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Research Paper

"Oral Leukoplakia: Insights into Prevalence, Risk Factors, and Evolving Management Approaches"

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ABSTRACT
Oral leukoplakia is considered the most common potentially malignant disorders that affect the oral cavity. Despite various surgical and non-surgical treatments that have been reported, there is no appropriate universal consensus and on the interval of follow-up of patients with this condition. Its management should begin with elimination of risk factors such as tobacco, betel chewing, alcohol abuse, superimposed candida infection over the lesion etc. Conservative treatment includes use of chemopreventive agents such as vitamins (vitamins A, C, E), fenretinide (Vitamin A analogue), carotenoids (betacarotene, lycopene), bleomycin, protease inhibitor, anti-inflammatory drugs, green tea, curcumin etc. Surgical treatment includes conventional surgery, electrocoagulation, cryosurgery, and laser surgery. The main purpose of its management is to avoid the malignant transformation.

Key Words: *Oral Leukoplakia , Prevalence, Malignant Transformation, Risk Factors, Conservative Management, Surgical Treatment, Chemopreventive Agents*

I. INTRODUCTION

Potentially malignant disorders of the oral cavity (OPMD) are a heterogeneous group of lesions associated with a variable risk of malignant transformation (MT) to invasive cancer. Leukoplakia (LE), lichen planus (LP), oral lichenoid lesions (OLL), oral erythroplakia (OE), oral submucous fibrosis (OSF), and proliferative verrucous leukoplakia (PVL) are among the most common of these lesions.[1]

The working group has defined OPMD as "any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer." OPMDs exhibit a broad range of clinical presentations, including colour variations (white, red, and mixed) and topographic changes

(plaque/plateau, smooth, corrugated, verrucous, granular, atrophic).[2]

Oral leukoplakia (OLK) is defined by the World Health Organization (WHO) Collaborating Centre in 2020 as “White plaques of questionable risk having excluded (other) known diseases that carry no increased risk for cancer”.[3]

EPIDEMIOLOGY

Leukoplakia is the most common premalignant lesion found in the oral cavity. The prevalence of leukoplakia shows high geographical and socio-demographical variance with approximately 1%-2% for all ages together. These are usually diagnosed after the fourth decade of life and are six times more common among smokers than among non-smokers.

The statistical analysis from several Indian studies shows the prevalence of leukoplakia ranges between 0.21% and 5.22% and the malignant transformation ranges from 0.13% to 10%.

ETIOLOGY

Several locally acting etiologic agents, including tobacco, alcohol, candidiasis, electro galvanic reactions, and herpes simplex and papillomaviruses, have been implicated as causative factors for leukoplakia.[4] Smoked or smokeless forms of tobacco contain carcinogen that bind to the epithelial DNA causing mutation, resulting in hyperkeratinisation and dysplasia. Heat stimulates keratinocytes causing hyperkeratinisation. Alcohol increases the permeability of oral mucosa, facilitating the penetration of carcinogens into the tissue. Oral leukoplakia can also accompany systemic disorders like hormonal disturbances, gastroaesofagal reflux, diminished saliva secretion or iron deficiency anemia.

CLINICAL PRESENTATION

The location of the OL was specified according to eight subsites into tongue, floor of mouth, lower lip, hard palate, buccal mucosa, upper alveolus and gingiva, lower alveolus and gingiva and multiples sites when more lesions were observed. A patch of oral leukoplakia may vary from a small and circumscribed area to an extensive lesion involving a large area of mucosa.

Homogenous leukoplakia is characterised by a uniform flat and thin white plaque/patch with well-defined margins and smooth surface which may be associated with shallow cracks/fissures of the surface keratin. Non-homogenous leukoplakia is characterised by irregular texture, which can include focal superficial ulceration, and ill-defined margins, carrying a higher risk of malignant transformation.

II. MANAGEMENT

CONSERVATIVE MANAGEMENT

The first step is the removal of etiological factors such as tobacco, alcohol, and betel quid chewing done through habit counseling.[5] Enameloplasty for sharp teeth and replacement of faulty restorations form the initial management in cases with chronic irritation-induced leukoplakia. The use of anti-fungal medication is useful in cases of Candida-associated leukoplakia. In case of low risk lesions, after 2-3 weeks of habit cessation, a clinical examination is repeated to assess the regression in size of lesion. If there is regression in size, then follow up is done initially every three months followed by every 6-12 months. Low risk lesion which is not regressing in size even after habit cessation or in cases of high risk lesion, biopsy is mandatory in order to assess the degree of epithelial dysplasia.[6] In cases which show no signs of dysplasia, then conservative treatment is advised. In cases of mild, moderate or severe dysplasia, both conservative and surgical treatment is advised. Oral leukoplakia presenting low to moderate malignant risk may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation.[7] In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended.
Non-surgical treatment can be considered as a good choice in homogenic lesions without dysplasia or as an initial treatment in other cases.

MEDICAL MANAGEMENT

1. Carotenoids

a. **Beta-carotene** is a vitamin A precursor. This carotenoid is commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges. The use of beta-carotene has been recommended for the prevention of potential malignant lesions. The potential benefits and protective effects against cancer are possibly related to its antioxidant action. It has been shown that beta-carotene has a better therapeutic clinical response in preventing oral leukoplakia lesions in smokers than in nonsmokers. A known side effect of excessive beta-carotene consumption is a change in skin color, which becomes very yellowish, called carotenoderma, which disappears in a few weeks after the reduction of consumption. 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.[8]

b. **Lycopene** is a fat-soluble red pigment found in tomatoes. 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. 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. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb anti oncogenes and stop cell division at the Go-G 1 cell cycle phase.[6] It has been reported that a daily dose of 8 mg of lycopene was more effective than 4mg a day. No systemic significant toxic effects of lycopene have been observed and there is no evidence of side effects from the treatment with lycopene.

2. Vitamins

a. **Retinoids (**Vitamin A/ Retinol) The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins.[7] Vitamin A is required in the normal pathway of epithelial cell differentiation and production of keratin. An association between vitamin A deficiency and the enhanced susceptibility to carcinogenesis was reported with an increased risk for developing different epithelial carcinomas. Supplementation with retinoids for oral leukoplakia treatment begin in the 1960s, however, this treatment was not widely accepted due to its side effects-hypervitaminosis, teratogenic effects, toxicity, and alterations in various organic systems. 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 300.000 IU of retinoic acid, a

clinical resolution of the 50% has been demonstrated. In a recent study the results obtained on using topical retinoid for the treatment of proliferative verrucous leukoplakia, involving variable concentration of tretinoin or isotretinoin in gel form (0.05% to 0.1%), are generally similar to those obtained with systemic retinoid.[8]

b. **Vitamin E** 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.[9]

c. **Vitamin C** has antioxidizing properties and reacts with superoxide produced as a result of the cell's normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. 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.[7]

3. Anti-neoplastic agents:

Bleomycin is a cytotoxic antibiotic which was first used for the treatment of neoplasms. It can be used as an alternative for treatment of oral leukoplakia. The most commonly adverse effects are muco-cutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin.[7] Topical administration of bleomycin usually reduces lesion size and has little toxic side effects. It is beneficial to use bleomycin adjuvant with the surgical procedure for extensive leukoplakia to decrease the size of lesion before surgery. This helps to avoid grafting after removal of the lesion and prevent the dysplastic change of benign form of lesion.

4. Polyphenols

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. It is known to suppress tumor initiation, promotion and metastasis in experimental models, and it can also act as an anti-proliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing apoptosis and micronucleation.[10]

Epigallocatechin gallate (EGCG), a major polyphenol found in green tea possesses antioxidant and chemo-preventive properties. Epigallocatechin gallate (EGCG) shows very promising results.

5. **Photodynamic therapy** is a non-invasive method of treatment for head and neck tumors and premalignant lesions. It is based on photo-chemical reaction, initiated by light activation of a photosensitizing drug causing tumor cell death. It requires the simultaneous presence of a photosensitizing drug (photosensitizer), oxygen, and visible light and it is a non-thermal reaction. The photosensitizer is administered systemically by intravenous injection or can be topically applied. After a period to allow the photosensitizer to collect in the target tissue, the photosensitiser is activated by exposure to low-power visible light of a drug specific wavelength.

III. SURGICAL MANAGEMENT

Conventional surgery- excision refers to scalpel excision of the lesion. This is followed by a primary closure or secondary healing in case of reduced mucosal defects or with a transposition of local mucosal flaps or even skin graft in case of large defects. Conventional surgery may not feasible for extensive lesions or those in certain anatomical locations.

Electrocoagulation can be used alone or as an adjuvant to scalpel surgery. Electrocoagulation produces thermal damage in the underlying and surrounding tissue, which causes postoperative pain and oedema, and leads to considerable tissue scarring.

Cryosurgery is a method of treatment which involves controlled tissue damage caused by low temperatures. This method locally destroys lesional tissue by freezing in situ by liquid nitrogen (N) or dinitrogen dioxide (N2O2). Initially, its use was limited to the treatment of cancer of the lip and oral cavity. At present, cryosurgery has an extensive application in the treatment of both benign and malignant lesions in the head and neck region. It has several advantages including bloodless treatment, a very low incidence of secondary infections, and a relative lack of scarring and pain. Furthermore, newly rebuilt epithelium is less likely to become cancerous again. It can also be used for high-risk group patients like those with a pacemaker, the elderly, and those with coagulopathies. In addition, it would be the first choice in the case of multiple and extensive lesions, areas of difficult surgical access, and areas where esthetics is important.

Recurrence after surgical management:

Recurrence after surgical treatment has been reported in 10%– 35% of cases. Various studies have shown that even after surgical management leukoplakia can recur in 13-42% of cases and malignant transformation can occur in 3– 11% of cases at the excision site.[11] The major factors promoting recurrence were non homogenous leukoplakia and the use of snuff. They also found that 9% of cases of recurrent leukoplakia transformed into

OSCC. A possible explanation for leukoplakia recurrence could be found in the concept of field cancerisation where genomic instability is present throughout the mucosa leading to a generalised increased risk of malignant transformation. The degree of dysplasia was not correlated to malignant transformation.[12]

Malignant transformation

The reported annual risk of malignant transformation of oral leukoplakia ranges from 2 to 3% or even much higher.[13] The most common sites for malignant transformation are the floor of the mouth, ventrolateral tongue, and soft palate. Candidal infection is one of the risk factors for malignant transformation.

Risk factor of malignant transformation

- Non-homogeneous clinical appearance
- Female gender
- Long-standing leukoplakia
- Idiopathic leukoplakia (non-smoking/non-drinking/non- chewing status)
- Location: lateral tongue and/ or floor of the mouth
- Size > 200 mm2
- Presence of epithelial dysplasia
- Presence of Candida albicans (chronic hyperplastic candidosis or candida leukoplakia)

IV. CONCLUSION

Early diagnosis, close monitoring, and management of patients with oral leukoplakia is imperative. Though surgery is still the main method to remove the lesions, there are a lot of important factors to understand and consider when choosing a therapy. This acts as a reminder that while current treatments are effective, they can always be improved by combining with non- invasive therapy.

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