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Oral Examination: An Important Adjunct to the Diagnosis of Dermatological Disorders

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Abstract**—**The oral cavity can be the site for early manifestations of mucocutaneous disorders (MD) or the only site for occurrence of these disorders. It can also exhibit oral lesions with simultaneous associated skin lesions. The MD involving the oral mucosa commonly presents with signs such as ulcers, vesicles and bullae. The unique environment of the oral cavity may modify these signs of the disease, thereby making the clinical diagnosis an arduous task. In addition to the unique environment of oral cavity, the overlapping of the signs of various mucocutaneous disorders, also makes the clinical diagnosis more intricate. The aim of this review is to present the oral signs of dermatological disorders having common oral involvement and emphasize their importance in early detection of the systemic disorders. The aim is also to highlight the necessity of oral examination by a dermatologist while examining the skin lesions. Prior to the oral examination, it must be imperative for the dermatologists and the dental clinicians to have the knowledge of oral anatomy. It is also important to know the impact of various diseases on oral mucosa, and the characteristic features of various oral mucocutaneous lesions. An initial clinical oral examination is may help in the early diagnosis of the MD. Failure to identify the oral manifestations may reduce the likelihood of early treatment and lead to more serious problems. This paper reviews the oral manifestations of immune mediated dermatological disorders with common oral manifestations.

Keywords**—**Vesiculobullous lesions, Desquamative gingivitis, Nikolsky's sign, Erythema

I. Introduction

THE oral mucosa, a specialized moist tissue lining the oral cavity, is in direct continuity with the skin at the vermillion border and the intermediate zone of the lip. It consists of a stratified squamous epithelium and an underlying connective tissue, a feature similar to the structure of the skin. Although the oral mucosa shares structural and functional features with the skin, it lacks stratum lucidum, hair and apocrine glands. The other conspicuous features of oral mucosa that are not analogous with the features of skin are the presence of taste buds and salivary glands. The epithelial cells of the oral mucosa have a high turnover rate, and the turnover rate endows this tissue with a higher healing capacity compared to the skin [2], [3].

The oral mucosa lining the oral cavity has characteristic regional variations. The various types of the oral mucosa are keratinized mucosa (gingiva and hard palate), non-keratinized mucosa (buccal mucosa, floor of the mouth, ventral surface of the tongue, intra-oral surfaces of lips, soft palate) and a specialized mucosa (dorsal surface of the tongue). The keratinized mucosa is either ortho-or parakeratinized, and it protects the mucosa from compression and friction arising in oral cavity. The specialized mucosa comprises taste buds for the perception of taste sensation. The epithelium maintains its structural integrity by renewal of the cells at the basal layer to replace the cells that are shed at the surface stratum corneum. The underlying juxtaposed connective tissue interdigitates with the epithelial tissue. The multiple interdigitations of epithelium with the connective tissue endows the oral mucosa with the integrity and strength to bear the shearing forces arising in the oral cavity during normal functional processes. The oral mucosa is kept moist by the salivary secretion, and this also helps to minimize the excessive accumulation of bacteria. The normal immunological homeostasis is maintained by cells such as neutrophils and lymphocytes [1], [3]-[5].

Oral health and disease are closely related with the status of general health. The oral cavity may be a source of inflammation or infection, and it can also be the site of systemic diseases, including diseases of the skin. The oral cavity can also reflect the disorders arising from the surrounding or para-oral tissues such as in Sjogren's syndrome. Both the skin and oral mucosa may vary in disease susceptibility. The disease susceptibility also varies in different sites of the oral cavity, e.g., masticatory mucosa of the oral cavity may be more vulnerable to diseases. Sometimes the disease affecting the skin may have also the associated oral manifestations e.g., ectodermal dysplasia, a disorder of the skin, may also show absence of teeth in the oral cavity. The diseases arising in oral mucosa may be modified by their complex organization and by the salivary environment [3], [6], [7].

II. Mucocutaneous Disorders Involving the Oral Cavity

The diseases occurring in the skin and the concomitant involvement of mucosa are grouped as mucocutaneous disorders (MD). The MD can involve the oral mucosa and may be the initial feature of the skin disease, the most florid clinical feature or the only sign of such disease. Sometimes the oral lesions can occur along with the skin lesions. These disorders have varied etiological factors, e.g., autoimmunity, reactivity, infection, nutrition and idiopathic factors; however, most of these have immune mediated pathogenesis. Mucocutaneous disorders can involve any site in the oral cavity, but 50% of these are seen on gingiva as desquamative gingivitis. The affected individual, in addition to presenting the involvement of oral mucosa and skin, may present the

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involvement of other mucosa sites that include the other mucosal surface, e.g., nasal mucosa, pharyngeal mucosa or the conjunctiva. The most common mucocutaneous disorders affecting the oral mucosa are lichen planus, pemphigus vulgaris, erythema multiforme, lupus erythematosus and a group of pemhigoid lesions [3], [8]-[12].

A. Clinical Signs and Symptoms of Mucocutaneous Disorders

The mucocutaneous conditions cause alterations in oral mucosa and present as ulcers, vesiculobullous lesions or blisters, polypoid growth, etc.; however, the most common signs of the autoimmune mucocutaneous disorders are blisters and ulcerations. The oral blisters may rapidly erode and leave ulcers that are often painful. The blisters produce much discomfort, as these interfere with swallowing, speaking and eating. The clinical examination reveals ulcers of irregular shape and size and are associated with the white striae. Several of these disorders share a common clinical manifestation, which is seen as desquamative gingivitis [8], [13].

III. Diagnostic Approach

The mucocutaneous disorders have overlapping signs and symptoms and this makes their diagnosis difficult. Moreover, the anatomical and functional peculiarities of oral mucosa add to the diagnostic dilemmas, e.g., the papular lesions of oral cavity may appear moist, while vesicular lesions may break down and ulcerate as they are exposed to trauma and infection. The histopathological diagnosis of the oral manifestations of the mucocutaneous condition may also be challenging because the oral lesions may show a different histopathological feature when compared to the histopathological features of the same disease seen in skin. [3], [6], [8],[14]

The accurate diagnosis of the lesion is usually started by obtaining the history of the present lesion and the patient's past medical and surgical history followed by an accurate intraoral and extraoral examination. In addition, a thorough evaluation of the clinico-pathological characteristics of each condition and laboratory investigations should be done. This will initiate a comprehensive differential diagnosis. [6] The immunofluorescence techniques have recently emerged as an important tool for the detection of immunoreactants in the tissues and for the presence of circulating autoantibodies. These techniques have helped in the diagnosis of immune mediated mucocutaneous disorders, but an initial clinical examination of the oral cavity for the oral mucocutaneous lesions is necessary. It gives the best opportunity to detect the immune mediated disorders in the early stages. The early detection and subsequent treatment may control the dissemination and involvement of skin and /or other body organs. [14], [16] The oral examination of the lesion is also important because the oral manifestations may be the early manifestations of a systemic condition or these may be a part of its essential diagnostic features. [3] The oral mucocutaneous conditions also need to be examined at an early stage, as these can be painful and cause functional limitations and can be life-threatening. [17]

This review explains the characteristic clinical manifestations of mucocutaneous disorders in the oral cavity, which should not be overlooked by a dermatologist, while examining skin lesions. The mucocutaneous disorders should also not be mistakenly diagnosed by a dental clinician.

IV. Lichen Planus

Lichen planus (LP) is a common chronic immune disorder affecting 0.5-2% of the population and involves the skin, hair, nails and mucous membrane. The mucous membrane lining the oral cavity is frequently affected. The other mucosal sites involved are the urethra, a vulvo-vaginal site, the oesophagus, the anus, the larynx, the nose and conjunctiva. Oral lichen planus (OLP) is seen more in individuals in their 4th – 5th decade of life with more involvement in women. [8], [18]-[20]

The aetiology is still not proven; however, the overwhelming evidence indicates the role of autoimmunity. The phenomenon of the autoimmune process is triggered by an antigen that alters the basal layer of cells of the oral mucosa. The antigen expression or unmasking of keratinocytes is induced by certain drugs; mechanical trauma; and contact with an allergen, bacterial or viral infection or some unknown agent. This event is followed by the migration of T lymphocytes (mostly CD8+T cells and some CD4+T cells) into the epithelium. The CD8+ T lymphocytes further are activated directly by antigen binding to the major histocompatibility complex on keratinocytes. The CD4+ cells are also activated as a result of an increase in the population of Langerhans cells and by upregulation of MHC-II. Interleukin IL-12 activates CD4+ cells, and this activates CD8+T cells. The activated CD8+T cells secrete tumour necrosis factor (TNF)-α and kill the basal keratinocytes through tumour necrosis factor, Fas-Fas- mediated or granzyme B-activated apoptosis. The migration of lymphocytes is facilitated by degranulation of mast cells and release of chymase, which in turn degrades the basement membrane. The lichen planus aetiology has also been associated with viral infections, e.g., herpes simplex virus, Epstein-Barr virus and Human papilloma. The most widely studied virus associated with lichen planus is HCV, but its role is still controversial, and the virus needs further studies to understand its role. Psychological disturbances also have been linked to this disease. [8], [21], [22].

A. Clinical Features

The skin or cutaneous lesion lichen planus (CLP) is seen in various forms and these types are mentioned as the 6 P's that include planar, purple, polygonal, pruritic, papules and plaques. The skin lesions manifest on the flexor surface of the wrists, firearms and legs. The classic type manifests as flat-topped papules that are shiny, red/purple-coloured with an adherent scale. The papules present whitish points or lace-like striae (Wickham's striae) on the surface. The lesions may be seen along the lines of trauma (Koebner phenomenon). Pigmentation is often seen in dark individuals after the disappearance of the cutaneous lesions, while pigmentation-inversus is also seen in white individuals. The other sites

involved in lichen planus include the scalp and nails, and rarely is there laryngeal, oesophagus and conjunctival involvement. [20], [23], [24]

Oral lichen planus (OLP) presents with varying symptoms ranging from asymptomatic to mild intolerance to spicy or salty foods and extremely painful lesions. It has a tendency to follow a chronic course punctuated with remissions and exacerbations. [8], [24] The OLP manifests in an array of forms such as reticular, papular, plaque, erosive, atrophic and bullous patterns. The common pattern or type of OLP is asymptomatic and is reticular. It is seen as white and keratotic lace – such as a pattern radiating from papules and surrounded by erythematous borders. Some cases of reticular OLP may progress into more erosive types. The papular type occurs as small white asymptomatic papules that may not be noticeable. The plaque type OLP appears as a white patch present mostly on the dorsum of tongue and buccal mucosa. It clinically resembles a leukoplakic lesion and is often seen in tobacco smokers. This type of OLP has been found to have a poor prognosis and less chance of remission. The reticular and papular plaque are asymptomatic types of OLP. The erosive variant presents as multifocal, erythematous ulcerations or erosions of the mucosa that are sometimes covered with a pseudomembrane and associated with white radiating striae. The erosive type of OLP is also accompanied by symptoms of pain and dysgeusia. The atrophic type is similar to the erosive type and has been grouped as erosive-atrophic LP and this lesion is more often seen affecting older aged individuals. A rare variant of OLP is also called bullous LP and is characterized by the appearance of bullae that rupture to leave painful and ulcerative surfaces. [8], [19], [20]

OLP lesions are frequently seen in buccal mucosa, especially involving the postero-inferior part (80-90%), and are seen as minute, opalescent papules, bilateral and multiple with symmetrical distribution. The other affected sites are the back of the tongue, lip mucosa and lip vermillion. The gingiva is the common site affected in atrophic/erosive types of OLP, and this involvement is called desquamative gingivitis. The painful atrophic/erosive lesions of gingiva may cause the patients to neglect their daily oral hygiene due to regular discomfort, and this in turn may increase the inflammation of gingival and periodontal disease. [25], [26] The OLP lesions may also appear at the sites of trauma (koebnerization) and can be exacerbated by dental procedures, ill-fitting appliances, heat and irritants released from tobacco smoke. Approximately 25% of OLP that occur may have associated involvement of the vulva, while 43-100% of vulvar involvement may have an associated oral involvement. The occurrence of oral and vulvar lesions is also known as the *vulvo-vaginal gingival syndrome* and females with this syndrome have reticular or erosive lichen planus involving gingiva, buccal mucosa, labial mucosa or the tongue. Males also present with lichen planus of the glans penis and associated OLP. Oral lichenoid lesions are a group of oral lesions that mimic the oral lichen planus lesions clinically; however, these represent the contact allergy of hypersensitivity reactions due to restorative materials and certain drugs. [8], [27]

B. Histopathological Features

The histology shows a hyperkeratotic or atrophic type of stratified squamous epithelium overlying a connective tissue stroma. The epithelium shows a typical saw-tooth appearance and thickening of the granular layer and liquefaction degeneration of basal keratinocytes and disruption of the basement membrane. The connective tissue shows a dense band of inflammatory cells (T lymphocytes) in the superficial part adjacent to basal keratinocytes or at the junction of the epithelial-connective tissue junction. [8], [23], [24], [28]

C. Diagnosis

Oral lichen planus needs to be differentiated from the erosive lichen planus, lichenoid reactions, lupus erythematosus, pemphigus, pemphigoid, erythema multiforme and chronic ulcerative stomatitis. The oral lichenoid lesions associated with the usage of drugs will resolve after the withdrawal of the drugs, while the proximity of the OLP - like lesions to the restorative material will justify the lichenoid reactions. It is suggested that the oral lichenoid drug reactions histopathologically show the diffuse inflammatory cells deep in the connective tissue. Oral lichen planus, on the other hand, shows the presence of a band of inflammatory cells in the superficial lamina propria of connective tissue. The lupus erythematosus (LE) lesions clinically resemble erosive OLP, but tend to be less symmetric. The keratotic striae in LE are more delicate and radiate from a central focus. Also the histopathological feature of LE reveals a perivascular infiltrate. The pemphigus and pemphigoid lesions have a similar clinical appearance as compared with the erosive /atrophic OLP, but these are not associated with white keratotic striae. Furthermore, Nikolsky's sign, a feature of pemphigus and pemphigoid, differentiates them from atrophic/erosive forms of OLP. Erythema multiforme may resemble the lesion of the bullous type of OLP, but the former is of acute onset and commonly involves labial mucosa. Chronic ulcerative stomatitis is differentiated from OLP with the help of direct immunofluorescence studies. [22]

A complete history and an oral examination are required to diagnose OLP. For confirmation of diagnosis, the patient with the classic reticular type of OLP needs no biopsy. However, the erosive type requires a biopsy for routine histopathology and immunofluorescence investigations. The biopsy is also indicated if the clinical presentation of the lesion changes or if the lesion does not respond to treatment. A biopsy may also be required to rule out other chronic white or ulcerative lesions. Individuals with OLP and lichenoid lesions need to be followed regularly due to the increased risk for transformation to a squamous cell carcinoma. Some report a low risk of malignant transformation and as high a risk as 5.3% [8], [24], [27], [29], [31].

V. Pemphigus

Pemphigus comprises a group of autoimmune disorders, affecting 0.1-0.5 individuals per 100,000 per year. These are characterized by the appearances of blisters involving skin and/or mucosal surfaces. Pemphigus has various subtypes: pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus and paraneoplastic pemphigus. The pemphigus vulgaris and paraneoplastic pemphigus show more common involvement of oral mucosa. [8], [32]

Pemphigus shows the destruction of cell-cell structures or desmosomes, which is initiated by the binding of autoantibodies with the cell-surface glycoproteins present in keratinocytes. These cell-surface glycoproteins are members of the desmoglein (DSG) subfamily of the cadherin and superfamily of adhesion molecules present in the desmosomes. The desmoglein molecules link to cytokeratins via desmoplakin and plakoglobin. In pemphigus, the Dsg1 and Dsg3 are the main targets that are destroyed, while the tissue-bound antibodies are IgG, IgA and complement deposits. The autoantibodies destroy and inhibit the adhesive functions of desmogleins leading to the loss of cell-cell attachment. A recent report suggests the correlation of high levels of desmoglein3 (Dsg3) with the severity of oral lesions. The breakdown of adhesion components leads to the detachment of epithelial cells, which is clinically seen as blisters, erosions or ulcers in the skin or oral mucosa. [8], [32]-[34] The initiating stimulus for the production of autoantibodies in pemphigus remains unclear; however, the predisposing factors include genetics, burns, irradiation, drugs, diet, viral infections, stress and increased levels of hormones [35].

A. Pemphigus Vulgaris

The pemphigus vulgaris [PV] is the most common variant in the group of pemphigus. It is characterized by the involvement of skin and oral mucosa. The disease is seen more commonly in the fourth and fifth decade of life. [32], [36], [37].

B. Clinical Features

The skin lesions, which appear later than oral lesions, are seen on the trunk, scalp and neck. These constitute blisters of varying diameter, tension and fragility. The PV skin lesions show a positive *Nikolsky's sign*-a feature in which there is induction of bullae on normal appearing skin, if firm lateral pressure is applied. As the bulla of the skin is subjected to pressure, the contents are released into the surrounding epidermis, and it further increases in size. *(Indirect Nikolsky's sign)*. The contents of the blisters or bullae turn opaque after 2-3 days and eventually these rupture leading to erosions that heal without scarring. The surrounding tissue becomes infected and may show the development of impetigo [38]-[40].

The oral lesions are seen in approximately 50% of cases and these may occur anywhere in the oral cavity, although the palate, buccal mucosa, ventral surface of tongue, lips and gingiva is often involved. Approximately 15% of cases have only oral lesions with no skin involvement. [38] The disease has an acute and a chronic form, with the acute form developing rapidly and fatal within weeks or months. The chronic form may have remissions and exacerbations and can persist for a period of years. Approximately 20% of the acute form of this disease can become converted to the chronic form and resolve. The oral lesions develop gradually as an intact bulla, but these rupture rapidly due to rubbing or slight trauma of the oral mucosa and these result in separation of epithelium and formation of an ulcer *(Nikolsky's sign)*. [41] Therefore, erosions and ulcerations instead of vesicles or bullae are the main manifestations of the oral PV [32], [38]. The collapsed vesicles or bulla roofs are often seen next to the areas of tooth contact, especially along the inner aspect of the lower and upper lip [42]. As the vesicles and bullae rupture, the lesion becomes painful. Patients often refrain from mastication and do not maintain proper oral hygiene. The ruptured lesions may be covered or uncovered with a white fibrin pellicle mingled with the debris of leukocytes [38], [41]. Gingival involvement may be seen as desquamative gingivitis or erosive gingivitis. This is seen as the ruptured areas showing peeling of the gingival tissue associated with ulcers and erosion on free gingiva. The lesions may persist for months before progressing to skin and other mucosal sites. The lesions of pemphigus may also mimic lesions of aphthae. Lesions may also occur in areas where mucosa is traumatized, especially the palate, tongue and buccal mucosa. The acute forms of PV affect the palate and orifice. The PV lesions, that arise initially as oral lesions have a poor prognosis. If the roof of the blister is removed by trauma, the raw denuded area takes more time to heal, but the lesions do not show scarring [8], [39]-[41].

C. Histopathological Features

Histopathology of oral pemphigus vulgaris shows a stratified squamous epithelium with a suprabasal cleft, intraepithelial separation and blister formation. Acantholysis is seen with the cells floating in the blister cavity. The basal cells, however, remain adherent to the lamina propria and present a typical *"Tombstone"* appearance. The blister cavity may contain infiltrate of eosinophils and acantholytic cells. An immunofluorescence investigation shows deposits of antigen-antibody complexes within the intercellular space [8], [33], [42].

D. Diagnosis

Pemphigus vulgaris (PV) needs to be differentiated from lichen planus (erosive type), erythema multiforme mucous membrane pemphigoid and linear IgA. The fragile blisters and the non–scarring lesions of oral mucosa with varying degrees of skin involvement are the characteristic clinical features of PV. In addition, the first site of the involvement of this disease is oral mucosa (70-90%), and the occurrence of the lesion is mostly at the sites of friction in the oral cavity. The pemphigus and pemphigoid occur as solitary erythematous lesions unassociated with white striae. The white striae are seen in the erosive forms of lichen planus. The erythema multiforme lesions have a sudden onset of ulcers and vesicles or bullae. Biopsies from perilesional sites are essential for diagnosis of PV. The clinical features of pemphigus and pemphigoid are

the same but these two lesions can be differentiated on the basis of the levels of the split or separation of the tissues. Diagnosis of PV is confirmed by histopathological examination that shows a suprabasilar split in the tissue sections, while the MMP shows a subepithelial split. The direct immunofluorescence or indirect immunofluorescence methods can detect tissue-bound and circulating autoantibodies against the intercellular junctions in the epidermis. In addition, the molecular specificity of pemphigus antibodies may be confirmed by quantitative immunoassays [8], [15], [16], [22], [43]-[45].

VI. Mucous Membrane Pemphigoid

Mucous membrane pemphigoid comprises a group of common chronic, autoimmune diseases, which exhibit sub-epithelial blisters on the erythematous or normal surface. In the past it was known by several names such as "benign mucous membrane pemphigoid" and "cicatricial pemphigoid" and "oral-gingival pemphigoid"; however, in reporting the results of the *First International Consensus on Mucous Membrane Pemphigoid (MMP)*, the recommended term used was Mucous membrane pemphigoid [38], [46], [47]. MMP affects approximately 2-5 individuals per 100,000 per year and usually affects older individuals, with an average of 50-60 years at the onset of the disease [47].

MMP begins with the targeting of specific adhesion molecules present in the hemidesmosomes at the basal epidermal keratinocytes and in the lamina lucida of the basal membrane by autoantibodies, e.g., collagen XII/BP180, BP230 and laminin332. The antibodies that target these antigens are: IgG C3 complement factor and IgA. The serum of the patients shows the combined circulating IgG and IgA, associated with severe and persistent disease. The immune reaction causes a sub-epithelial split and vesicle formation [8], [48].

A. Clinical Features

The disease is characterized by painful bullae appearing mostly on the mucosa with or without the involvement of skin. Patients often complain of bleeding, soreness, pain, dysphagia or peeling of mucosa [49]. Lesions often heal with scarring and hyper-pigmentation [50]. Oral mucosal involvement is seen in 90% of cases; however, the extraoral mucosal sites may also be affected. Approximately 65% of cases show conjunctival involvement and also large oral MMP patients develop ocular involvement. The oral involvement begins with the appearance of thicker, painful vesicles or bullae, which may not be seen in pemphigus. The disease commonly shows a *positive Nikolsky's sign*. The blisters occupy the full thickness of the epithelium and may be fluid-filled or sometimes blood-filled following trauma. These lesions eventually rupture and leave raw, large, superficial denuded and ulcerated areas of mucosa. The ulcerated areas are surrounded by an erythematous border and are covered by a pseudomembrane. These may persist from weeks to months, if untreated. The disease manifests throughout the oral cavity, however the gingival lesions represent the onset of the disease in the oral cavity. [51] The gingival involvement is manifested as desquamative gingivitis with varying signs and symptoms. A recent study showed the MMP as the second most common cause of desquamative gingivitis. The lesions can manifest as irregular erythema with mild discomfort and generalized erythema with painful bullae. The involvement of gingiva can lead to the loss of alveolar bone and subsequent tooth loss. The skin lesions are uncommon and appear on face, neck, scalp, trunk and extremities [8], [36], [38], [46]-[48].

B. Histopathological Features

Histopathology shows a cleft below the level of the basal cell layer at the lamina propria interface. The subepithelial lesions are seen associated with a mixed inflammatory infiltrate comprising lymphocytes, neutrophils and eosinophils. The direct immunofluorescence (DIF) microscopy of perilesional tissue shows the presence of IgG and C3 at the basement membrane zone, while the indirect immunofluorescence microscopy is negative [8], [42].

C. Diagnosis

The diagnosis of MMP is difficult and is based on clinical, histopathological and immunopathological investigations. The disease must be differentiated from blistering diseases such as pemphigus vulgaris, linear IgA disease, SJS and epidermolysis bullosa acquisita. The histopathological feature is non-specific while the DIF is more sensitive and specific than histopathology and electron microscopy. Immunoblotting, enzyme-linked immunosorbent assay and immunoprecipitation also help in diagnosis [8], [15], [48].

VII. Erythema Multiforme

ER is an immune mediated mucocutaneous disorder manifesting hypersensitive reactions to either infections or drugs, affecting individuals of 20-40 years of age. The onset may be later than 50 years or more. The incidence of erythema multiforme according to reports is found to occur in a range between .01% and 1 %, while the incidence of toxic epidermal necrolysis and of Steven-Johnson syndrome is 0.4-1.2 cases per million per year and 1-6 cases per million per year, respectively [8], [44], [52].

Erythema multiforme (EM) was considered to represent a spectrum of disorders of variable degrees of severity including EM major, EM minor, Steven-Johnson syndrome and toxic epidermal necrolysis (TEN). However, in recent years, reports have shown that EM major is different from SJS and TEN in terms of aetiology and clinical features. A consensus classification proposed by Bastuji-Garin et al. classifies EM into bullous EM, SJS, SJS/TENS, overlap TEN with spots and TEN without spots [56]. The EM major and SJS in children have been found to be caused by HSV infection or mycoplasma. In adults, EM major occurs as a result of HSV infection and SJS/TENS occurs due to exposure to drugs. The Stevenson-Johnson syndrome and toxic epidermal necrolysis that typically occur in adults represent the severe forms of the disease, but are less common. Minor EM occurs due to the

herpes virus but its severe episodes are seen associated with drugs [8], [26], [27], [53]-[56].

The lesions of EM occur due to the body response in the form of immunological hypersensitive reactions to infections, e.g., mostly HSV and mycoplasma pneumonia or drugs. The drugs labelled as causative factors are NSAID, sulphonamides, anti-epileptics and antibiotics. The actual mechanism by which these etiological agents trigger the disease is not clear, however genetic susceptibility and autoimmunity are suggested as the predisposing factors for the disease [8].

The immune response targets the different antigens after the exposure to drugs or infection, chiefly being the herpes simplex virus. The immune reaction mediated by CD8+ T lymphocytes and monocytes leads to characteristic target lesions and a wheel-like appearance. In cases of viral associated EM lesions, the inflammation is associated with the damage of blood vessels. The T lymphocytes also target antigen-expressing keratinocytes leading to their apoptosis and satellite cell necrosis [8], [34], [55].

A. Clinical Features

Erythema multiforme is self-limiting and it tends to resolve within 1-2 weeks and affects the age groups of the 20s or the 30s. There is a history of fever, malaise, myalgias, headache and cough occurring about one week before the onset. These prodromal symptoms are seen more commonly in cases of EM accompanied by mucosal involvement. The early lesions may begin with the eruption of red or pink macules on the skin and these may be associated with itching and burning. The eruptions may form papule and vesicles that collapse to form plaques. The central portion of the plaque becomes darker red, dusky or purpuric. The disease is also characterized by the appearance of symmetrical, erythematous, circular concentric rings resembling a bullseye (targetoid lesions) on the skin of distal extremities. Nevertheless, the erythematous lesions on skin appear in approximately 50 % of cases; the other lesions may be oral, genital or ocular mucosal erosions or combinations of these [38], [44], [54].

Most patients with EM (70%) of either major or minor form have oral involvement. The occurrence of these lesions in mucosal sites usually occurs along with the involvement of skin; it can, however, precede or follow the onset of skin lesions by several days [56].

The minor erythematous multiforme usually affects the skin with ‘typical target’ lesions with rare and mild involvement of oral mucosa. The oral involvement begins with the appearance of macules that evolve into vesicles, which rupture and form ulcers with a pseudomembrane formation. The upper and lower lips are swollen, blood–stained and with erosions and crusting. Intraoral lesions are limited to the anterior part of non-keratinized areas of the oral cavity. Lesions heal without scarring unless these are deep and necrotic. The complications associated with the appearance of oral lesions are pain, interference with speech, mastication and swallowing. The patient appears dehydrated as a result of an inability to ingest liquids. The erythema multiforme major has more severe and common oral lesions and usually more than two areas of mucosa are affected. Many investigators have reported the cases of isolated oral lesions of EM, without the involvement of the skin [57]. These lesions have been classified under a new category of oral EM, and it has been reported that the subsequent attacks of these lesions can produce more skin lesions. The favoured sites of oral manifestations of EM are labial mucosa, buccal mucosa, the tongue and the floor of the mouth. The oral lesions are erythematous, diffused macules and associated with oedema. The macules may evolve into blisters and undergo epithelial necrosis and ulcerations with pseudomembrane formation [8], [52], [56-58].

The SJS and TENS that are different from EM begin with prodromal symptoms of flu followed by diffuse, atypical target lesions with bullous central areas.

B. Histopathological Features

The histopathological findings of the affected mucosal tissue exhibit the liquefaction degeneration of basal epithelial cells and necrotic keratinocytes. There is an exocytosis of lymphocytes and infiltration of lymphocytes at the basement membrane zone. Early stages of the lesion show more blood vessel involvement in the form of dilatation and surrounding mononuclear infiltrates. The target lesions microscopically show necrosis of the tissue [8], [34], [55].

C. Diagnosis

The EM must be differentiated from PV, TENS and SJS. The abrupt clinical features of the disease are rapid onset, history of similar episodes, pleomorphic nature of the oral and skin lesions and spontaneous recovery along with the pattern of recurrences and lip involvement that can help in the clinical diagnosis. EM can also be suspected based on the aetiology and typical skin involvement. Diagnosis is also confirmed by immunofluorescent studies to exclude other vesiculobullous diseases [8], [48], [58].

VIII. Lupus Erythematosus

Lupus erythematosus (LE) is an immunological mediated condition associated with significant morbidity and mortality [59]. It has variable clinical manifestations ranging from a skin rash unaccompanied by extra cutaneous stigmata to one showing multiorgan involvement [60]. There is an interaction of multiple genetic and environmental factors that lead to occlusive vasculopathy and vasculitis. More than 95% of the individuals affected by LE show loss of tolerance to nuclear antigens with formation of antinuclear antibodies [8], [48].

LE has an unknown aetiology; however, it is initiated by a complex interaction of environmental and genetic factors. The exogenous triggering factors such as infections, smoking, drugs, vaccines, diet and exposure to UV light lead to the formation of antibodies. These antibodies bind to the cell surface, cytoplasm, nuclei and nucleic acids proteins and lead to inflammatory reactions and further destruction of cells and tissues. The characteristic pathogenic feature of LE is the inflammation of blood vessels in the form of occlusive vasculopathy and vasculitis [8], [61].

Lupus erythematosus (LE) is classically subdivided into the following subtypes: systemic LE and cutaneous (LE). The cutaneous type is further subdivided into chronic CLE (CCLE), subacute CLE (SCLE) and acute CLE (ACLE) [59].

A. Systemic Lupus Erythematosus

Systemic lupus erythematosus is an autoimmune and inflammatory disorder occurring in all age groups with a reported prevalence of approximately 20-150 per 100,000. It occurs in both sexes; however, 90% of new cases are child bearing women. [62]. There is involvement of many organ and systems leading to severe tissue and organ damage [63]. The clinical features range from mild cutaneous lesions to life-threatening manifestations involving organs. The skin involvement is seen in all of the affected individuals in form of sun-induced skin rashes in 40-50% of the cases. The commonly occurring classical rash forms over the malar and nose, while the nasolabial crease is spared. The lesions heal without scarring. The oral lesions are chronic, asymptomatic (up to 50% of cases) and are seen in a range of 9 to 54% of individuals affected by SLE. The lesions mostly affect the palate, buccal mucosa and gingiva, and they may or may not be symmetrically distributed in the oral cavity. The morphological features of the oral lesions include the appearance of macules, palatal erythema and erosions or ulcerations. The ulcerations in the oral cavity are asymptomatic in up to 50% of cases and are considered to be the predictors of systemic vasculitis and with a poor prognosis. The lesions can also appear as plaques with central erythematous areas surrounded by a white rim with radiating striae and occasional telangiectasia. Approximately 40% of cases show desquamative gingivitis and marginal gingivitis. The lesions may be painful, mimic lichenoid areas or even look like granulomas. The SLE has also been associated with the conditions such as xerostomia, stomatodynia, candidiasis and dysgeusia [8], [38], [48], [64], [65].

B. Chronic Cutaneous Lupus Erythematosus (CCLE)

CCLE has few or no systemic signs and symptoms with primarily involvement of skin and mucosa. The skin manifests round, distinct or well circumscribed scaly and atrophic plaques associated with follicular plugging mainly on the face, ears and scalp. The oral manifestations are seen in 3-20% of cases. These present as distinct, well-bordered round or irregular red areas, which can be ulcerated or atrophic. The lesions are asymmetric and involve palate, buccal mucosa and the tongue. The central erythematous lesional site is surrounded by fine white radiating keratotic striae. The chronic oral lupus can also show honeycomb plaques with mucosal scarring, intense keratotic white lesions and linear fissured ulcerative and keratotic lesions affecting buccal mucosa.

Subacute cutaneous lupus erythematosus (SCLE): This type of the disorder has intermediate features between those of SLE and CCLE. The lesions of SCLE are photo-distributed, non-scarring, erythematous, papulosquamous and/or annular, polycyclic that may occur along with mild extracutaneous manifestations. These lesions are well-demarcated, round, red patches, which may be depressed, and these heal without scarring. Oral manifestations are rare; however, the lesions may be seen involving the lip as diffuse red scaling plaques on the vermilion of the lip [38], [48], [60], [65].

The histopathology feature of oral lesions of LE shows a hyperkeratotic epithelium with atrophy of rete pegs. The underlying connective tissue is oedematous and has infiltrates of lymphocytes surrounding blood vessels in the lamina propria and in the deep part as well. There is increased thickness of the basement membrane zone and liquefaction degeneration of basal cells [8].

C. Diagnosis

The LE needs to be differentiated from oral lichen planus (OLP). The clinical examination can play an important role in differential diagnosis. The asymmetric distribution of oral lesions in SLE is an important clinical feature that can help in differentiating from a symmetric distribution of oral lesions in OLP. The involvement of the lip in LE is seen crossing the vermillion to the surrounding perioral skin. The OLP lesion is usually limited to the area of the vermilion border. The striae of LE are more delicate than the *whickham striae* of lichen planus. The band–like distribution of inflammatory infiltrates in the lamina propria juxtaposed to the epithelium is a characteristic feature of OLP, whereas the deep and perivascular infiltrate of inflammatory cells suggest LE. Immunofluorescence methods to detect immunoglobulins and complements at the basement membrane confirm the diagnosis [8], [48], [61].

IX. Conclusion

The oral mucosa is developmentally and structurally similar to skin and is affected by a number of skin diseases. The oral manifestations of the skin diseases may occur before or following the skin disease, or they may be an isolated disease and may contribute to the diagnosis. The oral signs of the skin disease may be overlooked by a dermatologist while examining the related skin lesions, or these may be misdiagnosed by a dental surgeon. There can be a consequent delay in the diagnosis and management. Therefore, it is mandatory for a dermatologist to take the proper history of the oral lesion and examine the oral cavity along with the skin examination. Before the oral examination, a dermatologist should know the anatomy and normal morphological alterations of the oral cavity. The dermatologist and the dental clinician should have sufficient skills to identify and diagnose the oral lesions. The dental clinicians together with dermatologists can play an important role by diagnosing the oral lesions and reduce the morbidity of a disease. This can also strengthen the interdisciplinary approaches in the management of such patients.

The oral cavity should be examined in a systemic manner that includes the lips, vestibule, buccal mucosa, labial mucosa, tongue, floor of the mouth, hard palate, soft palate and pillars of fauces followed by the examination of the gingiva and teeth. In addition to the oral examination, the paraoral tissues and the other surrounding tissues should be examined. The

inspection and palpation of perioral skin, lymph nodes, thyroid gland and the TMJ can give additional clinical information. Similarly, the assessment of the functioning of salivary glands should not be overlooked. All of the evaluations of oral and para-oral structures will eventually help in formulating a differential diagnosis. To reach a final diagnosis, comprehensive laboratory tests must be performed; however, the initial oral examination can give clues of the impending disease.

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