et al.*, 2005). Given the emerging importance of the microbiota to host development, it is speculated that these observed changes in microbial composition are contributing factors to the initiation and/or persistence of many of these diseases.

There are multiple ways that the structure of the microbial community can be influenced. This includes the genetics of the host, diet, infection, or medical interventions (such as antibiotics). The hygiene hypothesis originally proposed that antibiotic usage and lifestyle alterations that limit microbial exposure were predisposing populations of people in developed countries to

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Evaluation of simplified oral hygiene index of the elementary school students before fluoride mouthwash

Beatriz Rosana Gonçalves de Oliveira*, Luciano Martini, Cláudia Silveira Viera and Edo Hirata

*Centro de Ciências Biológicas e da Saúde, Universidade Estadual do Oeste do Paraná, Rua Universitária, 2069, 85819-110, Jd. Universitário, Cascavel, Paraná, Brazil. *Author for correspondence. E-mail: beatriz.oliveira@unioeste.br*

ABSTRACT. The State Program of fluoride mouthwashes for caries control was established in 1980 in elementary schools of Paraná State covering children 7-11 years old. Knowing the importance of removing bacterial plaque to reach the maximum desired effect of prevention, this study aimed to evaluate the Simplified Oral Hygiene Index, before applying the solution of Sodium Fluoride (NaF; 0.2%) in children from an elementary school in the city of Nova Aurora, Paraná State, by using disclosing dental plaque. This is a quantitative research, descriptive and exploratory whose data were obtained through a specific form, with 61 children and analyzed using descriptive statistics with distribution of absolute and percentage frequencies. Most children (60%) showed the worst results - regular and bad - with presence of plaque and risk of dental caries. Therefore, we should establish a prevention program in oral health that must involve parents and students. This program should be developed by health professionals inside the school, explaining about the etiologic factors, causes and consequences of plaque, the techniques of cleaning and maintenance of hygiene instruments, and the risks of the lack of proper hygiene in the oral cavity.

Keywords: disease prevention, fluorine, dental caries, school health, dental plaque.

Avaliação do índice de higiene oral simplificado (iho-s) de alunos do ensino fundamental antes do bochecho com flúor

RESUMO. O Programa Estadual de Bochechos com Flúor nas escolas de ensino fundamental do Paraná abrange crianças do ensino fundamental I e foi instituído em 1980 para controlar a cárie. Sabendo-se da importância da remoção da placa bacteriana para que se atinja o máximo efeito de prevenção desejado, esse trabalho objetivou avaliar o Índice de Higiene Oral Simplificado, momentos antes da aplicação do bochecho com solução de Fluoreto de Sódio (NaF) a 0,2% nas crianças de uma escola de ensino fundamental da cidade de Nova Aurora/PR, por meio de evidenciador de placa bacteriana. Pesquisa quantitativa do tipo descritiva e exploratória, cujos dados foram obtidos por meio de um formulário específico, com 61 crianças, e analisados por meio de estatística descritiva com distribuição de frequências absolutas e percentuais. A maioria das crianças (60%) apresentou os piores resultados – 'Regular e Ruim' – com presença de placa bacteriana e risco à cárie. É preciso, então, estabelecer um programa de prevenção em saúde bucal, alcançando pais e alunos, sensibilizando-os dos fatores etiológicos, causas e conseqüências da placa bacteriana, das técnicas de higienização e manutenção dos instrumentos de higiene e dos riscos de não se higienizar adequadamente a cavidade oral, utilizando-se dos profissionais da unidade de saúde no espaço da escola.

Palavras-chave: prevenção de doenças, flúor, cárie dentária, saúde escolar, biofilme dentário.

Introduction

The changes in sanitary practices are being consolidated as a result of the way the State respond, through actions in the area of public health, to social changes, to the needs and to the population health problems. In dentistry, the exclusion of the major part of the population to dental attendance had always been a problem, becoming evident the need to develop a low cost assistance, generalist which involves the prevention of oral diseases, in particular the caries and the periodontal disease, during the early years, assuming that, if the teeth had been kept healthy during the childhood, during the following periods all people would have conditions to take better care of their teeth.

Considering these assumption, the State Decree 3,046 developed in 1980 the School Health Program, which created the Mouthwashes with Fluorine Solution Program, using 0.2% sodium fluoride (NaF) solution, with a weekly periodicity, in primary schools of the Paraná State, as a way to reach all the children

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Review Article

The Microbiome in Connective Tissue Diseases and Vasculitides: An Updated Narrative Review

Rossella Talotta,[1] Fabiola Atzeni,[2] Maria Chiara Ditto,[1] Maria Chiara Gerardi,[1] and Piercarlo Sarzi-Puttini[1]

[1]*Department of Rheumatology, ASST Fatebenefratelli-Sacco, Milan, Italy*
[2]*IRCCS Galeazzi Orthopedic Institute, Milan, Italy*

Correspondence should be addressed to Rossella Talotta; rossella.talotta@asst-fbf-sacco.it

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Objective. To provide a narrative review of the most recent data concerning the involvement of the microbiome in the pathogenesis of connective tissue diseases (CTDs) and vasculitides. *Methods*. The PubMed database was searched for articles using combinations of words or terms that included systemic lupus erythematosus, systemic sclerosis, autoimmune myositis, Sjögren's syndrome, undifferentiated and mixed CTD, vasculitis, microbiota, microbiome, and dysbiosis. Papers from the reference lists of the articles and book chapters were reviewed, and relevant publications were identified. Abstracts and articles written in languages other than English were excluded. *Results*. We found some evidence that dysbiosis participates in the pathogenesis of systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, and Behçet's disease, but there are still few data concerning the role of dysbiosis in other CTDs or vasculitides. *Conclusions*. Numerous studies suggest that alterations in human microbiota may be involved in the pathogenesis of inflammatory arthritides as a result of the aberrant activation of the innate and adaptive immune responses. Only a few studies have explored the involvement of dysbiosis in other CTDs or vasculitides, and further research is needed.

1. Introduction

The human microbiota harboured by each person consists of 10–100 trillion symbiotic microbial cells, mainly bacteria in the gut, but also viruses, yeasts, protozoa, and even helminths. The sum of human microbes and their genes existing within and on the human body (collectively known as the microbiome) has been found to be a principal factor in human health and disease [1]. Humans and microbes have coevolved to establish a symbiotic relationship over time, but perturbations, known also as dysbiosis, may occur and drive several diseases, including autoimmune disorders. Over the last few decades, new insights provided by DNA sequence-based analyses of human microbial communities have renewed interest in mucosal immunology and suggest that alterations in the human microbiome can also affect the development of rheumatic diseases.

The concept that human microbiota may modulate systemic autoimmunity is not new, but the underlying mechanisms of autoimmune regulation by the microbiome are just beginning to emerge [2]. Studies of animal models published 30 years ago demonstrated a relationship between the development of inflammatory arthritis and the presence/absence of some intestinal bacteria [3, 4], and, more recently, many studies have drawn attention to the potential role of the oral microrganism *Porphyromonas gingivalis* in the development of rheumatoid arthritis (RA) [5]. A recent study of the lung microbiome in a cohort of patients with early RA has found distal airway dysbiosis similar to that detected in sarcoidol lung inflammation [6], but, although various studies have investigated the different composition of gut microbiota in patients affected by RA and spondyloarthritis (SpA), the complex mechanisms by which microbes influence the pathogenesis of autoimmune diseases are still unknown.

Connective tissue diseases (CTDs) encompass a wide group of immune-mediated diseases, characterized by the inflammation of the connective tissues of the body sustained

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Shared gut, but distinct oral microbiota composition in primary Sjögren's syndrome and systemic lupus erythematosus

Taco A. van der Meulen[a,*], Hermie J.M. Harmsen[b], Arnau Vich Vila[c,d], Alexander Kurilshikov[d], Silvia C. Liefers[e], Alexandra Zhernakova[d], Jingyuan Fu[d], Cisca Wijmenga[d], Rinse K. Weersma[c], Karina de Leeuw[e], Hendrika Bootsma[e], Fred K.L. Spijkervet[a], Arjan Vissink[a], Frans G.M. Kroese[e]

[a] Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands
[b] Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands
[c] Department of Gastroenterology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands
[d] Department of Genetics, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands
[e] Department of Rheumatology & Clinical Immunology, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands

A B S T R A C T

Objective: Alterations in the microbiota composition of the gastro-intestinal tract are suspected to be involved in the etiopathogenesis of two closely related systemic inflammatory autoimmune diseases: primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE). Our objective was to assess whether alterations in gut and oral microbiota compositions are specific for pSS and SLE.

Methods: 16S ribosomal RNA gene sequencing was performed on fecal samples from 39 pSS patients, 30 SLE patients and 965 individuals from the general population, as well as on buccal swab and oral washing samples from the same pSS and SLE patients. Alpha-diversity, beta-diversity and relative abundance of individual bacteria were used as outcome measures. Multivariate analyses were performed to test associations between individual bacteria and disease phenotype, taking age, sex, body-mass index, proton-pump inhibitor use and sequencing-depth into account as possible confounding factors.

Results: Fecal microbiota composition from pSS and SLE patients differed significantly from population controls, but not between pSS and SLE. pSS and SLE patients were characterized by lower bacterial richness, lower Firmicutes/Bacteroidetes ratio and higher relative abundance of *Bacteroides* species in fecal samples compared with population controls. Oral microbiota composition differed significantly between pSS patients and SLE patients, which could partially be explained by oral dryness in pSS patients.

Conclusions: pSS and SLE patients share similar alterations in gut microbiota composition, distinguishing patients from individuals in the general population, while oral microbiota composition shows disease-specific differences between pSS and SLE patients.

1. Introduction

Primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE) are systemic inflammatory autoimmune diseases that share epidemiological, clinical, pathogenic and etiological features [1,2]. The world-wide prevalence rates for pSS and SLE are 0.01–0.09% and 0.02–0.24%, respectively, with a female:male ratio of 10:1 for both diseases [3–6]. pSS is characterized by chronic inflammation of the exocrine glands, in particular the salivary and lacrimal glands, resulting in oral and ocular dryness (sicca) complaints [7,8]. In SLE, a wide range of symptoms can be present, such as skin rash, photosensitivity, arthritis, glomerulonephritis, pericarditis, neurologic and hematological symptoms [2]. Overlap of clinical symptoms is frequently observed in pSS and SLE patients [7,9,10].

Host genetics and environmental factors are important etiological factors in pSS and SLE. pSS and SLE patients share genetic risk loci which predisposes individuals to these diseases. Genetic risk loci for both pSS and SLE include *STAT4* and *IRF5* (involved in innate immunity), *IL12*A and *BLK* (involved in adaptive immunity) and *HLA class II* region [11–14]. Many more genetic risk factors are currently known for SLE than for pSS [11]. The majority of SLE genetic risk factors are involved in innate immune signaling (e.g. TLR7 and TLR9) and lymphocyte signaling (e.g. IL-10, CD80) [15].

Despite increasing knowledge on genetic risk factors, still relatively little is known about environmental factors involved in the development of pSS and SLE. In this respect, the microbial composition in the gut and oral cavity may be important factors in the etiopathogenesis of these two chronic inflammatory autoimmune diseases [16–20]. Several

* Corresponding author. Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, The Netherlands.
E-mail address: t.a.van.der.meulen@umcg.nl (T.A. van der Meulen).

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EVOLUTION AND MEASUREMENT OF SPECIES DIVERSITY*

*R. H. Whittaker***

Summary

Given a resource gradient (e.g. light intensity, prey size) in a community, species evolve to use different parts of this gradient; competition between them is thereby reduced. Species relationships in the community may be conceived in terms of a multidimensional coordinate system, the axes of which are the various resource gradients (and other aspects of species relationships to space, time, and one another in the community). This coordinate system defines a hyperspace, and the range of the space that a given species occupies is its niche hypervolume, as an abstract characterization of its intra-community position, or niche. Species evolve toward difference in niche, and consequently toward difference in location of their hypervolumes in the niche hyperspace. Through evolutionary time additional species can fit into the community in niche hypervolumes different from those of other species, and the niche hyperspace can become increasingly complex. Its complexity relates to the community's richness in species, its alpha diversity.

Species differ in the proportions of the niche hyperspace they are able to occupy and the share of the community's resources they utilize. The share of resources utilized is expressed in species' productivities, and when species are ranked by relative productivity (or some other measurement) from most to least important, importance-value or dominance-diversity curves are formed. Three types of curves may represent manners in which resources are divided among species: (a) niche pre-emption with strong dominance, expressed in a geometric series, (b) random boundaries between niches, expressed in the MacArthur distribution, and (c) determination of relative importance by many factors, so that species form a frequency distribution on a logarithmic base of importance values, a lognormal distribution. The forms of importance-value curves do not permit strong inference about resource division, but are of interest for their expression of species relationships and bearing on measurement of diversity.

Two aspects of alpha diversity are to be measured. Diversity in the strict sense is richness in species, and is appropriately measured as the number of species in a sample of standard size. Slope measurements, in contrast, express the steepness of the importance-value sequence. Of the slope measurements the Simpson index expresses dominance or relative concentration of the importance values into the first or first few species, whereas the Shannon-Wiener index expresses the relative evenness or equitability of the importance values through the whole sequence. A new index, expressing equitability as number of species per logarithmic cycle of the importance-value sequence, is suggested.

Given a habitat gradient (e.g. elevation or soil moisture conditions) species evolve to occupy different positions along this gradient. The various habitat gradients of a landscape may also be conceived as a multidimensional hyperspace, and species evolve toward occupation of different positions in this hyperspace. Along a particular habitat gradient species populations have scattered centers and usually overlap broadly, forming a community continuum or coenocline. Through evolutionary time additional species can fit themselves in along the coenocline. As they do so the extent of change in community composition along

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** Ecology and Systematics, Cornell University, Ithaca, New York, 14850, U.S.A.

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Reviews

Systemic sclerosis and its oral health implications

Agata Puzio[1,B,D–F], Brygida Przywara-Chowaniec[2,B–F], Lidia Postek-Stefańska[1,D–F], Katarzyna Mrówka-Kata[3,B,D–F], Karolina Trzaska[4,B,E]

[1] Department of Pediatric Dentistry, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland
[2] 2nd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland
[3] Department of Otorhinolaryngology and Oncological Laryngology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland
[4] Clinical Department of Internal Diseases, Dermatology and Allergology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Address for correspondence
Agata Puzio
E-mail: agata.puzio1@gmail.com

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Abstract

Systemic sclerosis (SSc) is a chronic, generalized disorder of the connective tissue. It is characterized by immune disorders, abnormalities of morphology and functions of small blood vessels, and the presence of inflammatory process. The pathogenesis of this disorder has not yet been fully understood. The classification criteria were established by The American College of Rheumatology (ACR). A number of clinical types are distinguished due to the diversity of the clinical picture. These types are characterized by a different course, presence of organ complications and prognosis. Connective tissue disorders are interdisciplinary conditions and, therefore, the subject of interest of different medical specialties, including dentistry. The oral cavity may be the place of pathological manifestations within soft and hard tissues. Such manifestations are the results or the primary symptom of systemic diseases. The relationship between the health of the oral cavity and systemic diseases has been frequently reported in the literature. Lesions in the oral cavity in patients with SSc are discussed in detail in the present paper. Management includes the administration of drugs that prevent tissue ischemia and post-ischemic consequences as well as drugs that inhibit inflammatory-immune processes and excessive collagen production.

Key words: connective tissue diseases, oral manifestations, systemic scleroderma

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Gastrointestinal and Hepatic Disease in Systemic Sclerosis

Tracy M. Frech, MD, MS and
University of Utah and Salt Lake Veterans Affair Medical Center, Department of Internal Medicine, Division of Rheumatology, Salt Lake City, Utah, USA

Diane Mar, MD
University of Colorado, Department of Internal Medicine, Denver, CO, USA

Keywords

Scleroderma; Systemic; Therapeutics; Gastrointestinal Diseases; Mouth Diseases; Esophageal Diseases; Stomach Diseases; Liver Diseases; Intestinal Diseases

Epidemiology

Systemic sclerosis (SSc, scleroderma) is a connective tissue disease characterized by vasculopathy, fibrosis, and immune dysfunction with a prevalence varying from 30 to 443 per million population (1). SSc classification criteria (2) do not incorporate the gastrointestinal tract (GIT) manifestations that are often present in this disease, despite the fact that GIT involvement produces substantial morbidity and is the most commonly involved internal organ in SSc (3). The GIT is the presenting disease feature in 10% of SSc, occurs during disease course in up to 95% of individuals, and is responsible for 6–12% of mortality in SSc patients (4). Malabsorption, gastroesophageal reflux, nausea, vomiting, diarrhea, and constipation are some of the GIT complications that occur in this population, and despite varying degrees of disease severity from mouth to anus, SSc GIT involvement significantly impairs quality of life in almost all patients (5, 6). Severe GIT involvement in up to 8% of SSc patients is associated with a high morbidity and poorer outcome (7, 8).

Pathogenesis and Pathophysiology

The specific pathogenesis of GIT involvement is complex and not adequately understood, but neuropathy progressing to myopathy with eventual fibrosis has been proposed (8). The pathophysiology of GIT involvement is thought to parallel other organ involvement in SSc with fibro-proliferative vascular lesions of small arteries and arterioles, increased production

Corresponding Author: Tracy M Frech, M.D., M.S., 4b200 SOM 30 N, 1900 E, Salt Lake City, UT 84132, Phone: 801 581 4334, Fax: 801 581 6069, tracy.frech@hsc.utah.edu.

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Scleroderma and the Oral Health Implications

Hajer Abdulhafid Derbi* and Gelsomina L Borromeo

University of Melbourne, Australia

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***Corresponding author:** Hajer Abdulhafid Derbi, University of Melbourne, Australia, Tel: 61 450314445; Email: hajer.derbi@unimelb.edu.au

Abstract

Patients with scleroderma present with a wide range of oral manifestations. This is due to the unique manifestations involving the oral soft tissues and resulting in restricted mouth opening, xerostomia, erosion of teeth, and periodontal disease. As a consequence, oral hygiene, providing dental treatment and fabrication of prosthetic appliances pose significant challenges primarily related to limited access and obliteration or shallowing of the mucobuccal folds. This paper presents the dental management and splint construction for a 41-year-old lady suffering from scleroderma.

Keywords: Scleroderma; CREST; Systemic sclerosis; Oral management; Limited mouth opening; Splint

Abbreviations: SSc: Systemic Sclerosis; CREST syndrome: Calcinosis, Raynaud's phenomenon, Oesophageal dysmotility, Sclerodactyly and Telangiectasia

Introduction

Scleroderma, or systemic sclerosis, is a chronic autoimmune disease characterized by inflammation, and vascular and fibrotic changes of the skin as well as internal organs [1-3]. This connective tissue disorder has been classified into two subsets: systemic scleroderma and localized sclerosis [4]. Localized scleroderma (sclerosis) is usually limited to skin lesions, and sometimes extends to involve the underlying muscle and bone. It is further subdivided into morphea, generalised, bullous, linear, and deep forms [4].

Systemic forms of scleroderma fall into the category of primary cutaneous sclerosis as designated by The American Academy of Dermatology. Systemic Sclerosis (SSc) can be further divided based on the extent of skin and internal organ involvement, into subcategories including diffuse SSc, which includes systemic scleroderma, and limited SSc, which includes CREST syndrome, involves calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia.

Patients with diffuse systemic sclerosis have extensive skin indurations with the possibility of near total organ system involvement. Cutaneous sclerosis is identified by a rapid development of symmetric skin thickening of the proximal and distal extremities, face and trunk together with internal organ involvement. Damage to the heart, kidneys, and lungs affect the course of the disease. Patients with limited cutaneous SSc typically have skin sclerosis that is restricted to the hands, and sometimes the face and neck. Patients may also have prominent vascular manifestations and frequently exhibit features of CREST syndrome. The pathological process evolves through oedematous, indurative, and atrophic phases sequentially over time, and as such, subtle differences exist between patients affected by this disease. It occurs more commonly in women (estimated female to male ratio, 4:1), and the age of peak onset is 30 to 50 years [5].

Scleroderma is an uncommon autoimmune disease affecting connective tissues, with an approximate prevalence of 20/100 000. It presents great challenges not only to the medical professionals but also the dental professionals with its profound impact on oral health. The current paper present dental management and splint construction for a 41 year old female, who was diagnosed with diffuse scleroderma.

Case Presentation

A 41-year-old female who was diagnosed in 2001 with Diffuse Scleroderma, Lichen sclerosis (vulva), minor Beta Thalassaemia, pulmonary interstitial fibrosis, and secondary Sjogren Syndrome was referred for ongoing oral health management by her general dentist to the Special Needs Clinic in 2014. Miss VK lived independently and had recently lost her job but was seeking further employment.

As a consequence of her condition, Miss VK was also suffering from depression managed with the Antidepressant Selective Serotonin and Norepinephrine Neuptake Inhibitor (SNRIs) desvenlafaxine 100mg. She was also prescribed a calcium channel antagonist (felodipine 10mg daily) to manage her Raynaud's phenomena and sclerodactyly. She reported dry eyes that were reviewed six monthly by an ophthalmologist who had prescribed eye lubricant drops and ointment. In addition, Miss VK was taking

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Critical Review
Oral Pathology

Orofacial manifestations of COVID-19: a brief review of the published literature

Esam HALBOUB[a]
Sadeq Ali AL-MAWERI[b]
Rawan Hejji ALANAZI[c]
Nashwan Mohammed QAID[d]
Saleem ABDULRAB[e]

[a]Jazan University, College of Dentistry, Department of Maxillofacial Surgery and Diagnostic Sciences, Jazan, Saudi Arabia.

[b]AlFarabi College of Dentistry and Nursing, Department of Oral Medicine and Diagnostic Sciences, Riyadh, Saudi Arabia.

[c]AlFarabi College of Dentistry and Nursing, Department of Oral Medicine and Diagnostic Sciences, Riyadh, Saudi Arabia.

[d]AlFarabi College of Dentistry and Nursing, Department of Restorative Dental Sciences, Riyadh, Saudi Arabia.

[e]Primary Health Care Corporation, Madinat Khalifa Health Center, Doha, Qatar.

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Corresponding Author:
Sadeq Ali Al-Maweri
E-mail: sadali05@hotmail.com

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Abstract: Coronavirus disease 2019 (COVID-19) has spread exponentially across the world. The typical manifestations of COVID-19 include fever, dry cough, headache and fatigue. However, atypical presentations of COVID-19 are being increasingly reported. Recently, a number of studies have recognized various mucocutaneous manifestations associated with COVID-19. This study sought to summarize the available literature and provide an overview of the potential orofacial manifestations of COVID-19. An online literature search in the PubMed and Scopus databases was conducted to retrieve the relevant studies published up to July 2020. Original studies published in English that reported orofacial manifestations in patients with laboratory-confirmed COVID-19 were included; this yielded 16 articles involving 25 COVID-19-positive patients. The results showed a marked heterogeneity in COVID-19-associated orofacial manifestations. The most common orofacial manifestations were ulcerative lesions, vesiculobullous/macular lesions, and acute sialadentitis of the parotid gland (parotitis). In four cases, oral manifestations were the first signs of COVID-19. In summary, COVID-19 may cause orofacial manifestations that might be the initial features in several cases. However, the occurrence of orofacial manifestations in COVID-19 seems to be underreported, mainly due to the lack of oral examination of patients with suspected and/or confirmed COVID-19. Oral examination of all suspected and confirmed COVID-19 cases is crucial for better understanding and documenting COVID-19-associated orofacial manifestations.

Keywords: COVID-19; Coronavirus; Oral manifestations, Review.

Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus 2019 disease (COVID-19) has caused an unprecedented global healthcare crisis. By the time of this writing, over 19 million people have been infected, and approximately 728,013 have lost their lives worldwide.[1] While most cases are either asymptomatic or affected with mild symptoms, a considerable fraction of cases develop severe respiratory symptoms, leading to acute severe respiratory distress (ASRD) and sometimes multiple organ failure.[2]

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Association between periodontitis and severity of COVID-19 infection: A case–control study

Nadya Marouf[1] | **Wenji Cai**[2] | **Khalid N. Said**[1] | **Hanin Daas**[3] | **Hanan Diab**[1] | **Venkateswara Rao Chinta**[4] | **Ali Ait Hssain**[4] | **Belinda Nicolau**[2] | **Mariano Sanz**[5] | **Faleh Tamimi**[3]

[1]Department of Dentistry, Oral Health Institute, Hamad Medical Corporation, Doha, Qatar

[2]Faculty of Dentistry, McGill University, Montreal, QC, Canada

[3]College of Dental Medicine, QU Health, Qatar University, Doha, Qatar

[4]Hamad Medical Corporation, Doha, Qatar

[5]ETEP Research Group, Faculty of Odontology, University Complutense of Madrid, Madrid, Spain

Correspondence
Faleh Tamimi, College of Dental Medicine, Qatar University, Building H12 annex, P.O. Box 2713, Doha, Qatar.
Emails: fmarino@qu.edu.qa; Faleh.tamimimarino@mcgill.ca

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Abstract

Aim: COVID-19 is associated with an exacerbated inflammatory response that can result in fatal outcomes. Systemic inflammation is also a main characteristic of periodontitis. Therefore, we investigated the association of periodontitis with COVID-19 complications.

Materials and Methods: A case–control study was performed using the national electronic health records of the State of Qatar between February and July 2020. Cases were defined as patients who suffered COVID-19 complications (death, ICU admissions or assisted ventilation), and controls were COVID-19 patients discharged without major complications. Periodontal conditions were assessed using dental radiographs from the same database. Associations between periodontitis and COVID 19 complications were analysed using logistic regression models adjusted for demographic, medical and behaviour factors.

Results: In total, 568 patients were included. After adjusting for potential confounders, periodontitis was associated with COVID-19 complication including death (OR = 8.81, 95% CI 1.00–77.7), ICU admission (OR = 3.54, 95% CI 1.39–9.05) and need for assisted ventilation (OR = 4.57, 95% CI 1.19–17.4). Similarly, blood levels of white blood cells, D-dimer and C Reactive Protein were significantly higher in COVID-19 patients with periodontitis.

Conclusion: Periodontitis was associated with higher risk of ICU admission, need for assisted ventilation and death of COVID-19 patients, and with increased blood levels of biomarkers linked to worse disease outcomes.

KEYWORDS
Covid-19, death, ICU admissions, periodontitis, ventilation

1 | INTRODUCTION

Coronavirus SARS-CoV-2 is a strain of the severe acute respiratory syndrome-related coronavirus (SARr-CoV), member of the Coronaviridae family and the responsible agent of the disease referred as 2019 coronavirus disease (COVID-2019). This emerging respiratory tract infection has resulted in over 75 million confirmed cases and almost 1.6 million deaths as of Dec 22th, 2020 (WHO, 2020b).

While most patients with COVID-19 present mild symptoms (Huang et al., 2020), nearly 14% of confirmed cases develop severe conditions requiring hospitalization and oxygen support, 5% need

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Prelude to Oral Microbes and Chronic Diseases: Past, Present and Future

Kalina R Atanasova[1] and **Özlem Yilmaz**[1,2,*]

[1] Department of Periodontology, University of Florida, Gainesville, FL 32610, USA

[2] Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610, USA

Abstract

Associations between oral and systemic health are ancient. Oral opportunistic bacteria, particularly, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have recently been deviated from their traditional roles and arguably ascended to central players based on their participations in complex co-dependent mechanisms of diverse systemic chronic diseases risk and pathogenesis, including cancers, rheumatoid-arthritis, and diabetes.

Keywords

Oral Microbes; *P. gingivalis*; *F. nucleatum*; Cancer; Chronic diseases; dysbiosis; small molecule danger signaling

1. Introduction

The oral microbial communities have evolved along with *Homo sapiens* and developed together with our dietary and hygienic habits over millions of years [1]. The first documented dental procedures date back to Neolithic times only about 8000 years BC [2] and dentistry and medicine have been linked in ancient records dating back to Egyptian times approximately 4000 years BC [3]. The importance of oral health for holistic wellbeing is also not a novel concept, as ancient civilizations of the Mediterranean, for example, had already noticed that teeth problems are associated with reproduction problems in women [4], and Hippocrates treated joint pain with tooth extractions (460-377 BC). With the discovery of microorganisms, and their causative link to diseases in the early 17th and throughout 18th century, the association between oral health and oral microbiota, became even more pronounced [3]. The concept of the single-pathogen causality became fashionable among the scientific community and Robert Koch postulated the criteria to establish a causative relationship between a microbe and disease. However many diseases and conditions remained unexplained by single pathogens. Moreover, with the development of the modern molecular tools the concept of the microbiome and the balance of the microbial communities that colonize the human body came to light [5, 6]. Currently the links between the oral microbial consortia and their interactions with the host in the maintenance of homeostasis

* Correspondence : Özlem Yilmaz, Department of Periodontology, College of Dentistry, And Emerging Pathogens Institute, University of Florida, Gainesville, FL, 32610-0434, Tel: (352) 273 8003, oyilmaz@ufl.edu.