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Ruminating the Pathway of Oral Leukoplakia- A Review

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ABSTRACT-

Oral leukoplakia (OL) grabs the place of being one of the most common oral potentially malignant disorders of the oral mucosa. As a result of differences in tobacco and dietary habits the annual percentage of malignant transformation varies in different parts of the world. The tongue and the floor of the mouth can be considered to be high-risk sites with regard to malignant transformation of leukoplakia in some parts of the world, while this does not have to be the case in other parts of the world.Management of this condition remains a variable and includes local, topical, and systemic therapies such as anti-oxidants, carotenoids, and antifungal therapies.Cessation of tobacco consumption habits, as being the most common etiological factor of OL, has shown to be an effective measure with regard to the incidence of oral cancer as well. Hence, in view of many predominantly white or white lesions of the mucosa of oral cavity, it is a great challenge for the oral health care professionals to clinically identify and diagnose a leukoplakia, being a potentially (pre) malignant lesion. In this review, we will be throwing light on the periphery and core of oral leukoplakia.

Keywords: - oral leukoplakia, precancerous lesion, epithelial dysplasia

INTRODUCTION

Oral leukoplakia (OL) is one of the most common and important potentially malignant disorders (PMD) of the oral mucosa. It can be defined as "a predominant white lesion of the oral mucosa that cannot be characterized as any other definable lesion."[1,2]The term leukoplakia means white patch (leuko-white, plakia-patch). It is considered as a premalignant lesion, but recently it is linked to being a broader term for common usage of tobacco in the form of smoking or chewing. The lesion possesses a high-risk of malignant transformation if the risk factors are not eliminated.[3]Leukoplakia consists of two forms: Homogeneous and the non-homogeneous type. Homogeneous leukoplakia is characterized by a uniform flat white lesion, thin in appearance, having a smooth, wrinkled or corrugated surface throughout the lesion, whereas non-homogeneous leukoplakia is a mixture of white-and-red lesion that may be either irregularly flat, nodular, or verrucous.[4]The characteristic histologic findings of leukoplakia include epithelial hyperplasia, and/or hyperkeratosis, with or without epithelial dysplasia or carcinoma.[5]The annual rate of malignant transformation of leukoplakia is estimatedto be 1.36% (0.69-2.03%).[6]Certain clinical characteristics such as lesion type, size, and site, dysplasia, and tobacco use have been associated with the increased malignant potential of leukoplakia.[1]

The World Health Organization (WHO) defined the term "potentially malignant disorders" as the risk of malignancy being present in a lesion or condition either during the time of initial diagnosis or at a future date.[3,7]While WHO defined leukoplakia as "a white plaque of questionable risk having excluded (other)

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known diseases or disorders that carry no increased risk for cancer."[3,8,9]Various risk factors have been associated with the rise of leukoplakia which include all forms of tobacco use forms, including cigar, cigarette, beedi, and pipe.[10] Some other synergistic risk factors include alcohol consumption, chronic irritation, fungal infections such as candidiasis, oral galvanism due to restorations, bacterial infections, sexually transmitted lesions like syphilis, combined micronutrient deficiency, viral infections, hormonal disturbances, and ultraviolet exposure.[10] It has been reported that many potentially malignant disorders may give rise to oral squamous cell carcinoma. Hence a correct and proper diagnosis along with treatment at the right time of potentially malignant disorders may help prevent malignant transformation of these lesions.[3] In this review, we will be discussing in depth about the periphery and core of oral leukoplakia.

THE EPIDEMIOLOGY OF LEUKOPLAKIA

Incidence and prevalence of Leukoplakia

Gupta *et al*,[11] in the year 1992, found the prevalence of leukoplakia in a wide range population. While in India, it was found to occur in 0.2% and 4.9% of the population present over 15 years of age.[11]Another researcher named Bánóczy in the year 1983 found that the prevalence of leukoplakia in adult population varied between 0.6% and 3.6%.[12] Downer and Petti explored an annual oral cancer incidence rate attributable to leukoplakia between 6.2 and 29.1 cases per 100,000 people.[13]

Martorell-Calatayud *et al*.[14](2009), found the prevalence of OL ranging from 0.4% to 0.7% of the population.[13] Feller and Lemmer in the year 2012 found the prevalence and malignant transformation of OL ranging from 0.5% to 3.46%and 0.7% to 2.9% respectively.[14,34]

Brouns *et al*. (2013), alsofound out the prevalence of OL of 2% approximately with an annual malignant transformation of approximately 1%.[15]

Age and gender aspects of leukoplakia

Bánóczy (1977) found the incidence of malignant transformation to be 5.8% in women and 2.1% in men. He also found a higher incidence rate amongst habitual smokers or drinkers.[16]Bánóczy also found the risk of malignant transformation to be greater in women as compared to males.[16]He explored that the age range for occurrence of leukoplakia is within the age-group of 51-60 years with a male:female ratio of 3.2:1.[16]

Espinoza (2003) found a higher prevalence of leukoplakia in men after 50 years of age.[17]Espinoza *et al*. stated the prevalence of leukoplakia in all the age groups but with an increased prevalence in the geriatric population, ranging from 0.35% to 18.6%.[17]Downer and Petti found the prevalence of leukoplakia to be more in males as compared to females with a prevalence ratio of 3.22.[13]

Liu *et al*. (2010) implied that the peak incidence of leukoplakia was in the fifth decade of human life (33.0%) by conducting a study on 218 patients. He found out the gender ratio to be equal.[6]Brzak *et al*. in the years 1997-2007 carried out a study by including 12,508 patients and found that women were predominantly affected than men.[18]

In India, the prevalence of leukoplakia varies from 0.2% to 4.9%. The lesion has a greater male prediction than females occurring within the age range of 35-45 years. Less than 1.3% of leukoplakias in India are of idiopathic origin.[19, 21]

In less than 1% of men below the age of 30 years suffer from leukoplakia, but the prevalence increases strikingly to 8% in men over the age of 70 years. The prevalence in women past the age of 70 is approximately two percent. The most common sites for occurrence of leukoplakia are the buccal mucosa, alveolar mucosa, and lower lip; however, lesions in the floor of mouth, lateral tongue, and lower lip are most prone to have dysplastic or malignant changes[20, 21].

CLASSIFICATION

According to BANOCZY (1977)[22]leukoplakiacan be classified into-

A. **Type I - Leukoplakia Simplex**- a uniform raised plaque formation, varying in size, with regular edges.

B. **Type II**–**LeukoplakiaVerrucosa** - a lesionwithslightlyraised, rounded, red or white excrescence thatmaybedescribed as granules or nodules.

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C. **Type III - Leukoplakia Erosiva**- it is characterized by verrucous proliferation raised above the mucosal surface.

According to WHO 1980[23]

1) **Homogenous leukoplakia** - Lesion that is uniformly white and unscrapable.
2) **Non-homogenous leukoplakia** - Lesion predominantly white and speckled with red.

PAPE et al (1994)[22]

A. Homogenous: Complete white lesion.
i. Flat- having a smooth surface.
ii. Corrugated- like a beach at ebbing edge.
iii. Pumice like- with a pattern of fine lines
iv. Wrinkled - like dry, cracked mud surface.

B. Non- Homogenous:
i. **Proliferative & Verrucous**- slow growing, papillary proliferations, above the mucosal surface that may be heavily keratinized.
ii. **Ulcerated**- Lesion exhibits red area at the periphery of which white patches are present.
iii. **Nodular** - Characterized by white specks or nodules on erythematous base.
iv. **Erythroleukoplakia** - leukoplakia is present in association with erythroplakia.

According to WHO (1998)[23]

- **Thin, smooth leukoplakia**- Translucent thin gray soft flat plaques usually with sharply demarcated borders.
- **Thick, fissured leukoplakia**- 2/3 of white plaques has distinctly white appearance, fissured and is leathery to palpation.
- **Granular, verruciform of leukoplakia**- Lesions have surface irregularities of nodular or granular nature with verrucous appearance.
- **Erythroleukoplakia-** Lesion showing intermixed red and white areas.

According to WHO (2002) depending on the probability of a malignant change and prognosis of these lesions as -

a. **Phase I**: thin, smooth leukoplakia - better prognosis.
b. **Phase II**: thick, fissured leukoplakia – mild prognosis
c. **Phase III**: proliferative verrucousleukoplakia (PVL) - higher malignant transformation rate- moderate prognosis
d. **Phase IV**: erythroleukoplakia - poor prognosis

WARNAKULASURIYA et al (2007)[23]

- Homogeneous leukoplakia
- Non - Homogenous leukoplakia
- Speckled leukoplakia
- Nodular leukoplakia
- Verrucousleukoplakia

Staging System[23]

WHO in 2005 recommended a clinical staging system for oral leukoplakia (OL system) on the lines of TNM staging by taking into account the lesion size (L) and the histopathological features (P) of the lesion.

I.(L - Size of leukoplakia) as-

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L1 -Size of leukoplakia is < 2cm

L2 - Size of leukoplakia is 2 - 4 cm

L3 - Size of leukoplakia is >4cm

Lx - Size of leukoplakia is not specified

II.(P - Pathology)

Px - Dysplasia not specified in pathology report

P0 - No epithelial dysplasia

P1 - Mild to moderate epithelial dysplasia

P2 - Severe epithelial dysplasia

OLEP Staging System[21]

Stage I L1P0

Stage II L2P0

Stage III L3P0 or L1/L2P1

Stage IV L3P1or any LP2.

General Rules of the OLEP Staging System[21]

In case of doubt concerning the correct L or P category to which a particular case should be allotted, then the lower (i.e. less advanced) category should be chosen. In cases of multiple biopsies of single leukoplakia or biopsies taken from multiple leukoplakias, a highest pathological score of the various biopsies should be used.[21] Leukoplakia is purely a clinical terminology and histopathologically it is reported as epithelial dysplasia. WHO in the year 2005 proposed five different grades of epithelial dysplasia based on architectural disturbances and cytological atypia as follows-

a. Squamous Hyperplasia - benign lesion.

b. Mild Dysplasia - better prognosis.

c. Moderate Dysplasia.

d. Severe Dysplasia.

e. Carcinoma In-situ - poor prognosis.

Recently, it has been proposed to modify the above 5- tier system into a binary system of 'high risk' and 'low risk' lesions so as to improve clinical management of these lesions.

Etiopathogenesis Of Leukoplakia

1) LOCAL FACTORS

i. Tobacco- is the main etiologic agent for leukoplakia and is available in mainly two forms: smoked and smokeless. The smoked form of tobacco contains carbon monoxide, thiocyanate, hydrogen cyanide, nicotine and the metabolites of these constituents whereas the smokeless form contains nitrosamine, polycylic aromatic hydrocarbons and nitrosoproline. The smoked tobacco is available in the forms of bidi, chilum and cigarette whereas the smokeless tobacco is available in the forms of dry snuff, moist snuff, niswar, naas, mishri, khaini quid (tobacco + slaked lime). The chemical constituents of tobacco in conjunction with its combustion end products such as tars and resins are irritating substances which are capable of causing leukoplakia.Over around 300 carcinogens identified in tobacco smoke or in its water-soluble components are expected to leach into saliva. The majorly studied among them include aromatic hydrocarbons, benzopyrene and the tobacco specific nitrosamines, N-nitrosonornicotine (NNN), nitrosopyrrolidine (NYPR), nitrosodimethylamine (NDMA) and 4-(methylnitrosamine)-1-(3-pyridyl)- 1-

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butanone (NNK).Benzopyrene being the most powerful carcinogen is found in amounts of 20-40mg per cigarette.[21]

ii. **Alcohol:** It seems to have a strong synergistic effect along with tobacco in oral cancer production, but has not been associated with leukoplakia. It causes the oral mucosa to dehydrate and also increases the ambient temperature of the oral cavity thereby making the oral mucosa more vulnerable to the carcinogenic effects of tobacco. Alcohol itself contains hydrocarbons and nitrosamines.[21]

iii. **Sanguinaria:** It is capable of causing true leukoplakia. It is a herbal extract used in the toothpaste and mouth rinse. It can cause true leukoplakia. This type of leukoplakia is called sanguinaria-associated keratosis and is usually located in the maxillary vestibule or on the alveolar mucosa of the maxilla.[21]

iv. **Trauma:** Continuous trauma or local irritation to the oral mucosa can cause leukoplakia. The factors associated with irritation may be malocclusion, ill-fitting denture, sharp broken teeth, hot or spicy food, root piece, etc. Chronic mechanical irritation may produce a whitish lesion having a roughened keratotic surface termed as frictional keratosis. The most prone sites for such trauma are the buccal mucosa and less often the alveolar ridge.[21]

v. **Candidiasis:** The association of Candida albicans with leukoplakia, has been reported very frequently and more commonly with the nodular type. Local factors such as tobacco smoking, denture wearing or occlusal friction may be associated with the occurrence of candidal leukoplakia. Tobacco smoking may cause candidal colonization due to increased keratinization, reduced salivary IgA concentration or decreased PMNL function.

vi. **Regional & Systemic Factors:**

- **Tertiary Syphilis**

White patches are seen on the tongue. Syphilitic glossitis is observed. Atrophy of the

filiform and fungiform papillae occurs.

- **Deficiency of vitamin A,B complex, C,E beta-carotene**

a) Nutritional Deficiency: Sideropenicanemia may be the disposing factor for the occurrence of leukoplakia.

b) Viral Infection: The possible implication of human papilloma virus in the etiology and potential for the malignant transformation of oral premalignant lesion has been studied extensively and it was reported that the likelihood of detecting HPV was 2-3 times higher in precancerous oral mucosa and 4-5 times higher in squamous cell carcinoma than in normal oral epithelium. The possible viral etiology of oral leukoplakia had been first suggested by light microscopic examination of HPV suggestive changes.

Clinical Features of Leukoplakia

People older than 40 years of age are usually affected by leukoplakia. Its prevalence increases rapidly with age, especially for males and as many as 8% of men older than 70 years of age reportedly are affected.

Leukoplakia can occur in any of the sites in the oral cavity, but most commonly occurs on the buccal mucosa, gingiva and vermilion border of the lip (actinic cheilitis) and less likely occurs on the the lips and palate, maxillary mucosa, retromolar area, floor of the mouthand tongue are less likely sites. The latter two sites account for almost 93% of leukoplakia with dysplasia or carcinomatous change. The sex distribution for leukoplakia quite is variable. Males are more commonly affected in some countries, while this is not the case in the western world. Less than 1% of men below the age of 30 have leukoplakia. The male -to-female ratio is reported to be about 3:1 to 6:1. Leukoplakia can occur either solitary or multiple.

The earliest form of leukoplakia is thin and appears as a slightly elevated grayish-white patch which may be either well-defined or it may gradually blend into the surrounding normal mucosa. Later with the progression of the lesion, it becomes thicker and whiter, sometimesdeveloping as leathery appearing patchhaving surface fissures. Some leukoplakias have irregularities on their surface and are referred to as granular or nodular leukoplakias while others develop a papillary surface and are known as verrucous or verruciformleukoplakia.[21, 24]

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Clinical Appearance

a. Homogenous Leukoplakia: It presents as a localized lesion or extensive white patch that may have a relatively consistent pattern throughout. Surface of lesion is described variously as corrugated ("like a beach at ebbing tide") with a pattern of fine lines ("cristae"), wrinkled ("like dry, cracked mud") or papillomatous. The homogeneous type occupies about 84% of all the leukoplakias.[21](FIGURE 1)

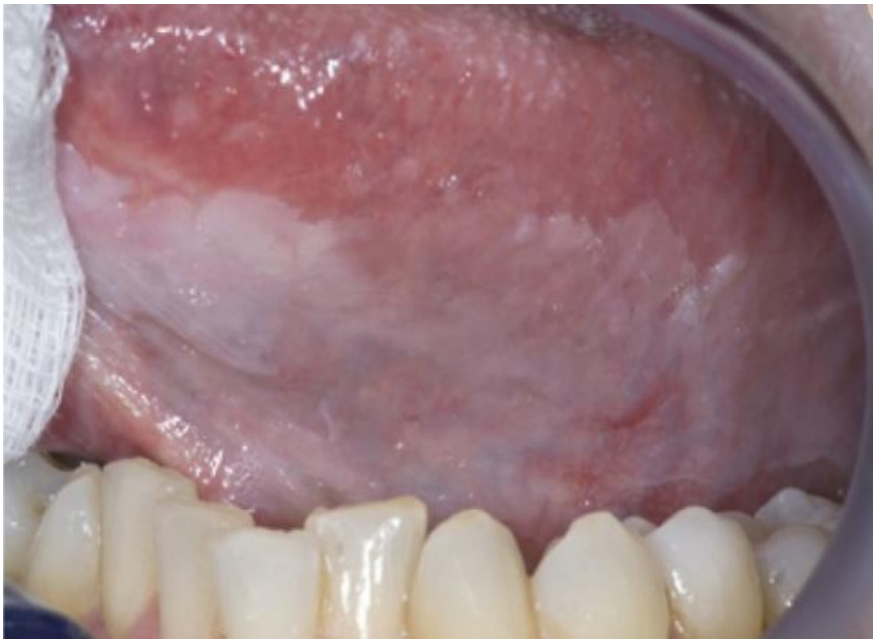

Figure 1- Homogenous Leukoplakia On Ventral Surface Of Tongue

b. Non-homogenous Leukoplakia:

- **Nodular leukoplakia**- It is also called as speckled leukoplakia and is characterized by small white specks or nodules lying on an erythematous base. The nodules may be very fine (Speckled), pinhead sized or even larger. About 3% of leukoplakias are of the nodular type. This type of leukoplakia is associated with a high malignant transformation rate.[21](FIGURE 2)

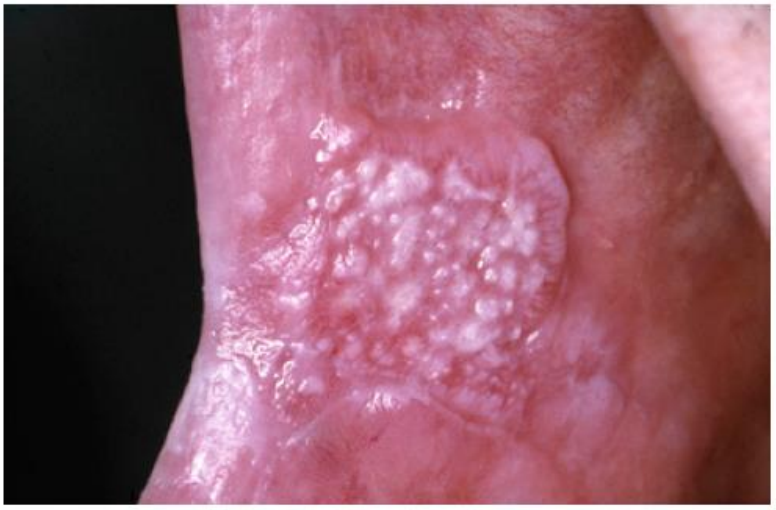

Figure 2- Non-homogeneous, nodular, leukoplakia

Verrucousleukoplakia: It presents as a thick white lesion with papillary surfaces in the oral cavity. These lesions are heavily keratinized and are most commonly seen in older adults in the 6th to 8th decades of life.[21] (FIGURE 3)

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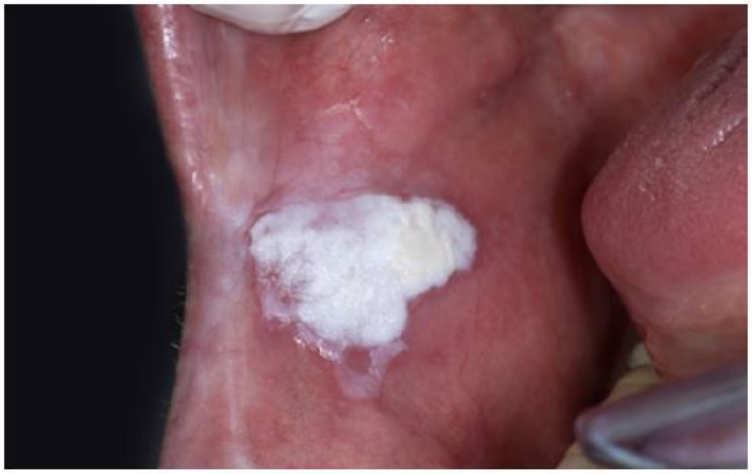

FIGURE 3- Non-homogeneous, verrucous leukoplakia.

- **Proliferative Verrucous Leukoplakia (PVL) :** It is a unique type of clinical oral leukoplakia. It possesses quite an enigmatic etiology. It is far more aggressive in fashion than other forms of leukoplakia. Batsakis JG et al. in the year 1999reported its aggressiveness related to a high recurrence rate, and also to a very high level of relentless progression from a localized simple keratosis to an extensive oral disease along with squamous carcinomas of verrucous or conventional squamous cell type.[24](Figure 4)

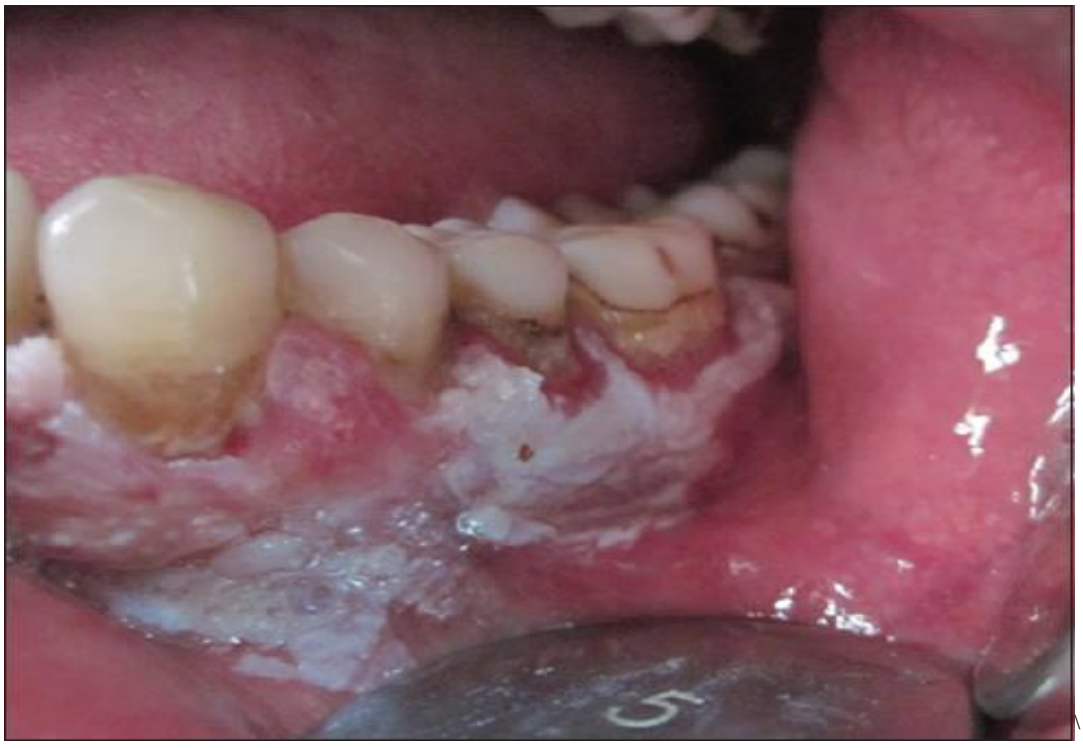

Figure 4:Proliferative Verrucous Leukoplakia (PVL) -Irregular keratotic growth involving gingiva and alveolar mucosa (posterior extension of growth)

- **Candidal Leukoplakia:** It is an extremely chronic form of oral candidiasis which presents as a firm, white, leathery plaquemainly found on the buccal mucosa, lips and tongue. Differentiation of candida leukoplakia from other forms of leukoplakia is done on the basis of PAS staining for hyphae and antibody studies. Epithelial dysplasia occurs 4 to 5 times more frequently in candida leukoplakia than in leukoplakia in general. Carcinomatous change, which occurs up to 40% more frequently in candida leukoplakia, is a characteristic of the speckled lesions. (Figure 5)

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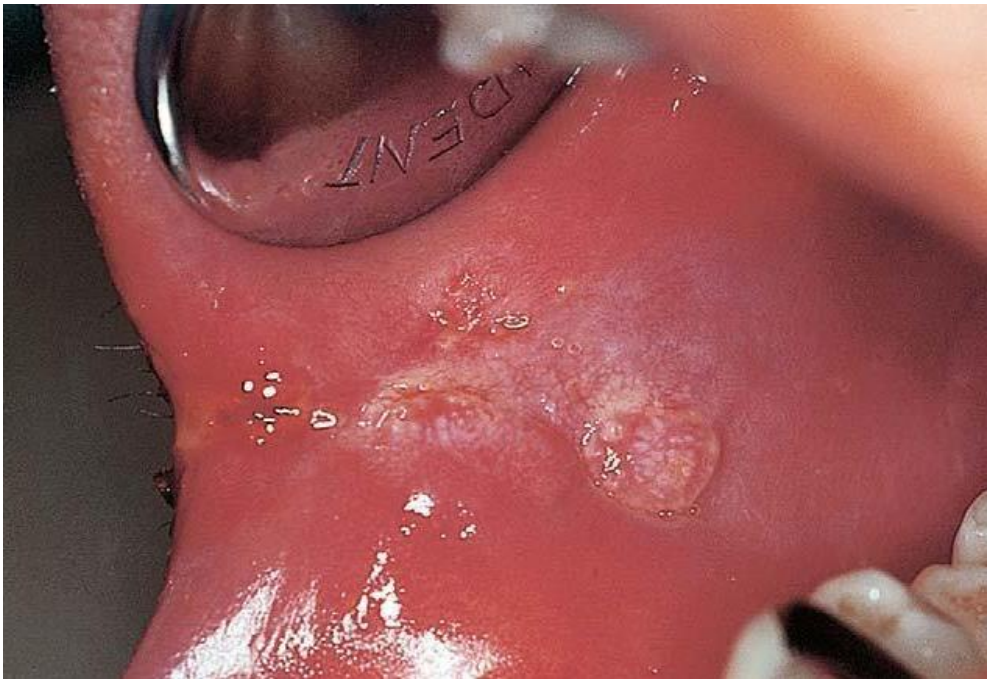

Figure 5: Candidal leukoplakia on right buccal mucosa

DIAGNOSING LEUKOPLAKIA

Leukoplakias are diagnosed on the basis of a proper case history and clinical examination. Taking biopsy of all suspected lesions of leukoplakia is very mandatory as it confirms the diagnosis so that proper treatment can be planned. In cases of large lesions, incisional biopsy should be done including some adjacent normal tissue, where as in cases of small lesions, excisional biopsy should be the choice. To select the appropriate biopsy site toluidine blue and vizilite can be used. The primary significance of incisional biopsy in such lesions is to detect the presence or absence of dysplasia, grade of dysplasia if present, as dysplasia, carcinoma in situ or invasive carcinoma cannot be predicted clinically. In cases of large sized lesions, if in inaccessible sites, at multiple sites, incisional biopsy is done mandatorily if the lesion is non homogenous. It also helps in excluding other recognized white lesions. The site of the biopsy should be from symptomatic area and if the lesion is asymptomatic, it should be taken from red or indurated areas .[25,26,27]

Differential Diagnosis

Lesions that must be included in differential diagnosis of leukoplakia should be lichen planus, leukoedema, white sponge nevus, syphilitic mucous patch, discoid lupus erythematosis, verruca vulgaris, chemical burn, and chronic cheek bite .[25-27]

Histopathological Features

Leukoplakia is basically a clinical term. The histopathological sections of leukoplakia comprise epithelial hyperplasia and surface hyperkeratosis (hyperparakeratosis or hyperorthokeratosis). Epithelial dysplasia may be seenin which may range from mild to severe, based on its presence leukoplakia is of two type's dysplastic and non dysplastic [25-27.] The criterion used for dysplasia are listed in [TABLE 1][28]

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Criteria used for diagnosing dysplasia

CYTOLOGY	ARCHITECTURE
Abnormal variation in nuclear size (anisonucleosis)	Irregular epithelial stratification
Abnormal variation in nuclear shape (nuclear pleomorphism)	Loss of polarity of basal cells
Abnormal variation in cell size (anisocytosis)	Drop-shaped rete ridges
Abnormal variation in cell shape (cellular pleomorphism)	Increased number of mitotic figures
Increased nuclear-cytoplasmic ratio	Abnormal superficial mitoses
Increased nuclear size	Premature keratinization in single cells (dyskeratosis)
Atypical mitotic figures	Keratin pearls within rete pegs
Increased number and size of nucleoli	Basal cell hyperplasia
Hyperchromasia	

Table 1- Criteria for diagnosing dysplasia

Verrucous leukoplakia is difficult to differentiate from verrucous carcinoma as it shows papillary surface projections and broad reteridges, PVL initially resemble leukoplakias but as the lesion progresses it resembles more like squamous cell carcinoma [26]

POTENTIAL FOR MALIGNANT TRANSFORMATION

Various studies have shown 0.6 to 20% rate of malignant transformation of leukoplakia. The factors responsible for increasing the transformation rate are[26, 27, 29]

1. **Age**: Transformation rates were found to be increasing with increasing age.
2. **Size**: Large size lesions (more than 20mm) are associated with high transformation rates.
3. **Habits**: It was found that smokers have greater malignant transformation than non smokers.
4. **Site**: The risk of transformation varied with the site, high risk areas being floor of mouth and tongue, low risk areas being buccal mucosa and commissures.
5. **Gender**: Females (6%) had higher transformation rates than male (3.9%).
6. **Clinical type:** Non homogenous types and PVL showed higher rates than homogenous type.
7. **Epithelial Dysplasia:** is considered as the most important factor for malignant transformation. Dysplastic leukoplakias showed a higher risk of malignant transformation as compared to non-dysplastic leukoplakias.
8. **Candida*:*** Leukoplakia with candida super infection showed higher malignant risk.

Treatment

Counselling the patient to complete cease the habits (tobacco or alcohol) is the primary step towards management of leukoplakia. The treatment may be conservative or surgical.

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Conservative Treatment: Can be done by [30,31]

1. **Enameloplasty**-so as to smoothen any sharp teeth or replacement of faulty restorations so as to avoid trauma.
2. Vitamin therapy (A, C and E) has a protective effect on the epithelium.
3. Prescribing retinoids
4. Advising consumption of lycopene (a protein that interferes in cell cycle sequence by blocking the growth factor receptor signalling)
5. β carotenes (react with oxygen and form an unstable molecule, which is resistant to the action of oncogenic free radicals)
6. In case of candidal leukoplakia nystatin therapy can be the treatment of choice.
7. Topical bleomycin, a cytotoxic antibiotic has been used in treatment of oral leukoplakia
8. Photodynamic therapy, which uses a photosensitizing drug like Aminolaevulinic acid (ALA), oxygen and visible light which causes destruction of exposed cells by a nonfree radical oxidative process.

Recurrences of the lesion were seen even after treating the patients conservatively. The treatment of the patients whether surgically or non surgically was based mainly on presence and extent of epithelial dysplasia.

Surgical Treatment: Various forms of surgical treatment include

1. **Surgical excision** is the treatment of choice and mostly performed procedure in cases of leukoplakia
2. **Disadvantage**-Its main disadvantage is scar formation
3. **Cryosurgery**- with liquid nitrogen has been successfully used in treatment of leukoplakia, its principle of action being freezing of lesions
4. **Laser therapy**: studies have shown that Co_2 laser therapy due to its excellent healing properties, lack of postoperative complications like bleeding and low recurrence rates is superior to other forms of treatment.

Follow up of the patients should be done frequently. Studies have shown that surgically treated patients have less chance of malignant transformation than those treated nonsurgically[32,33]

CONCLUSION

Oral leukoplakia is one of the most common potentially malignant disorders. A proper history and a thorough clinical examination can help in the diagnosis of this lesion. Biopsy of such lesions should be carried out and it should be differentiated with other white lesions. Early detection of leukoplakia is necessary as it shows high malignant transformation rates. New non invasive methods such as salivary markers in the detection of transformation should be carried out to control this lesion.

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