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REVIEW PAPER

Autoimmune diseases and their various manifestations in the oral cavity – a systematic review

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ABSTRACT

Introduction and aim. Oral manifestation of the disorder is the leading cause of common initial features of most autoimmune diseases. Therefore, this study aimed to present different oral manifestations of selected autoimmune diseases.

Material and methods. We systematically reviewed the etiology, signs and symptoms, oral manifestations, epidemiology, diagnosis, treatment plan, and prognosis. We searched the articles on PubMed, Google Scholar and Web of Science for the following search term: Behcet's disease, lichen planus, mucous membrane pemphigoid and bullous pemphigoid, pemphigus vulgarisms and paraneoplastic pemphigus, rheumatoid arthritis, Sjögren's syndrome, IgG4-related disease, systemic lupus erythematous, and granulomatosis with polyangitis.

Analysis of the literature. We conducted that the disorder's oral manifestation causes most autoimmune illnesses' earliest symptoms.

Conclusion. Clinical-pathological is a piece of requisite knowledge for the dentist to recognize and diagnose in the early phase of the symptoms.

Keywords. autoimmune diseases, Behcet's disease, lichen planus, lupus erythematous, rheumatoid arthritis, Sjögren's syndrome

Introduction

Autoimmune diseases are a complex group with various, often multifactorial, etiologies. The immune system loses the ability to recognize its antigens from foreign ones and produces antibodies against its own cells. They are chronic inflammatory diseases with subsequent active stages and remission involving multiple organs, especially the skin, joints, connective tissue, and oral cavity. The oral manifestations could be the initial character in the early stage of the disease, and the dentist could be the first who discovers the lesion intraorally and extra orally.[1,2] However, some disorders have similar oral lesions, and a differential diagnosis is needed to distinguish the difference.[3] Also, it is indispensable to understand the oral manifestation of autoimmune disease and its characteristics due to the diseases may also lead to fatal in some cases. Acquire detailed knowledge of the oral manifestation of autoimmune diseases and their features would help the dentist recognize and make an early phase of symptoms diagnosis to build an integral future treatment plan for the patients.[1,4]

Aim

To address these needs, we comprehensively present and discuss selected autoimmune diseases that involve oral and maxillofacial areas. In addition, the study aims to present detailed characteristics of the oral manifestation of autoimmune diseases.

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Material and methods

We conducted a systematic review to identify all case-control studies correlating with autoimmune disease. First, we searched the articles on PubMed, Web of Science, Google Scholar with the data from 2010 to 2021 with the following search term: "autoimmune diseases," "oral manifestation," "oral lesions," "immunosuppressive drug," "Behçet's disease," lichen planus," "pemphigoid," pemphigus," "rheumatoid arthritis," Sjögren's syndrome," IgG4-related diseases, systemic lupus erythematosus," granulomatosis with polyangitis.", by distributing the diseases into eight sections. For each section, we mention the autoimmune disease as the following: etiology, signs and symptoms, oral manifestation, epidemiology, diagnosis, treatment, and prognosis.

Analysis of the literature

Behçet's disease

Behçet's disease (BD) is a chronic inflammatory autoimmune vasculitis and involves multiple systems. Its etiology is still unknown. The lesions include skin, oral mucosa, genital, gastrointestinal, and neurological systems. BD is characterized by at least two of the three key typical factors: oral ulcers, genital ulcers, and eye inflammation. The critical characteristics of BD are ocular lesions with inflammation known as uveitis and conjunctivitis and oral and genital ulcerations. Ocular lesions are present in 30–70% of the cases.[1] Oral lesions could be the initial sign of the disease.[1,2] Chen et al mentioned that the human leukocyte antigen HLA-B51 is related to BD. It also presents greater chances of having ocular lesions and a lesser chance of genital involvement.[4] Environmental factors such as smoking, diet, stress, and infection can also trigger BD.[3] BD patients with vasculitis have found a more significant tumor necrosis factor (TNF)-α and local neutrophil infiltration and mononuclear endothelial cells.[3,5] Recurrent aphthosis is the most common manifestation in the oral cavity for BD individuals.[6] Oral aphthosis is present on the lips, mucosa, tongue, and soft and hard palate.[1] The oral lesions are ulcers of the oral mucosa indistinguishable from the conventional aphthae of the oral mucosa. They are painful and characterized by the cyclic presentation.[1] The oral lesions are usually the initial manifestation. Their diagnosis is a key factor and permits a more favorable prognosis. Many patients present their onset during childhood.[1] Conversely, their differential diagnosis is challenging, considering oral aphthous lesions are common in the general population. Some aphthous lesions could be linked to HIV, Crohn's disease, sarcoidosis, and lupus, given that the dual-site-specific ulcerations seem to be the unique sign to differentiate the BD from different pathologies associated with aphthous lesions.[1] There are three types of oral ulcers of BD, minor aphthae presenting approximately 3 to 10 mm in diameter with erythematous halo, major aphthae developing into 1-3 cm in diameter and healing with scar tissue, and herpetiform ulcers clustering ulcers similar to HSV infection with numerous lesions.[7,8]

Some articles related to BD epidemiology mentioned that its higher incidence is detected in Middle East and Asian populations.[2,3] The population is mainly from the countries along with Silk Road.[9] The highest prevalence is in Turkey (20-420 per 100.000).[6] BD impacts more males than females; the ratio is 1.5-5:10.[9] Greco et al. mentioned that BD is a common disease in males from Middle Eastern countries; females from Japan and Korea demonstrate a higher frequency of BD.[1] BD shows up in third to the fourth decade of life, and the first onset is around the second to third decades.[9]

The BD diagnostic tests are approaches used in clinical practice—three characteristics of ulcers of uveitis of ocular involvement, oral mucosa, and genital ulcerations.[1,5] The pathergy test shows positive when intradermal puncture on the skin forms an erythematous pustule or papule in forty-eight hours.[5] The oral ulceration of the mucosa could be related to HIV, HSV, Crohn's disease, pemphigus vulgaris, and lichen planus.[6] Therefore, dentists should perform a differential diagnosis like biopsy on patients because oral aphthosis is similar to other conditions.[5]

BD treatment is based on administering immunosuppressive drugs, corticosteroids, and anti-inflammatory drugs. The immunosuppressive drug mainly treats BD, and systemic and topical steroids are for anti-inflammation and pain control.[1,3] Colchicine and glucocorticoids can be the first management line for mucocutaneous lesions. Azathioprine, Apremilast, TNFα inhibitors, and interferon-α are used for the second line.[4] Özdede et al. mention that oral lesion treatment with Apremilast demonstrated around seventy-three percent of oral bioavailability. Both in 12 weeks and 24 weeks, applied with the Apremilast group, showed reduced pain compared to the placebo group.[5] Biological drugs tocilizumab, daclizumab, and adalimumab manage B-cell-mediated inflammatory factors[8] BD patients are suggested to use a chlorhexidine mouth rinse to maintain oral hygiene and avoid food irritating the oral mucosa.[9]

Patients with BD harm their quality of life, especially in oral lesion involvement. The BD shows a life-threatening relapse, which can result in death. Early Diagnosis of BD from the oral manifestations can prevent multiple organ involvement.[1] Management with immunosuppressing drugs can improve the prognosis of BD.[5]

Lichen planus

Another autoimmune disease involving the oral cavity is lichen planus (LP). LP is a chronic disease with oral mucosa membranes and cutaneous inflammation.[10] It was

first mentioned by Erasmus Wilson in 1869. LP is mediated by the lymphocyte T cell with an unclear etiology with a higher count of CD4+ and CD8+ in patients.[10,11,12] Forty-five percent of the individuals with oral-involved lichen planus have presented dry mouth (xerostomia) and lower salivary gland function, and eighty-seven percent of them experienced insufficient salivary flow. Oral lichen planus (OLP) is sometimes accompanied by other autoimmune diseases.[10] The OLP involving the gingiva shows desquamative gingivitis.[12,13] Sometimes, accompanied mouth-burning sensation negatively affects patients' quality of life.[13] OLP can also be irritated by spicy or acidic and salty foods.[8,14] Some factors could also induce OLP, such as medications, dental materials, and viruses (HIV, hepatitis B virus [HBV], and hepatitis C virus [HCV]).[12,15] Some authors described that Aquaporins (AQP) is a channel cell protein that works as an intercellular water permeability. In OLP patients, a significant increase in the AQP3 gene prevents xerostomia.[10] Management of pregnant women with OLP should consider the risk to the mother and fetus. The United States Food and Drug Administration has a risk factor classification for the fetus at three trimesters.[11]

The OLP is commonly presented in the tongue, gingiva, buccal, and labial mucosa.[11,13,16] There are six types of OLP: reticular form, plaque form, atrophic form, bullous form, erosive form, and papular form.[11,13,14] In OLP patient, the manifestation exhibit desquamative gingivitis, saw-tooth rete pegs, and buccal mucosa with Wickham's striae for the reticular formation. Sallow ulceration and deep erosion lesions with erythema can also be observed.[12,13]

The prevalence of LP is around 0.22-5% of the world population, and 60% show up with OLP. The range of age is from 30 to 80 years old.[13] It has a higher frequency in females between the 5th and 6th decades of their lives. One of the articles mentions that one of the reasons is that females experience menopause around the 5th decade, and the estrogen level changes making the mucosa change.[15,17] The ratio between men and women is 1:2 or 1:3.[12,14]

Direct immunofluorescence can be found deposition of IgG, IgM, C3, or fibrinogen at the basement membrane zone (BMZ) and the deposition of IgM in the colloid bodies. The indirect immunofluorescence will be negative.[13,18] Oral lichenoid lesion (OLL) is an immune-related disease on the oral mucosa induced by systemic drugs or dental materials (dental amalgam or resin).[12,15,18] Oral manifestations of OLL have a similar clinical feature to OLP. The differential diagnosis should include clinical and histological, and pathological criteria. OLP is familiar with bilateral and symmetric oral manifestation; OLL is involved with unilateral and localized and doesn't involve cutaneous lesions.[18] Under the microscope, OLP exhibits band-like T lymphocyte cell infiltration in the sub-epithelial layer and degenerated basal cells in the Civatte bodies.[13,18]

Treatment of OLP is quite challenging due to the potential side effects of commonly used drugs. If the patient is pregnant, it is important to ensure the health and well-being of both the mother and the developing fetus undergo drug management.[11] For managing OLP, topical corticosteroids such as clobetasol propionate, fluocinolone, and triamcinolone are used to control the local pain, but it shows that they show a potentially harmful effect on the fetus. Systemic steroids can be considered as well.[8,11] Immunosuppressant drugs like tacrolimus and cyclosporine are effective treatments for an erosive type of OLP. But it also shows an adverse effect on the fetus.[11] Chu et al. mention that oral isotretinoin in the dose of 0.25–1 mg/kg per day can effectively manage the OLP.[19] In turn, White et al. mention no significant benefits of curcumin therapy compared with placebo.[13]

OLP is a chronic immune-mediated disease that can last more than twenty years. There is no requirement for treating the patient with an asymptomatic condition. Patients with OLP have fewer than 5% developing oral squamous cell carcinoma.[12,18] Therefore, OLP patients are suggested to have regular check-ups and reassessment for the oral lesion conditions.[18]

Mucous membrane pemphigoid and bullous pemphigoid

Pemphigoid is an autoimmune disease that causes blistering of the skin and mucous membranes.[1,13] There are two main types of pemphigoid: bullous pemphigoid (BP) and mucous membrane pemphigoid (MMP). BP primarily affects the skin, with blistering typically occurring on the arms, legs, and torso. In contrast, MMP predominantly affects the mucous membranes, such as the mouth, eyes, nose, throat, and genitals.[14,20] In MMP), the most commonly targeted protein is collagen XVII, a basement membrane zone (BMZ) component in the skin and mucous membranes. However, antibodies in MMP can also target other proteins in the BMZ, including laminin 5, 6, and 3, as well as BP antigens 180 and 230 kDa.[8,14] In contrast, bullous pemphigoid (BP) is often triggered by certain medications, radiotherapy, and ultraviolet radiation.[17,21] It is characterized by large, tense blisters on the skin that can be itchy and painful. The antibodies in BP typically target BP antigens 180 and 230 kDa, also components of the BMZ.[14,20] Both MMP and BP are autoimmune diseases characterized by the production of autoantibodies against proteins in the BMZ, leading to blistering and erosions. However, they differ in their clinical presentation and the specific proteins targeted by the autoantibodies.

Most cases with mucous membrane pemphigoid exhibit the oral mucosa as the initial lesions. The pain accompanied by an erosive blister, is easily ruptured on

the affected side and left with a scar after healing the wound.[12] Bagan et all. mention that the commonly affected sites include gingiva, buccal mucosa, and hard and soft palate. About 51.6% of patients present the size of a lesion smaller than 3 cm.[21] Most of BP cases present erythematous cutaneous lesions with pruritus and blisters.[12,20] It affects people from the 6th to 8th decades. The female exhibits a higher chance of being diagnosed with the disease.[13,18] The ratio between women and men is 2:1.[8,13] Schifter et al. described that pemphigoid frequency is three times higher than pemphigus. And it's rare for the kids.[12] The prevalence is from 5 to 7.5 for every 10.000 population.[12]

For mucous membrane pemphigoid, the direct immunofluorescence shows that IgG and C3 are deposited in the layer of the basement membrane. It also can be observed that lymphocytes and granulocytes infiltrate the subepithelial layer.[12] We can discover the epithelial separate from connective tissue as well.[1]

BP demonstrates extensive infiltration with the vesicle and degeneration of epithelial cells in the basement membrane zone.[20] Direct immunofluorescence exhibits IgG and C3 deposition; indirect immunofluorescence can discover circulating antibodies.[12] Desquamative gingivitis is characteristic of pemphigus vulgaris, lichen planus, and pemphigoid.[21] Compared to pemphigus, there is no histopathological characteristic of acantholysis.[14] It is noticed that it's less frequency of involvement of gingiva, and the blister is more fragile in pemphigus individuals.[1,22]

Topical drugs corticosteroid is one of the managements of the pemphigoid. We can apply systemic steroids in some severe cases as the treatment plan.[1] Previous studies noticed that 88% of patients were treated with topical corticosteroids for mucous membrane pemphigoid, and 12% were managed with systemic therapy.[22] It is postulated that depleting the B-lymphocytes is one strategy to manage the disorder. Rituximab is directed against the specific antigen CD20 of B cells and rapidly uses up circulating B cells. Another benefit is cutting down the usage of steroids and reducing side-effect.[23] BP can be fatal for patients.[12] MMP shows the potential to cause ocular lesions and damage the eyes' anatomical structure, leading to blindness. Therefore, the patient must have a regular check-up due to the chance of relapse.[1,14,18] Therapy with mild conditions shows a better prognosis treated with topical corticosteroid medicine. Severe cases must be treated with systemic treatment.[12,18]

Pemphigus vulgaris and paraneoplastic pemphigus

Pemphigus is a chronic inflammation of autoimmune diseases involving the supra epithelial layer with the desmosome in a vesiculobullous shape. It exhibits a specific phenomenon called acantholysis.[1,18] Also known as Tzanck cells.[8]

Pemphigus is a group of autoimmune diseases that affect the skin and mucous membranes, and there are six different types. Pemphigus vulgaris (PV) and paraneoplastic pemphigus (PNP) are two of the most common types and are often the focus of research and clinical practice.[8,18,24]

PV is autoantibody that target desmosomal proteins, particularly desmoglein 1 and 3, and 130, 160-kDa cadherin, which plays a critical role in maintaining the adhesion between keratinocytes in the epidermis and mucous membranes.[14,18] When the antibodies attack these proteins, the adhesion between cells is disrupted, forming intraepithelial blisters, which can cause erosions and ulcers. Schifter et al. noticed that desmogleins dominate the oral cavity, and PV affects the oral cavity and is the first location then extended to the cutaneous.[14]

PNP is a rare autoimmune disease often associated with an underlying neoplasm, particularly hematologic malignancies such as non-Hodgkin's lymphoma.[25] Autoantibodies in PNP target various skin and mucous membrane proteins, including desmoplakin I and II, essential components of desmosomes.[12,18] In addition to skin and mucosal lesions, PNP can also affect other organs, such as the lungs and the gastrointestinal tract, leading to severe complications.

PV is more prevalent in females, with an estimated incidence of 1 to 5 cases per 1.000.000 population, and most commonly affects individuals in their fourth to sixth decade of life.[1,18] The Jewish population has a higher chance of being diagnosed.[8,14] Conversely, PNP does not show a gender preference and typically affects individuals in their fourth to seventh decade of life.[25] It can present with lesions on various oral sites, including the buccal or lingual mucosa, hard or soft palate, lips with vermillion border, or tongue. The lesions can be erythematous, vesicles, erosion, or ulcerations, typically accompanied by pain.[1,8,18] The buccal mucosa is the most commonly affected site, while the tongue is a less common site of involvement.[26] PV is characterized by a positive Nikolsky's sign, which is the slippage of the top layer of skin on gentle pressure.[14] Conversely, pemphigoid presents with ulceration and erosion in the oral mucosa, often mimicking oral lichenoid reaction.[12,18]

Approximately 45% of PNP patients show oral lesions as the first site.[12] The manifestations of the vermillion border with crusting and erosion are similar to other autoimmune diseases, such as erythema multiforme or Steven-Johnson syndrome.[25] Overall, dentists play a crucial role in identifying and recognizing oral manifestations of autoimmune diseases and performing a differential diagnosis to provide an accurate diagnosis and appropriate treatment plan.

The oral manifestation of pemphigus can be confused with oral lichen planus (OLP) and mucous membrane pemphigoid. Direct and indirect immuno-

fluorescence (DIF and IIF) can differentiate the differences. In DIF, IgG antibodies can be discovered with net-like features. The microscopy also shows a specific tombstone-like pattern resulting from separating the supra-epithelial layer and underlying connective tissue.[1,8,18] Desquamative gingivitis is one of the features of pemphigus vulgaris. The gingiva surface is without peels and is accompanied by erythema. However, 84% of mucous membrane pemphigoid cases can also exhibit desquamative gingivitis, while only 26% of pemphigus vulgaris cases have this characteristic.[22] Therefore, a biopsy is needed to confirm the diagnosis, as this feature is not specific to pemphigus.[12,27] Compared to pemphigus vulgaris, the histopathology of pemphigus foliaceus is mainly in the BMZ layer, with features of supra-epithelial blister and acantholysis.[18,25] In DIF, the deposition of IgG, IgM, and C3 can be discovered in the BMZ.[8,12,25]

Corticosteroids are commonly used in the management of pemphigus and PNP.[1,18] It is important to recognize the potential severity of these conditions and the need for prompt and appropriate treatment. Immunomodulatory therapies like rituximab and azathioprine are effective in managing pemphigus, while surgical removal of tumors may be necessary in cases of PNP.[8] Good oral hygiene is also crucial in managing these conditions.[8] It is concerning to hear that without treatment, the death rate of pemphigus can be as high as 90%.[14] However, appropriate medication therapy can significantly reduce the life-threatening fatal rate to 5-10%.[8,18,28] It is also important to consider the patient's age as a factor in their prognosis, with elderly patients potentially having a less favorable outcome.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is another autoimmune disease with possible oral manifestation. It is a chronic inflammatory autoimmune disease. The clinical features mainly involved multiple joints bilaterally and were accompanied by morning stiffness that persisted for more than an hour.[2,7,29] The etiology of RA is still unknown. Still, smoking and infection can be environmental factors that trigger RA.[2] Cheng et al. described that dysbiosis of *Porphyromonas gingivalis* can result in the onset of RA. *P. gingivalis* induced the production of anti-citrullinated protein antibodies, which will be the essential factor in increasing the risk of RA.[30] 67.6% of RA individuals can be involved in the temporomandibular joint (TMJ).

The characteristics exhibit swelling of joints, pain, and limited jaw motion. If the young patient is diagnosed with juvenile RA, the TMJ could show underdeveloped mandible bone, ankylosis, and malocclusion with anterior open bite.[2,7,8] Approximately 70% of RA patients present with oral candidiasis; some show a lower salivary flow rate accompanied by halitosis.[31,32] The oral condition with xerostomia negatively affects Oral-Health-Related Quality of Life, especially in physical pain and psychological disability.[32] Compared to healthy individuals, a higher frequency of severe periodontal status, more significant bleeding, worsened gingival inflammation, and deeper pockets are detected in RA patients.[33]

In epidemiology, X-chromosomal is the risk factor for RA, so the female has a higher chance of RA. The incidence of RA in the 5th and 6th decades is the most frequent.[34] RA impacts more female; the ratio between female to male is 3:1 to 4:1.[2]

The diagnosis of rheumatoid arthritis often involves a combination of factors, including a positive result on the anti-citrullinated protein antibody test, joint involvement, and blood tests to measure inflammation (such as CRP and ESR).[2,29] However, it is important to note that other conditions can have similar symptoms and may need to be ruled out before a definitive diagnosis can be made. For example, skin lesions may be present in conditions such as psoriatic arthritis, systemic sclerosis, and systemic lupus erythematous. Muscle pain may suggest polymyalgia rheumatica or fibromyalgia, which can have similar symptoms to rheumatoid arthritis.[29]

In the RA treatment, NSAID and acetaminophen would be the suggestions for pain control.[2,8] Biological medication for immune suppression is used to manage hypersensitivity reactions.[8] Anti-TNF-α agents reduce immune-mediated inflammation and are also helpful in controlling the disorder.[31] Möller et al. noticed that dysbiosis of oral microbial in periodontitis patients is linked to RA, but periodontal treatment is no significant effect on RA.[33]

RA is associated with an increased risk of periodontal diseases, and controlling carbohydrate consumption and maintaining good oral hygiene is important for managing this risk in RA patients.[34] Regular dental appointments can also help with prophylaxis and monitoring the oral health of RA patients.[33] It's important for RA patients to work closely with their healthcare providers, including dentists, to manage both their RA and oral health.

Sjögren's syndrome

Sjögren's syndrome (SS) is an autoimmune rheumatic disease primarily affecting the exocrine gland responsible for producing tears and saliva. The local infiltration of B-lymphocytes can be found in the affected sites.[35-39] This damage can result in dry eyes and dry mouth and induces xerostomia and xerophthalmia.[1,2] The reduction in saliva production can increase caries rate and plaque accumulation, and long-term dry mouth can contribute to oral candidiasis.[36] While the etiology of Sjögren's syndrome is not fully understood, it is believed to be an autoimmune disorder where the body's immune system

mistakenly attacks its own tissues. Viral infections such as Epstein–Barr virus, HCV, and Coxsackie A virus have been suggested as possible environmental triggers for the disease. [36,40]

SS can cause salivary dysfunction, which reduces saliva production. This reduction in saliva flow can result in various oral health issues, including an increased risk of dental caries and periodontal diseases. Due to insufficient saliva, individuals with SS may also experience taste alteration, halitosis, and difficulties with chewing, swallowing, and speaking.[2,8] The condition may lead to xerostomia with taste alteration; rampant caries and advanced periodontitis are also one of the main reasons that decrease patients' living quality.[41-43]

Oral candidiasis is a fungal infection that can occur in individuals with SS due to reduced saliva flow and altered oral microbiota. It can present with erythematous or pseudomembranous features, and conditions such as median rhomboid glossitis and angular cheilitis may also be present.[1,2,43] Around 34% of individuals with SS may experience bilateral swelling or enlargement of the parotid glands, the most prominent salivary glands in front of the ears.[36] This swelling is often painless but can lead to discomfort and cosmetic concerns. SS is more prevalent in females than in men, with an estimated ratio of approximately 9:1.[1,2] It typically affects women in their 5th or 6th decades of life, although it can occur at any age.[7,43] The prevalence rate of SS is approximately 60.82 per 100,000 population, although this can vary depending on the population studied and the diagnostic criteria used.[36]

The autoantibodies anti-Sjögren A (SSA) and anti-Sjögren B (SSB) are commonly used in the diagnosis of SS.[1,44] These autoantibodies can be detected in the blood of individuals with SS and are considered a critical factor in diagnosing the condition. To confirm a diagnosis of SS, patients should meet two out of three conditions: xerostomia (dry mouth), keratoconjunctivitis sicca (dry eyes), and rheumatoid arthritis or another autoimmune disease.[1] Other tests may be performed to assess salivary function, such as salivary flow rate measurements or salivary gland biopsies.

The diagnosis of SS involves a combination of clinical evaluation, physical examination, and various diagnostic tests. Two common methods for diagnosis are biopsy of the minor salivary glands from lips and reduced salivary flow rate.[36,44] A labial salivary gland biopsy is included into SS diagnostic criteria and is based on the detection of focal lymphocytic sialadenitis. Although microscopic pattern of SS is representative for all minor as well as major salivary glands, currently only labial salivary gland biopsy is the SS criterium. It results from simply surgical approach of labial salivary glands.[45,46] Another diagnostic criterium is a positive Schirmer's test result, which is less than 5 mm in 5 minutes, indicates dry eyes.[2,8] The American-European Consensus Group SS criteria is widely used and include six criteria: 1) dry eyes, 2) dry mouth, 3) positive result of Schirmer's test, 4) labial minor salivary gland biopsy, 5) reduced salivary flow or diffuse sialectasias, and 6) positive result of autoantibodies SSA or SSB. These criteria help clinicians make an accurate diagnosis of Sjögren's syndrome.[38,39]

Xerostomia, or dry mouth, is a common symptom that can be caused by various conditions other than Sjögren's syndrome. Some systemic diseases, such as other autoimmune diseases, AIDS, and diabetes, can have similar characteristics to xerostomia. Additionally, certain medications can cause dry mouth as a side effect. Other conditions, such as HCV and amyloidosis, can also cause salivary gland enlargement and sialadenitis, which may mimic some of the symptoms of Sjögren's syndrome. Therefore, performing a differential diagnosis to rule out these conditions and accurately diagnose Sjögren's syndrome is important.[1,8]

Managing Sjögren's syndrome involves various approaches, depending on the symptoms and severity of the disease. Corticosteroids are commonly used to manage the symptoms of Sjögren's syndrome, while biological agents such as rituximab and azathioprine may be used for immunosuppression.[1,36,47] For xerostomia, cholinergic agonist drugs can be used to stimulate saliva production, while sugar-free gum and topical fluoride can help soothe the dry mouth and promote remineralization.[48] Antifungal medications can be used to treat oral candidiasis, and antimicrobial mouth rinse can help control bacterial growth in the mouth.[2,8] Hydroxychloroquine, a medication used to treat malaria, can also be used to treat autoimmune diseases such as Sjögren's syndrome by targeting innate immunity pathways.[47] Due to the risk of dental caries and periodontitis associated with xerostomia, patients with Sjögren's syndrome should maintain good oral hygiene, and dentists should recommend regular dental check-ups and caries prophylaxis.[1,48,49] In severe cases of Sjögren's syndrome, systemic manifestations such as renal failure, cardiovascular disease, lymphoma, and vasculitis can occur, which may increase the risk of mortality.[35,36] Therefore, early diagnosis and appropriate management of Sjögren's syndrome are essential to prevent these complications and improve patient outcomes.

IgG4-related diseases

Another group of autoimmune diseases are immunoglobulin G4 (IgG4)-related diseases (IgG4-RD). They constitute a group of immune-mediated entities that can affect many organs at nearly any anatomic site. However, head and neck area is the second most common site of IgG4-RD after the pancreas. The occurrence of IgG4-RD in the head and neck area is estimated at 20%.[50,51]

They are chronic, systemic, fibro-inflammatory diseases of unknown etiology. All IgG4-RD are characterized by the formation of infiltrations composed mainly of IgG4+ plasma cells, CD4+ and CD8+ T cells and by fibrosis in the organs that are affected. Depending on the organs involved, these infiltrations lead to organ dysfunction and a special clinical presentation. In the head and neck area Mikulicz's disease (MD) and Küttner's tumor (KT) are their main manifestations. The basic and entry criterion for both MD and KT diagnosis is the involvement of a set of salivary glands. KT is defined as less severe manifestation of the IgG4-RD in the head and neck area with the predominant fibrosis of affected salivary glands. KT is an enlargement and sclerosing sialadenitis of the submandibular glands (SMG). In turn, MD is usually a symmetrical enlargement of the lacrimal glands, parotid and SMG, and sometimes sublingual glands with the symptoms of dry mouth and ocular dryness. However, salivary secretion in MD is normal or decreased to a lesser extent. Both MD and KT as IgG4-RD may be confused with malignancy, infection or SS and vasculitis.[51] Moreover, in the past, MD was treated as a subtype of primary Sjögren's syndrome (pSS). Xerostomia is not the predominant symptom and the diagnostic criterion in MD contrary to SS. Furthermore, in contrast to pSS, the target of autoimmune attack in MD and KT is the parenchyma of the major salivary gland.[51,52] Microscopic examination and serum IgG4+ levels are diagnostic steps allow MD and KT to be distinguished from pSS. These entities also have different epidemiological characteristics. IgG4-RS, contrary to SS, mainly affects men in middle age. The median age of the onset of IgG4-RD is 58 years. The male–female ratio is approximately 5:1. The characteristic features of IgG4-RD are the slow progression of the disease and a good response to steroid therapy.[53] MD is characterized by idiopathic, bilateral, symmetrical and painless diffuse swelling of the lacrimal, parotid and SMG. This swelling lasts for at least 3 months. In MD, gland swelling is persistent, while gland swelling in SS is periodic. Enlargement of the salivary glands in MD is more frequent than in SS. KT is considered to be a subtype of MD. In KT, the swelling is well localized and limited mainly to the SMG. It presents with a firm, painless mass in the neck, which mimics the neoplastic process of SMG. Hard and painless salivary gland swelling is the predominant symptom. KT is characterized by asymptomatic bilateral swelling of the SMG. KT could be histopathologically diagnosed by strong lymphocytic infiltration and fibrosis in the SMG either with or without sialolith. Moreover, salivary duct obstruction, salivary stasis, sialolithiasis and secretory dysfunction play a role in the etiology of KT. Both KT and MD are characterized by increased serum IgG4+ levels > 135 mg/dl that has been defined as a general diagnostic criterion of all IgG4-RD. Lymphoplasmacytic infiltrations of uncertain etiology in the salivary glands fulfils the entry criterion for both MD or KT.[52-54]

Systemic lupus erythematous

Systemic lupus erythematosus (SLE) is an immune-mediated inflammatory disease that can affect multiple organs, with the skin being the most commonly involved. A characteristic skin feature of SLE is the butterfly rash, which appears on the face.[1,2] Recent research has suggested that changes in the gut microbiome may be associated with SLE and may offer an alternative method for diagnosing the disease.[55]

SLE patients are more likely to experience mental health issues, functional limitations, and physical pain compared to the general population, as evidenced by the oral-health-related quality of life questionnaire.[31,56] The most common oral manifestation of SLE is the presence of erythematous plaques with peripheral telangiectasia, which may occur on the buccal mucosa, gingiva, palate, and lips.[2,12] SLE patients may also experience recurrent oral aphthous ulcers, which can cause significant discomfort.

Periodontitis is a common oral health issue in SLE patients, with up to 70% of individuals diagnosed with the disease.[7] High CRP levels may be associated with periodontitis in SLE patients.[9] Xerostomia, or dry mouth, is also prevalent in SLE patients and can negatively impact their quality of life.[31,56] Spicy and hot foods may irritate oral lesions and trigger a burning sensation in SLE patients.[57]

SLE disproportionately affects black females in the United States and is most commonly diagnosed in individuals in their 4th decade of life.[1,2,57] The prevalence of SLE ranges from 12 to 50 in every 100.000 population and is more common in females than males, with a female-to-male ratio of approximately 4.5:1 to 8:1.[2,7,8,41,57]

Direct immunofluorescence is an important diagnostic tool for SLE as it can detect the deposition of immunoglobulin and complement proteins in the basement membrane, a characteristic feature of the disease.[2,13,28] Path histology can also examine tissue samples from affected organs or tissues to identify characteristic changes such as hyperkeratosis and thickening of the basal and spinous cell layers. However, it is important to note that the oral lesions associated with SLE, such as mucosal ulcers and recurrent aphthous stomatitis, can have a similar appearance to other oral lesions, such as lichenoid lesions or leukoplakia. Therefore, a thorough evaluation of the patient's clinical history and systemic symptoms, such as kidney dysfunction and joint pain, is necessary to make an accurate diagnosis of SLE.[2,18]

Corticosteroids are commonly used to manage oral lesions in SLE, including RAS and ulceration.[2,41] However, alternative treatments such as anti-malarial including

Table 1. Manifestations and management of selected autoimmune diseases

Disease	Diagnostic methods	Oral manifestation	Treatment
Behect's disease	HLA-B51 detection Criteria consist of oral ulcerations plus any 2 of the following recurrent genital ulcers, eye lesions, skin lesions Positive pathergy test	Recurrent oral aphthous ulcers	NSAID, Steroids: glucocorticoids (topical or systemic), Immunosuppressants: Azathioprine, Apremilast, TNF-α inhibitor Interferon-α
Mucous membrane pemphigoid and bullous pemphigoid	Direct immunofluorescence (Linear immunoglobulin G and complement C3 at basement membrane zone) Indirect immunofluorescence (Linear immunoglobulin G and/or immunoglobulin A at basement membrane zone)	Desquamative gingivitis, oral buccal and lingual mucosa, lips, and tongue Subepithelial separation of epithelium from connective tissue Positive Nikolsky sign	Steroids: topical steroids Systemic with dapsone and prednisone. Immunosuppressants: azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab
Pemphigus vulgaris and paraneoplastic pemphigus	Direct immunofluorescence (Pemphigus vulgaris: IgG and C3 deposit in suprabasal layer; Paraneoplastic pemphigus: IgG and C3 deposit in BMZ) ELISA for the detection of antibodies HLA-DR4 detection	Desquamative gingivitis, superficial blisters and erosions on the palate, tongue, and labial/buccal mucosa Dyskeratosis, Acantholysis (Tzanck cells), Basal cells are separated from connective tissue with tombstones pattern Positive Nikolsky sign	Steroids: topical steroids Systemic with dapsone and prednisone. Immunosuppressants: Azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab
Rheumatoid arthritis	Rheumatoid factor (RF) Anti-citrullinated peptide antibodies HLA-DRB1 detection	High risk of periodontitis TMJ dysfunction (surface erosion; ankylosis with an anterior open bite) Myofacial pain Reduced salivary flow rate (xerostomia) Oral candidiasis	NSAID: Ibuprofen, Naproxen Immunosuppressive medication: Rituximab, Azathioprine, TNF-α antagonists Antifungal drugs
Sjögren's syndrome	American-European Consensus Group criteria ANA, anti-SSA/Ro, anti-SSB/La Minor salivary gland biopsy and serology Schirmer's test Dry eyes Dry mouth Reduced salivary flow	Xerostomia with taste alterations Rampant caries Salivary gland pathology difficulty with chewing and swallowing oral candidiasis burning mouth complaints	Steroids: topical/systemic steroids Immunosuppresive drugs: Azathioprine, Cyclosporine, Hydroxychloroquine Antifungal drugs: nystatin Adjunctive therapy: topical fluoride, 2% Chlorhexidine mouth rinse
Mikulicz disease and Küttner tumor	Serum levels of IgG4 Histopathological examination	Billateral, painless swelling of parotid, submandibular and sublingual glands, lacrimal glands (Mikulicz disease) Severe fibrosis of submandibular gland, asymmetric swelling	Steroids: Systemic steroids Good response to steroids Immunosuppresive drugs
Systemic lupus erythematosus	ANA, anti-dsDNA, anti-Sm, Direct immunofluorescence: Depositions of IgG or IgM in the basement membrane zone Hyperkeratosis, lymphocytes infiltration in basal cell layer	Oral lesion common buccal mucosa, lips, gingival, Plaque or macules in red Oral aphthous ulceration Periodontitis xerostomia Possible transformation to squamous cell carcinoma	Steroids: topical/systemic steroids Immunosuppressants: Azathioprine, cyclophosphamide Adjunctive therapy: vitamin D and Ca^{2+} supplements Improvement of oral hygiene
Granulomatosis with polyangitis	Granuloma in the respiratory tract Necrosis and inflammation of the small vessels Glomerulonephritis induce kidney failure Anti-neutrophil cytoplasmic antibodies	Strawberry gingivitis Alveolar bone resorption Tooth loss Ulceration on oral mucosa, hard palate, soft palate and tongue.	Steroids: prednisone NSAID Immunosuppressive drugs : Cyclophosphamide, Rituximab
Lichen planus	Direct immunofluorescence (Deposition of immunoglobulin G, IgM, complement C3, or fibrinogen at basement membrane zone; deposition of immunoglobulin M in the colloid bodies),	Buccal and lingual mucosa, lips, tongue, and gingiva with erosions or ulcerations. Saw-tooth epithelial ridges, with desquamative gingivitis Striated white lesions (reticular variant) with or without erythematous	Corticosteroids: topical, systemic, Immunosuppressants: tretinoin cyclosporine, pimecrolimus, tacrolimus, TNF-alpha inhibitors Antimicrobials: Chlorhexidine, povidone-iodine, miconazole, nystatin Others: vitamin A

anti-malarial, NSAID drugs, and immunosuppressive medications such as azathioprine, mycophenolate, and cyclophosphamide can also be used to manage SLE.[8,58] Adjunctive therapies, such as vitamin D and calcium supplements, may also be recommended for SLE patients.[58] Additionally, isotretinoin can effectively manage skin lesions associated with SLE.[19] SLE patients need to be aware of the potential side effects of long-term corticosteroid use, including avascular necrosis and the risk of secondary infection after undergoing immunosuppressive therapy. SLE patients with chronic ulceration should also be monitored closely, as there is a potential risk of transformation into squamous cell carcinoma.[2,58] Therefore, it is important for SLE patients to have regular follow-up appointments with their healthcare provider and to report any changes or new symptoms.[2,8,58]

Granulomatosis polyangitis

Granulomatosis with polyangitis (GPA), previously known as Wegener's granulomatosis, is a chronic autoimmune disease characterized by necrosis of granulomatous lesions and inflammation of the vessels, particularly in the respiratory tract and kidneys.[59] The etiology of the disease is unknown, but environmental factors such as hydrocarbons and crystalline silica have been suggested as possible triggers.[60] The disease was first mentioned by Klinger in 1931, and Wegener provided a more detailed description of its symptoms in 1936.[41,61]

GPA is a rare disease; only a small percentage of affected individuals develop oral manifestations.[62] The most common oral manifestation is hyperplastic gingivitis, which is also known as "strawberry gingivitis."[59] This condition is characterized by gingiva enlargement, bleeding, and pain. In addition to hyperplastic gingivitis, ulcers on the oral mucosa, hard and soft palate, and tongue can also be seen in some patients.[59,60] However, the involvement of the parotid and submandibular glands is rare.[61,62] Periodontitis can also develop in GPA patients, leading to further bone resorption and tooth loss. Therefore, it is important for dentists to be aware of these oral manifestations and to refer patients for further evaluation and treatment if necessary.

GPA prevalence is around 5 per 100.000 population.[58] The disease is usually diagnosed in the 4th or 5th decade of life, and there is no gender predilection.[59,] These criteria include the presence of granuloma in the respiratory tract, necrosis, inflammation of small vessels, and glomerulonephritis that can lead to kidney failure.[27,58] Microscopy may reveal local infiltration of lymphocytes and neutrophils in the gingiva, which dentists must differentiate from malignant tumors or Hodgkin's lymphoma.[59,60] Cytoplasmic-staining ANCA (anti-neutrophil cytoplasmic antibodies) is crucial in distinguishing GPA from gingival hyperplasia, vascular proliferation, and squamous cell carcinoma.[63,64]

Immunosuppressive drugs such as cyclophosphamide are recommended to manage GPA, typically at 2 mg/kg per day.[27] This medication helps to reduce the immune system's response that is causing inflammation. Steroids such as prednisone (at the dose of 1 mg/kg per day) or NSAIDs (non-steroidal anti-inflammatory drugs) can also be used to alleviate pain.[27,29,62] Rituximab, a monoclonal antibody, is another effective treatment option for GPA cases.[60,64] It works by targeting and killing the abnormal immune cells that are attacking the body's tissues. Without treatment, the fatal rate of GPA is approximately 82%, with a 5-month survival time. Interrupted therapy can lead to the relapse of GPA and may result in multiple organ damage.[62,63] Therefore, diagnosing the disease early and beginning treatment promptly to prevent kidney failure and death is crucial (Table 1).[29]

Conclusion

As the dentist may be the first healthcare professional to identify these symptoms, they must provide an accurate diagnosis and appropriate treatment plan to improve the patient's quality of life. Autoimmune diseases can present with a wide range of oral symptoms, making the differential diagnosis a critical aspect of the dentist's role. In some cases, the characteristics of different disorders may overlap, further emphasizing the importance of clinical expertise in distinguishing between them. As an integrated multidisciplinary team member, the dentist can collaborate with other healthcare professionals to provide comprehensive care for patients with autoimmune diseases. Early disease management can help prevent further complications and improve the patient's overall outcome. Table 1 likely includes additional information regarding the specific autoimmune diseases that may present with oral manifestations and their respective characteristics, which can assist dentists in making a more accurate diagnosis and developing a tailored treatment plan.

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Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

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