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MEDICAL MANAGEMENT OF ORAL LEUKOPLAKIA: AN UPDATED REVIEW OF LITERATURE

Dental Science

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ABSTRACT

Leukoplakia is the most frequent potentially malignant lesion of the oral mucosa. Its diagnostic and therapeutic present a challenge for dentist. The aim of this article is to present a review of the management of oral leukoplakia according to the contemporary standards. Management of oral leukoplakia should begin with elimination of predisposing habits. The main purpose of oral leukoplakia management is to avoid malignant transformation of the lesion or if this happened to detect this in early stages.

KEYWORDS

Leukoplakia, Management, Predisposing, Pre- Cancerous, Malignant Transforation

INTRODUCTION:

Leukoplakia has been studied for many years and is commonly agreed upon as representing the most common pre-malignant oral mucosal lesion. Leukoplakia has evolved as a clinico-pathologic concept over many years, with the current clinical designation being accepted worldwide[1]. According to the World Health Organization (WHO) in 1978, oral leukoplakia is defined as a white lesion that cannot be clinically or pathologically be characterized as any other disease[2,3,4,5]. In 2012, "Van der Waal" proposed a new definition, which includes the histological confirmation: "A predominantly white lesion or plaque of questionable behavior having excluded, clinically and histopathologically, any other definable white disease or disorder" [2]. About 15%–48% of the squamous cell carcinomas of the oral cavity are developed from innocent-appearing precancerous lesions, and approximately 60% are present as white keratotic lesions [6, 7]. Early identification of the oral precancerous lesions, particularly in high-risk individuals, is important to prevent further morbidity and to improve the oral health-related quality of life. The purpose of this article is to highlight the reader about the recent updates of management protocols for oral leukoplakia.

DIAGNOSTIC CHALLENGES:

As a result of the WHO definition of oral leukoplakia, the accuracy of the clinical diagnosis largely depends on the experience of the clinician. Ideally, a diagnosis of oral leukoplakia should be the result of close collaboration between clinicians and pathologists [7, 8]. It is extremely important to accurately diagnose and differentiate other reactive or inflammatory keratotic conditions(table 1) from leukoplakias because of the precancerous nature of the latter, which requires close follow-up or complete removal. Taking a careful history and clinical and histopathologic examinations of all such white lesions will enable the clinician to arrive at a final diagnosis which is ultimately a key for effective management[9].

Table1 : WHITE LESIONS OF THE ORAL CAVITY[9]

Developmental	Cannon white sponge nevus Hereditary benign intraepithelial dyskeratosis Other congenital genodermatoses (eg, pachyonychia congenita)
Reactive or frictional	Leukoedema Contact desquamation Frictional keratosis: MMO, BARK Hairy tongue Associated with tobacco use: nicotinic stomatitis, smokeless tobacco keratosis
Infectious	Candidiasis Hairy leukoplakia (associated with EBV)
Immune mediated	Lichen planus Lichenoid lesions Benign migratory glossitis
Autoimmune	Lupus erythematosus Chronic graft-vs-host disease
Metabolic	Uremic stomatitis Palifermin-associated hyperkeratosis
Malignant and OPMD	Keratosis of unknown significance Dysplastic leukoplakia SCC Verrucous carcinoma

Abbreviations: BARK, benign alveolar ridge keratosis; EBV, Epstein-Barr virus; MMO, morsicatio mucosae oris; OPMD, oral potentially malignant disorders; SCC, squamous cell carcinoma.

MALIGNANT POTENTIAL:

Some factors may contribute to increase the chance of the OL becoming malignant and these include the following.

(1) Gender: female patients tend to present a higher risk of developing the malignant form.
(2) A long standing lesion: a lesion that is resistant to the treatments and what persist for long time may have worse prognosis than recent.
(3) OL in sites of high risk: lesions in the floor of mouth, ventrolateral tongue and soft palate have a high risk of malignant transformation.
(4) OL among nonsmokers (idiopathic): non-smokers with OL have an increased rate of malignant ransformation in relation to OL in

smokers.

(5) Nonhomogenous OL-type: non-homogenous OL lesions have a mixed color of white and red alterations, and an exophytic, papillary, or verrucous aspect; regardless of treatment, they exhibit a high.
recurrence rate and often eventually transformation to squamous cell carcinoma [4, 12].

(6) Epithelial dysplasia: OL with moderate and severe dysplastic lesions had a significantly higher risk of developing a squamous cell carcinoma than OL without epithelial dysplasia or with mild epithelial dysplasia [7, 9, 12].

The overall frequency of malignant transformation rate of oral leukoplakia varies between 15.6% and 39.2%. A speckled leukoplakia has maximum malignant transformation rate. The annual average of malignant transformation rate of oral leukoplakia is 1% in various populations with the highest reported rate of 43% [13]. In general, the thicker the lesion the greater the chance of having dysplastic changes [14].

TREATMENT OPTIONS:

Any treatment of oral leukoplakia should begin with **elimination of risk factors** such as tobacco abuse, betel chewing, alcohol abuse, superimposed candida infection over the lesion etc. Up to 60% of leukoplakias regress or totally disappear if tobacco use is stopped. Leukoplakias induced by smokeless tobacco may resolve if the habit is stopped [15].

Conservative treatment includes use of chemopreventive agents such as vitamins (vitamins A, C, E), fenretinide (Vitamin A analogue), carotenoids (beta-carotene, lycopene), bleomycin, protease inhibitor, anti-inflammatory drugs, green tea, curcuma etc [15,16]. The use of photodynamic therapy has been also reported. Careful and routine follow-up observations of leukoplakia are appropriate in conjunction with elimination of any risk-associated behavior or habits. In case of no improvement, treatment should become more invasive [15].

CAROTENOIDS:

They are hydrophobic particles that have little or no solubility in water.

Beta Carotene:

It is a vitamin A precursor which is commonly found in dark green, orange or yellow vegetables such as spinach, carrots, sweet potato, mango, papaya, and oranges [15,17]. 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. It has been shown that beta-carotene has a better therapeutic clinical response in preventing oral leukoplakia lesions in smokers than in nonsmokers [17]. The only known effect of excessive beta-carotene intake is a state in which the skin becomes strongly yellowish, the so-called carotenodermy, which disappears in a few weeks after the reduction of consumption [12,18]. Some studies report that clinical resolution of oral leukoplakia ranges from 4% to 54%, with dosages regimes from 20 to 90mg/day of beta-carotene in time periods from 3 to 12 months [15,17,19].

Lycopene:

Lycopene is a fat-soluble red pigment found in some fruit and vegetables [15]. The greatest source of lycopene is tomato. In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to play a protective role against progression of dysplasia by inhibiting tumor cell proliferation [19]. 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 cardio-vascular diseases.A study evaluated lycopene in oral leukoplakia for a three months period, with dosages regimes from 4mg/day and 8mg/day and patients had clinical resolution 25 and 55%, respectively [15,20].

VITAMINS:

Vitamin A:

The most biologically, naturally occurring retinoid is vitamin-A. Vitamin A, also known as retinol, is an alcohol that can be converted into an aldehyde (retinal) or retinoic acid [15]. 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. Hypervitaminosis occurs when consumption exceeds the liver's capacity to store retinoids [12,21]. The topical use of 13-cis retinoic acid has been shown to be effective in resolving oral leukoplakia. But they are limited because recurrences appear after short periods of cessation of the treatment. In the systemic use with dosage of 300000 IU of retinoic acid, a clinical resolution of the 50% has been demonstrated [12,17].

Vitamin E:

Vitamin-E is the collective term for a family of chemical substances that are structurally related to alpha-tocopherol. Alpha-tocopherol, the major constituent of Vitamin E has anti-tumor proliferation capacity as well as function as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids[15,22]. It is found in plant oil, margarine, and green leaves[15,17,22]. It was found that high doses of vitamin E supplementation (> 400 IU/d) may increase all cause mortality and should be avoided. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women[15,22].

Vitamin C:

L-AA(L-Ascorbic Acid) 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 [12]. 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 concentration in serum leukocytes [15,22].

Fenretinide :

The compound N- (4-hydroxyphenyl) retinamide, also known as fenretinide (4-HPR) was synthesized in the United States in 1960 and is used for treating leukoplakia. It has proven to be less toxic than many other vitamin A analogues. 4-HPR is well tolerated, and no local or distant side effects are observed. A characteristic feature of 4-HPR is its ability to inhibit cell growth through the induction of apoptosis with mechanisms that may be both receptor-dependent and receptor-independent. This compound is used for the chemo-preventive treatment of various diseases, and has been studied and tested in clinical trials for the treatment of OL. Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of leukoplakia of 12 patients [12,15,17,22].

ANTI-NEOPLASTIC AGENTS:

Bleomycin:

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 . The most commonly adverse effects are mucocutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin. 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 [12,15].

POLYPHENOLS:

Curcumin:

Curcumin has been used for thousands of years in traditional Indian medicine. Curcumin reportedly possesses several pharmacological properties, including anti-inflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemo-sensitizing, radio-sensitizing, and wound healing activities. Small doses of curcumin are taken daily as a spice by the population in many Asian countries. In India, where the average intake of curcumin can be as high as 100 mg per day, no toxicities or adverse effects have been reported or studied at the population level. However the doses administered in clinical trials are expected to be rather higher than those normally consumed [12,15,17].

Green Tea Polyphenols:

Epigallocatechin gallate (EGCG), a major polyphenol found in green tea possesses antioxidant and chemo-preventive properties. It shows very promising results. According to one study, 29 out of 59 patients with oral leukoplakia were randomized to use a mixed tea extract orally as well as a topical tea extract. After the 6-month trial, the oral lesions had decreased in size in almost 40% of the patients treated, which was associated with a decrease in proliferation in the treatment

group on histopathologic examination[12,15,17].

Photodynamic Therapy:

Photodynamic therapy (PDT) is a non-invasive method for the treatment of premalignant lesions and head and neck cancers. The principle of PDT is a nonthermal 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. There are several photosensitizers which have been developed and approved in time: (1) Photofrin; (2) 5- Aminolaevulinic acid (ALA); (3) Verteporfin ;(4) Foscan. Patients were treated with topically applied 10% ALA and light from an argon-pumped dye laser. Irradiation was performed in several (6-8) sessions using light at 635 nm wavelength, delivering a total dose of 100 J/cm2 per session. A complete response was obtained in 10 out of 12 treated patients. One recurrence was observed during 6 months[12,15,24,25].

CONCLUSION:

The main purpose of oral leukoplakia management is to avoid malignant transformation of the lesion or if this happened to detect this in early stages. Several clinical trials have investigated the treatment of leukoplakia with use of supplements. Although the administration of retinoic acid and beta-carotene has some efficacy to resolve leukoplakia, the studies were based on small samples and short periods of follow-up. There is a lack of randomized clinical trials that assess the effectiveness of nonsurgical treatment of OL. At this time, randomized controlled trials for nonsurgical treatment of leukoplakia demonstrate no evidence of effective treatment in preventing malignant transformation and recurrence. It reinforces that even after clinical resolution, leukoplakia should be regularly followed.

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