Oral Manifestations of Autoimmune Diseases
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Abstract
Many autoimmune diseases have oral manifestations. The oral lesions are the initial and early manifestations in few autoimmune diseases. These oral manifestations must be properly recognized if the patient is to receive appropriate diagnosis and referral for treatment. Failure to identify these oral manifestations may reduce the likelihood of early treatment and lead to more serious problems. This paper reviews the oral manifestations of various autoimmune diseases.

Keywords: Autoimmune disease; Hematological disorders; Scleroderma; Dermatologic diseases; Mucocutaneous; Pemphigus.


Introduction
The term autoimmune disease is ideally applied to those cases where it can be shown that autoimmune process contributes to pathogenesis of disease rather than situations where apparently harmless autoantibodies are formed following tissue damage. Autoimmune disease is controlled by genetic and environmental factors. Both of these affect susceptibility to autoimmunity at three levels: (1) The overall reactivity of the immune system (2) Specific antigen and its presentation and (3) Target tissue.

Autoimmune diseases occur in up to 3-5% of the general population. They are common in females for which, the reason is unknown. They are classified as organ-specific or multisystem. In organ-specific the immune system reacts against an antigen which is present in only one organ eg: thyroxine which is present in only thyroid. One important feature of some organ-specific autoimmune disease is the tendency for overlap, such that an individual with one specific syndrome is more likely to develop a second syndrome. Eg: there is high incidence of pernicious anemia in individuals with autoimmune thyroiditis. In systemic or non organ specific autoimmune diseases the pathologic lesions are found in multiple organs and tissues. Eg: systemic lupus erythematosus (SLE) which involves kidneys, joints, skin, blood vessels and central nervous system. Autoimmune diseases can affect virtually any site in the body and accordingly their clinical presentation varies widely. Therefore, each disease is usually considered separately.

ORGAN-SPECIFIC AUTOIMMUNE DISEASES
I) Hematological disorders
Autoimmune Hemolytic Anemia (AIHA) is characterized by the presence of autoantibodies directed to antigens on the individuals own red cell membrane, and by evidence of decreased red cell survival mediated by the red cell autoantibody. AIHA was the first autoimmune disorder in which an autoantibody was clearly shown to be involved in its pathogenesis. AIHA is most often idiopathic. Oral manifestations include deposition of blood pigment in the enamel and dentin of the developing teeth, giving them a green, brown or blue hue. The stain is intrinsic and does not involve teeth or portions of teeth developing after cessation of hemolysis.

Immune Thrombocytopenic Purpura (ITP) is an autoimmune disorder characterized by a low platelet count and mucocutaneous bleeding. ITP is classified as primary and secondary and as acute and chronic. Adult-onset and childhood-onset immune thrombocytopenic purpura are strikingly different. Affected children in childhood-onset ITP are young and previously healthy and they typically present with the sudden onset of petechiae or purpura a few days or weeks after an infectious illness. In more than 70 percent of children, the illness resolves within six months, irrespective of whether they receive therapy. By contrast, immune thrombocytopenic purpura in adults is generally chronic, the onset is often...
insidious, and approximately twice as many women as men are affected.10

Oral manifestations are gingival bleeding; petechiae, mucocutaneous bleeding and haemorrhage into tissues.11 Petechiae occur in the oral mucosa more commonly on the palate and appear as numerous tiny, grouped clusters of reddish spots only a mm or less in diameter. Oral surgical procedures mainly extractions are contraindicated because of excessive bleeding and should be carried out only after the deficiency is compensated.3

II Gastrointestinal diseases
Pernicious anemia is the most common cause of vitamin B12 deficiency. Vitamin B12 deficiency has many causes and the term pernicious anemia applies only to the condition associated with chronic atrophic gastritis.12 Glossitis is the most common oral manifestation of pernicious anemia. Tongue is smooth and beefy red because of atrophic glossitis.12 With glossitis, glossodynia and glossoporysis there is gradual atrophy of the papillae of the tongue which leads to smooth and bald tongue referred as hunter’s glossitis or Moeller’s glossitis. Taste sensation also may be diminished.3, 13

III Dermatologic diseases
Pemphigus Vulgaris: Pemphigus is a group of potentially life-threatening autoimmune mucocutaneous diseases characterized by epithelial blistering affecting cutaneous and/or mucosal surfaces, the term being derived from the Greek Pemphix (bubble or blister).14 Oral lesions in Pemphigus are common and early manifestations in about 50% of the patients.15 Cutaneous lesions develop 5 months after oral lesions and in some patients oral lesions are the only manifestation.16, 17

Lesions typically run a chronic course, causing blisters, erosions, and ulcers.18 Intact bullae are uncommon in the mouth.9, 19 Initially vesiculobullous, the oral lesions readily rupture, new bullae develop as the older ones rupture and ulcerate.20 Thus erosions and ulcers are the main features and are seen primarily in the buccal mucosa, palate, and lips.21, 22 Ulcers heal without scarring.14, 23

Bullous Pemphigoid is a subepidermal skin blistering disease characterized immunohistologically by dermal-epidermal junction separation, an inflammatory cell infiltrate in the upper dermis, and autoantibodies targeted toward the hemidesmosomal proteins BP230 and BP180.24 Oral lesions begin as bullae, but they tend to rupture sooner, probably as a result of constant low-grade trauma to which the oral mucosa is subjected. Large, shallow ulcerations with smooth, distinct margins are present after the bullae rupture. Sometimes erosions are confined to the gingiva creating a picture of chronic desquamative gingivitis.25

Cicatral Pemphigoid (CP) or mucous membrane pemphigoid (MMP) is a rare chronic autoimmune subepithelial blistering disease characterized by erosive lesions of mucous membranes and skin that result in scarring of at least some sites of involvement.26 The term cicatrical is derived from the word cicatrix, meaning “scar.”24 Oral mucosa is the most frequent site of involvement in patients with cicatrical pemphigoid and it is often the first site affected. Lesions involve the gingiva, buccal mucosa, and palate. The most frequent oral manifestation is desquamative gingivitis (DG). Chronic soreness is common, being especially worse when acidic foods are eaten. There is gingival erythema and loss of stippling, extending apically from the gingival margins to the alveolar mucosae. The desquamation may vary from mild, almost insignificant small patches to widespread erythema with a glazed appearance. In severe disease, adhesions may develop between the buccal mucosa and the alveolar process, around the uvula and tonsillar fossae and between the tongue and floor of the mouth. Gingival involvement can result in tissue loss and periodontal complications.26, 27

Psoriasis is a chronic inflammatory skin disease with a strong genetic basis, characterized by complex alterations in epidermal growth and differentiation and multiple biochemical, immunologic and vascular abnormalities.28 Oral manifestations are rare in psoriasis. Oral psoriasis involves 2% of psoriatic patients and usually it is observed with the onset of cutaneous lesions and progresses with them.28 Oral lesions of psoriasis are commonly seen on lips, buccal mucosa, palate, gingiva and floor of the mouth.9 Four types of oral lesions of psoriasis are described- (1) well-defined, gray to yellowish white, tiny, round to oval lesions; (2) lacy, circinate, white elevated lesions on the oral mucosa and the tongue paralleling skin lesions; (3) fiery red
erythema of the oral mucosa including the tongue seen primarily in the acute form of psoriasis; and (4) a geographic tongue that occurs more frequently among patients with psoriasis than without. Many reports of oral psoriasis show no consistent lesion pattern. Patterns range from raised, white, scaling lesions predominantly on the palate or buccal mucosa to well-demarcated, flattened, erythematous lesions with a slightly raised, white, annular or serpiginous border. Oral lesions may disappear quickly or they may undergo exacerbations or remissions concomitantly with skin lesions. Diagnosis of oral psoriasis is best made when the clinical course of the oral lesion parallels that of the skin disease and is supported by microscopic findings such as parakeratosis, acanthosis, elongated rete ridges, thinning of the suprapapillary plate and migration of polymorphonuclear leukocytes through the epithelium forming intraepithelial microabscesses (Munro abscesses).

Epidermolysis Bullosa Acquisita is a chronic subepidermal blistering disease associated with autoimmunity to type IV collagen with anchoring fibrils located at the dermal-epidermal junction. Epidermolysis bullosa acquisita will present mostly with skin bullae and vesicles. Oral lesions are rare. oral mucosa when involved will form large hemorrhagic bullae, most commonly on the buccal mucosa which heal with scar formation.

Oral Lichen Planus (OLP) is present in 70-77% of dermatological patients with LP (Lichen Planus). There are six recognized oral manifestations: (1) Reticular, (2) Papular, (3) Plaque, (4) Atrophic, (5) Erosive, (6) Bullous. The first three forms are white forms and the latter three forms are red forms and are associated with significant symptoms and usually require either topical or systemic immune suppressive therapy. Reticular lichen planus is most common type. Lesions consist of radiating white or gray, velvety, threadlike papules in a linear, annular or retiform arrangement forming typical lacy, reticular patches, rings and streaks over the buccal mucosa and to a lesser extent on the lips, tongue and palate. A tiny white elevated dot is frequently present at the intersection of the white lines, known as the striae of Wickham. Because of interlacing white lines it is named as reticular lichen planus. Papular type is rare and present as small white raised papules of 0.5-1.5mm in diameter. Plaque type of OLP appears as homogenous white patches which resemble leukoplakia. Radiating striae may be seen on the periphery. This type commonly affects the dorsum of the tongue and buccal mucosa. Atrophic Lichen Planus presents as a diffuse red or erythroplakic lesion. The lesion may appear as a mixture of clinical subtypes. Sometimes the atrophy and ulceration are confined to the gingival mucosa, producing the reaction pattern called desquamative gingivitis. In erosive lichen planus erosions are often extensive, irregular and affect mainly the lingual and buccal mucosa and are often associated with white lesions. Gingival involvement produces desquamative gingivitis. Bullous lichen planus is the least common type of OLP. The bullae range from mm to cm in diameter. They tend to rupture leaving ulcerated and painful surfaces. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae.

Erythema Multiforme is a reactive mucocutaneous disorder in a disease spectrum that comprises a self-limited, mild, exanthematic, cutaneous variant with minimal oral involvement to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis. The exact cause is unknown. In about 50% of the cases there can be either a preceding infection of herpes simplex or mycoplasma pneumoniae or there may be exposure to any of the drugs and medications particularly antibiotics and analgesics. These agents may trigger the immunologic derangement that produces the disease. Oral manifestations of EM range from tender superficial erythematous and hyperkeratotic plaques to painful deep hemorrhagic bullae and erosions.

SYSTEMIC AUTOIMMUNE DISEASES

Systemic lupus erythematous is a chronic, multi-systemic disease of unknown etiology. It is characterized by the production of autoantibodies and immune complexes leading to protean systemic manifestations. Genetic, hormonal, racial and environmental factors all contribute to SLE. Oral lesions of SLE develop in 5% to 25% of patients. The lesions usually affect the palate, buccal mucosa and gingiva. Sometimes they appear as lichenoid areas, but they may also look nonspecific or even somewhat granulomatous. Involvement of the vermilion zone of the lower lip (lupus cheilitis) is sometimes seen. Varying degrees of...
ulceration, pain, erythema and hyperkeratosis may be present. Other oral complaints are xerostomia, stomatodynia, candidiasis, periodontal disease and dysgeusia.25,40

Oral or nasopharyngeal ulceration is recognized as a major diagnostic manifestation of SLE by the American Rheumatism Association Committee on Diagnostic and Therapeutic Criteria. These ulcerations are generally painless and often involve the palate. Purpuric lesions such as ecchymoses and petechiae may also occur. In up to 30% of patients with SLE, salivary gland involvement may occur concomitantly, leading to secondary Sjogren's syndrome and severe xerostomia.41

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disorder that may affect many tissues and organs like skin, blood vessels, heart, lungs and muscles. But principally attacks the joints, producing a nonsuppurative proliferative and inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints. Although the cause is unknown, autoimmunity plays a role in its chronicity and progression.13 The TMJ is affected to some degree in more than 40% of persons with rheumatoid arthritis. If TMJ is involved it is usually bilateral and occurs late in the disease. The signs and symptoms are less severe than in other joints and include stiffness, crepitation, pain or ache, tenderness and limitation of mouth opening.25 Pain of TMJ rheumatoid arthritis is not related to motion but rather to pressure on the joint. Clenching the teeth on one side produces pain of the contralateral joint. Subluxation or ankylosis is less frequent in the TMJ than in other joints, but gross destruction of the condylar heads may be so severe that mandibular micrognathia causes a receding chin and malocclusion may develop.25

Sjogren syndrome (SS) is a chronic disease characterized by dry eyes and dry mouth resulting from immunologically mediated destruction of the lacrimal and salivary glands.13 Oral manifestations of SS are grouped under subjective symptoms and objective symptoms. Subjective symptoms include dry mouth, termed xerostomia a dominant clinical oral symptom of SS.42 Severity of this dryness varies from patient to patient.25 Other manifestations include increased liquid intake, chewing difficulty, particularly with dry foods, sensitivity to acids and voice alteration. Patients report burning and tingling sensations in the mouth with frequent voice hoarseness and a change in the sense of smell. Oral manifestations reduce self-esteem, affect work productivity and alter quality of life.42,43 Objective oral manifestations of SS include dry oral mucosa, the inability to produce saliva, and difficulty in talking. Approximately 70% of patients exhibit dental caries and 85% manifest oral infections, particularly oral candidiasis. Patients also exhibit an inability to distinguish between normal, bitter and sweet tastes. The tongue may be dry, red, fissured. The lips may be cracked and have a tendency to peel.42,44

Scleroderma is a chronic disease characterized by diffuse sclerosis of the skin, gastrointestinal tract, heart, muscle, lungs, and kidney. The lips of a patient with scleroderma may appear to be pursed due to constriction of the mouth aperture, thus making it difficult to open the mouth.41 Tongue becomes stiff and board like, causing difficulty in eating and speaking. Gingival tissues are pale and firm.9

Reiter's Syndrome is characterized by presentation of polyarthritis, ocular lesions and aseptic urethritis. Although approximately 80% of the patients with Reiter's syndrome possess HLA-B27 and it has been found that most of the HLA-B27 negative patients of this disease possess HLA-B7, Bw22, B40, B42 or B60, which are crossreactive with HLA-B27.45 The oral lesions occur in less than 20% of patients with this disorder.45 Lesions appear as painless, red, slightly elevated areas sometimes granular or even vesicular with a white circinate border on buccal mucosa, lips and gingiva. The lesions may be mistaken for recurrent aphthous ulcers. The palatal lesions appear as small, bright purpuric spots which darken and coalesce. Lesions on the tongue closely resemble geographic tongue.9

Behcet's disease is an inflammatory disorder of unknown cause, characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. All these common manifestations are self-limiting except for the ocular attacks.46 The oral lesions are painful and very similar in appearance to recurrent aphthous ulcers.47 Ulcers are round, few mm to a cm in diameter having an erythematous
border and covered by yellowish exudates occurring on soft palate and oropharynx.9, 46

Recurrent aphthous stomatitis (RAS) is a common disease characterized by the development of painful, recurring solitary or multiple ulcerations of the oral mucosa.9, 47 RAS is a common oral disorder. RAS affects 5-66% of the population.46 Based upon the clinical manifestations recurrent aphthous stomatitis has been classified into four categories: (1) Recurrent aphthous minor (2) Recurrent aphthous major (3) Recurrent herpetiform ulcerations and (4) Recurrent ulcers associated with Behcet's syndrome.9, 48

The minor aphthous ulcer begins as a single or multiple superficial erosions covered by a gray membrane having a well-circumscribed margin surrounded by an erythematous halo. The lesion is very painful and interferes with eating.9, 46, 48 The number of lesions present in any one patient during a single outbreak may vary from one to over 100. Size varies from 3-10 mm in diameter.9, 48 Common sites are the buccal and labial mucosa, buccal and lingual sulci, tongue, soft palate and pharnx. Ulcers are uncommon on gingiva and hardpalate.9, 48, 50

Recurrent aphthous major ulcers are large, oval, painful which may exceed 1cm in diameter and may approach upto 3cm, usually 1-10 in number occurring on the lips, cheeks, tongue, soft palate and fauces.51 These ulcers persist for up to 6 weeks and heal on scarring.9, 52, 46 These patients show a high incidence of antibodies to oral mucosa.47, 48 Recurrent herpetiform ulcers are characterized by crops of multiple small, shallow ulcers, often up to 100 in number, which may occur at any site in the oral cavity.51

Conclusion
Autoimmune diseases often present with abnormalities of the structures of the mouth and jaws. Proper diagnosis is necessary to initiate the correct treatment and the dentist should have good knowledge of oral manifestations of autoimmune diseases for the correct diagnosis and treatment. In this article we have outlined oral manifestations of autoimmune diseases.

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