

ORAL SIGNS IN MUCO-CUTANEOUS DISORDERS- REPORT OF THREE CASES AND REVIEW OF LITERATURE

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Abstract—According to Sir William Osler, Mouth is the mirror of the body which reflects systemic diseases. The oral mucosa may be affected by a variety of mucocutaneous diseases and oral lesions may occur first or very early in several mucocutaneous disorders. The erosive gingival lesions associated with vesiculobullous diseases such as lichen planus, cicatricial pemphigoid, and pemphigus vulgaris have been collectively referred to as "Desquamative gingivitis." Gingival desquamation is a clinical sign in which the gingiva appears reddish, painful, glazed and friable with destruction of the epithelium. This gingival desquamation is due to various disease processes in gingiva. The disease process may be a localized disease of gingiva or a systemic disease which manifests in the gingiva. It is important to be aware of this rare clinical entity so as to distinguish desquamative gingivitis from plaque induced gingivitis which is an extremely common condition, easily recognized and treated daily by the dental practitioner. Accurate diagnosis and effective treatment of these lesions may greatly diminish or reverse disease progression. This paper gives a detailed overview of Desquamative gingivitis- It's clinical presentation, possible causes, diagnosis and treatment.

Keywords—Muco-cutaneous diseases, Desquamative gingivitis, Oral lichen planus, pemphigus vulgaris, Mucous membrane pemphigoid.

I. INTRODUCTION

Oral mucocutaneous conditions are a group of disorders which are observed in the dental practice. Oral mucosal manifestations may be the initial feature, or the only sign of such diseases. In other cases, lesions occur in both the skin and mucosae, with several clinical manifestations involving the tissues.¹ Mucocutaneous lesions are Non-plaque induced gingival lesions and constitute a subgroup of gingival manifestations of systemic conditions. All these disorders share two features in common: an immune-mediated pathogenesis and possibly common clinical appearance. This common clinical

appearance is called 'Desquamative gingivitis'. Desquamative gingivitis is a clinically relevant entity because it can affect oral health and can be a feature of systemic disease. There is no evidence that Desquamative gingivitis per se can cause attachment loss and alveolar bone destruction.² As opposed to plaque induced gingivitis, Desquamative gingivitis is more common in middle aged to elderly females, is painful, affects the buccal / labial gingiva predominantly, frequently spares the marginal gingiva but can involve the whole thickness of the attached gingiva and its clinical appearance is not significantly altered by traditional oral hygiene measures or conventional periodontal therapy alone.³ Chronic desquamative gingivitis was first described by Tomes and Tomes in 1894.⁴ "Desquamative gingivitis" is a descriptive term, first introduced by Prinz in 1932 that indicates the presence of erythema, desquamation, erosion, and blistering of attached and marginal gingiva.⁵ Desquamative gingivitis is not considered a definitive diagnosis because it is a clinical manifestation of several disorders, as suggested by Glickman and Smulow in 1964⁶ and confirmed recently by others.⁷ The main characteristic of desquamative gingivitis is an extensive desquamation and / or erosion of the buccal aspect of attached gingival of anterior teeth.⁸ Desquamative gingivitis is now recognized to be mainly a manifestation of a number of disorders ranging from vesiculobullous diseases to adverse reactions to a variety of chemical or allergens.³ Overall, Mucous membrane pemphigoid, Oral lichen planus, and Pemphigus vulgaris are the most common causes of desquamative gingivitis, with the first two accounting for about 80% of cases.³ Other disorders manifesting as desquamative gingivitis include dermatitis herpetiformis, linear IgA disease, chronic ulcerative stomatitis, erythema multiforme, pyostomatitis vegetans, epidermolysis bullosa acquisita, and Kindler syndrome; similar appearance may be seen in reactions to various mouthwashes, chewing gums,

medications, and dental materials and in candidosis, lupus erythematosus, plasma cell gingivitis, Crohn's disease, sarcoidosis, some leukaemias, and even some factitious lesions.³ Use of clinical and laboratory parameters have revealed that approximately 75% of desquamative gingivitis cases have a dermatologic genesis. However, many of these autoimmune conditions do present with oral manifestations primarily.⁹ Differential diagnosis of desquamative gingivitis can include various diseases of fungal, viral, bacterial origin.³ Nisengard and Levine¹⁰ cited the following as the standard in making a clinical diagnosis of DG: (1) Gingival erythema not resulting from plaque, (2) gingival desquamation, (3) other intraoral and sometimes extraoral lesions, and (4) complaint of sore mouth, particularly with spicy foods. Hence it is of utmost importance to identify the disease responsible for desquamative gingivitis to establish appropriate therapeutic approach and management.

II. CASE 1

A 45 year old female patient reported to the department of Oral Medicine and Radiology with a chief complaint of burning sensations in the upper gingival region since 09 months. History reveals that patient was asymptomatic 09 Months back when she developed burning sensations in the maxillary gingival region. The burning sensations were particularly increased on intake of hot and spicy foods. History also reveals that the patient was under depression for some personal family reasons. There was no associated history of vesicle formation in any area of oral cavity. There were no associated skin, ocular and genital lesions. Patient had received medications, but there was not much improvement in the patient's symptoms. On clinical examination, there was areas of desquamation involving marginal and attached gingiva in relation to 11,23,24,25 & 14,15,16. (Figure 1) (Figure 2) (Figure 3) The desquamated area was surrounded by minute radiating whitish striations. The area showed bleeding on probing. Application of gentle pressure did not induced the formation of new lesion. Considering the history of 9 month duration, areas of desquamation with radiating white striations without formation of vesicle, provisional diagnosis of Erosive Lichen Planus can be given. After the patient was informed about the disease and getting her approval, incisional biopsy was made from maxillary right posterior gingival region. Histopathological features were consistent with the diagnosis of Lichen Planus. (FIG 4) The patient was subjected to thorough oral prophylaxis and oral hygiene instructions. Thereafter,

the patient was prescribed topical application of high potency steroids (Clobetasole propionate) 3 times daily for one month. Tablet Cetzine (antihistaminic) once daily for 15 days and once daily tablet of chelating agent (Supracal) was also given to the patient. The patient was reviewed every 2 weeks for the first one month. The lesions had subsided with topical steroids within 4 weeks of starting the treatment. (FIG 5) (FIG 6). The patient was asked to stop the topical application and reinforcement of oral hygiene instructions was given. Since the lesions can recur, the patient was under observation for 6 months and the lesions showed no signs of recurrence.



Figure 1



Figure 2



Figure 3



Figure 6

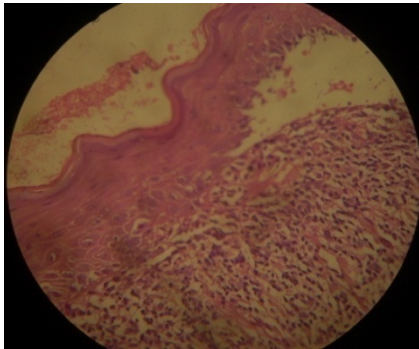


Figure 4



Figure 5

LEGENDS:

Figure 1, 2 & 3 - Erythematous & ulcerated areas involving the marginal & attached gingiva in relation to 11,23, 24, 25 & 14,15 & 16.

Figure 4 - basal cell degeneration with saw tooth shaped rete pegs.

Figure 5 & 6 - Healed lesions after topical steroid therapy

III. CASE 2

A 56 year old female patient reported to the oral medicine and radiology department with a complaint of chronic oral ulcerations since past two years. Her medical history was significant for diabetes, but the patient was not on medication. Thorough history taking revealed that the ulcerations showed remissions and exacerbations over a period of time. Initially bullae formation had occurred and the bullae have ruptured to form areas of erosions. On clinical examination, cutaneous involvement was non significant. Other sites such as the conjunctival, nasal, genital and oesophageal mucosa were also free of lesions. Intra-oral examination revealed diffuse irregular ulcer on lower lip extending till the mucocutaneous junction and the inner aspect of lower labial mucosa (Figure 7). Two (02) thin walled, fluid filled bullae on the lower labial mucosa, which on pressure ruptured with bleeding (Figure 8). Mucosa over the lower lip peeled on lateral pressure (positive nikolsky's sign). Multiple irregular ragged ulcers on palatal mucosa and a solitary bullae on soft palate which on pressure ruptured with bleeding surface

(Figure 9). Generalised areas of desquamation of the marginal and attached gingiva with bleeding on probing was noticed (Figure 10). There was paleness of right and left buccal mucosa with areas of fibrin covered irregular erosions and fibrosis (Figure 11 & 12). The patient had poor oral hygiene and was in extreme discomfort and in debilitated state. Based on a history of bullae formation, multiple chronic ulcerations, positive nikolsky's sign and apparent fragility of the oral mucosa experienced during clinical examination, the condition was differentially diagnosed as- Pemphigus vulgaris, mucous membrane pemphigoid and bullous lichen planus. After taking the consent from the patient, an incisional biopsy was taken from the lower lip region. Histopathological examination revealed suprabasilar blister formation associated with acantholysis (Figure 13 & 14). The patient did not agreed for immunofluorescence studies. Hence, a final diagnosis of Oral pemphigus vulgaris was made. Treatment regimen included thorough oral prophylaxis, kenalog-orabase ointment 3-4 times daily for topical application, along with dilute betadine mouth wash, tab cetzine twice daily and multivitamins once daily for one month. The patient was reviewed every 2 weeks for the first one month. The lesions had subsided with topical steroids within 4 weeks of starting the treatment. The patient was asked to stop the topical application and reinforcement of oral hygiene instructions was given. Since the lesions can recur, the patient was under observation for 06 months and the lesions showed no signs of recurrence.



Figure 7



Figure 8



Figure 9



Figure 10



Figure 11

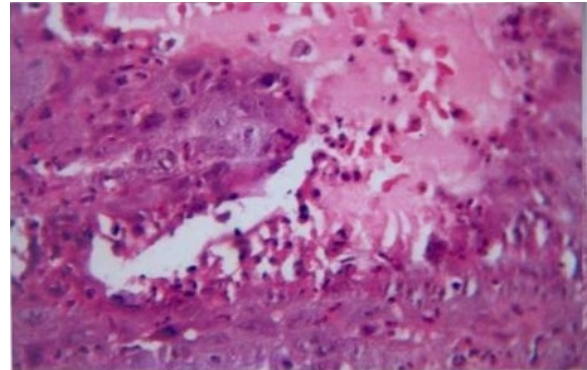


Figure 14



Figure 12

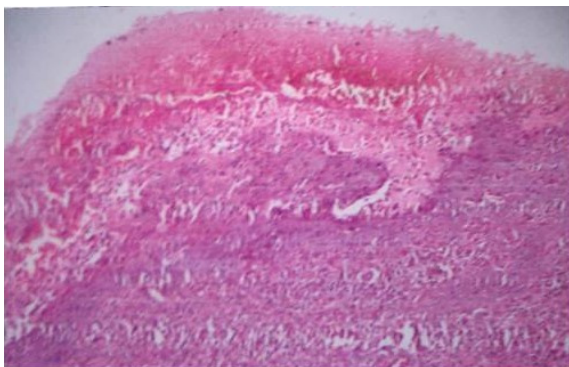


Figure 13

LEGENDS:

Figure 7 - Diffuse irregular ulcer on lower lip extending till mucocutaneous junction.

Figure 8 - Flaccid fluid-filled blister on lower lip with a positive Nikolsky's Sign.

Figure 9 - Multiple irregular ulcers on hard palate with solitary bullae on soft palate.

Figure 10 - Desquamative erythematous areas involving the marginal and attached gingiva in relation to upper anterior teeth.

Figure 11 - Multiple irregular erosions on right buccal mucosa

Figure 12 - Multiple irregular erosions on left buccal mucosa

Figure 13 & 14 - Typical features of suprabasilar split with acantholysis suggestive of intra-epithelial blistering disorder.

IV. CASE 3

A 57 year old female patient reported to the department of Oral medicine and Radiology with a complaint of burning sensation and tenderness in the gums on intake of spicy food for the past 9 months. The patient had also noticed the formation of blisters on the gums on and off which would break off on their own. The medical history was not significant and she was otherwise in good health. There were no associated ocular, cutaneous or genital lesions.

Intraoral examination revealed an erythematous and inflamed labial gingiva in relation to 11, 12, 21, 22. (Figure 15) There was an area of desquamation involving the buccal aspect of free, marginal and attached gingiva in relation to 24,25,26 & 27 along with the presence of an intact haemorrhagic bullae on the buccal attached gingiva in region of 25,26. (Figure 16) Gentle manipulation of the normal mucosa induced a positive Nikolsky's sign. The patient's oral hygiene was poor and gingiva showed bleeding on probing with no attachment loss. Faint white striae could be seen bordering the desquamated area in some part. Provisional diagnosis of MMP was made. Differential diagnosis included bullous pemphigoid, mucous membrane pemphigoid and bullous lichen planus. After an informed consent from the patient, an incisional biopsy was taken from the perilesional gingival tissue for histopathologic and immunofluorescent studies. Histopathological picture showed parakeratinised stratified squamous epithelium of variable thickness along with presence of subepithelial cleft and basal cell degeneration in few areas. Connective tissue stroma showed band of intense chronic inflammatory cells (plasma cells) along with areas of vascularity and hemorrhage. (Figure 17 & 18) Direct immunofluorescence showed a linear deposition of IgG and C3 at the dermo-epidermal junction. (Figure 19 & 20) The clinical, histopathological and immunofluorescent interpretations confirmed the diagnosis of Mucous membrane pemphigoid. The patient was subjected to thorough oral prophylaxis and oral hygiene instructions. Thereafter, the patient was prescribed topical application of high potency steroids (Clobetasole propionate) 3 times daily for one month and vitamin supplements. The patient was reviewed every 2 weeks for the first one month. The lesions improved considerably with topical steroids within 4 weeks of starting the treatment. (Figure 21 & 22) The patient was asked to stop the topical application and reinforcement of oral hygiene instructions was given. Since the lesions can recur, the patient was under observation for one year and there was no recurrence.



Figure 15



Figure 16

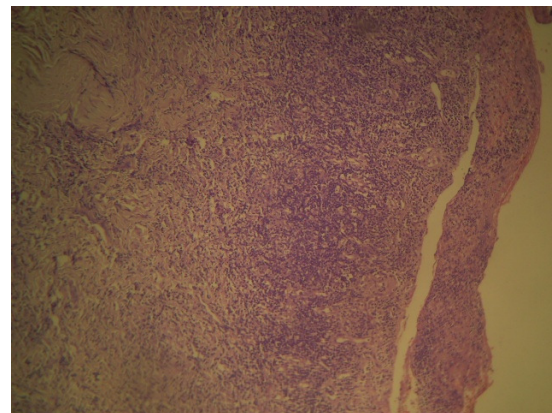


Figure 17

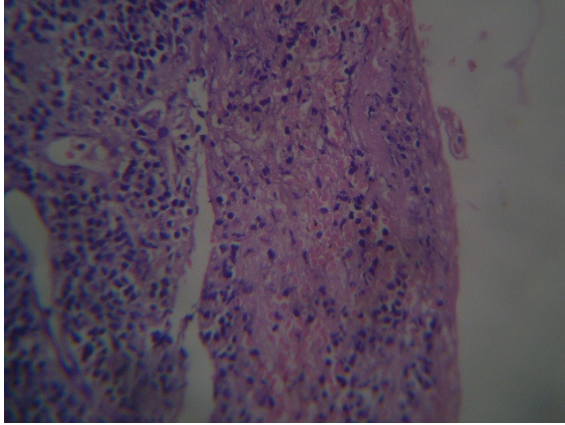


Figure 18



Figure 21

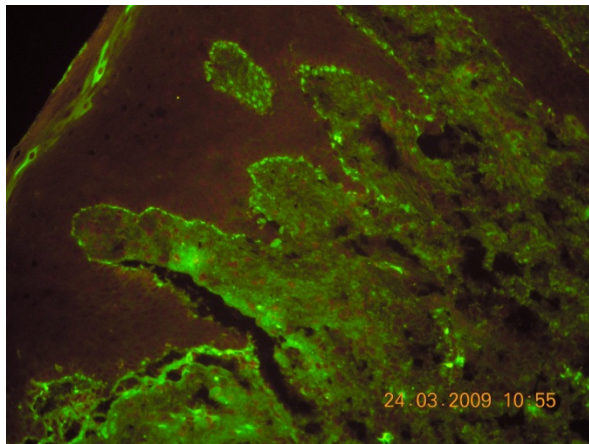


Figure 19



Figure 22

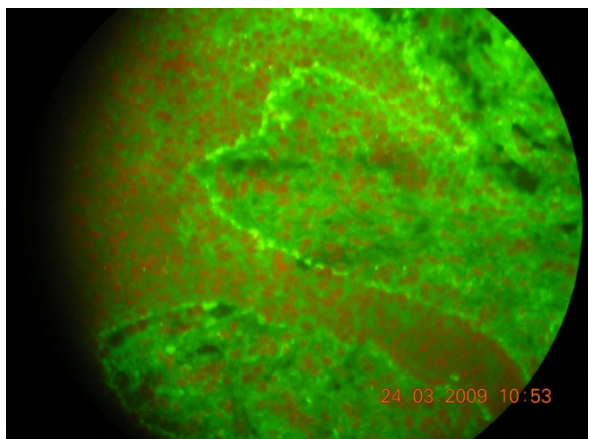


Figure 20

LEGENDS:

Figure 14 - Erythematous labial gingiva in relation to maxillary incisor teeth.

Figure 15 - Blood tinged bulla with desquamative gingivitis seen in respect to left maxillary posterior teeth.

Figure 16 & 17 - Histopathology showing sub-epithelial cleft and basal cell degeneration, along with chronic inflammatory cells and hemorrhagic areas.

Figure 18 & 19 - Direct immunofluorescence showing a linear deposition of IgG and C3 at the dermo-epidermal junction.

Figure 20 & 21- Healed mucosal lesions following institution of topical steroid therapy.

V. DISCUSSION

ORAL LICHEN PLANUS

Lichen planus is a common muco-cutaneous disorder, more frequent within the oral cavity, where it appears as either white reticular, or erosive lesions¹¹. In the majority of patients with oral lichen planus (OLP) there is no associated cutaneous lichen planus or lichen planus at other mucosal sites. This may be called "isolated" OLP.¹² The term "Lichen Planus" was coined by the British physician Erasmus Wilson in 1869.¹³ Since Lichens are primitive organisms of symbiotic algae and fungus, and planus in latin refers to "Flat". Most patients who experience this disorder are middle-aged or elderly, and 60 % are female.¹²

ETIOPATHOGENESIS

The exact etiology is not known (2). However, OLP is a T-cell mediated auto-immune disorder in which auto-cytotoxic CD8 T cells triggers the apoptosis of oral epithelial cells, leading to chronic inflammation.¹³

PREDISPOSING FACTORS:

1)HEPATITIS C VIRUS Infection: HCV infection is more common in Erosive Lichen Planus. HCV viral sequences have been found in the serum of patients with OLP; and HCV was shown to occasionally replicate in Oral Lichen Planus tissue, possibly contributing to the pathogenesis of mucosal damage.¹⁴

2)PSYCHOLOGICAL FACTORS: OLP patients exhibit higher levels of anxiety, depression, stress and psychological disorders. The levels of anxiety and salivary cortisol of OLP patients are high, thus establishing the relationship of OLP and stress.¹⁴

3)ORAL LICHENOID REACTIONS:

a)Dental restorative materials: Amalgams, composite resins, cobalt, gold and even flavouring agents may lead to oral lichenoid reactions.¹⁴

b)Drugs: NSAIDS, ACE inhibitors(captopril), beta blockers, Penicillamine may be implicated as a cause. However, lichenoid reactions are usually unilateral and resolves on discontinuation of the offending factors.¹⁵

4)MECHANICAL TRAUMA: Dental procedures, friction from sharp cusps, rough dental restorations, poorly

fitting prosthesis and deleterious oral habits are exacerbating factors. KOEBNERS PHENOMENON, where the lesions develop in response to trauma, explains why erosive lesions are common in areas subjected to trauma.(buccal mucosa and lateral border of tongue).¹⁴

5) PLAQUE AND CALCULUS: May result in worsening gingival lesions LP and are associated with a higher incidence of erosive lesions.

6) DIABETES AND HYPERTENSION: There is no literature supporting the association of LP with Diabetes and Hypertension. However GRINSPAN'S SYNDROME is the association of LP, Diabetes and Vascular Hypertension.¹⁶

A)EXTRA-ORAL MANIFESTATIONS:

1)CUTANEOUS LESIONS: consists of purple, pruritic, polygonal papules, often overlined by radiating lines (WICKHAM'S STRIAE).¹⁶ Skin lesions develop several months after the appearance of oral lesions and are usually self limiting. Genital mucosa is the most common extraoral site of involvement.

VULVOVAGINAL-GINGIVAL SYNDROME- is the association of LP of vulva, vagina and gingiva in female patients. Patients usually complains of burning, pain, vaginal discharge dyspareunia.¹⁴

PENO-GINGIVAL SYNDROME- is the male counterpart of vulvovaginal-gingival syndrome.¹⁴

2)SCALP AND HAIR FOLLICLES: Lichen planopilaris / Graham's little syndrome represents LP involvement of scalp and hair follicles, resulting in scarring alopecia.¹⁴

3)NAILS: Thinning and ridging of the nail plate and splitting of the distal free edge of the nail. Healing with scar produces PTYERGIUM.¹⁴

4)ESOPHAGEAL LESIONS: Dysphagia is the commonest feature. Chronic pain and strictures may also be seen.

B) ORAL MANIFESTATIONS:

The clinical evaluation of the oral lesions is based on the six clinical forms described by Andreason: reticular, papular, plaque, atrophic, erosive, and bullous.¹⁷ Mucosal lesions, which are multiple, generally have a symmetric distribution, particularly on the mucosa of the cheeks, adjacent to molars, and on the tongue mucosa, less frequent on the labial mucosa (lichenous cheilitis) and on the gums (desquamative gingivitis).¹⁷ The most common form

is reticular type with characteristic slender white radiating interlacing striations.¹⁸ The lesions frequently occurs bilaterally and are mostly asymptomatic.¹⁸ Erosive LP most often appears as a mixture of intensely erythematous mucosa with large areas of irregularly shaped ulceration with a whitish-yellowish pseudomembrane.¹⁹ Erosive and atrophic LP results in burning sensations. Erythematous lesions that affect the gingiva cause desquamative gingivitis, the most common type of gingival LP. The plaque like forms of LP may resemble leukoplakia, particularly proliferative verrucous leukoplakia and appears as slightly raised or flat area on oral mucous membrane.²⁰ Desquamative gingivitis as a presenting feature is most commonly noticed in oral lichen planus.³ The gingiva may be the only site of involvement in about 10% of cases. The atrophic form of OLP presents often on the gingival giving the classical appearance of desquamative gingivitis. The whole thickness of the attached gingiva upto the muco gingival junction may be affected. The gingival tissues appear erythematous with occasional areas of erosions and possibly white striae at the periphery. Patients may complain of persistent soreness of the gums which is made worse by spicy foods or when carrying out daily oral hygiene procedures. The latter may become restricted to the point that plaque induced gingivitis and periodontitis sets in, confusing the clinical picture. However, it is important to note that the immunological reaction occurring in lichen planus doesnot result in clinical attachment loss and periodontitis.²¹ The most common site of plaque like LP is tongue. Bullous LP is extremely rare form in oral cavity..The bullae rupture almost immediately , leaving an ulceration on a bed of inflamed mucosa. Bullous LP most commonly affects the posterior buccal mucosa.²⁰

MALIGNANT POTENTIAL:

The most important complication of OLP is the development of Oral squamous cell carcinoma.²² The first case of carcinoma arising in LP of oral mucosa was described by HALLAPEAU in 1910.²³ The risk of malignant transformation varies from 0.4% to over 5% a period of 5 – 20 years. Accumulation of inducible nitric oxide synthetase with 8-nitroguanine and 8-oxo-7,8-dihydro-2' deoxyguanosine in oral epithelium in OLP may cause oxidative and nitrative damage to DNA and could be the basis of malignancy. The risk of malignant transformation is independent of the clinical type of OLP or the treatment used.²⁴

DIAGNOSIS:

1)CLINICAL DIAGNOSIS: is sufficient to establish a diagnosis of OLP, if characteristic oral and skin lesions are present.

2)HISTOPATHOLOGY:¹⁴

Essential features:

- superficial band like infiltrate of T lymphocytes
- Basal cell liquefaction degeneration
- Normal epithelial maturation pattern

Additional features:

- SAW TOOTH rete pegs
- Civatte /colloid bodies
- Separation of epithelium from lamina propria
- Max josph spaces

3)IMMUNOFLOURESCENCE OF PERI-LESIONAL MUCOSA:¹⁴

- Fibrin and shaggy fibrinogen in a linear pattern at basement membrane zone
- Cytoids in the absence of deposition of fibrinogen

TREATMENT:

Generally, no medication is necessary for the benign form of this disease (reticular lichen planus). In the case of severe pain and a burning sensation, high-potency topical corticosteroids remain the most reliably effective treatment modality. Oral hygiene and corrective dentistry play a major role in the management of OLP and consultation with a dentist or oral medicine specialist is helpful.¹⁴

DRUG TREATMENT:

Drug treatment with topical steroids is preferred due to fewer side effects. Systemic steroids may be used if the lesions are extensive,or there are recalcitrant disease.

TOPICAL CORTICOSTEROIDS:

Most effective topical steroids are the medium potent steroids (triamcinolone), high potent steroids (fluocinolone acetonide) and superpotent halogenated steroids (clobetasol propionate). Elixir forms are also used such as dexamethasone, triamcinolone and clobetasol. These are used for diffuse oral involvement, elderly patients or for patients having difficulty in applying the medications. The greatest difficulty in using topical steroids is is the lack of mucosal adherence for a sufficient period of time. Therefore, topical steroids may be used with adhesive pastes (orabase).¹⁴ A regular follow up should be done for prolonged use of topical steroids for the following adverse effects:

- a)secondary candidal infection
- b)Tachyphylaxis(diminished biological effectiveness)

- c) Adrenal suppression
- d) atrophy of the oral mucosa

INTRALESIONAL STEROIDS:

Used for intractable erosive OLP lesions. Triamcinolone acetonide (10-20 mg / ml) is used and repeated every 2-4 weeks. Frequent steroid injections are painful and may result in an unwanted systemic dose.¹⁴

SYSTEMIC STEROIDS:

Should be reserved for recalcitrant cases of Erosive or Erythematous OLP or for widespread OLP with skin, genital, scalp or esophageal involvement. Daily doses of 40-80 mg is usually sufficient to achieve a response.¹⁴

OTHER TOPICAL AGENTS:

a) **TOPICAL CYCLOSPORINE** (100 mg / ml as a mouth rinse) may be beneficial in recalcitrant OLP cases. Systemic absorption is generally low, but it is expensive and less effective than topical steroids in inducing clinical improvement in OLP.¹⁴

b) **TOPICAL TACROLIMUS:** is a steroid free topical immunosuppressive agent. It was used primarily for atopic dermatitis. The exact mode of action is not known they inhibit T cell activation and proliferation. Burning is the most common side effect with tacrolimus. Other side effects include carcinogenicity, mutagenesis and infertility.²⁵

c) **TOPICAL RETINOIDS:** Tretinoin and isotretinoin are used for erosive-atrophic forms. Side effects include teratogenicity and liver dysfunction.

OTHER THERAPIES:

PUVA THERAPY - Oral psoralen-UVA (PUVA) therapy with low doses of UV-A may also be used. PUVA is a combination therapy that consists of exposing patients to psoralen and then exposing the skin to long wave ultra-violet radiation.

-CROSSURGERY- has also been used, particularly in erosive drug resistant OLP, but the lesions may develop in healing wounds and result in scars.

-LASER THERAPY- CO₂ lasers are used to treat multicentric lesions or lesions in difficult areas.

ADDITIONAL DRUG THERAPY:

Griesofulvin, Thalidomide, Levamisole and Dapsone may also be used.

SURGERY:

Resection may be done for isolated plaques or non-healing erosions. Free soft tissue grafts have been used for localized areas of erosive OLP. However, periodontal surgery have been reported to provoke OLP.

PEMPHIGUS VULGARIS

The term "Pemphigus", is derived from the greek word pemphix (bubble or blister)¹⁶ and vulgaris is derived from latin word (common)⁹. Pemphigus is a potentially life threatening disease that causes blisters and erosions of the skin and mucous membranes²⁶. Pemphigus vulgaris is the most common form and frequently involves the mouth. The main importance of PV is that it typically runs a chronic course, almost invariably causing blisters, erosions, and ulcers on the oral mucosa and skin.²⁷ The oral lesions are often the first sign of the disease, and they are the most difficult to resolve with therapy. Thus, the oral lesions are the "first to show and the last to go"⁹. Death occurred most frequently in elderly patients and in patients requiring high doses of corticosteroids who develop infections and bacterial septicemia, mostly from staph. Aureus (fluid and electrolyte loss)²⁶.

EPIDEMIOLOGY:

Pemphigus is an uncommon disease with an incidence rate ranging from 0.5 to 3.2 per 100,000 per year.²⁸ Although pemphigus vulgaris is usually considered a disease of adults, it has been reported in neonants²⁹ and infants³⁰. Genetic predisposition linked to HLA class II alleles may occur, as it is more frequently seen in certain ethnic groups and within families. Ashkenazi jews and people of Mediterranean origin are at an increased risk.³¹

PATHOGENESIS:

Pemphigus vulgaris is an autoimmune disorder in which there is deposition of mainly IgG class antibodies intracellularly, as well as damage to desmosomes by antibodies directed against the extracellular domains of cadherin-type epithelial cell adhesion molecules, particularly desmoglein 3. Since oral epithelium largely expresses DS 3; but skin expresses DSG 1 as well as DSG 3, damage to DSG 3 by antibodies results in oral lesions at an early stages but skin integrity maintained by DSG. However, if damage to DSG 1 antibodies appear, cutaneous lesions appear and the disease tends to be more severe³². The appearance of serum antibodies against DSG 1 heralds involvement of skin and mucosa other than oral. The immune reaction against these

glycoproteins causes a loss of cell to cell adhesion (ACANTHOLYSIS) resulting in the formation of INTRAEPITHELIAL BULLAE²⁶. The mechanism by which antidesmoglein antibodies cause the loss of cell-cell adhesion is controversial. Some believe the binding of the PV antibody activates proteases, whereas recently, it is considered that PV antibodies directly block the adhesion function of the desmogleins²⁶.

PREDISPOSING FACTORS:

Most cases of pemphigus are IDIOPATHIC, but triggered by

1. DRUGS:33

- Captopril

- Penicillamine (immunogenicity is caused by SULPHYDRYL groups which resembles molecular structure of desmoglein 3 ; crossreactivity)

- Rifampicin

- Phenyl butazone

2. Radiation

3. Surgery

4. Diet particularly garlic³⁴

5. Emotional stress

6. Viruses – HHV 8³⁵

7. Emotional stress

8. Pesticide exposure

9. Pregnant females³⁶

CLINICAL FEATURES:

PV affects the mucosa and the skin, resulting in superficial blisters and chronic ulcerations. Various mucosal surfaces may be involved, including ocular, nasal, oral, pharyngeal, laryngeal, upper respiratory, and anogenital mucous membranes³⁷. Classic lesion is flaccid thin walled bullae that may arise on normal or erythematous skin /mucous membrane²⁶. The bulla are fragile & break readily leaving denuded areas of variable size that tend to enlarge as the epithelium detaches from the dermis at the periphery. Such

vesicles and bullae rupture easily on the skin, so that the most common skin lesions seen are erosions, which may be widespread. Skin lesions consists of WEEPING bulla that bursts, crusts and recur in the same area and spread to adjacent regions. The formation of a lesion after gentle mechanical pressure (blowing air / applying pressure with mirror handle) on affected tissue may be used as a diagnostic tool in the assessment of patients presenting with oral ulcerations. This test is known as NIKOLSKY'S SIGN, named after Pyotr Vasilyewich nikolsky, who first described this sign in 1896³⁸. (may also be seen in MMP, Epidermolysis bullosa). ASBOC-HANSEN SIGN : When finger is applied directly over an intact blister it produces lateral spread of lesion.

ORAL MANIFESTATIONS:

80-90% of patients with pemphigus vulgaris develop oral lesions sometime during the course of disease, and, in 60% of cases, the oral lesions are the first sign²⁶. Oral lesions usually begins as a vesicle or bulla. Early oral lesions may consist of a single hemorrhagic bulla or shallow ill defined irregular ulcers. However a whitish superficial covering which is the collapsed roof of a bulla is consistent and characteristic finding. Blisters, which rapidly lead to chronic erosions and ulcers³⁹, are seen mainly in the buccal mucosa, palate, ventral surface of tongue and lips³. Pemphigus should be considered whenever there are multiple persistent oral erosions, but in the early stages, the erosions may be recurrent⁴⁰. Advanced signs usually consist of severe desquamative or erosive gingivitis⁴¹, but gingival lesions are uncommon at the onset or may appear as isolated blister or erosions, or both, mainly on free gingiva, and may be difficult to recognize as bullous lesions⁴². Lips may be covered by thick hemorrhagic crusts. In advanced cases, the lesions may resemble ERYTHEMA MULTIFORME. Gentle lateral pressure applied to an area adjacent to the affected site forms a blister resulting in a positive nikolsky's sign⁴³. Distal extension from oral cavity can occur effecting oesophagus, pharynx, larynx producing dysphagia and odynophagia⁴⁴. In the present case flaccid fluid filled bullae was seen on the lower lip and a positive nikolsky's sign was also elicited. Areas of desquamation involving the marginal and attached gingival which showed bleeding on probing were also seen. The oral lesions were the only presenting symptoms without skin or any other mucosal involvement.

-IMMUNOFLORESENCE STUDIES :The clinical diagnosis was always confirmed by direct and indirect immunofluorescence⁴⁸.

ASSOCIATION WITH OTHER DISORDERS:

PV may occasionally be associated with other auto-immune disorders, particularly rheumatoid arthritis, myasthenia gravis, lupus erythematosus, pernicious anaemia⁴⁵, herpes simplex infection and internal malignancies(SCC).

DIAGNOSIS:

-CLINICAL EXAMINATION: in patients with PV and active blistering, firm sliding pressure with a finger separates normal-looking epithelium (nikolsky's sign), but this is neither completely sensitive nor specific.

-BIOPSY: Best done on intact vesicle or bulla less than 24hr old. Specimens taken from the advancing edge of the lesion where areas of characteristic SUPRABASILAR ACANTHOLYSIS is seen²⁶.

In P. VULGARIS, intercellular edema develops in epithelial cells, dissolution of intercellular bridges occurs, and the widening of intercellular spaces occurs which causes separation between cells and formation of blister above basal cell layer (supra basilar split)⁴⁶

The present case showed typical histological features of intraepithelial blistering disorder with supra-epithelial split and acantholytic cells.

- TZANK SMEAR :

The base of blister is scrapped and examined for acantholytic cells. The free floating rounded or ovoid acantholytic cells has an enlarged , hyperchromatic centrally or eccentrically situated nucleus. Basal cells are tightly attached to basal lamina but loose their attachment to one another, producing a TOMB STONE appearance⁴⁷. Relatively fewer inflammatory cells are seen in P. vulgaris compared with other bullous diseases.

-COMPRESSED AIR TEST :

Application of a stream of compressed air to the oral mucous membrane of gingival tissues may cause a shimmering of the outer tissues followed by formation of bleb or a blister.

DIRECT IMMUNOFLORESENCE:

Florescence labeled antihuman immunoglobulins are placed over the pt's tissue specimen. Circulating antibodies of IgG type, bound to the intercellular cement region of the oral mucosa were detected. In case of PV the technique will detect antibodies usually IgG & compliment bound to the surface of Keratinocytes²⁶.

INDIRECT IMMUNOFLORESENCE:

Serum from a pt is placed over a prepared slide of an epidermal structure(usually monkey oesophagus). The slide is then overlaid with flouroscein tagged antihuman gama globulin. Pt with PV have antikeratinocyte antibodies against intercellular substance that show up under a fluorescent microscope. The titer of antibody has been directly related to level of clinical disease. The test distinguishes pemphigus from pemphigoid & other chronic oral lesions²⁶.

-UPPER GASTROINTESTINAL ENDOSCOPY: may be useful in identifying oesophageal involvement⁴⁹.

-ELISA :

Can detect Dsg1 & Dsg3 in serum samples²⁶.

-IMMUNOPRECIPITATION AND IMMUNOELECTRON MICROSCOPY

The targeted antigen recognised by autoantibodies is 130KD glycoprotein identical to Desmoglein.

TREATMENT MEASURES:

Periodontal therapy is an essential part of overall treatment of pemphigus. Optimal oral hygiene is important because the gingival involvement may present an exaggerated response to bacterial plaque. Oral lesions are difficult to treat because of trauma to the surface epithelium whenever the patient eats.

DIET CONSIDERATIONS -

Patients on steroid therapy are monitored for weight gain and advised low salt, low fat , low calorie diet . Also advised increased consumption of potassium and protein rich meals.

-Corticosteroids form the mainstay of treatment in Pemphigus cases. In patients with *P. vulgaris* there is pronounced imbalance of helper T – T suppressor ratio, which is restored by corticosteroid therapy⁵⁰. Oral lesions of Pemphigus Vulgaris may respond partially to topical or intralesional corticosteroids. Systemic corticosteroids. (1-2 mg/kg/day) remain the mainstay of therapy of patients with oral lesions. Corticosteroids with less adverse effects are preferred eg .Deflazacort⁵¹ . In cases of severe disease 80mg daily Prednisolone may be used.

-Combining corticosteroids (Prednisolone or prednisone) with immune-suppressive agents, such as cyclosporine, methotrexate, azathioprine and cyclophosphamide makes it possible to use much smaller doses of the corticosteroids and thereby reduces the chance for steroid- related complications⁵². Dapsone has been used in treating cutaneous pemphigus vulgaris⁵³. Plasminogen activator may have a role in pemphigus, drugs such as Tranexamic acid, which prevents conversion of Plasminogen to Plasmin may be effective in treating pemphigus⁵⁴.

-Plasmapheresis : is done with cyclosporin or cyclophosphamide. This process removes circulating antibodies. It affects B cell proliferation. Plasmapheresis has been used in patients who are refractory to therapy with steroids in doses of 2mg/kg/day. The low levels of antibodies resulting from plasmapheresis cause a rebound effect where new antibodies are produced in excess of the original levels. However , this rebound effect can be controlled by administration of an immunosuppressive agent⁵⁵.

Photopheresis : where in WBC's are photoinactivated with methoxsalen and UV-A in an extra corporeal system.

PUVA : Administration of 8-MethoxyPsoralen followed by exposure of peripheral blood to Ultraviolet radiation.

Intravenous Pulse therapy of corticosteroids- IV methyl Prednisolone 1gm daily/5days⁵⁶

Intravenous Immunoglobulins : Proved successful & safe in steroid resistant PV⁵⁷

Newer drugs.⁵⁸

-Cholinergic agonists (modulates autoimmune response which require autoreactive helper T cells that regulate IgG isotope switching)

-Rituximab (Anti CD20 monoclonal antibody)

-Proteinase inhibitors

-Chimeric molecules (for specific recognition & elimination of autoimmune B cells targeting Dsg3 specific T cells)

Our patient was advised thorough oral prophylaxis and oral hygiene reinforcement was emphasized. Topical steroids along with daily dose of Cetzine and multivitamins was prescribed. The patient was reviewed for 6 months and there were no signs of recurrences.

MUCOUS MEMBRANE PEMPHIGOID

Cicatricial pemphigoid is a rare chronic autoimmune subepithelial blistering disease characterized by erosive lesions of mucous membranes and skin that result in scarring of at least some sites of involvement.^{59,60,61} In the past, MMP was known by several terms, including “benign mucous membrane pemphigoid”, “cicatricial pemphigoid”, and “ocular or oral-gingival pemphigoid”. However, in reporting the results of the First International Consensus on Mucous membrane pemphigoid, Chan and others⁶² recommended the term “mucous membrane pemphigoid” because the disease may not be benign when it causes blindness from ocular involvement or death from laryngeal scarring⁶³; it may not be scarring , as in gingival involvement; and it may affect a number of mucous membranes such as the oral and nasal mucosa, pharynx, anus, genital mucosa, esophagus and trachea. The skin may be affected, but is always a minor component. The incidence of MMP has been estimated to be between 1.5 to 9.6 cases per 100,000 / year⁶⁴. It appears to manifest more commonly in females than males at a ratio of 2:1 and in an estimated 83% to 100% of cases, the oral cavity is involved⁶². The mean age of onset is 50 years or older. However, case reports of mucous membrane pemphigoid in children and young adults exist.⁶⁵

The patient , in our case report was a female of 57 years of age.

ETIO-PATHOGENESIS

MMP is an autoimmune disorder, usually of unknown cause but occasionally triggered by drugs^{66,67} and occasionally associated with other autoimmune diseases⁶⁸. There may be no known racial or geographic predilections, but there may be an immunogenetic background and an association with HLA DQB1*0301,⁶⁹ which is especially notable in ocular pemphigoid.

The pathophysiologic mechanism of MMP is complex and poorly understood. There is clearly a defect in the immune regulation involving the formation of autoantibodies directed against antigens, which are normal components of the basal membrane zone. The separation of the epithelium from the underlying tissue within the Basal membrane zone may be the result of a direct cytotoxic action or the effect of lysosomal proteolytic enzymes⁴⁴. Cellular immunity and cytokines also play a role in the pathogenesis of MMP. The cytokine tumor necrosis factor-alpha (TNF- α) is thought to play a prominent role in the pathogenesis of MMP^{70,71}. The chronic overproduction of TNF- α was recently implicated in the pathogenesis of MMP and other autoimmune blistering disorders⁷¹. Consequently, MMP may not be a distinct disease entity but, rather, a series of syndromes with different causes and pathogenetic mechanisms.⁷²

CLINICAL MANIFESTATIONS

1. MUCOUS MEMBRANES

The Mouth is the most frequent site of involvement in patients with MMP, and it is often the first site affected. Lesions in the mouth often involve the gingiva, buccal mucosa, and palate; other sites such as the alveolar ridge, tongue, and lips are also susceptible.⁷³

Desquamative gingivitis is the main oral feature of MMP⁷⁴ and may be the presenting feature⁷⁵. A recent cohort study⁷⁶ of patients presenting with DG found MMP to be the second most common underlying disorder accounting for 14% of cases, whereas lichen planus was the most common underlying disorder, accounting for 70.5% of DG patients. DG is a fairly common disorder in which the gingivae are desquamated. Chronic soreness is common and can be worse with the intake of spicy foods⁷⁷. The clinical appearance is of gingival erythema and loss of stippling, extending apically from the gingival margins to the alveolar mucosae. The desquamation may vary from mild, almost insignificant small patches to widespread erythema^{78,79} with a glazed appearance.

Vesicles or bullae may also occur elsewhere on the oral mucosa in MMP, and there can be positive Nikolsky sign⁷⁹ elicited by palpation with a finger, mouth mirror or periodontal probe. The blisters rupture quickly, leading to pseudomembrane-covered, irregularly-shaped erosions, which are the second most common manifestation after DG. Erosions have a yellowish slough and are surrounded by an inflammatory halo⁶². Persistent extensive erosions may be present in the buccal mucosa and

especially the palate, but unlike those of pemphigus vulgaris cause little discomfort.

In severe cases, adhesions may develop between the buccal mucosa and the alveolar process, around the uvula and tonsillar fossae, and between the tongue and the floor of the mouth.

When lesions involve the frenulum, ankyloglossia or limited mobility of the tongue may result.

Some patients may have lesions of other stratified squamous epithelia, such as the larynx, esophagus, there may also be nasal, vulval, penile or anal involvement.⁸⁰

Nasopharyngeal lesions can result in discharge, epistaxis, excessive crust formation, impaired airflow, chronic sinusitis, scarring and tissues loss.

Laryngeal involvement may present as hoarseness, sore throat, or loss of phonation. Chronic laryngeal erosions, edema, and scarring may result in supraglottic stenosis and airway compromise that eventually necessitates tracheostomy.⁸¹

Involvement of the esophagus in mucous membrane pemphigoid is rare and is usually found in patients with a disseminated form of the disease. The most common alterations are the involvement of multiple mucous membranes or esophageal strictures. The esophagus is affected in only 2-13% of cases of mucous membrane pemphigoid. It may develop years after onset of the disease; however, esophageal involvement alone is very rare.⁸²

Although involvement of the genital and / or rectal mucosae in MMP patients is rare, it can be a source of substantial pain and morbidity. Rare cases of urethral stricture, vaginal stenosis, and anal narrowing have been developed as a consequence of this disease.

Ocular manifestations have been quite common in some stomatologic units, the incidence ranging from 3% to 48%^{83,84} these are important in as much as they culminate in blindness. Eye involvement usually begins as chronic conjunctivitis with symptoms of burning, irritation, and excess tearing.⁸⁰ Vesicles are rarely seen in conjunctiva, whereas ulceration is seen only in advanced aggressive diseases. Scarring after repeated fibrosis can lead to the fusion of the sclera and palpebral conjunctivae (Symblepharon) or of the superior and inferior palpebrae (ankyloblepharon). The conjunctiva may contract and invert the eyelid margins (entropion) leading to inversion of eyelashes onto the corneal surface with subsequent irritation (trichiasis). The damaging combination of entropion and trichiasis may lead to blindness.⁸⁰

2. SKIN

Skin involvement occurs in about one-third of MMP patients.⁸⁰ When it occurs, two patterns of

involvement may be seen: 1) widespread blistering similar to that seen in BP 2) Recurrent vesicles most commonly affecting the scalp, head, neck and upper trunk. However, unlike BP, skin involvement is not a dominant feature of the disease. Instead mucous membrane involvement with progression to scarring of involved sites is usually its presenting and most prominent feature.

In the present case, the patient presented with desquamation of marginal and attached gingiva with a blood filled bullae and a positive Nikolsky sign. Desquamative gingivitis was the only presenting manifestation in our case, without the presence of any other oral, ocular, genital or cutaneous lesions.

DIAGNOSTIC CRITERIA

Accurate diagnosis is based on the history, examination, and biopsy with histologic and direct immunofluorescent (DIF) examination.

Histologically, biopsy specimens from patients with MMP demonstrate a sub basilar separation of the epithelium from the underlying connective tissue. Sub-epithelial vesicle formation and vacuolation in the basal lamina occur below intact epithelium. In contrast to lichen planus, the inflammatory infiltrate is non-specific in nature, consisting of lymphocytes, plasma cells, and neutrophils.⁸⁵

Histopathological features in the present case, showed subepithelial cleft and basal cell degeneration, along with band of intense chronic inflammatory cells (plasma cells) and areas of vascularity and hemorrhage.

Direct immunofluorescence testing of MMP specimen usually show a linear deposition of complement (usually C3) and IgG or other immunoglobulins at the basement membrane zone⁶⁰. Intact epithelium and connective tissue are critical in evaluating a specimen with DIF techniques.

Serum IIF testing has been believed to be of little diagnostic value in MMP since circulating basement membrane antibodies are often not detected.⁸⁶ The sensitivity of IIF can be improved using normal human skin or mucous membrane incubated with 1mol/l NaCl solution as a substrate, thus separating the epithelium from the connective tissue at the site of lamina lucida (known as salt split)²⁶. This technique can also help in differentiating between antigens located on the epidermal side (MMP) of the split and those located on the dermal side (EBA) with the provision of additional details for the diagnosis.²⁶

Direct immunofluorescence features in our case, showed linear deposition of IgG and C3 at the dermo-epidermal junction.

TREATMENT MEASURES

The factors to be taken into account in treating MMP are its location, severity and progression rate. In low risk patients with lesions confined to the oral mucosa and/or skin, topical corticosteroids are advised, such as 0.1% triamcinolone acetonide, 0.05% fluocinolone acetonide, or 0.05% clobetasol propionate in orabase, applied 3-4 times a day during 9-24 weeks. In patients with isolated erosions, intralesional corticosteroid injections (triamcinolone in 5-10 mg/ml solution) can be used. In subjects presenting gingival lesions in the form of desquamative gingivitis, 0.05% clobetasol propionate is recommended, with nystatin 100,000 IU to avoid candidiasis overinfection.^{87,88} When MMP affects the palate, esophagus or nasal mucosa, beclomethasone dipropionate or budesonide (50-200 µg) can be prescribed.⁸⁷ Topical 0.1% tacrolimus in pomade, associated to prednisone 40 mg/ day via the oral route has been reported to offer good results, with resolution of the lesions after three months of treatment, and offering a preventive effect against the disease⁸⁹. Depending on the patient response, other alternatives can be considered, such as 100 mg of doxycycline a day for 8 weeks, or minocycline 50-100 mg/ day during 3-39 months, and nicotinamide 2-3 g/day^{87,88}. In high risk patients with multiple oral lesions, rapidly progressing spread of the disease to other mucosal membranes such as the eyes, genital, esophagus or nasopharyngeal zone, or recurrent lesions, the administration of prednisone 1-2 mg/kg/day, with gradual dose reduction, and immune suppressors such as cyclophosphamide (0.5-2 mg/kg/day), azathioprine 1-2 mg/ kg/day, or mycophenolate mofetil 2-2.5 g/day has been described.^{87,88,90,91} Another treatment option is dapsone (50-200 mg/day) for 12 weeks.⁹¹ Treatment is started with 25 mg during three days, followed by 25 mg increments every three days until reaching a dose of 100 mg, followed by boosting of the dosage to 150 mg⁸⁸. Blood test monitoring is important in order to avoid the appearance of side effects⁹¹. Other drugs that have been used include methotrexate, which at low doses prevents the progression of conjunctival cicatrization in 72% of all patients, tumor necrosis factor-alpha, leflunomide or sulfonamide (regarded as an alternative to dapsone, administered at a dose of 1.5-3 g/day). Less commonly used options in turn are intravenous immunoglobulins (1-2 g/kg/cycle), plasmapheresis in patients with eye lesions refractory to corticosteroids and immune suppressors and, as a last option, surgery to avoid complications such as blindness, esophageal strictures or upper airway stenosis⁸⁷. A case report⁹² with 8 years of follow up presented the successful

management of a patient with both periodontal disease and MMP through the use of topical corticosteroids and standard periodontal therapy including scaling and root planning and surgical treatment. Recently a case report⁹³ demonstrated that Low level laser therapy (LLLT) may improve healing after the application of a local corticosteroid for a period of 12 months. The basic principle of LLLT is based on the biostimulation or biomodulation effect,⁹⁴ which considers that irradiation at a specific wavelength is able to alter cellular behavior.⁹⁵

The patient in the present case underwent thorough oral prophylaxis and was treated with topical steroids and vitamin supplements for one month. The lesions showed dramatic improvement after steroid application. Regular follow up was done and the lesions showed no signs of recurrence.

VI. CONCLUSION

The clinical features of dermatoses or mucocutaneous disorders where desquamative gingivitis is a presenting manifestation have been described in this paper. Correct diagnosis of these conditions entails taking a detailed history, coupled with a thorough intraoral and extraoral examination, along with histopathology and Immunofluorescence studies. The gingival lesions are usually treated by improved oral hygiene measures and occlusive topical corticosteroid therapy.

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