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Review Article

Immune mediated Lesions of the oral cavity: A scrupulously researched review

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ABSTRACT

Oral mucosa may be the first site to manifest protean signs and symptoms in immune mediated diseases. Therefore, it is of paramount importance to have a thorough and vast knowledge about various diseases. It is the role of Oral and Maxillofacial Diagnostician to diagnose the lesions according to their salient features. In this review article, we aim to describe the immune mediated oral lesions, their clinical features, investigations and management.

1. Introduction

Immunology is the study of the molecular cells, organs and system for the identification and removal of foreign materials. Immunological response is variable and can be due to difference in age, nutrition and genetic factors. The confirmation of the lesion can be done by performing a biopsy. [1,2]

2. Classification of Immune Mediated and Autoimmune Diseases

The oral immune mediated and autoimmune lesions can be classified as follows; [3]

1. Hypersensitive reaction
2. Pemphigus vulgaris
3. Cicatricial or mucocutaneous pemphigoid
4. Cutaneous, bullous pemphigoid
5. Linear IgA Disease
6. Epidermolysis bullosa Acquisita
7. Erythema multiforme
8. Systemic Lupus erythematosus
9. Scleroderma
10. Bechets syndrome
11. Sjogren's Syndrome
12. Lichen planus

3. Hypersensitive Reaction

The surface of oral mucosa is continuously exposed to many infectious agents, however the immune system does not react to it. This unresponsiveness / tolerance is due to energy or functional unresponsiveness, apoptosis, and the suppression of immune system by regulatory T-Cells. The most serious, life threatening hypersensitive reaction that initiates immediately after exposure to the allergen is known as Anaphylaxis. It presents as swelling of the lips, tongue, cheek or ulcerations and formation of blisters or erythema on the oral mucosa. [4,5]

Treatment: It is primarily treated by intramuscular application of a dose of 0.3 to 0.5 mg adrenaline (body weight range 30 to 50 kg) at the outer upper thigh. In an unstable patient, i.e. in case of respiratory and/or circulatory arrest, intravenous administration of

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adrenaline should be given. Other management modalities include administration of Dopamine, Noradrenaline and vasopressin. H1 antihistaminics like dimetindene (0.1 mg/kg bw) and clemastine (0.05 mg/ kg bw) and glucocorticoids are also used in the management of anaphylaxis.[6–10]

4. Pemphigus Vulgaris

Pemphigus vulgaris is an immune mediated disorder affecting the skin ad mucosa.

Etiopathogenesis: Etiology is multifactorial and can be associated with stress, genetic susceptibility, hormones or drug induced. Presence of immunoglobulin G antibody against desmosomal components like desmoglein -1 & desmoglein -1 is seen in patients with pemphigus leading to alteration in adhesion of the cell molecules causing intraepithelial blisters.[11,12] The disease predominantly involves females and in the 4^{th} to 5^{th} decade of life.[11,13,14]

Clinical features: Oral mucosal lesions precede the cutaneous lesions. The buccal mucosa is is most commonly involved followed by soft palate, lower lip, tongue and gingva. It appears as superficial vesicles or blisters which break rapidly due to masticatory forced leading to erosion of the oral mucosa causing burning sensation. Nikolsky phenomenon is positive which is detachment of large area of the surface with the formation of blisters by exerting a slight pressure on the epithelium.[14]

Diagnosis: Pemphigus can be easily confused with aphthae, lichen planus, candidiasis and pemphigoid. Hence, it is mandatory to perform an indirect immunoflourescence in which the antibodies are detected in patient's serum and is seen as 'Chicken wire' pattern. Direct immunoflourescence helps in detecting intercellular deposits of IgGMA and C3 protein. Laboratory methods for diagnosis include tzanck smear to detect acantholytic cells.[15,16]

Treatment: Pemphigus is managed by local and systemic corticosteroids. The treatment is aimed in two phases: loading phase to control the disease and a maintenance phase. The treatment is initially started with application of paste, ointment or a mouthwash either alone or in conjunction with systemic treatment. In severe and extensive cases, systemic corticosteroids are the first line of treatment starting with 0.5-2mg/kg of prednisone. Depending upon the response, the dose is altered to a minimum therapeutic dose to avoid side effects.[17,18]To avoid long term complications of steroids, immunomodulatory drugs like azathioprine, cyclophosphamide, cyclosporine, methotrexate can be added in the treatment regimen. The response to Rituximab 1gm I.V at two week interval has shown promising results.[19,20]Titration of the circulating antibodies should be done to evaluate the response to treatment and progression of disease.[21]

5. Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is an immune mediated blistering disease.

The oral mucosa is involved along with genitals, eyes and skin. The disease shows autoantibodies mostly IgA and IgG along with C3 Complement C3 against mucosae and epithelial basal membranes.[11,12]

Oral Findings: Gingiva is most commonly affected giving rise to a clinical condition of Desquamative Gingivitis. However, it is not diagnostic. The oral mucosa shows erythema or true ulcerations involving the attached gingival. Erythematous lesions are also seen on palate, buccal mucosae, lips, tongue and pharynx.[11] Patient may experience burning and inability to chew and eat food. The bullae in pemphigoid are less brittle therefore they may remain in the oral cavity for more than 48 hours.[22,23]

Diagnosis: The diagnosis is based on clinical and histological samples. The histologic examination reveals detachment of the epithelium from the underlying connective tissue. Immunoflourscence can be used to distinguish between lichen planus, pempphigus, periodontal diseases and SLE. It reveals intense inflammatory infiltration of plasma cells and eosinophils in connective tissue.[11]

Treatment: The treatment of the disease depends on the area of involvement. In minor or less extensive lesions, topical corticosteroids gel application can be advised. Along with corticosteroids, dapsone can be given. In severe cases, pulse therapy can also given. It is important to monitor and follow up the patient on a regular basis to assess the presence of eye lesions to prevent the ocular damage.[11,23]

5.1. Linear IgA Disease

Linear IgA Disease is a mucocutaneous autoimmune disease that shows linear deposition of IgA and disruption of the dermoepidermal junction causing tense blisters.[24] The disease shows a bimodal occurrence, first occurring within the first 10 years and adult occurrence between 60 & 65 years.[25]

It could be idiopathic or drug induced. Drugs involved are antibiotics, antihypertensives, and nonsteroidal anti-inflammatory agents. Most commonly involved is Vancomycin.[26]In addition, associations with lymphoproliferative disorders, infections, ulcerative colitis,and systemic lupus erythematosishave been reported.[27–33]

Diagnosis: The disease can be confirmed with clinical, histopathological and immunological data. Direct immunofluorescence demonstrate the presence of IgA deposits along the basement membrane zone in a linear pattern.[34]

Treatment: Management varies with the degree of involvement and identification of inciting factors. The

mainstay treatment modality is to remove the offending drug agent, which alone can help in gradual resolution of the skin lesions.[35] The drug therapy include dapsone which is the first line of treatment with the dose of 50-150mg/d in adults. It shows resolution of symptoms within 72 hours. Dapsone is given after assessment of Glucose-6-phosphate dehydrogenase as deficit patients carry a risk of developing haemolytic anaemia. Therefore, a complete blood cunt with differential and liver function tests should be obtained before the initiation of therapy.[36] Other treatment options are less substantiated and include sulfonamides, prednisone, colchicine,tetracyclines and nicotinamide.[37–40] Systemic therapy is required until patients show clinical remission with gradual tapering toward treatment cessation.

6. Epidermolysis Bullosa Acquisita

It is an acquired, autoimmune, cutaneous subepidermal blistering disease that primarily involves the skin and sometimes mucous membranes. The disease exhibits no racial or gender predilection and often presents in the fourth to fifth decades of life.[41]

Clinical findings: It is characterized by formation of blisters following mild mechanical trauma. It can also present systemic complications such as ocular, genital and oropharyngeal infections, involving difficulty in swallowing.[26,42]

Diagnosis: The hallmark of the disease shows presence of autoantibodies (mainly IgG class) to type VII collagen, a major component of anchoring fibrils at the dermal-epidermal junction. The disease occurs in approximately 5% of unselected patients with basement membrane zone antibodies.[41]

Treatment: Children respond to high dose of corticosteroids and steroid sparing drugs. The cutaneous lesions respond to dapsone alone.[43]

7. Erythema Multiforme

This is a self limiting disease characterized by target lesions on the mucous membrane and skin.[44]

Etiology: It is an immune mediated disorder presenting hypersensitive reactions to viral and fungal infections and medication such as NSAIDS's, penicillins, alopurinol, barbiturates, chemotherapeutic agents, carbamazepines and cephalosporins.[45]

Oral findings: It manifests as multiple irregular ulcers or vesicles are surrounded by erythematous margin and covered with white or yellow exudates. They usually affect the lingual, buccal, and/or labial mucosa, and less frequently the floor of the mouth, palate and the gingivae. Patients may complain of trismus, dysphonia, dysarthria, and/or dysphagia. Painful crusting ulcerations are seen on the lips.[44,46] Severe forms of EM are Stven Johnson Syndrome, Toxic Epidermal Necrolysis (TEN) that shows extensive mucosal involvement.

Histopathological section shows intercellular edema of superficial connective tissue with subepidermal vesicle. Liquefaction degeneration with superficial epithelium or corneal areas. Basal cell degeneration is seen.

Diagnosis: Blood investigation show raised ESR, decrease CD4+ cells.[47]

Treatment: The treatment is aimed at treating the underlying cause. In case of lesions due to HSV infection, antiviral agents may be indicated in herpes associated EM, and a 5 day course of acyclovir 200 mg five times daily at the first sign of lesions, or 400 mg four times daily for 6 months, or continuous treatment using valacyclovir, 500 mg twice a day, is useful for prophylaxis. Tetracycline 250 mg four times a day for at least 1 week may be indicated in EM related to Mycoplasma pneumoniae.

Mouthwashes containing local anesthetic and mild antiseptic compounds may help in relieving painful oral symptoms. Patients with severe EM should be treated with systemic corticosteroids (prednisolone 0.5–1.0 mg/kg/day tapered over 7–10 days) or azathioprine, or both or other immunomodulatory drugs such as cyclophosphamide, dapsone, cyclosporine, levamisole, thalidomide or interferon-α.[48,49]

8. Systemic Lupus Erythematosus

Systemic lupus erythematosus is a severe autoimmune inflammatory disease with various clinical presentations affecting predominantly females.[50]

Etiopathogenesis: The disease involves cell mediated immunity followed by humoral immunity leading to deposition of immune complex triggering an inflammatory reaction causing functional impairment of the organs.[11,51]

Clinical Features: It may appear as erythema on the sun exposed areas. A characteristic Butterfly or Malar rash is located on the nose and cheek is seen. Healing is seen as a central scar. Multiple organs are involved leading to arthralgia and arthritis of the joints, eyes show retinal damage due to vasculitis leading to retinal nerve damage. Renal involvement leads to kidney damage thereby compromising patient's health.[52,53]

Oral Findings: Oral lesions show a central erythema with a border forming radiating white striae and peripheral telangiectasia appearing as discoid lesions. It may also appear as desquamative gingivitis, marginal gingivitis or erosive mucosal lesions.[54,55]

Diagnosis: Serum can be used to assess the presence of Anti nuclear Antibodies (ANA's). Blood stream shows LE Cells. These are mature neutrophils with spherical inclusions. It has to be differentiated with erythema multiforme, lichen planus, vesiculobullous lesions, traumatic or smoker's keratosis, verrucous carcinoma, lichenoid reactions to restorations.

This can be distinguished through histological and immunohistochemical confirmation as a standard criteria for a definitive diagnosis.[55,56]

Treatment: Salicyclates can be advised in mild cases. Drugs like steroids, hydroxychloroquine, steroid sparing drugs like azathioprine and cyclosporine can be used to maintain the states of remission and alleviation of symptoms and reversal of inflammation.[57,58]

9. Sjogren's Syndrome

Sjogren's syndrome affects salivary and lacrimal glands leading to lymphocytic infiltration and destruction of the exocrine glands.[11]

Etiology: The disease triggers humoral and cell mediated immunity leading to activation of B cells followed by immune complex formation and autoantibody production. It affects females predominantly (9:1). It has bimodal peak of occurrence, just after the menarche and after the menopause.[10,59–61]

Clinical Features: The manifestations may be only confined to mouth and eyes and it could also be associated autoimmune damage. 50% is associated with rheumatoid arthritis and systemic lupus erythematosus.[10] The involvement of eyes and oral is primary Sjogren's syndrome, the addition of any other autoimmune issues is Secondary Sjogren's Syndrome.

Oral symptoms include dry mouth, lack of saliva leading to development of cavities which can build up plaque accumulation can cause opportunistic infections leading to bacterial and fungal infection like candida. Gingival inflammation and ulcerations are also seen.[10,62,63]

Oral signs include dryness of eyes causing xerophthalmia and keratoconjunctivities leading to ocular infections. Patients also present with Raynaud's phenomenon, a condition causing bluish discoloration of the tips of fingers and toes in cold water due to vasoconstriction.[10]

Diagnosis: The diagnosis is primarily clinical, supported by oral presentation and laboratory investigations. The classification made by Shiboski et al. is most commonly used and is endorsed by the American College of Rheumatology.[64,65] The diagnosis can be confirmed when 2 out of the listed conditions are identified: xerostomia, keratoconjunctivitis sicca and rheumatoid arthritis. Assessment of salivary flow rate and biopsy of the minor salivary glands are basic investigations to confirm the syndrome.[10,66] Ophthalmic evaluation like Rose Bengal test and BUT test are necessary to detect keratoconjunctivitis sicca. Regular follow ups should be made mandatory as patients with Sjogren's syndrome are prone to developing lymphoma and Waldenstrom macroglobulinemia.[10,66] Laboratory findings show 90% positive Rheumatoid Factor, anti-Sjogren A/ Anti-Ro and Anti Sjogren B/ Anti -La.[66]

Treatment: The treatment is aimed at treating clinical signs. Most commonly, corticosteroid and immunosupresive therapy is given for alleviation of symptoms. The salivary substitutes like pilocarpine 5mg three times a day and cevimiline 30mg three times a day, installation of an air humidifier and salivary substitute mouthwashes can be prescribed to stimulate salivary production. Anti fungal medications can be given in case of opportunistic candidal infections. Periodic follow with the dentist is recommended for evaluation of hard and soft tissue changes.[67–69]

10. Behcet's Syndrome

First described by Hulusi Behcet in 1937 as an inflammatory disease of unknown etiology. It is characterized by recurrent aphthae, genital ulcerations, uveitis and cutaneous lesions. It may be associated with less frequent systemic manifestations like gastrointestinal, central nervous system, vascular and joint infections.[10,70]

Etiopathogenesis: Altered immunoregulation causes activation of T lymphocytes and macrophages in association with NK cells which leads to both cellular and humoral immunity leading to Type III hypersensitivity reactions.[71,72]

It usually affects individuals in their 30s and shoes no gender predilection. Topographically, it is commonly seen to affect the Mediterranean and Asian population with marked prevalence in Turkey. The disease shows the presence of autoantibodies in association with HLAB5 and B51.[10,73]

Clinical Features: Oral lesions manifest before involvement of any other organ. The lesions appear as aphthous ulcers in multiple numbers on the soft palate occurring on the soft palate, lips, tongue, gingiva, oral mucosa and oropharynx. The ulcers appear with a necrotic yellowish base with raised edges with surrounding erythema. Ulcers persist for several days and heal without scarring.[74,75]

Genital lesions appear in females mainly and appear on the vulva and vaginal wall. Cutaneous manifestations present as erythematous nodules, papules, vesicles, pustules, folliculitis and are positive in the pathergy test, a non specific hypersensitivity skin reaction induced by needle prick within 1-2 days. The orbital involvement show posterior uveitis, retinal vasculitis, conjunctivitis, optic neuritis and retinal arthritis. Involvement of the articular joints such as knees, ankles, wrists which manifest as inflammatory episodes. The syndrome may involve the CNS leading to convulsions and meningoencephalitis in advanced cases.[73,76–78]

Treatment: The main goal of therapy in patients with BD is to induce and maintain remission and improve patients' quality of life. Selecting treatment is based on the organ involved and the assessment of the severity of the disease.

For oral ulcers, the treatment can be started with topical colchicines and dapsone. If sufficient response

is not observed, oral thalidomide, predisone and methotrexate can be prescribed but the patient should be kept on regular follow up to assess the degree of toxicity. Severe cases can be treated with cyclosprorines, azathioprine, cyclohosphamide and IFN-alpha. The treatment requires a multidisciplinary approach due to systemic involvement.[77,78]

11. Oral Lichen Planus

Lichen planus is a mucocutaneous disease involving the skin and mucous membrane. The cutaneous lesions are self limiting whereas the oral lesions are chronic, exhibits periods of remission and exacerbation is a potentially malignant disorder.[79]

Etiopathogenesis: It is believed that an abnormal T cell mediated immune response against the basal cells of the epithelium that are recognized foreign by the body due to antigenic variation.The antigen binds toCD8+ T cells Via MHC II present on the surface of keratinocytes. Other factors include psychological stress, systemic medications like beta blockers, NSAID's, oral hypoglycemics, genetics, hepatitis C virus and dental amalgam, resinous dental materials, composite restorations that can cause lichenoid reactions.[80–84]

Clinical Features: It is seen predominantly affecting females from 3^{rd} to 7^{th} decade. It mostly involves the buccal mucosa, gingival and tongue. Clinically, 6 types are present: Reticular (fine white striae cross each other in the lesion), atrophic (areas of erythematous lesion surrounded by reticular components), papular type, bullous type, plaque type, erosive or ulcerative type. The reticular type of oral lichen planus is often asymptomatic, only can be seen clinically. Ulcerative type in which erythematous areas are seen surrounded by reticular elements.Grayish white lines can be seen around the surface of the lesion known as Wickham's striae.[85–89]

Oral Findings: It presents as whitish gray radiating lines mostly bilateral presentation. Mostly, 80% buccal mucosa is involved, 65% tongue, 20% lips, <10% floor of the mouth and palate. The reticular form has a better prognosis as 40% of cases has spontaneous remission, the erosive type being long standing and with frequent exacerbations and severe pain and complications.[90,91]

Investigations: Clinical examination with a thorough history, followed by tissue biopsy is routinely sufficient for the diagnosis of oral lichen planus. Histopathological examination from the biopsy of the site of lesion reveals the diagnosis of lichen planus. The direct immunofluorescence of lichen planus shows "Linear pattern" in the basement zone and exhibit positive fluorescence with antifibrinogen. IgA, IgG, complement C3 were seen on colloid bodies. Indirect immunofluorescence aids in the detection of antibodies in the circulating blood of the lichen planus patient. The circulating antibodies that react and bind to the basal cells of the epithelium gives rise to the "annular fluorescence" or the "string of pearls" appearance.[92,93]

Treatment: Different drugs have been used in the form of topical and systemic application for the treatment of OLP. Topical application of corticosteroids, immunosuppressives, retinoids, and immunomodulators are used for management of the localised lesion. In severe cases, systemic administration of metronidazole, griseofulvin, and hydroxychloroquine, some retinoids and corticosteroids is recommended. Holistic treatment modalities like Tulsi, Green tea, Honey, aloe vera have shown remarkable results in the management of OLP.[94–96]

High dysplastic or severe cases can be managed by Surgical excision, cryotherapy, CO_2 laser, and ND:YAG laser.[97]

12. Conclusion

Oral lesions secondary to immune dysregulaton can affect the psychological, economic and the quality of living in the patients. It is of utmost importance to diagnose and treat them to reduce the morbidity of the affected patients.

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14. Conflict of Interest

The authors declare no conflict of interest.

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