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AN UPDATED REVIEW ON ORAL LEUKOPLAKIA

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Abstract:

Oral leukoplakia, the most commonly occurring potentially malignant disorder of the oral mucosa. The WHO (1997) defined leukoplakia as "a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion". The present review covers the incidence, etiological factors, classification, diagnostic criteria in assessing and finally the management strategies aimed at preventing and treating oral leukoplakia.

Key Words: Oral Leukoplakia, Pre-Leukoplakia, Potentially Malignant Disorders, Tobacco & Malignant Transformation

Introduction:

Leukoplakia defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion [1] Leukoplakia has been recognized by two forms: Homogeneous and the Non-homogeneous type. Homogeneous leukoplakia has predominantly white lesion of uniform flat, thin appearance, smooth, wrinkled or corrugated surface throughout the lesion, whereas non-homogeneous leukoplakia has been a mixture of white-and-red lesion that may be either irregularly flat, nodular, or verrucous. [2]

Incidence:

- ✓ During the year 1992, Gupta et al., reported that in India, leukoplakia was found in 0.2% and 4.9% of the population presented over 15 years of age.[3]
- ✓ Bánóczy (1983) found that the prevalence of adult population varied between 0.6% and 3.6%.[4]
- ✓ Downer and Petti found an annual oral cancer incidence rate inferable to leukoplakia between 6.2 and 29.1 cases per 100,000 people.[5]

Etiology Associated with Oral Leukoplakia:

Tobacco, Alcohol, Candida albicans, Human papilloma virus (HPV) and Nutritional deficiency are the most common etiologies attributed or linked with leukoplakia.Tobacco is a well established etiologic factor associated with oral leukoplakia. Leukoplakia is more frequently found in smokers of tobacco than in non-smokers. There is a direct relationship between tobacco usage and the prevalence of oral leukoplakia. Reducing or cessation of tobacco use may result in the regression or disappearance of oral leukoplakia (Gupta et al 1995).[6] Schepman et al. found that smokers have 6 times higher risk of developing leukoplakia than non-smokers, despite lesions of non-smokers having a greater probability to transform into oral cancer.[7]

Alcohol by itself is an independent etiological factor in the development of oral leukoplakia, is still questionable. Alcohol, may be synergistic to other well known etiological factorslike tobacco and physical irritants. Soames and Southam reported mutations of p53 in the cells from dysplastic areas of some leukoplakias in individuals who smoke and drink heavily.[8]

The role of Candida albicans as an etiological factor in leukoplakia and its malignant transformation is still unclear. Various evidence has been presented to justify an etiologic role for candida in neoplastic transformation, which includes among others the catalytic transformation in-vitro of the carcinogenic nitrasamine, N-nitrosobenzyl-methylamine, by stains of C. albicans demonstrated to be selectively associated with leukoplakia. About 10% of oral leukoplakia elate the clinical and histological criteria for chronic hyperplastic candidiasis (candidal leukoplakia). Epithelial dysplasia is reported to occur four to five times more commonly in candida leukoplakia than in leukoplakia in general. However, this change is more frequently seen in the speckled variant than in homogeneous leukoplakia and malignant change is more a characteristic of the speckled lesion than that of candidal super-infection.[9]Bánóczy said reported that Candida albicans infection and the coexistence seemed to play a role in malignanttransformation among the etiological factors, and leukoplakia found the highest risk of developing into cancer (25.9%).[10] Krogh et al. have found that higher nitrosation potentials of candidal organisms can be isolated from non-homogeneous leukoplakias than homogeneous forms.[11]

The conducive role of viral agents like Human papilloma virus (HPV) strains 16, 18 in the pathogenesis of oral leukoplakia has also been discussed, particularly with regard to exophytic verrucous leukoplakia (Palefsky JM et al 1995). Caldeira*et al*. (2011) found a high-risk factor of leukoplakia for malignant transformation is the infection with human papilloma viruses as the expression of oncogenic proteins such as human papillomavirus-16L1 can promote carcinogenesis.[9]

Serum levels of vitamin A, B12, C, betacarotene, and folic acid were significantly low in patients with oral leukoplakia compared to controls, whereas, serum vitamin E was not (Ramaswamy G et al 1996). [9] Bánóczy (1977) also observed statistically decrease in serum levels of Vitamin A, B12, C, beta carotene, and folic acid in patients with oral leukoplakia compared to controls.[10] Soames and Southam reported that the changes of developing leukoplakia were more in the areas of epithelial atrophy and the conditions associated with mucosal atrophy included iron deficiency, some vitamin deficiencies, and oral submucous fibrosis.[9]

Relatively little is yet known with regard to possible genetic factors in the development of oral leukoplakia. Activation of oncogenes and deletion and injuries to suppressor genes and genes responsible forDNA repair will all contribute to a defective functioning of the genome that governs cell division. Following a seriesof mutations, a malignant transformation may occur.[12]

Clinical Aspects:

Preleukoplakia is defined as a low grade or very mild reaction of the oral mucosa, appearing as a grey or greyish-white, but never completely white area with a slightly lobular pattern and with indistinct borders blending into the adjacent normal mucosa (Pindborg et al 1968).[13]

Clinical Classification:

The various forms of leukoplakia and its subdivisions (WHO 1980):

(A) Homogeneous: Lesions that are uniformly white.

(B) Non-Homogenous: Lesions in which part of the lesion is white and rest appears reddened.Alternatively, a more elaborate sub-division may be used such as:

Homogenous:

- ✓ Smooth
- ✓ Furrowed (fissured)
- ✓ Ulcerated

Non-Homogeneous Nodulo – Speckled: Well demarcated raised white areas, interspersed with reddened areas. When recording leukoplakia, space has been allowed in the recording form for three different sub-divisions:

- ✓ Homogenous - Smooth And Fissured
- ✓ Homogenous - Ulcerated
- ✓ Non Homogenous - Nodulo-Speckled

Various Forms of Leukoplakia:

- ✓ **Proliferative Verrucous Leukoplakia (PVL)**: Hansen et al. (1985) first described PVL is a distinct clinical form of leukoplakia which has a high rate of malignant transformation which was described by the WHO. It is multifocal progressive lesions, found in women, frequently affecting the lower gingival, tongue, buccal mucosa, and alveolar ridge[1]
- ✓ **Oral Erythro-Leukoplakia (OEL)** is a non-homogenous lesion of mixed white and red components. Defined as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease'. Shows a higher malignant transformation potential than homogeneous leukoplakia [1]
- ✓ **Sublingual Keratosis**: Soft white plaque in the sublingual region with a wrinkled surface, an irregular but well-defined outline and sometimes a butterfly shape[14]
- ✓ **Candidal Leukoplakia (CL):** is a chronic, discrete elevated lesion which are palpable, translucent, whitish areas to large, dense, opaque plaques, hard and rough ontouch[15]
- ✓ **Oral Hairy Leukoplakia (OHL)** or Greenspan lesion: Greenspan et al. first described OHL in 1984, which is characterized by whitish patches with a corrugated or hairy surface and most commonly present on the lateral borders of the tongue. Caused by the reactivation of a previous Epstein-Barr virus infection.[16]

Overall Risk Factors for Malignant Transformation in Leukoplakia:

Warnakulasuriya*et al.* enlistedthe following as a riskfactor for malignant transformation in PMD.[1]

- ✓ 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 *C. albicans*
- ✓ Presence of epithelial dysplasia.

A Modified Classification and Staging System for Oral Leukoplakia:

A proposal for a modified classification and staging system for oral leukoplakia (OLEP) was presented by van der Waal et al 2000 in which the size of the leukoplakia and the presence or absence of epithelial dysplasia are taken into account.[17] Altogether four stages are recognized.

L-Size of Leukoplakia:

- ✓ L 1 - size of leukoplakia is < 2cm
- ✓ L2 - size of leukoplakia is 2 - 4 cm
- ✓ L3 - size of leukoplakiais>4cm
- ✓ Lx - size of leukoplakia is not specified.

P – Pathology:

- ✓ PO - No epithelial dysplasia
- ✓ P1 - Distinct epithelial dysplasia
- ✓ Px - Dysplasia not specified in pathology report

OLEP Staging System

- ✓ Stage I - L 1 PO
- ✓ Stage II - L2 PO
- ✓ Stage III - L3 PO or L1L2 P1
- ✓ Stage IV - L3 P1

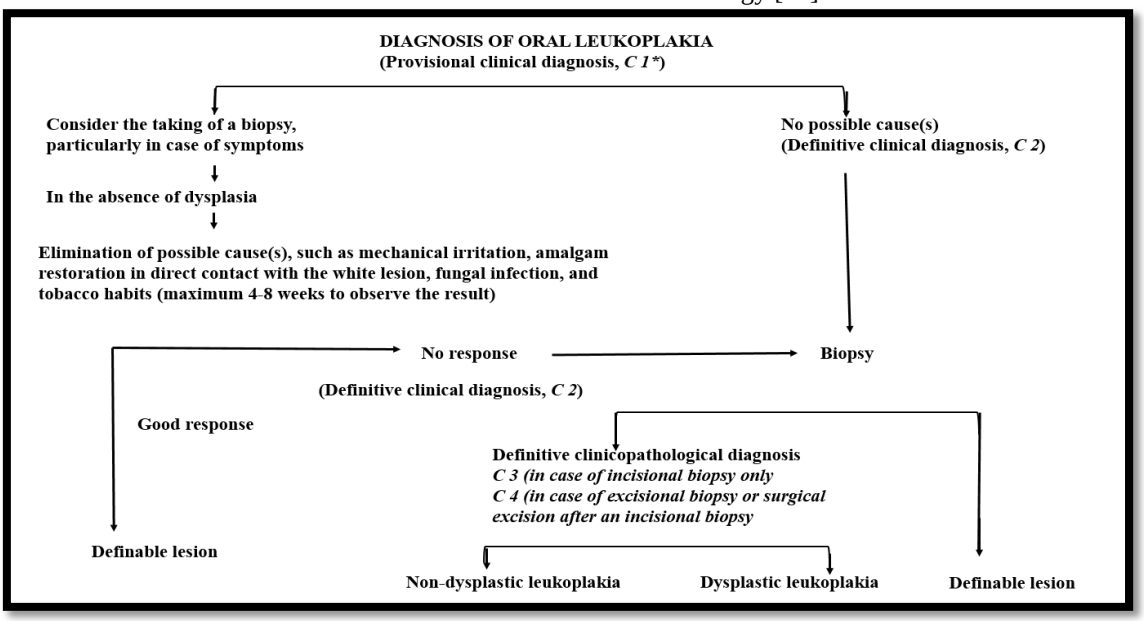
Diagnostic Strategies:

Elimination of Possible Cause: Oral clinician should first try to rule out any of the definable white lesions before accepting a definitive clinical diagnosis ofleukoplakia. Recently, Van der Waal in his review reported about certainty(C) factors for diagnosing leukoplakia(Table 1& Figure 1)[18]**.** He said a provisional diagnosis was made when a lesion at the initial clinical examination could not be clearly diagnosed as either leukoplakia or any other disease. In case of a provisional clinical diagnosis, Certainty factor 1 was assigned. A definitive clinical diagnosis of leukoplakia was made after unsuccessful elimination of suspected etiological factors or in the absence of such factors, assigning Certainty factor 2. Certainty factor 3 was assigned when histopathological examination of an incisional biopsy did not show the presence of any other diseases. In case of an excisional biopsy or surgical excision, performed after an incisional biopsy, Certainty factor 4 was assigned based on histopathological examination of the surgical specimen. It goes without saying that in epidemiological studies a Certainty factor 1, based on a single oral examination, is acceptable, while in scientific studies, e.g. comparing different treatment results, Certainty factor 4 will be required, if feasible. Apparently, the recommendation to use a Certainty factor has not been widely accepted in the recent literature [19], although the use of such factor is common practice in cancer registries.

Table 1: Certainty (C)-factor of a diagnosis of oral leukoplakia [18]

C1	Evidence from a single visit, applying inspection and palpation as the only diagnosis means (Provisional clinical diagnosis), including a clinical picture of the lesion.
C2	Evidence obtained by a negative result of elimination of suspected etiologic factors, e.g. mechanical irritation, during a follow-up period of 6 weeks (Definitive clinical diagnosis)
C3	As C2, but complemented by pretreatment incisional biopsy in which, histopathologically, no definable lesion is observed (Histopathologically supported diagnosis)
C4	Evidence following surgery and pathologically examination of the resected specimen

Figure 1: Diagnosis of oral leukoplakia adapted from van der Waal I(2015). Oral leukoplakia, the ongoing discussion on definition and terminology [18]



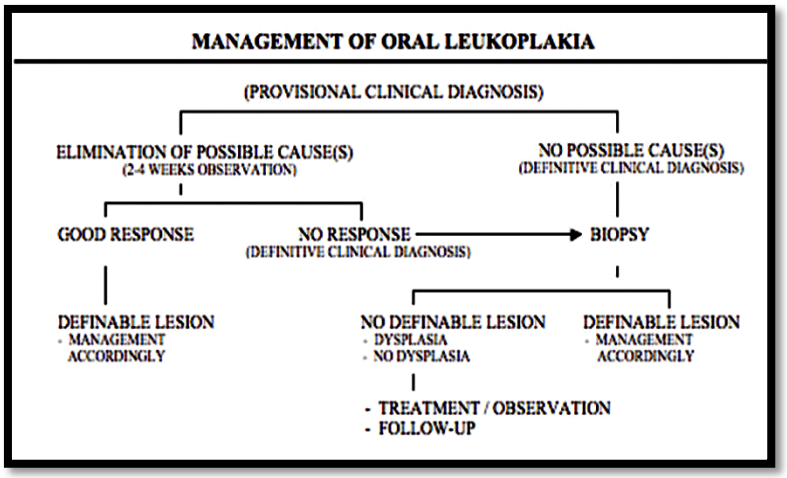
Chair Side Diagnostics: The use of toluidine blue staining or Lugol's iodine and exfoliative cytology are of limited value when dealing with leukoplakia.[13]

The Biopsy: Biopsy is the golden standard till date in diagnosing any oral lesions**.** In homogeneous leukoplakia, the value of histological examination might to some extent be questioned. The occurrence of epithelial dysplasia is rather low in homogeneous leukoplakia subtype, as is the risk of future malignant transformation. But this cannot be taken as anaxiom in all cases since atleast in certain cases it proves to be otherwise. Therefore, the taking of a biopsy in homogeneous leukoplakia should be the standard rule. In non-homogeneous leukoplakia, biopsy should be taken at the site of symptoms, if present, and / or at a site of redness or induration. [13]

Treatment Modalities:

Abstaining the afflicted or suspected person from tobacco and alcohol intake is mandatory.Apart from the surgical excision, various treatment modalities are available, such as cryosurgery, C02 - laser surgery, retinoids and other drugs, and recently photodynamic therapy. Van der Waal and Axéll stated if the patient had a white lesion in oral mucosa, the clinician would first try to rule out any of the definable white lesions before accepting a distinct clinical diagnosis of leukoplakia. A 2-4 weeks interval to observe the possible regression or disappearance of a white lesion after elimination of possible causative factors, including smoking habits, seems a fully acceptable period of time for the general practitioner before taking a biopsy or before referring the patient to a specialist for further advice(Figure 2).[20]

Figure 2: Management of oral leukoplakia/erythroplakia. Adapted from van der Waal I, Axéll T.(2002) Oral leukoplakia: A proposal for uniform reporting [20]



Antifungals: Cawson (1996) reported that leukoplakia showed drastic improvement and disappearance of a significant number of their cases with polyene-nystatin (tablets) dissolved slowly in the mouth.[21] Ramanathan et al. suggested that the candida-associated leukoplakia or speckled leukoplakia may show response to topical antifungal agents (including imidazoles).[22] Lamey et al. (1994) reported that oral leukoplakia with epithelial dysplasia resolved within 11 days of systemic treatment with fluconazole antifungal agent.[23] Garber found anti-candidal treatment strategy was helpful in ruling out a possible fungal etiology for lesions. In immuno-compromised hosts, candidal lesions may require the use of more toxic agents like Amphotericin B.[24]Nystatin therapy given in CL. 500,000 IU twice daily with 20% borax glycerol or 1% gentian violet or mouth rinses with chlorogen solution showed anadequate response.[25]

Antioxidants: Beta-carotene is a vitamin A precursor is used in treatment of leukoplakia due to its potential benefits and protective effects against cancer are possibly related to its anti-oxidizing action. In a study by Blaggana et al., using beta-carotene, in a therapeutic dose of 75,000 to 300,000 IU for a duration of 3-month is advised, and also suggested that 13-cis-retinoic acid a synthetic analog of Vitamin A, given in doses of 1.5-2 mg/kg body weight for 3 months showed good results.[25] Lycopene is a carotenoid without provitamin A action, fat-soluble red pigment found in some fruit and vegetables. The greatest known source of lycopene is tomatoes. Blaggana et al., In his 3 months follow-up study reported that lycopene appeared to be a promising agent in the management of Leukoplakia.[25]

Lasers: Lodi and Porter showed in a review of various treatments for leukoplakias that carbon dioxide (CO2) LASER vaporization showed maximal while CO2 LASER evaporation showed minimal recurrence of leukoplakia. However, cryosurgery and conventional blade surgery showed up to 22% and 13% recurrence rates, respectively. [26]

Bleomycin: A cytotoxic antibiotic, was first used for the treatment of neoplasms of the penis and scrotum, but has also been employed for squamous cell carcinoma of the head and neck region, oesophagus, and skin [27]. Eight patients with leukoplakia were treated by the daily application of a 0.5% (w/v) solution of bleomycin sulphate in dimethyl sulphoxide (DMSO). After 12 to 15 applications, the white patch peeled off and the resultant raw surface was epithelialized over the following 14 days, repeated histopathological examination

showed a significant reduction of dysplasia and keratinisation [28]. The use of topical 1% bleomycin in DMSO was evaluated for the treatment of dysplastic oral leukoplakia. Bleomycin was applied once daily for 14 consecutive days to lesions of the oral mucosa in 19 patients, immediate post-treatment 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. [29].

Photodynamic Therapy (PDT): Is a noninvasive method for the treatment of premalignant lesions and head and neck cancers. The principle of PDT is a non-thermal photochemical reaction, which requires the simultaneous presence of a photosensitising drug (photosensitiser), oxygen, and visible light. After a period to allow the photosensitiser to collect in the target tissue, the photosensitiser is activated by exposure to low-power visible light of a drug-specific wavelength. The light source is supplied by a portable diode laser and the light is transmitted via laser fibresto or into the tumour,results in the destruction of cells by a non-free radical oxidative process. These reactive oxygen species (ROS) may damage crucial cell components, such as structural proteins, enzymes, DNA, and phospholipids. PDT is a cold photochemical reaction, and the photosensitising agents are of inherently low systemic toxicity. PDT damage heals mainly by regeneration rather than scarring. Due to the organ preserving principle of PDT, important structures are maintained with good functional and cosmetic outcome [30-32].

Conclusion:

Tobacco usage over several decades remains a dominant etiologic factor associated with oral leukoplakia. Alcohol acts as synergistic factor with other known causes in prompting occurrence of leukoplakia. Habitual counseling and behavioral management are most essential methods of prevention aimed at preliminary level. Priority exits to arrive at a proper confirmatory diagnosis of oral leukoplakia, by eliminating it from a huge plethora of white lesions mimicking oral leukoplakia. This is possible only with a thorough knowledge about the disease, its associated etiological factors, proper diagnostic method and early treatment strategies that would help in preventing a leukoplakia from undergoing malignanttransformation.

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