OROPHARYNGEAL NON SCRAPABLE WHITE LESIONS- A DIAGNOSTIC DILEMMA

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ABSTRACT-

White lesions of the oral cavity are commonly encountered in routine clinical dental practice. Common white lesions may cause diagnostic dilemma. White lesions are usually focal, multifocal, striated or diffuse. Diagnosis of these lesions is extremely important, as some of these lesions may represent early stages of malignancies. Clinical diagnostic skills and good judgment forms the key to successful diagnosis and management of white lesions of the oral cavity. This review article lists the non scrapable white lesions affecting or pharyngeal mucosa ranging from normal variants of oral mucosa to those which are malignant; it also highlights the specific features of each of these lesions.

KEY WORDS- Potentially malignant disorders, Non scrapable lesions, White lesions, malignant transformation.

INTRODUCTION-

White lesions of the oral cavity are most commonly seen by dental professionals in day to day dental practice. It includes some physiological variations, systemic conditions, infections, malignancies and other lesions. The importance of early diagnosis of these will lesions help in preventing its complications. White lesions of the oral mucosa obtain their characteristic appearance because of a thickened layer of keratin (hyperkeratosis), superficial debris on oral mucosa, blanching caused by reduced vascularity and loss of pigmentation due to acquired causes [1]. The treatment ranges from reassurance by the clinician to management of potentially malignant disorders.

The consensus views of the Working Group are presented here. The term, potentially malignant disorders, was recommended to refer to precancer as it conveys that not all disorders described under this term may transform into cancer [2].

White lesions are seen in the oral cavity and are mainly found as an incidental finding on routine examination. They may be benign, potentially malignant in nature. Review of the literature has shown that there are very few epidemiological studies on oral mucosal lesions and in particular white lesions. Few prevalence related studies have been done on potentially malignant conditions, rarely correlating their clinic pathologic correlation [3, 4].

COMMON NON-SCRAPABLE WHITE LESIONS

1. LINEA ALBA-

The linea Alba (Latin for *white line*), is a horizontal streak on the buccal mucosa at the level of occlusal plane. It usually extends from the lip commissure to the posterior teeth. [5]It is a common finding and most likely associated with pressure, frictional irritation, or trauma from the facial surfaces of the teeth. It may be found in individuals who chew tobacco, and may be mistaken for a lesion requiring treatment.[5]

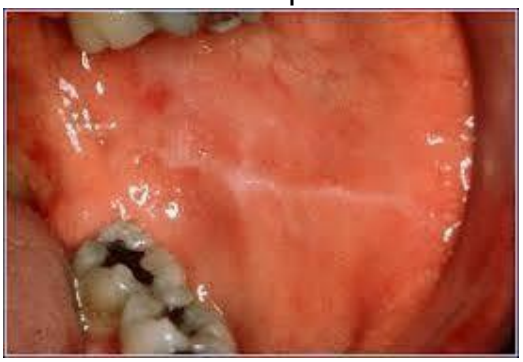
CLINICAL MANIFESTATIONS [5]-

- The linea alba is usually present bilaterally
- It is restricted to dentulous areas

- It presents an asymptomatic, linear elevation, with a whitish colour, at the level of the occlusal line of the teeth

TREATMENT [5]-

Treatment is not required.



F Fig.1 White keratotic linear line at occlusal level.

Fig. 2 White keratotic line at occlusal level

LEUKOEDEMA-

Leukoedema (also spelled **leucoedema**)[6] is a blue, grey or white appearance of mucosa, particularly buccal mucosa.It is a harmless and very common condition. Because it is so common, it has been argued that it may in fact represent a variation of the normal appearance rather than a disease [7] but empirical evidence suggests that leukoedema is an acquired condition caused by local irritation. [8]

ETIOLOGY-

The cause is unknown [7] but it is thought to be caused by intracellular edema of the superficial epithelial cells coupled with retention of superficial parakeratin. Although leukoedema is thought to be a developmental condition, it may be more common and more pronounced in smokers, and becomes less noticeable when smoking is stopped. It may also develop in areas subject to repeated subclinical irritation, caused by low grade irritants such as spices, oral debris or tobacco [8].

CLINICAL MANIFESTATIONS-

There is a diffuse, gray-white, milky opalescent appearance of the mucosa which usually occurs bilaterally on the buccal mucosa. Less often, the labial mucosa, the palate or the floor of mouth may be affected. The surface of the area is folded, creating a wrinkled, white streaked lesion.[7] Leukoedema usually start to appear around age 2 to 5; however, it is not often noticeable until adulthood. [8] Clinically Leukoedema presents as asymptomatic, folds or white lines crisscross the affected area. The buccal mucosa is the most common site for Leukoedema; however, it can extend to the labial mucosa, floor of the mouth, and pharyngeal areas. [8] Other mucosal surfaces can be affected, such as vagina and larynx. Leukoedema cannot be wiped off; however, it can be eliminated temporarily by stretching of the mucosa, which is referred to as clinical stretch test. [8]

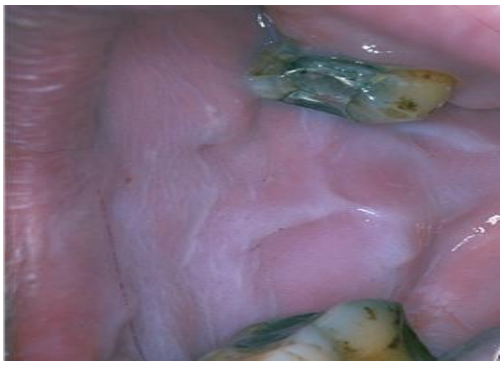


Fig.3 Folded appearance of leucoedema on buccal mucosa

TREATMENT-

Leukoedema is considered to be a normal variation; therefore, no treatment is required for this condition. [8]

DIFFERENTIAL DIAGNOSIS-

Clinical examination readily differentiates leukoedema from leukoplakia since there is no loss of pliability or flexibility of the involved tissues. [9] Leukoedema is distinguished from lichen planus by stretching the buccal mucosa [10]. Areas exhibiting leukoedema will either disappear or persist upon stretching, whereas lesions of lichen planus will become more

pronounced. Leukoedema should also be differentiated from white sponge nevus and habitual cheek-biting (pathomimia morsicatio buccarum) [11, 12] .White sponge nevus is a

relatively uncommon lesion, and the buccal mucosa appears thickened and folded. [13]

FRICTIONAL KERATOSIS-

Frictional keratosis is a reactive white lesion caused by prolonged mild irritation of the mucous membrane. It shows rough and frayed surface, upon removal of the offending agent, the lesion resolves in 2 weeks. Biopsies should be performed on these lesions that do not heal to rule out a dysplastic lesion [14,15].

ETIOLOGY-

It is mostly caused by acute trauma which in turn causes ulcers while chronic trauma causes hyperkeratosis. The etiology for frictional keratosis is habitual cheek biting, orthodontic appliance, ill-fitting denture, broken cusp, rough edges of a carious tooth or malaligned teeth [16].

CLINICAL MANIFESTATIONS-

Clinical features are at first a patch which is pale translucent later it becomes dense and white, mostly they occur in areas that are commonly traumatized like buccal mucosa along the occlusal line, lips, lateral margins of tongue.[16]

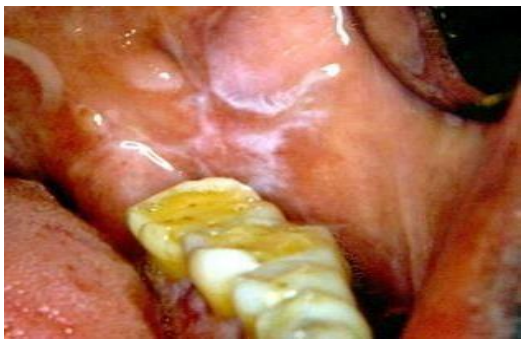


Fig.4 Frictional keratosis in retromolar region adjacent to sharp tooth

TREATMENT-

Frictional keratosis is one of the most commonly associated traumatic oral lesions by sharp edges of the tooth. Removal of cause for irritation is required. Many of them are harmless and do not require any treatment other than reassurance from the side of the clinician. But still a small minority roughly 4% are potentially dangerous if left unattended.[15]Following diagnostic algorithm for oral white lesions, if the lesion after monitoring for 6 weeks still persists, biopsy has to be performed and if results indicate keratosis with no dysplasia then proper follow-up and review are necessary.[17]

LEUKOPLAKIA-

DEFINITION AND TERMINOLOGY-

In 1978, oral leukoplakia has been defined by the World Health Organization (WHO) as: 'A white patch or plaque that cannot be characterized clinically or pathologically as any other disease. [18]

ETIOLOGY -

Tobacco plays important role in etiology. Whether the use of alcohol by itself is an independent etiological factor in the development of oral leukoplakia, is still questionable [20-24].The role of Candida. albicans as a possible etiological factor in leukoplakia and its possible role in malignant transformation is still unclear.[24-28] The role of viral agents in the pathogenesis of oral leukoplakia has been noticed, particularly with regard to exophytic, verrucous leukoplakia.[29,30] In a study from India, serum vitamin levels of vitamin A, B12, C, beta carotene and folate acid were significantly decreased in patients with oral leukoplakia compared to controls, whereas serum vitamin E was not.[31]Loss of heterozygosity (LOH) of the chromosome arms 3p and 9p are associated with increased malignant potential in oral leukoplakia (Emilion et al, 1996; Mao, 1997; Zhang and Rosin, 2001). Fifty percent of leukoplakia contains allelic loss of either the 3p or 9p chromosome arms 4(Rosin et al, 2000; van der Riet, 1994) [32].

CLINICAL MANIFESTATIONS-

The site distribution shows world-wide differences, that are partly related to gender and tobacco habits [19, 33, 34, 38].In general, two clinical variants of leukoplakia are being recognized, the homogeneous and the non-

homogeneous type. Transitions or changes among the different clinical variants of oral leukoplakia may occur [36, 37]

Homogeneous leukoplakia has been defined as a predominantly white lesion of uniform flat, thin appearance that may exhibit shallow cracks and has a smooth, wrinkled or corrugated surface with a constant texture throughout [18]. Non-homogeneous leukoplakia has been defined as a predominantly white or white-and-red lesion ("erythroleukoplakia") that may be irregularly flat, nodular or exophytic. The nodular lesions are characterized by white patches or nodules on a erythematous base [39], while the exophytic lesions have irregular blunt or sharp projections [18].

The adjective "non-homogeneous" is applicable both to the aspect of colour, i.e. a mixture of white and red changes ("erythroleukoplakia") and to the aspect of texture, i.e. exophytic, papillary or verrucous. With regard to the latter lesions, no reproducible clinical criteria can be provided to distinguish (proliferative) verrucous leukoplakia from the clinical aspect of verrucous hyperplasia or verrucous carcinoma [40, 41]. Furthermore, a diagnosis of proliferative verrucous leukoplakia can only be made retrospectively after new lesions have developed [2].The homogeneous type is usually otherwise asymptomatic, whereas the non-homogeneous (mixed white and red) leukoplakias are often associated with mild complaints of localised pain or discomfort. In the presence of redness or palpable induration, malignacy may already be present [38].

MALIGNANT TRANSFORMATION-

In a study from India, an annual malignant transformation rate of 0.3% has been reported.[35]In studies from Western countries somewhat higher figures have been mentioned; an annual malignant transformation rate of approximately 1% is probably a reasonable average figure for all types of leukoplakia together. Non homogenous type [35] nearly always transforms into verrucous carcinoma or squamous cell carcinoma and may do so in a protracted course of over 10–15 years.

Reported risk factors of statistical significance for malignant transformation of leukoplakia, listed in an at random order (not applicable in the individual patient)[35]

- Female gender
- Long duration of leukoplakia
- Leukoplakia in non-smokers (idiopathic leukoplakia)
- Location on the tongue and/or floor of the mouth
- Size > 200 mm^2
- Non-homogeneous type
- Presence of Candida albicans
- Presence of epithelial dysplasia

VARIOUS FORMS OF LEUKOPLAKIA - Clinical types [2]-

Two main clinical types of leukoplakia are recognized

1. Homogeneous
2. Non-homogeneous leukoplakia.

Non homogeneous varieties includes

- speckled: mixed, white and red, but retaining predominantly white character
- Nodular: small polypoid outgrowths, rounded red or white excrescences
- Verrucous: wrinkled or corrugated surface appearance.

However, those with mixed white and red plaques should be recognized as having a higher risk status. These are to be denoted as **erythroleukoplakia.**

- Proliferative verrucous leukoplakia (PVL) presents with multiple, simultaneous leukoplakias ; as the disease is visibly multifocal and frequently covers a wide area. This clearly fits with the proposed terminology of potentially malignant disorder' rather than struggling to list PVL under lesions' or as a condition

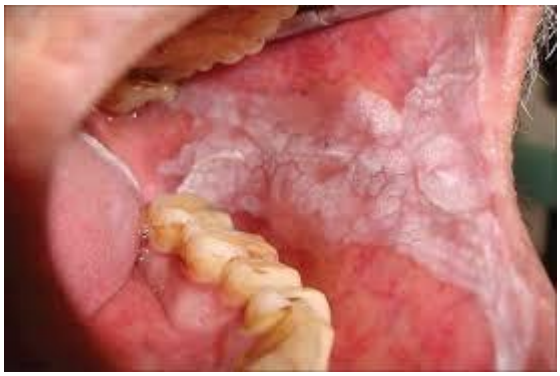


Fig.5 Homogenous leukoplakia on buccal mucosa

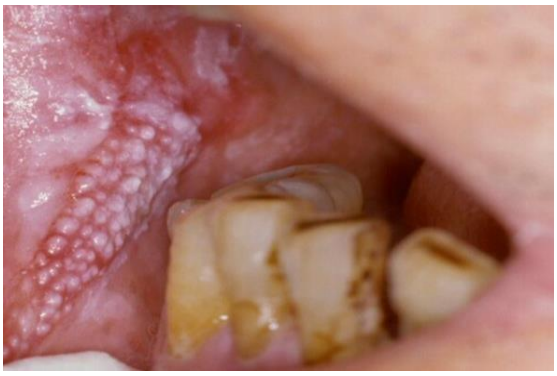


Fig.6 Non-homogenous leukoplakia

TREATMENT [2] –

White patch

Exclude other known conditions /disorders/diseases based on history and examination

Provisional clinical Diagnosis of leukoplakia

Biopsy → Other known disorder confirmed

Other known disorder Excluded

Revise diagnosis to other disease/ disorder

Leukoplakia with dysplasia
Leukoplakia without dysplasia

Carotenoids[39]

1. **Beta-Carotene-** Betacarotene is a vitamin A precursor. The use of beta-carotene has been recommended in order to prevent Oral Leukoplakia and possibly oral cancer. The potential benefits and protective effects against cancer are possibly related to its antioxidizing action. This function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals.

2. **Lycopene-** Lycopene is a carotenoid without provitamin A action. This is a fat-soluble red pigment found in some fruit and vegetables. The greatest known source of licopene is tomatoes, which are widely employed in cooking. There is a positive relationship between lycopene consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardiovascular diseases. Lycopene has the uncommon feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent. Due to this property, studies have been enthusiastically conducted with lycopene, in order to find out whether or not it could be an alternative to protect patients against the damaging effects of free radicals. In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to be an anticancer mechanism.

   No systemic significant toxical effect of lycopene has been observed and there is no evidence of side effects from the treatment with lycopene. Lycopene is a promising candidate in reducing cancer and chronic diseases in human beings; however, further research is needed to clarify its potential

function in human health, according to the following criteria.

(1) Factors influencing the uptake of lycopene in the diet, including the way it interacts with othercarotenoids.

(2) Human metabolism and the possible function of the metabolites and cis-trans isomers.

(3) Mechanisms of the direct or indirect modulation of cancer.

(4) Studies based on evidences of treatment in human beings.

(5) Mechanisms of lycopene deposition in human tissues.

(6) Lycopene effects in the immunological system.

Vitamins [39]

1.L-Ascorbic Acid (Vitamin C)-

L-ascorbic acid (L-AA), the so-called vitamin C, is found in citrus fruits such as kiwi, strawberries, papaya, and mango. The current US recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults. It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of the L-AA(L-ascorbic acid)concentration in serum leukocytes. L-AA has antioxidizing properties and reacts with superoxide produced as a result of the cells' normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. L-AA toxicity does not occur, since vitamin is water-soluble and a decrease in absorption efficiency occurs when consumption exceeds 180 mg/day.

2.α-Tocoferol (Vitamin E)-

α-Tocoferol (AT) is the commonest and most active form of vitamin E. It is found in plant oil, margarine, and green leaves. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women. Its absorption rate is reduced when consumption exceeds 30mg/day. α-Tocoferol is an effective antioxidant at high levels of oxygen,protecting cellular membranes fromlipidic peroxidation.

3. Retinoic Acid (Vitamin A)-

The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. Vitamin A exists in the human body as various interconvertible compounds, notably retinal (essential for vision) and retinol, which is the most potent analogue and the main form of storage and transportation. Retinoic acid is obtained from carotene and animal products such as meat, milk, and eggs, which, while in the intestine, are converted, respectively, into retinal and retinol. The absorption of retinoids increases by up to 50% when ingested with food. Retinoids are transported in the blood by plasmatic proteins. Hepatic metabolization is achieved via the action of cytochrome P- 450. Hypervitaminosis occurs when consumption exceeds the liver's capacity to store retinoids. Topic retinoids were initially tested against diseases related to keratinization. 13-cRA was used for the first time against acne, in 1969. The so-called "retinoic dermatitis" is the main side effect of tretinoin, this leads to cutaneous irritation characterized by erythema, scaling, ardency, and/or pruritus. "Retinoic dermatitis" occurs frequently, and patients ought to be previously instructed with regard to itsoccurrence.

Bleomycin[39]

Bleomycin, a cytotoxic antibiotic.The use of topical 1% bleomycin in dimethyl sulphoxide DMSO was evaluated for the treatment of dysplastic OL. Bleomycin was applied once daily for 14 consecutive days to lesions of the oralmucosa in 19 patients. It was well tolerated with minor mucosal reactions. Immediate posttreatment biopsies showed that 75% of patients had resolution of dysplasia. Ninety-four percent of the patients attained at least partial clinical resolution. After a mean follow-up period of 3.4 years, 31.6% of patients had no clinically visible lesions. In 2 patients (11%), malignant transformation occurred. Topical bleomycin in treatment of OL was used in dosages of

0.5%/day for 12 to 15 days or 1%/day for 14 days.

TREATMENT GUIDELINES FOR LEUKOPLAKIA

Longshore and Camisa[42]

1. Eliminate all contributing factors
2. Absence of dysplasia or presence of mild dysplasia -surgical excision/laser surgery of the lesions on the ventral/lateral tongue, floor of the mouth, soft palate, and oropharynx. Close observation and follow-up for all other anatomic locations
3. Presence of moderate or severe dysplasia - surgical excision or laser therapy is preferred treatments
4. Red lesions (Erythroplakia/ leukoerythroplakia) - Surgical removal is best
5. Proliferative verrucous leukoplakia - Complete surgical excision/laser surgery if possible
6. Follow-up for all lesions.

ORAL LICHEN PLANUS-

Lichen planus is a common mucocutaneous disease. It was first described by Wilson in 1869 and is thought to affect 0.5–1% of the world's population.[43] Oral lichen planus is a chronic disease that can persist in some patients for a long time. In contrast to cutaneous lichen planus, the oral form may persist for up to 25 years.[89] It affects woman more often than men in a ratio 2:3.[45,46]

CLASSIFICATION-

Andreasen[44] divided oral lichen planus into six types: reticular, papular, plaque-like, erosive, atrophic, and bullous. The reticular, papular and plaque-like forms are usually painless and appear clinically as white keratotic lesions. The erosive, atrophic and bullous forms are often associated with a burning sensation and in many cases can cause severe pain. A detailed history and observation of the clinical features of the disease are usually sufficient to establish the diagnosis.

a. RETICULAR ORAL LICHEN PLANUS-

The most common type of oral lichen planus is the reticular form.

Characteristically, it presents as a series of fine, radiant, white striae known as 'Wickham striae', which may be surrounded by a discrete erythematous border. [45, 46] The buccal mucosa is the site most commonly involved. The striae are typically bilateral in a symmetrical form on the buccal mucosa. They may also be seen on the lateral border of the tongue and less often on the gingiva and the lips. Reticular lichen planus is likely to resolve in 41% of cases.[47]

b. PAPULAR ORAL LICHEN PLANUS -

The papular form presents as small white pinpoint papules about 0.5 mm in size. It is rarely seen and because the lesions are small it is possible to overlook them during a routine oral examination. [47]

c.PLAQUE-LIKE ORAL LICHEN PLANUS

Plaque-like lesions resemble leukoplakia and occur as homogenous white patches.It may can be slightly elevated or smooth, irregular and multifocal. The primary sites are dorsum of tongue and buccal mucosa. This form is significantly more common among tobacco smokers. [48] The lesions are often discovered incidentally by the patient or by a clinician during a routine oral examination.

d. ATROPHIC ORAL LICHEN PLANUS

The atrophic type of oral lichen planus is diffuse, red and there are usually white striae around the lesion. Such striae that radiate peripherally are usually evident at the margins of the atrophic zones of the lesion. The atrophic form can display a symmetrical patchy distribution over all four quadrants. The lingual gingiva is usually less severely involved. This condition can cause a burning sensation particularly when in contact with certain

foods. About 12% of atrophic lesions will resolve spontaneously.[47]

e. BULLOUS ORAL LICHEN PLANUS -

Bullous oral lichen planus appears as small bullae or vesicles that tend to rupture easily. The bullae or vesicles range from a few millimetres to several centimetres in diameter. When they rupture they leave an ulcerated, painful surface. This form is rarer than the other forms of oral lichen planus. It is commonly seen on the buccal mucosa, particularly in the posteroinferior areas adjacent to the second and third molar teeth. The next most common site is the lateral margins of the tongue. The lesions are rarely seen on the gingiva or inner aspect of the lips.[47]

f. EROSIVE ORAL LICHEN PLANUS-

Erosive oral lichen planus is the second most common type. The lesions are usually irregular in shape and covered with a fibrinous plaque or pseudomembrane where there is erosion. The periphery of the lesion is usually surrounded by reticular or finely radiating keratotic striae. It is painful when the pseudomembrane or fibrinous plaque is disturbed. It is thought that erosive oral lichen planus has a greater potential to undergo malignant change. [96] It has been reported that only the atrophic and erosive forms of lichen planus undergo malignant change, and this may be because of the atrophic nature of the mucosa rather than the specific disease.[47]

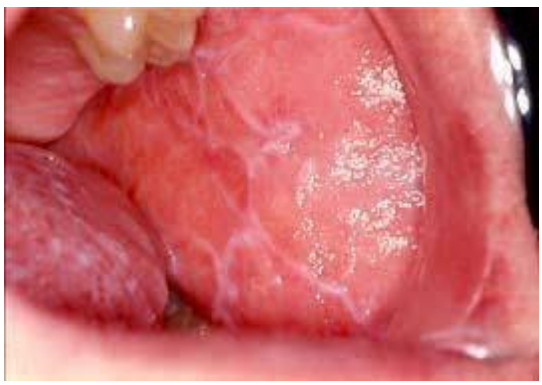


Fig.7 Reticular pattern in lichen planus

ETIOLOGY OF ORAL LICHEN PLANUS

Although the aetiology has not been fully elucidated, an immunologically induced degeneration of the basal cell layer of the oral mucosa has been suggested. In the past,

Fig.8 Erosive lichen planus on buccal mucosa

speculation about the aetiology covered a wide range of possibilities including trauma, specific bacteria, syphilis, parasites, viruses, mycotics, allergies, toxicity, neurogenic, hereditary and psychosomatic disorders. [51]

Diabetes mellitus and hypertension have been described when associated with oral lichen planus as 'Grinspan syndrome'. [52] In addition, it can be seen in several members of one family, but this does not suggest that oral lichen planus is a hereditary disease.

DIFFERENTIAL DIAGNOSIS OF ORAL LICHEN PLANUS –

Clinically, the differential diagnoses should include

- lichenoid reactions
- leukoplakia
- squamous cell carcinoma
- pemphigus
- mucous membrane pemphigoid
- candidiasis

Lichenoid reactions in the oral cavity are invariably drug-induced lesions.The erosive or atrophic types that affect the gingiva should be differentiated from pemphigoid, as both may have a desquamative clinical appearance. Lupus erythematosus often has white plaque-like lesions with an erythematous border. In some cases, erythema multiforme can resemble bullous lichen planus, but it is more acute and generally involves the labial mucosa.

MALIGNANT TRANSFORMATION OF ORAL LICHEN PLANUS -

There is some controversy regarding its malignant potential. There seems to be a slightly higher incidence of oral squamous cell carcinoma in patients with oral lichen planus than in the general population.[53] The actual overall frequency of malignant transformation is low, varying between 0.3% and 3%.[55] The forms that more commonly undergo malignant transformation are the erosive and atrophic forms.[49,54]

- Silverman et al., [58] in a survey of 570 patients followed for a mean of 5.6 years, reported malignant transformation in seven patients. The lichen lesions in five of the seven patients were considered to be either erosive or atrophic.
- Holmstrup et al., in a survey of 611 patients followed for a mean of 7.5 years, reported nine cases of malignant transformation. Six of these patients had a combination of the reticular and atrophic forms, one had a combination of the reticular, atrophic and erosive forms and two had a combination of the reticular and plaque-like forms.
- The numerous reports range from 0.4% to 5.6%.[57,58]
- About 2% of patients develop squamous cell carcinoma.[60]
- Nevertheless, Eisenberg and Krutchkoff[59] reported in their review that there was 'no inherent predisposition for oral lichen planus to become malignant', whereas in the same journal Holmstrup stated that the controversy was over because there was an 'increased risk of oral cancer development'.

MANAGEMENT OF ORAL LICHEN PLANUS-

I. Non-Surgical Management Of Oral Lichen Planus-

Corticosteroids – Intralesional corticosteroids-

Topical corticosteroids are of limited value for some cases of oral lichen planus. In such cases, it may be appropriate to use topical corticosteroids in combination with intralesional preparations. Zegarelli[63] combined the use of topical and intralesional corticosteroids in seven patients, resulting in complete improvement in five patients. However, intralesional corticosteroids have some contraindications, including atrophy of tissue and secondary candidiasis after frequent injections.

Systemic corticosteroids -

Systemic corticosteroids are of great value when there has been an acute exacerbation of symptoms and are often used in combination with topical corticosteroids. Because of the immediate effect of systemic corticosteroids and their inherent toxicity, adverse effects are common even after a course as short as two weeks.[64] The most common adverse effects include gastrointestinal upset, mood alteration, polyuria, insomnia and shakes.[65] Changes in blood pressure and blood glucose concentrations have been reported in a few patients.[61] Patients who take systemic steroids for a long time, particularly in high doses, should be monitored regularly.

Retinoids -

Retinoids were first used for the treatment of asymptomatic, white, reticulated oral lichen planus by Gunther. [66] Vitamin A was applied locally to the lesions with good results. Tretinoin is the most readily available topical retinoid.

Cyclosporin-

Damage to the basement membrane in oral lichen planus is the result of the production of lymphokines such as interferon gamma by activated T lymphocytes. Cyclosporin is an immunosuppressant and reduces the production of lymphokines.[61] It inhibits the proliferation and function of T lymphocytes. Its main adverse reaction is renal dysfunction as a result of prolonged use, so patients taking cyclosporin need to be monitored closely The primary side-effect of cyclosporin therapy was reported to be transient sensations of burning on the mucosal surface of the lesion. [67]

THE SURGICAL MANAGEMENT OF ORAL LICHEN PLANUS-

Cryosurgery and carbon dioxide laser ablation have been suggested for the surgical treatment of oral lichen planus. However, excision should not be a primary method of treatment as it is an inflammatory condition that can recur. In addition, surgical management is not suitable for the erosive and atrophic types because the surface epithelium is eroded. Surgical treatment is more applicable to the plaquelike lesions, because the affected surface epithelium can be removed easily. [67]

CHRONIC HYPERPLASTIC CANDIDIASIS-

Lehner (1964, 1967)[68,69] recognized the presentation of chronic candidal infection in the form of leukoplakia and introduced the term "candidal leukoplakia." The terms "chronic hyperplastic candidosis" (CHC) and "candidal leukoplakia" (CL) appear to have been synonymously used until the mid-1980s (Cawson, 1966a,b; Cawson and Lehner, 1968) [70,71]. Several authors preferred the term "candidal leukoplakia" to describe lesions confined to the mouth alone. In recent times, however, the term "candidal leukoplakia" appears to have lost currency, and most histopathologists prefer the term "chronic hyperplastic candidosis/candidiasis".

CLINICAL MANIFESTATIONS-

The most common and arguably the classic clinical presentation of CHC is a white plaque that cannot be scraped off and presenting most frequently in the commissural regions of the oral mucosa. However, other oral sites can be infrequently affected. The lesion can be differentiated from oral leukoplakia of idiopathic origin, since appropriate antifungal therapy usually leads to resolution of the condition.

CHC presenting as leukoplakia appears as well-demarcated, palpable, raised lesions that may vary from small translucent whitish areas to large opaque plaques that cannot be rubbed off.
Some or all areas of the plaque may have a smooth, homogenously white surface, and if this feature predominates, the lesion is referred to as a homogenous leukoplakia. However, the
Surface often has erythematous areas intermingled with white areas that, more often than not, possess a nodular characteristic. Such lesions are referred to as nodular or speckled leukoplakia.

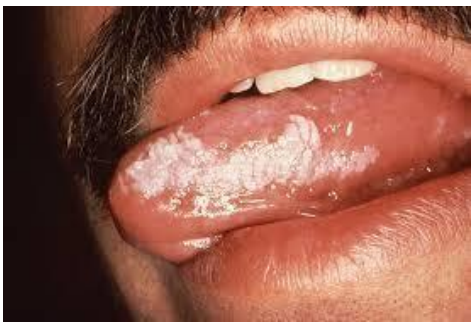


Fig.9 white hyperplastic candidiasis on lateral border of tongue

TREATMENT AND PROGNOSIS

GENERAL MEASURES TO ELIMINATE PREDISPOSING FACTORS

Since tobacco smoking has been clearly shown to be linked to the causation of many/most leukoplakias, and to candidal

leukoplakias in particular, elimination of this habit is an important

Step in the management of CL-

Prostheses, particularly maxillary dentures, act as reservoirs of *Candida* and have been shown to be linked to a high prevalence of CL. Although requesting patients to abandon their dentures is not a realistic option, preventive measures such as not wearing the prosthesis at night, together with stringent denture hygiene, should be encouraged to prevent candidal colonization of the denture surface. Patients using a steroid inhaler for medical reasons should be advised to rinse their mouths or drink water soon after using the inhaler (Spector *et al.*, 1982; Ellepola and Samaranayake, 2001) [72, 73].

SPECIFIC TREATMENT OF CHRONIC HYPERPLASTIC CANDIDAL LEUKOPLAKIA-

Antifungal therapy

Cawson and Lehner (1968)[74], in their first report on CL, claimed improvement and disappearance of a significant number of their cases of leukoplakia with polyene-nystatin (tablets) dissolved slowly in the mouth. Lamey *et al.* (1989) [75] reported a case of CL with a significant degree of epithelial dysplasia that resolved within 11 days of systemic treatment with the triazole antifungal, fluconazole. Holmstrup and Bessermann (1983) [76] reported that, following antifungal therapy, nodular lesions of the commissural areas showed the highest recurrence rate after 12 months.

WHITE SPONGE NEVUS-

White sponge nevus (WSN) is a rare hereditary leucokeratosis that was first described by Hyde in 1909[77]; the term white sponge nevus was first coined by Cannon in 1935[78].It is also known as cannons disease, oral epithelial nevus, white folded dysplasia of mucous membrane.

CLINICAL MANIFESTATION-

The onset of WSN is early in life, and both sexes are affected equally. Lesions of WSN are easily recognised and clinically important; the lesions appear as bilateral white spongy plaques, typically found on the buccal mucosa, and the patients report no painful symptoms. The lesion can be found in other common sites, including the tongue, floor of the mouth and alveolar mucosa [79]. The disease are characterised by white, thickened, folded and spongy lesions of the oral mucosa, although the oesophageal, laryngeal, nasal and anogenital mucosa can also be affected [80]. The WSN plaques are considered benign because the lesions are asymptomatic and painless in many cases, although they may undergo alternate periods of remission and exacerbation due to infections. This disorder often manifests in early childhood and exhibits no gender preference. WSN occur on the surface of the skin, including the oral mucosa and anal mucosa, among other areas.

TREATMENT AND PROGNOSIS-

Although WSN patients experience no significant physical pain, they often complain of an altered

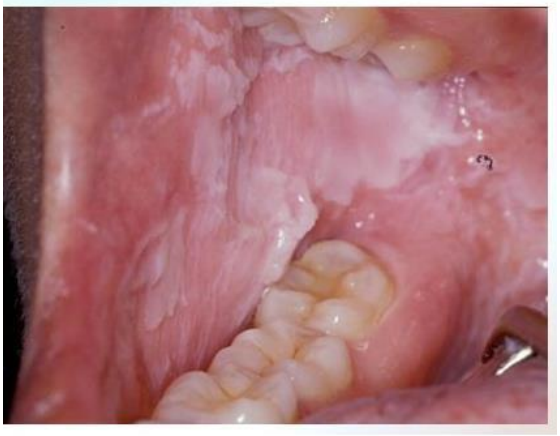


Fig.10 White, folded appearance of White sponge nevus

texture to their mucosa. Azithromycin, tetracycline and penicillin have exhibited some clinical effects [81]. A case of WSN exhibiting significant improvement following penicillin administration has been reported [82]. McDonagh et al. first reported that tetracycline medicines were effective in four WSN patients [83]. Another report stated that oral tetracycline rinse improved the symptoms of WSN [84].Subsequently, WSN was successfully treated with a tetracycline mouth rinse [85]. Long-term low dose systemic

antibiotic therapy maintained the remission of WSN [86]. To date, systemic antibiotics or local applications of retinoic acid have provided limited benefits, but both are poorly effective. Dufrasne et al. described a case of effective surgical resection, and the patient was free of recurrence 2 years later [87]. WSN may be treated with chlorhexidine [88]. Meanwhile, WSN patients should perform a careful oral hygiene to reduce infection in the oral cavity. The proper diagnosis and treatment of this rare disease will require the combination of clinical history, clinical examination and pathologic findings.

DISCUSSION-

A wrong diagnosis may lead to wrong treatment, which may not only cause physical trauma to the patient but may also be fatal especially in lesions with malignant potential. Considering the serious nature of the potentially malignant lesions, we suggest thorough clinical examination and accurate diagnosis is essential. Planning appropriate treatment can help in prevention of conversion of simple lesions into malignancies. The primary goal of this article is learning the process of clinical diagnosis of non scrapable white lesions.

Linea alba has its unique appearance as seen at occlusal plane on buccal mucosa. The clinical diagnostic test for leucoedema is it could be disappears on stretching and it is racial. The frictional keratosis is associated with history of trauma and etiological cause is apparent, mostly reversible on removing the cause. Leukoplakia is potentially malignant lesion, careful diagnosis and treatment is essential. Oral Lichen Planus is usually associated with Wickham's striae and can be differentiated from other lesions. Antifungal therapy resolves Chronic Hyperplastic Candidiasis is diagnostic. White Sponge Nevus is noted in early life, family history, large areas involved, genital mucosa may be affected.

CONCLUSION-

White lesions in oropharyngeal region can range from genetic disorder to potentially malignant disorders. Differentiating these lesions clinically is extremely important as treatment and prognosis is highly variable. Many lesions involving the oral mucosa are benign and do not require treatment. These include developmental conditions like white sponge nevus, frictional keratosis, linea Alba, etc. In contrast potentially malignant lesions like leukoplakia, lichen planus require intervention depending on potential mortality and morbidity.

REFERENCES-

1. Panat SR, Yadav N, Aggarwal A. White lesions of oral mucosa-diagnostic dilemma. Journal of Dental Sciences & Oral Rehabilitation. 2011;08-10.
2. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36:575-80.
3. Freitas MD, Blanco- Carrion A, Gandara- Vila P, Antunez-Lopez J, GarciaGarcia A, Gandara Rey JM. Clinicopathlologic aspects or oral leukoplakia in smokers and non smokers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006; 102(2):199-203.
4. Mehta FS, Daftary DK, Shroff BC, Sanghvi LD. Clinical and histological study of oral leukoplakia in relation to habits: A five year follow up. Oral Surg Oral Med Oral Pathol. 1969;28(3);372-88.
5. Martínez AD, García-Pola MV. Epidemiological study of oral mucosa pathology in patients of the Oviedo School of Stomatology. Medicina oral: organo oficial de la Sociedad Espanola de Medicina Oral y de la Academia Iberoamericana de Pathology Medicina Bucal. 2002;7(1):4-9.
6. Scully C. Oral and maxillofacial medicine: the basis of diagnosis and treatment. Churchill Livingstone Elsevier; 2008.
7. Neville BW, Damm DD, Allen CM, Bouquot JE. Odontogenic cysts and

8. tumors. Oral and maxillofacial pathology. 2002;3:678-740.
9. Madani FM, Kuperstein AS: Normal variations of oral anatomy and common oral soft tissue lesions Evaluation and management. Med Clin N Am.2014;1-18.
10. Russ HC. Oral leukoplakia: a review of the literature. Journal of Oral Surgery. 1957;1 5:40-49.
11. Crawley EP, Kerr DA. Lichen planus. Oral Surg Oral Med Oral Pathol. 1952;5:1069-1076.
12. Banoczy J. Oral leukoplakia and other white lesions of the oral mucosa related to dermatological disorders. J Cutan Pathol. 1983;1 0:238-256.
13. Duncan SC. Leukoedema of the oral mucosa. Possibly an acquired white sponge nevus. Arch Dermatol. 1980;1 16:906-908.
14. Cannon AB. White nevus of the mucosa (naevus spongiosus albus mucosae). Archives of Dermatology and Syphilis. 1935;31:365-370.
15. Jayanthi P, Ranganathan K. Differential diagnosis of white lesions of oral mucosa. J Orofac Sci 2010:2(2);58-63.
16. Joshy VR, Hari S. White lesions of the oral cavity – diagnostic appraisal & management strategies. Journal of Clinical Dentistry 2005;1(1):27-30.
17. Regezi J, Sciubba J, Jordan R. Oral Pathology, clinical pathologic correlations – 5th Edition. Elsevier Publishers.
18. Lee KH, Polonowita AD. Oral white lesions: Pitfalls for diagnosis. MJA 2009; 190: 274-7.
19. van der Waal I. Oral leukoplakia, the ongoing discussion on definition and terminology. Med Oral Patol Oral Cir Bucal. 2015 Nov 1;20 (6):685-92.
20. Gupta PC, Mehta F S, Daftary DK et aL, Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. Community Dental and Oral Epidemiology. 1980;8:287-333.
21. Gupta PC. Epidemiologic study of the association between alcohol habits and oral leukoplakia. Community Dental and Oral Epidemiology. 1984;12:47-50.
22. Evstifeeva, T. V. and Zaridze, D. G., Nass use, cigarette smoking, alcohol consumption and risk of oral and oesophageal precancer. Oral Oncology, European Journal of Cancer. 1992;28:29-35.
23. Kulasegaram R, Downer MC, Jullien J A, Zakrzewska JM and Speight PM. Case-control study of oral dysplasia and risk habits among patients of a dental hospital. Oral Oncology, European Journal of Cancer.1995;31:227-231.
24. Blot WJ, Winn DM, Fraumeni JF. Oral cancer and mouthwash. J Natl Cancer Inst. 1983;70:251–253.
25. Kabat GC, Hubert JR and Wynder E L. Risk factors for oral cancer in women. Cancer Research. 1989;49:2803-2806.
26. Kramer IR. Precancerous conditions of the oral mucosa. A computer-aided study. Annals of the Royal College of Surgeons of England. 1969;45(6):340.
27. Krogh P, Hald B and Holmstrup P. Possible mycological etiology of oral mucosal cancer: catalytic potential of infecting Candida albicans and other yeasts in production of N-nitrosobenzylmethylamine. Carcinogenesis. 1987;8:1543-1548.
28. Field EA, Field JK, Martin MV. Does Candida have a role in oral epithelial neoplasia?. Journal of Medical and Veterinary Mycology. 1989;27(5):277-94.
29. Hornstein OP, Gräbel R. Häufigkeit und prognostische bedeutung der candida-besiedelung oraler leukoplakien. Dtsch Z

31. Mund Kiefer GesichtsChir. 1992;16:112-6.
32. Miller CS and White DK. Human papillomavirus expression in oral mucosa, premalignant conditions, and squamous cell carcinoma. A retrospective review of the literature. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology Endod. 1996;82:57-68.
33. Palefsky JM, Silverman Jr S, Abdel-Salaam M, Daniels TE, Greenspan JS. Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. Journal of oral pathology & medicine. 1995;24(5):193-7.
34. Ramaswamy G, Rao VR, Kumaraswamy SV, Anantha N. Serum vitamins' status in oral leucoplakias—a preliminary study. European Journal of Cancer Part B: Oral Oncology. 1996;32(2):120-2.
35. Mithani SK, Mydlarz WK, Grumbine FL, Smith IM, Califano JA. Molecular genetics of premalignant oral lesions. Oral diseases. 2007;13(2):126-33.
36. Silverman S, Bhargava K, Mani NJ, Smith LW and Malaowalla AM. Malignant transformation and natural history of oral leukoplakia in 57,518 industrial workers of Gujarat, India. Cancer, 1976, 38, 1790 1795.
37. Banoczy J, Sugar L. Longitudinal studies in oral leukoplakias. Journal of Oral Pathology & Medicine. 1972;1(6):265-72.
38. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral oncology. 2009;45(4):317-23.
39. Bfindczy J and Sugfir L. Progressive and regressive changes in Hungarian oral leukoplakias in the course of longitudinal studies. Communit Dental and Oral Epidemiology. 1975;3:194-197.
40. Sdubba JJ. Oral leukoplakia. Critical Reviews in Oral Biology & Medicine. 1995;6(2):147-60.
41. Van der Waal I, Schepman KP, Van der Meij EH, Smeele LE. Oral leukoplakia: a clinicopathological review. Oral oncology. 1997;33(5):291-301.
42. Ribeiro AS, Salles PR, da Silva TA, Mesquita RA. A Review of the Nonsurgical Treatment of Oral Leukoplakia. International Journal of Dentistry.2010;1-10.
43. Hansen LS, Olson J A and Silverman S. Proliferative verrucous leukoplakia. Oral Surge13', Oral Medicine, Oral Pathology, 1985, 60, 285 298.
44. Shear M and Pindborg JJ. Verrucous hyperplasia of the oral mucosa. Cancer. 1980;46:1855-1862.
45. Longshore SJ, Camisa C. Detection and management of premalignant oral leukoplakia. Dermatol Ther. 2002;15:229-35.
46. Bouquot JE, Gorlin RJ. Leukoplakia, lichen planus, and other oral keratoses in 23 616 white Americans over the age of 35 years. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1986; 61: 373–381.
47. Andreasen JO. Oral lichen planus. A clinical evaluation of 115 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1968; 25:31–42.
48. Scully C, el-Kom M. Lichen planus: review and update on pathogenesis. J Oral Pathol Med. 1985; 14: 431–458.
49. Strassburg M, Knolle G. Diseases of the oral mucosa. Quintessence Int 1974; 5: 53–60.
50. Bricker SL. Oral lichen planus. a review. Semin Dermatol. 1994; 13: 87–90.
51. Thorn JJ, Holmstrup P, Rindum J, Pindborg JJ. Course of various clinical

forms of oral lichen planus. A prospective follow-up study of 611 patients. J Oral Pathol Med. 1988; 17: 213–218.
52. Marder MZ, Deesen KC. Transformation of oral lichen planus to squamous cell carcinoma: a literature review and report of case. J Am Dent Assoc. 1982; 105: 55–60.
53. Pogrel MA, Weldon LL. Carcinoma arising in erosive lichen planus in the midline of the dorsum of the tongue. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1983; 55: 62–66.
54. McCarthy PL, Shklar G. Diseases of the Oral Mucosa, 2nd edn. Philadelphia: Lea and Febiger, 1980.
55. Grinspan D, Diaz J, Villapol LO et al. J. Lichen ruber planus of the buccal mucosa. Its association with diabetes. Bull Soc Fr Dermatol Syphiligr. 1966; 73: 898–899.
56. Silverman S Jr, Griffith M. Studies on oral lichen planus. II. Follow-up on 200 patients, clinical characteristics, and associated malignancy. Oral Surg Oral Med Oral Pathol Oral.
57. Barnard NA, Scully C, Eveson JW, Cunningham S, Porter SR. Oral cancer development in patients with oral lichen planus. J Oral Pathol Med. 1993; 22: 421–424.
58. Sloberg K, Jonsson R, Jontell M. Assessment of Langerhans' cells in oral lichen planus using monoclonal antibodies. J Oral Pathol Med. 1984; 13: 516–524.
59. Silverman S Jr, Gorsky M, Lozada-Nur F. A prospective follow-up study of 570 patients with oral lichen planus: persistence, remission, and malignant association. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1985; 60: 30–34.
60. Murti PR, Daftary DK, Bhonsle RB, Gupta PC, Mehta FS, Pindborg JJ. Malignant potential of oral lichen planus: observations in 722 patients from India. J Oral Pathol Med. 1986; 15: 71–77.
61. Salem G. Oral lichen planus among 4277 patients from Gizan, Saudi Arabia. Community Dent Oral Epidemiol. 1989; 17: 322–324.
62. Eisenberg E, Krutchkoff DJ. Lichenoid lesions of oral mucosa. Diagnostic criteria and their importance in the alleged relationship to oral cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1992; 73: 699–704.
63. Zegarelli DJ. The treatment of oral lichen planus. Ann Dent. 1993; 52: 3–8.
64. Eisen D. The therapy of oral lichen planus. Crit Rev Oral Biol Med. 1993; 4: 141–158.
65. Sleeper HR. Intralesional and sublesional injection of triamcinolone acetonide for oral lichen planus. Yale J Biol Med. 1967; 40: 164–165.
66. Zegarelli DJ. Multimodality steroid therapy of erosive and ulcerative oral lichen planus. J Oral Med. 1983; 38: 127–130.
67. Lozada F, Silverman S Jr, Migliorati C. Adverse side effects associated with prednisone in the treatment of patients with oral inflammatory ulcerative diseases. J Am Dent Assoc. 1984; 109: 269–270
68. Silverman S Jr, Lozada-Nur F, Migliorati C. Clinical efficacy of prednisone in the treatment of patients with oral inflammatory ulcerative diseases: a study of fifty-five patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1985; 59: 360–363.
69. Gunther SH. Vitamin A acid in treatment of oral lichen planus. Arch Dermatol. 1973; 107: 277.

70. Mollaoglu N. Oral lichen planus: a review. British Journal of oral and maxillofacial surgery. 2000 Aug 1;38(4):370-7.
71. Lehner T et. al. Chronic candidiasis. Br Dent J. 1964;116:539-545.
72. Lehner T.et.al. Oral candidosis. Dent Pract. 1967;17:209-216
73. Cawson RA.Chronic oral candidiasis and leukoplakia. Oral Surg Oral Med Oral Pathol 1966;22:582-591.
74. Cawson RA. Chronic oral candidosis, denture stomatitis and chronic hyperplastic candidosis. In: Symposium on Candida infections. Winner HI, Hurley R, editors. London: Livingston. 1966;22:138-53.
75. Spector SL, WANGAARD C, Bardana Jr EJ. The use of cultures and immunologic procedures to predict oropharyngeal candidiasis in patients on steroid aerosols. Clinical & Experimental Allergy. 1982;12(3):269-78.
76. Ellepola AN, Samaranayake LP. Inhalational and topical steroids, and oral candidosis: a mini review. Oral diseases. 2001;7(4):211-6.
77. Cawson RA, Lehner T. Chronic hyperplastic candidosis-candidal leukoplakia. Br J Dermatol. 1968; 80:9-16.
78. Lamey PJ, Lewis MA, MacDonald DG. Treatment of candidal leukoplakia with fluconazole. British dental journal. 1989;166(8):296
79. Holmstrup P, Bessermann M. Clinical, therapeutic, and pathogenic aspects of chronic oral multifocal candidiasis. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 1983;56(4):388-95.
80. Hyde JN. An unusual naevus of the tongue in a five-year-old boy. J Cutan Dis. 1909;27:256.
81. Cannon AB. White sponge nevus of the mucosa (naevus spongiosus albus mucosae). Archives of Dermatology and Syphilology. 1935;31(3):365-70.
82. Frithiof L, Bánóczy J. White sponge nevus (leukoedema exfoliativum mucosae oris): ultrastructural observations. Oral Surgery, Oral Medicine, Oral Pathology. 1976;41(5):607-22.
83. Jorgenson RJ, Levin LS. White sponge nevus. Archives of dermatology. 1981;117(2):73-6.
84. Songu M, Adibelli H, Diniz G. White sponge nevus: clinical suspicion and diagnosis. Pediatric dermatology. 2012;29(4):495-7.
85. Alinovi A, Benoldi D, Pezzarossa E. White sponge nevus: successful treatment with penicillin. Acta dermato-venereologica. 1983;63(1):83-5.
86. McDonagh AJ, Gawkrodger DJ, Walker AE. White sponge naevus successfully treated with topical tetracycline. Clinical and experimental dermatology. 1990;15(2):152-3.
87. Lim J, Ng SK. Oral tetracycline rinse improves symptoms of white sponge nevus. Journal of the American Academy of Dermatology. 1992;26(6):1003-5.
88. Becker LR, Lutz C, Erbard H, Bröcker EB, Hamm H. White sponge naevus successfully treated with tetracycline mouth rinse. Acta dermato-venereologica. 1997;77(5):413.
89. Lamey PJ, Bolas A, Napier SS, Darwazeh AM, Macdonald DG. Oral white sponge naevus: response to antibiotic therapy. Clinical and experimental dermatology. 1998;23(2):59-63.
90. Dufrasne L, Magremanne M, Parent D, Evrard L. current therapeutic

approach of the white sponge naevus of the oral cavity. Bulletin du Groupement International pour la Recherche Scientifique en Stomatologie et Odontologie. 2011; 50(1):1-5.

91. Satriano RA, Errichetti E, Baroni A. White sponge nevus treated with chlorhexidine. The Journal of dermatology. 2012; 39(8):742-3.

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