REVIEW

Autoimmune Diseases Affecting the Orofacial Region – An Overview

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Abstract

Introduction: Diseases result from abnormal divergence of the normal structural and functional well-being of an organism. It can be brought about by physical, biological, chemical, genetic, or autoimmune causes. Autoimmune diseases occur when the body's defence system targets its own healthy cells and tissues. The clinical signs and symptoms vary depending on the target tissues. Oral lesions such as ulcers, blisters, mucositis, and gingivitis are seen in many autoimmune diseases and may be an early sign, first recognized by the dental surgeon.

Objective: To review the various autoimmune diseases affecting the orofacial region and update the clinicians about their oral manifestations.

Materials and Methods: Case reports, review articles and original research papers published in various electronic databases like PubMed, Cross reference, Google scholar, and data collected from books are compiled in this review article.

Result and Conclusion: This review gives an overview of some of the common autoimmune diseases affecting the head and neck region, their pathogenesis, clinical features, histopathological features and laboratory findings.

Keywords: Autoimmune, vesicles, bullae, desmosomes, immunofluorescence, oral, immunohistochemistry.

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Introduction

An immune response is brought about when an antigen is detected and processed by the Antigen Presenting Cells (APC) for activation of other immune cells. Autoimmune diseases (AD) involve the targeting of self-antigens by the host immune system. In AD, the body's defense mechanism fails to distinguish 'self' from 'non-self' antigens leading to the production of autoantibodies. The clinical manifestations of AD vary greatly depending on the organs it affects.[1] Oral manifestations are often a primary sign of autoimmune diseases.[2]

Classification of autoimmune disease

AD can be classified based on the location as organ-specific / localized and organ-non-specific /systemic. (Table 1)

Mechanism of autoimmune disease

AD evolves in varying degrees through three phases - initiation, propagation, and resolution.

Initiation

Patients in the initiation phase of the disease are usually unaware of clinical symptoms (subclinical). This phase involves

- Genetic susceptibility: Gene polymorphisms play an important role. For example, Interleukin (IL23R) gene polymorphisms have been reported in ankylosing spondylitis, Behcet's disease, Crohn's disease, psoriasis, and ulcerative colitis.[3] Genetic alterations in a single gene can result in ADs, as in Autoimmune Polyendocrine Syndrome (APS; AIRE mutation), Immunodysregulation Polyendocrinopathy Enteropathy X-linked Syndrome (IPEX; FOXP3 mutation), and autoimmune lymphoproliferative syndrome (Fas/ Fas ligand mutation).[4,5]
- Environmental trigger: Infections have a major role in AD – examples include the hypothesized association of Epstein Barr Virus (EBV) infection in multiple sclerosis and periodontal infections in rheumatoid arthritis. Theories proposed to explain this association involves epitope spreading, antigen complementarity, and excessive innate/ pattern recognition receptor activation.[1,6]
- Immunological factors: Failure of immune tolerance can initiate autoimmunity. This involves the Major Histocompatibility Complexes (MHC) from Chromosome 6.[7]

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Propagation

This phase is characterized by self-perpetuating inflammation and tissue damage resulting from cytokine production, epitope spreading, and a disrupted effector T cell/ regulatory T cell (Teff/Treg) balance.[1] These lead to a catastrophic inflammatory loop1 and AD.

Resolution

Autoimmune reactions can resolve with the activation of cell-intrinsic (inhibitory pathways) and cell-extrinsic (Tregs) mechanisms that limit effector responses and restore T effector/T regulator balance.[8] Patients in this phase may also enter into a cycle of relapse and remitting disease as a result of a disturbed balance between pathogenic effector responses and regulation.[1] (Figure 1)

Autoimmune diseases affecting the oral cavity

Many ADs manifest early in the oral cavity. ADs affecting the orofacial region include connective tissue disorders like systemic lupus erythematosus, Sjögren's syndrome, scleroderma, and vesiculobullous lesions like pemphigus, pemphigoid, epidermolysis bullosa acquisita, linear Ig A disease, dermatitis herpetiformis, and chronic ulcerative stomatitis, rheumatoid arthritis, dermatomyositis, and polymyositis.[9]

1. Systemic Lupus Erythematosus

Lupus erythematosus is a chronic multi-system collagen vascular disease affecting the body's connective tissue and blood vessels. The word 'lupus' is derived from the Latin word 'wolf'. The disease is named so because the malar rash on the face resembles the pattern of markings of a wolf. Females are more susceptible than males. The global prevalence of SLE ranges between 12 and 50 per 100,000 varying between location and ethnicities.[10] Lupus erythematosus can present clinically as systemic lupus erythematosus (SLE) or Cutaneous lupus erythematosus (CLE). Two common methods of classifying lupus are the American College of Rheumatology and Systemic Lupus International Collaborating Clinics. (Table 2)[11] (Table 3)[12] SLE is primarily a type III hypersensitivity reaction triggered by nuclear and cytoplasmic autoantigens that result from exposure of keratinocytes to ultraviolet light.[13, 14]

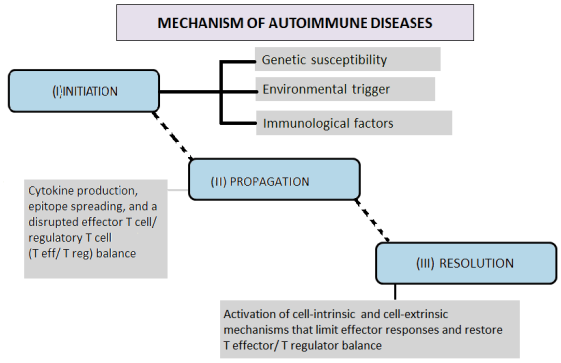

Fig. 1: Mechanism of autoimmune diseases

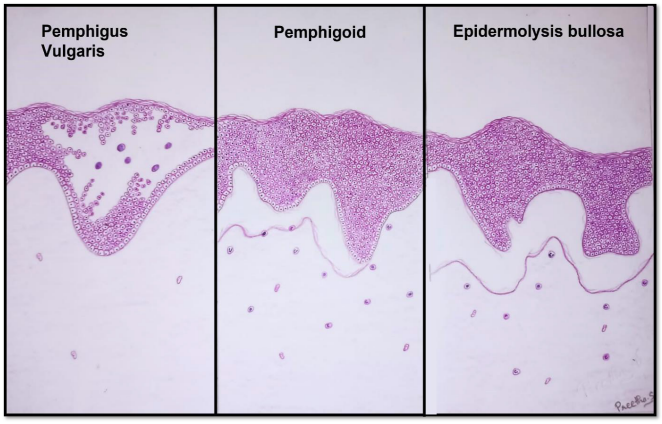

Fig. 2: Histopathological Images of Pemphigus vulgaris, Mucous membrane Pemphigoid, Epidermolysis bullosa. Image courtesy: Dr. S. Preetha

Clinical Features: SLE patients show a wide range of mucocutaneous, renal, neuropsychiatric, cardiovascular infections, and hematological manifestations.[15] The complications of systemic manifestations include cardiovascular problems, renal failure, and stroke. Patients with SLE have antiphospholipid antibody that predisposes them to thromboembolic events such as stroke and myocardial infarction.[16] These patients may also present with photosensitivity, serositis, arthritis, seizures, and psychosis.

Extraoral erythematous patches across the bridge of the nose and malar region of the face appear in a characteristic butterfly pattern.[17] Oral lesions include recurrent infections like pneumonia, urinary tract infections, cellulitis, tuberculosis, mouth ulcers, TMJ disorders, osteonecrosis of the mandible, and dental caries.[18,19] Oral lesions occur in the buccal mucosa, hard palate, gingiva, and lips. They may present as classical plaques with central erythema surrounded by a white rim with radiating keratotic striae, telangiectasia, and varicose or bullous forms.[20] Desquamative gingivitis, marginal gingivitis, or erosive mucosal lesions have been reported. Xerostomia, hematological disturbances, angular cheilitis and oral candidiasis may also be present.[21] Macrocheilia, facial numbness, paresthesia, pain, and salivary gland infection like focal parotid necrosis have been reported.[15,22]

Histopathological features: Hyperkeratosis, thickening of the basement membrane, liquefaction necrosis of the basal cells, and interface mucositis with superficial and deep perivascular lymphocytic inflammation are commonly seen.[23]

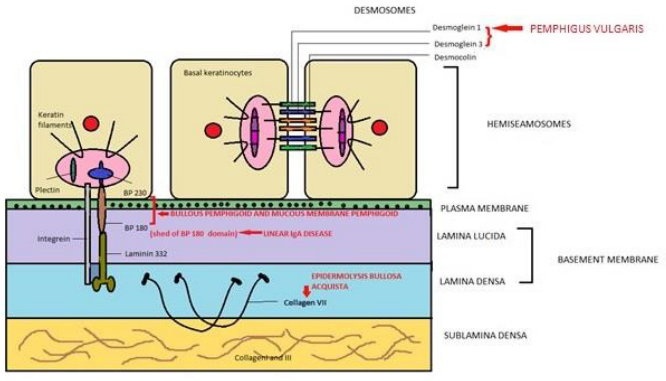

Fig. 3: Components of the basement membrane to which autoantibodies are targeted during an autoimmune attack in vesiculobullous lesions.

Laboratory Tests: Serological levels of Anti-nuclear antibody (ANA), Anti-DNA, Anti-Smith (Anti-Sm), antiphospholipid (APL) antibody are useful indicators of the disease.[23] Their presence is useful in the classification criteria of SLE. In addition, tests are done to evaluate hemolytic anemia and proteinuria.[24,25]

2. Sjögren's Syndrome

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by dysfunction and destruction of exocrine glands. Salivary glands and lacrimal glands are commonly affected. It is characterized by lymphocytic infiltration and immunological hyperactivity.[26] It is named after Dr. Henrik Sjögren, a Swedish Ophthalmologist who first described this condition. Sjögren's syndrome has a predilection to occur in middle-aged women than in men with a female-to-male ratio of 9:1.[27] There are two variants of Sjogren's syndrome: Primary Sjögren's syndrome and secondary Sjögren's syndrome. Primary Sjögren's syndrome is a long-lasting systemic autoimmune disorder characterized by focal lymphocytic infiltration of the salivary glands and lacrimal glands resulting in xerostomia and xerophthalmia respectively. Secondary Sjögren's syndrome is characterized by a triad of keratoconjunctivitis sicca, xerostomia, and other autoimmune systemic disorder like rheumatoid arthritis.[28] The etiopathogenesis of SS is not known but genetic, environmental, immunological, hormonal, and microbial components may act as triggering factors. B cell hyperactivity in SS leads to the accumulation of autoantibodies, hypergammaglobulinemia, and the development of lymphoid foci in inflamed tissues.[29]

Table 1: Classification of Autoimmune diseases
(Modified from Harsh Mohan. Essentials of Pathology for Dental Students. 5TH Edition. Jaypee Brothers Medical Publishers (P) Ltd. 2017)

TYPE OF AUTOIMMUNE DISEASE	EXAMPLES
Organ non-specific (systemic)	1. Rheumatoid arthritis 2. Systemic lupus erythematosus 3. Scleroderma 4. Inflammatory myopathies (dermatomyositis, polymyositis) 5. Sjogren's syndrome 6. Wegener's granulomatosis
Organ specific (Localized) 1. Haematologic diseases	1. Idiopathic thrombocytopenic purpura 2. Autoimmune hemolytic anemia 3. Pernicious anemia
2. Alimentary tract	1. Crohn's disease 2. Ulcerative colitis 3. Autoimmune atrophic gastritis in pernicious anemia
3. Endocrine glands	1. Grave's disease 2. Type 1 diabetes mellitus 3. Addison's disease 4. Hashimoto's thyroiditis
4. Others	1. Myasthenia gravis 2. Autoimmune orchitis 3. Autoimmune encephalomyelitis 4. Autoimmune skin disease • Pemphigus • Pemphigoid • Behcet's disease • Lichen planus • Chronic ulcerative stomatitis • Linear Ig A disease • Epidermolysis bullosa acquisita • Dermatitis herpetiformis 5. Lupoid hepatitis

Clinical Features: Skin, nasal and vaginal mucosae are dry due to the autoimmune destruction of the mucosal acini. Patients with SS have an increased risk of developing non-Hodgkin's lymphoma.[30] In the oral cavity, SS presents as dysgeusia, stomatopyrosis, and tingling sensation, especially on the tongue. In 80% of cases, kerato-conjunctivitis sicca is the first sign followed by xerostomia. Lack of saliva leads to caries and plaque accumulation. The teeth and gums should be protected from collateral damage as a result of xerostomia.[14] Oral mucosa may exhibit erosive lesions with pale, corrugated buccal mucosa and angular cheilitis.[15] About 25-66% of patients with SS have enlarged parotid or submandibular glands.[31]

Histopathological Features: The histopathology reveals hypertrophic glands with the replacement of gland tissue by the lymphocytes and presence of epimyoepithelial islands.[32]

Laboratory test: Serological tests for anti-IgG antibodies SS-A, SS-B, Salivary flow estimation, and biopsy of minor salivary gland are the definite tests for SS.[31]

3. Pemphigus

In Pemphigus, autoantibodies target the desmosomes. Desmosomes maintain cell-to-cell junction. Pemphigus clinically presents as blisters that evolve into painful erosions of skin and mucous membrane.[33] The term 'Pemphigus' is derived from the Greek word 'pemphig' or 'pemphix' meaning 'pustule'. Pemphigus has a global incidence of 0.1-3.2/per 100000 population.[34] Pemphigus can be broadly classified as (i) Pemphigus vulgaris and its variant pemphigus vegetans (ii) Paraneoplastic pemphigus (iii) Pemphigus foliaceus.[35]

3a. Pemphigus vulgaris

Pemphigus vulgaris (PV) causes superficial blisters and erosions that can occur at any oral site, the palate, tongue, and oral mucosa are often involved.[36] It is caused by the autoantibodies directed against the desmosomes (desmogleins 1 and 3). 37 (Figure 3)

Clinical Features: Skin lesions are found in the trunk, groin, and in pressure points where flaccid blisters develop and eventually rupture causing painful erosions.[14] Mucosal lesions are usually located in the oral and pharyngeal mucosa, conjunctiva, larynx, nasal mucosa, and vagina.[38] Blisters rupture causing chronic painful ulcers that bleed.[39]

Histopathological Features: Acantholytic cells - Tzanck cells, intraepithelial cleft, and tombstone appearance of the basement membrane.[40, 41] (Figure 2)

Table 2: European League Against Rheumatism/ American College of Rheumatology Systemic Lupus Erythematosus Classification Criteria. (EULAR/ACR -2019 Criteria) [11]

Entry criterion

Antinuclear antibodies (ANA) at a titre of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE

If present, apply additive criteria

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and 10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score.§

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria>0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 or low C4	3
Low C3 and low C4	4
SLE- specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

TOTAL SCORE

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

§ = additional criteria within the same domain will not be counted; * = in an assay with 90% specificity against relevant disease controls. Anti-β2 GPI = anti–β2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA

Laboratory Test: Direct Immunofluorescence demonstrates intercellular IgG and C3 deposition in a netlike or lattice-like pattern within the stratified squamous epithelium. ELISA detects circulating IgG autoantibodies in patients' serum.[17] Clinically, Nikolsky's sign is positive.

3b. Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) presents as painful, florid oral mucosal erosions and ulcers and occurs as a result of a combined humoral autoimmune response and cellular immune response.[42,43,44]

Clinical Features: It is usually associated with hematological malignant tumors such as lymphomas, leukemia, and malignant melanoma.[23] Extraoral lesions involve the conjunctiva, genitals, pharynx, and esophagus.[43,45] The bronchial mucosa sloughs and occludes bronchial lumina and alveoli causing bronchiolitis obliterans. Oral lesions include hemorrhagic erosions typically affecting the lateral part of the tongue and lip vermillion border.[29, 44]

Histopathological Features: Intraepithelial and subepithelial clefting were associated with suprabasal acantholysis.[42]

Laboratory Test: Direct Immunofluorescence shows deposition of IgG and/or C3 at the intercellular epithelial cell surface alone or in combination with a granular-linear deposition of IgG or complement at the basement membrane zone. Indirect Immunofluorescence detects circulating IgG antibodies against intercellular surfaces.[17] Clinically, Nikolsky's sign is positive.

4. Pemphigoid

The basement membrane consists of various components like laminin, integrin, plectin, and collagen fibers. The collagen XVII fibers along with the other components are involved in stabilizing the basement membrane to the underlying connective tissue matrix. Pemphigoid is a chronic, subepithelial blistering disorder characterized by autoantibodies against the structural components of the surface epithelial junction.[23] Pemphigoid encompasses mucous membrane pemphigoid and bullous pemphigoid.

Table 3: Systemic Lupus International Collaborating Criteria for classification of Systemic lupus erythematosus (SLICC)[12]

CLINICAL CRITERIA	IMMUNOLOGICAL CRITERIA
1. Acute cutaneous lupus	1. ANA above laboratory reference range
2. Chronic cutaneous lupus	2. Anti-dsDNA above laboratory reference range
3. Oral ulcers: palate	3. Anti-Sm
4. Nonscarring alopecia	4. Antiphospholipid antibody
5. Synovitis in 2 or more joints	5. Low complement (C3, C4)
6. Serositis	6. Direct Coombs tests positivity without hemolytic anemia
7. Renal (Urine protein/ creatinine or RBC casts)	REQUIREMENT: Must have 4 or more criteria (at least 1 clinical and 1 laboratory) or biopsy proven Lupus nephritis with positive ANA or Anti-dsDNA
8. Neurologic (seizures, psychosis others)	
9. Hemolytic anemia	
10. Leukopenia (< 4000/ mm^3 at least once)	

4a. Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a heterogeneous group of systemic, autoimmune inflammatory diseases that affects the stratified squamous epithelium of mucosa and skin.[46] It most frequently (85%) involves the oral mucosa of the patients.[47] It is predominantly seen in females.[48, 49, 50] The blisters result from Ig G auto-antibodies directed against collagen XVII and dystonin leading to the destruction of hemidesmosomes responsible for the attachment of the epidermis and epithelium to basement membranes.[46,51] (Figure 3)

Clinical Features: There is pain and dysphagia associated with rupture of bullae.[23] It affects the oral, conjunctival, vaginal, and laryngeal mucosae. Oral lesions involve the gingiva, buccal mucosa, palate, lip, alveolar ridge, and tongue and present as erythema, erosions covered with pseudo-membrane, ulcers, and intact vesicles or bullae.[47] Gingival lesions appear as desquamative gingivitis. Lesions in the oral cavity usually heal in 7 to 10 days and seldom scar.[52] Ocular lesions if untreated can lead to blindness due to keratinization.

Histopathological features: Sub-epithelial clefting with hyperplastic or atrophic epithelium with diffuse, dense, chronic inflammatory cell infiltrate in lamina propria.[39]

Laboratory Test: Direct Immunofluorescence shows continuous, linear deposition of IgG and/or C3, and sometimes IgA along the basement membrane zone. Indirect immunofluorescence detects circulating autoantibodies in the patient's serum.[47]

4b. Bullous pemphigoid

Bullous pemphigoid, a chronic subepidermal blistering disease that mainly affects the elderly. It is characterized by autoantibodies (Ig G/ Ig E) that target collagen alpha 1 (XVII) chain (previously known as BP180 or BPAG2) and dystonin (previously known as BP230 or BPAG1) (Figure 3). The degradation of the collagen alpha 1 chain and activation of the complement cascades causes the blister.[53]

Clinical Features: The disease is acute with lesions occurring predominantly in lip commissures, oral mucosa, pinna, axillae, inguinal areas, and foot.[54] It is characterized by large, tense bullae that may begin as erythematous macule, or plaques.[55]

Histopathological Features: On examination, there is a detachment of basal keratinocytes from the dermis and subepithelial cleavage with leucocytic infiltrate.[39] (Figure 2)

Laboratory Tests: Direct immunofluorescence reveals linear deposits of IgG or C3 at the dermal–epidermal junction. ELISA shows circulating autoantibodies specific to collagen XVII/ BP180, BP230/dystonin, laminin 332.[53] Clinically, Nikolsky's sign is positive.

5. Epidermolysis Bullosa Acquisita (EBA)

EBA is an acquired, chronic, bullous mucocutaneous condition. The autoantibodies, mainly IgG are directed against type VII collagen in the basement membrane.[23,29,56] (Figure 3)

Clinical Features: Lesions appear in sites of trauma like

Table 4: Summary of Autoimmune Diseases affecting the orofacial region.

LESION	PATHOGENESIS	ORGANS AFFECTED	MAJOR CLINICAL PRESENTATION IN ORAL CAVITY	LABORATORY DIAGNOSIS	TREATMENT
SYSTEMIC LUPUS ERYTHEMATOSUS	A type III hypersensitivity reaction triggered by endogenous autoantigens.[13,14]	Skin Mucous membrane Kidney Heart Brain[15,16]	Mouth ulcers, Desquamative gingivitis, honeycomb-like plaques, xerostomia, angular cheilitis, focal parotid necrosis.[19,20,21]	Elevated levels of ANA, Anti- DNA, Anti-Smith, and APL antibody in patient's serum. [23]	Prophylactic medication to prevent cardiac damage includes anti-coagulant therapy and antibiotic prophylaxis. [78] Systemic corticosteroids -Prednisolone Hydroxychloroquine Immunosuppressants-azathioprine and cyclophosphamide.[21]
SJÖGREN'S SYNDROME	B cell hyperactivity. The genetic, environmental, immunological, hormonal, and microbial components act as triggering factors.[29]	Skin Mucous membrane Eyes. [30]	Kerato-conjunctivitis sicca, xerostomia, angular cheilitis, enlargement of parotid and submandibular glands. [14,15,31]	Salivary flow estimation, Biopsy of minor salivary glands, test for Anti-Ig G, SS-A, SS-B in patient's serum.[11]	Systemic corticosteroids. Anti-inflammatory drugs Cyclophosphamide. Saliva stimulating drugs (pilocarpine/ cevimeline).[79] Saliva replacement with sugar-free chewing gums, and candies. Fluoride toothpaste
PEMPHIGUS VULGARIS	Autoantibodies are directed against desmogleins 1 and desmogleins 3.[37]	Skin Mucous membrane Eyes[38]	Blisters, painful ulcers.[39]	DIF demonstrates intercellular IgG and C3 deposition in a netlike or lattice-like pattern within the stratified squamous epithelium. ELISA detects circulating IgG autoantibodies in patient serum.[37] Clinically, Nikolsky's sign is positive.	High-dose corticosteroids Immunosuppressants like cyclosporin, and azathioprine. Intravenous immunoglobulin[80] Early lesions in the oral cavity are treated by periodontal therapy. Proper oral hygiene maintenance. [81]
PARANEOPLASTIC PEMPHIGUS	Develop due to combined humoral autoimmune response and cellular immune response.[43,44]	Skin Mucous membrane Hematological tumors.[13,43,45]	Hemorrhagic erosions at the lateral part of tongue and vermillion border.[29,44]	DIF shows deposition of IgG and/or C3 at the intercellular epithelial cell surface alone or in combination with a granular-linear deposition of IgG or complement at the basement membrane zone. IIF detects circulating IgG antibodies against intercellular surfaces.[37] Clinically, Nikolsky's sign is positive.	

MUCOUS MEMBRANE PEMPHIGOID	IgG autoantibodies are directed against collagen XVII and dystonin.[46,51]	Skin Mucous membrane Eyes	Erythema, erosions, ulcers, desquamative gingivitis.	DIF shows continuous, linear deposition of IgG and/or C3, and sometimes IgA along the basement membrane zone. IIF detects circulating autoantibodies in patient's serum. [47]	Systemic corticosteroids Immunosuppressants like cyclosporin, and azathioprine. Antibiotics like tetracycline, erythromycin and niacinamide. Oral lesions treated with topical corticosteroids. [68]
BULLOUS PEMPHIGOID	Autoantibodies (Ig G/ Ig E) are targeted against BP180 and BP230.[53]	Skin Mucous membrane.[54]	Ulcers, erythematous macules, or plaques.[55]	DIF reveals linear deposits of IgG or C3 at the dermal-epidermal junction. ELISA shows circulating autoantibodies specific to collagen XVII/ BP180, BP230/ dystonin, and laminin 332.[39] Clinically, Nikolsky's sign is positive.	
EPIDERMOLYSIS BULLOSA ACQUISTA	Autoantibodies directed against type VII collagen.[5,29,56]	Skin Mucous membrane [29,57]	Blisters, erosion, tooth loss, mandibular contraction with limited extent.[29]	DIF shows linear deposition of Ig G antibodies. IIF detects circulatory autoantibodies.[23]	Topical and systemic corticosteroids with immunosuppressants like rituximab or cyclophosphamide.
LINEAR IgA DISEASE	An autoimmune blistering disease characterized by linear deposition of IgA at the basement membrane	Skin Mucous membrane[59,60]	Multiple painful ulcers, erosive cheilitis, desquamative gingivitis.[59,60]	DIF shows linear deposition of IgG antibodies.[23]	Systemic corticosteroids Intravenous immunoglobulin. Oral glucocorticoids with dapsone are used to treat oral lesions. [15]
DERMATITIS HERPETIFORMIS	Inflammatory cascade following exposure to gluten results in IgA autoantibodies directed against epidermal transglutaminase.[61]	Skin Scalp Mucous membrane[23]	Lesions occur in areas of trauma.[23]	DIF shows granular deposits of IgA along the dermo-epidermal junction. IIF detects IgA autoantibodies. [23]	Gluten-free diet. Topical corticosteroids. Oral antibiotics.

elbow, knees, and dorsal surface of hands and feet and heal with scarring.[57] Oral lesions may include blisters, erosions, tooth loss, and mandibular contraction to a limited extent.[29]

Histopathological Features: Subepidermal blisters with chronic inflammatory cell infiltrate are present.[23] (Figure 2)

Laboratory Tests: Direct immunofluorescence shows linear deposition of Ig G antibodies in the basement membrane zone. Indirect Immunofluorescence is done to detect circulatory autoantibodies.[23] Different ELISA systems are developed for the detection of circulating anti-collagen VII IgG antibodies.[58]

6. Linear Ig A disease

Linear Ig A disease is an autoimmune blistering disease characterized by linear deposition of Ig A at the basement membrane zone. (Figure 3)

Clinical Features: Lesions involve the skin and mucous membrane. Oral mucosal lesions appear as multiple, painful blisters that rupture to form ulcers. Erosive cheilitis and desquamative gingivitis are seen.[59,60]

Histopathological Features: Subepithelial cleft with inflammatory cell infiltrate comprising predominantly neutrophils is seen.[23]

Laboratory Tests: Direct immunofluorescence shows linear Ig A deposition in the dermo-epidermal junction. Indirect immunofluorescence binding of IgA autoantibodies to the

CHRONIC ULCERATIVE STOMATITIS	Autoantibodies against 70-kD, a nuclear protein are developed which interrupts the normal maintenance of epithelium.	Skin Mucous membrane.[23]	Gingival soreness, desquamative gingivitis. [23]	DIF shows granular deposition of Ig G in the nuclei of keratinocytes. IIF detects circulating autoantibodies.[23]	Topical and systemic corticosteroids. Hydroxychloroquine.
RHEUMATOID ARTHRITIS	Interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) have been implicated in RA pathogenesis.[65,66]	Joints[67]	TMJ involvement causes limited mouth opening, malocclusion, inflammation of the pre-auricular region, and intercapsular crepitus. Synovitis[50,63]	DIF detects rheumatoid factors. Blood investigation.[67]	Systemic corticosteroids Immunosuppressants. TMJ disorders are treated medically using analgesics, NSAIDs, and antirheumatic drugs. [68] Surgically it can be corrected by prosthetic joints. Prophylactic antibiotic therapy.[15]
SCLERODERMA	Excessive collagen deposition, vascular abnormalities, and fibrotic degenerative changes.[69]	Skin Muscles Internal organs.[68]	Firm pale gingiva, stiff tongue, dysphagia, microstomia, xerostomia, periodontal diseases.[72]	Elevated levels of antinuclear antibodies antitopoisomerase I (Scl70), anticentromere, anti-RNA polymerase III, anti-U3-fibrillarin, anti-endothelial cell, anti-fibroblast, antimatrix metallo proteinase in patient's serum. [68,69]	Skin lesions are treated by D-penicillamine, interferon-gamma and cyclophosphamide.[82] Mouth stretching exercises may help with reduced mouth opening
POLYMYOSITIS AND DERMATOMYOSITIS	PM is an idiopathic, autoimmune disease and DM is systemic complement-mediated microvasculopathy.[74,75]	Muscles Mucous membrane[68,71]	Macroglossia, xerostomia with ulceration, and atrophy of the tongue. Squamous cell carcinoma of the tongue. Prominent blood vessels, and gingival telangiectasia. Dysphonia, dysphagia, with aspiration, and hypersalivation.[72,76]	Elevated levels of creatinine kinase and autoantibodies, Muscle biopsy, antibody profile. [52] Anti-nuclear antibodies, Muscle-specific antibodies (MSAs) including anti-signal recognition particle (anti-SRP) and anti-Jo-1 help confirm the diagnosis. Biopsy changes of muscle fiber necrosis and endomysial fibrosis with inflammatory infiltrate visible. [75]	High dose corticosteroids Immunosuppressants-methotrexate, azathioprine, cyclophosphamide Intravenous immunoglobulin

epidermal side of salt-split skin.[23]

7. Dermatitis herpetiformis

Dermatitis herpetiformis is an AD that arises as a papulovesicular lesion on the elbow, knees, back, scalp, and buttocks. Lesions look similar to those caused by Herpes hence the name Herpetiformis. It is characterized by an inflammatory cascade that follows exposure to gluten which results in Ig A autoantibodies directed against epidermal transglutaminase.[61]

Clinical Features: It presents an itching and burning blister

of the skin. Oral lesions are rare and occur in areas of trauma.[23]

Histopathological features: Inflammatory cell infiltrate seen at the dermo-epidermal junction in the upper dermis predominantly of neutrophils and eosinophils.[23] The blister formation is due to the granulocytes that form typical papillary micro abscesses.[62]

Laboratory Tests: Direct Immunofluorescence shows granular deposits of Ig A along the dermo-epidermal junction. Indirect Immunofluorescence detects IgA autoantibodies against endomysium, which recognize the epidermal transglutaminase (TG3) and tissue transglutaminase (TG2).[63]

8. Chronic ulcerative stomatitis

Chronic ulcerative stomatitis is a rare mucocutaneous disorder that presents with painful, vesicular, and ulcerative lesions. It is characterized by autoantibodies against a 70-kD nuclear protein which interrupts the normal maintenance of epithelium.

Clinical Features: It affects the tongue, buccal mucosa, and gingiva. Gingival soreness and desquamative gingivitis are seen. The ulcers present as patchy zones of erythema and streaky keratosis.[23]

Histopathological features: Atrophic mucosal epithelium with saw-toothed rete ridges, leukocytic exocytosis, and a dense band of mixed inflammatory cell infiltrate are seen.[64]

Laboratory Tests: Direct Immunofluorescence reveals a speckled, fine granular deposition of Ig G in the nuclei of keratinocytes. Indirect Immunofluorescence is done to detect circulating autoantibodies.[23]

9. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease affecting the synovial membrane of diarthrodial joints.[15] The pathogenesis most likely involves genetic and environmental factors. An infectious trigger in which there is an exposure to the periodontal microbe Porphyromonas gingivalis has been hypothesized in RA.[2] Inflammatory mediators such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) have been implicated in RA pathogenesis.[65, 66]

Clinical Features: It begins with fatigue, anorexia, and generalized weakness followed by synovitis in joints, hands, wrists, knees, and feet.[67] Temporomandibular joint involvement is seen rarely in RA. There is malocclusion, limited mouth opening, joint stiffness, inflammation of the pre-auricular region, and intracapsular crepitus.[52] RA is a progressive disease that causes severe pain and joint damage.[2]

Histopathological Features: Hyperplasia of synovial lining cells, chronic infiltration by macrophages and lymphocytes.[68]

Laboratory Tests: Direct Immunofluorescence detects rheumatoid factors at the early stage or during the course of the disease. Blood investigation reveals normochromic, normocytic anemia, and increased ESR rate.[67]

10. Scleroderma

Collagen is a widely distributed protein found in the body that provides strength and support to the tissues. Scleroderma is an autoimmune connective tissue disease associated with excessive collagen deposition, vascular abnormalities and fibrotic degenerative changes in the muscles, joints and other internal organs.[69] It causes skin induration and thickening. The Greek word 'scleros' means 'hard' and 'derma' means 'skin'. Orofacial involvement is reported in 80% of the patients.[70] Scleroderma is a multilateral disease caused by immunological abnormalities with specific chronic inflammatory immune cells and fibroblast dysfunction leading to fibrosis of the skin and internal organs.[68] Oral submucous fibrosis was previously described as Idiopathic scleroderma of the mouth.[71]

Clinical Features: One of the first signs is the Raynaud phenomenon, a vasoconstrictive event triggered by emotional distress or exposure to cold. Oral manifestations include firm and pale gingiva, stiff tongue, dysphagia, and microstomia (purse-string appearance).[72] Xerostomia, dental caries, and periodontal disease are also seen.

Histopathological features: Microscopic examination reveals dense collagen deposition in the involved tissues. Complications include loss of normal tissue function and fibrosis of internal organs.[73]

Laboratory Tests: Serological tests reveal autoantibodies like antinuclear antibodies, antitopoisomerase I (Scl70), anticentromere, anti-RNA polymerase III, anti-U3-fibrillarin, anti-endothelial cell, anti-fibroblast, anti-matrix metalloproteinase.[68,69]

11. Polymyositis and Dermatomyositis

Polymyositis (PM) is an idiopathic, systemic autoimmune multifactorial disease of the connective tissue.74,75 Dermatomyositis (DM) is a systemic complement-mediated microvasculopathy.[75]

Clinical Features: Both PM and DM cause impairment of the pharyngo-laryngeal muscles resulting in dysphonia and dysphagia, with aspiration and hypersalivation.[76] Clinically, there is macroglossia, xerostomia with ulceration and atrophy of the tongue, and rarely squamous cell carcinoma of the tongue.[72,76] Oral lesions include ulcers, edema, erythema, prominent blood vessels, and gingival telangiectasia.

Histopathological features: In Polymyositis chronic mononuclear inflammatory infiltrate in the muscle fibers is seen on histopathological examination. An increase in perimysial and endomysial connective tissue, increased variation in fiber diameter, and scattered necrotic and regenerative muscle fibers are seen.[77] Dermatomyositis presents with mild perivascular chronic inflammatory infiltrate.[75]

Laboratory Tests: Serological tests detect increased levels of muscle enzymes, especially creatinine kinase and autoantibodies. Muscle biopsy and antibody profile are also undertaken.[52] Anti-nuclear antibodies, Muscle-specific antibodies (MSAs) including anti-signal recognition particle (anti-SRP) and anti-Jo-1 help confirm the diagnosis. Biopsy changes of muscle fiber necrosis and endomysial fibrosis with inflammatory infiltrate visible.[75]

Conclusion

Oral lesions can be the earliest signs of autoimmune diseases. In some cases, the oral cavity may be the only place where the signs and symptoms become evident. Early and accurate diagnosis is important for the management and treatment of the disease. Therefore, a comprehensive understanding is essential for the dentist and health care professionals for early diagnosis and appropriate management of autoimmune diseases.

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