Oral Leukoplakia: A Therapeutic Challenge-An Update

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Abstract:

Owing to the stressful life patterns leading to harmful oral habits, dentistry is witnessing an upsurge in various lesions, particularly leukoplakia. Though it is the most common precancerous lesion, yet it poses a major diagnostic and therapeutic challenge. An attempt has been made to comprehensively lay down the clinical relevance, presentations, and the therapeutic modalities available, employing a molecular approach for optimal clinical management of the disease.

Key words: Leukoplakia, white patch, tobacco chewing, precancerous.

Introduction:

Based on work by the Pindborg school[1], WHO defined leukoplakia as a whitish patch or plaque that cannot be characterized, clinically or pathologically, as any other disease and which is not associated with any other physical or chemical causative agent except the use of tobacco. The literature, however, strongly indicates the role of alcohol, viruses and systemic conditions, thus needing further investigations[2,3]. Oral cancer accounts for approximately 650,000 new cases each year[4] with no reported improvement in the survival rate in the last 30 years[5]. The 5-year survival rate has reached 80% in cases detected at the initial stage, 40% in cases of regional involvement, and less than 20% in cases with distant metastasis[4]. The delay in diagnosis is yet another manipulative factor occurring due to the fact that patients often do not seek oral care for an unusual oral situation which is coupled lack of knowledge about these lesions among health professionals[6]. Nowadays, certain authors recommend that an initial clinical diagnosis of leukoplakia should be considered provisional and confirmed histologically if the lesion persists after 2-4 weeks and when all other possible etiologic risk factors have been ruled out[7].

World Health Organization in collaboration with the Center for Oral Cancer and Precancer in the United Kingdom in May 2005 replaced the term “pre-cancerous lesions” to “potentially malignant disorders” which included oral leukoplakia among other diseases[8]. Dentists therefore play an important role in early detection of malignant and premalignant conditions and providing timely therapeutic intervention to institute prevention.

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Clinical features:

Most commonly, older age group males in the age group of 35-45 years are affected. Prevalence in India is 0.2-4.9 percent, with most common sites as buccal mucosa and commissures, followed by lips, tongue, palate, alveolar ridge, floor of mouth, soft palate and gingiva\(^9,10\).

Clinical Types: Homogenous: It is also called as leukoplakia simplex. It accounts for 84 percent of cases. Morphologically it appears as a localized lesion with extensive white patch, with a relatively consistent pattern throughout. Leukoplakias which are seen amongst clay pipe smokers and betel quid chewers are generally of homogenous type.

Ulcerated leukoplakia: It occurs in 13 percent of cases. Appearance is characterized by red area, which at times exhibit yellowish areas of fibrin, giving the appearance of ulceration.

Nodular leukoplakia: It is also called as leukoplakia erosiva or speckled leukoplakia. A mixed red and white lesion is seen, in which small keratotic nodules are scattered over an atrophic patch of oral mucosa.

Verrucous leukoplakia: It is also called as leukoplakia verrucosa. It is a white lesion with a broken down surface due to multiple papillary projections, which may be heavily keratinized. In due course of time erythematous component may develop in the lesion.

Malignant potential:

It is higher in women (6%) than men (3.9%), due to involvement of endogenous factors. Leukoplakia associated with habit of chewing tobacco shows higher rate of transformation as compared to others. In buccal mucosa and commissure region 1.8 percent malignant transformation occurs. In lip and tongue region 16 to 38.8 percent malignant transformation occurs. The annual malignant transformation rate has been determined to be 0.1% to 17%\(^11,12\). Less than half (33% to 42%) of leukoplakias which undergo malignant change, does so within 2 years of diagnosis\(^13\) and the incidence of malignant transformation has been discovered to increase with the duration of follow up\(^14\).

Nodular dysplasia has higher risk of malignant transformation than other clinical types. Idiopathic leukoplakia and candida-associated leukoplakia have also been identified as high risk cases.

Management:

Lodi et al\(^15\) proposed a comprehensive treatment plan for patients demonstrating a variety of high to low risk potential of conversion into malignant lesion as:

Active
- Surgical removal of the lesion, including surgical excision, laser surgery, cryotherapy.
- Topical medical treatment, including anti-inflammatory agents, antimycotic agents, carotenoids and retinoids, cytotoxic agents, etc.
- Systemic medical treatment.
- Removal of predisposing habits (e.g. tobacco, alcohol, etc.).
- Other treatment (e.g. photodynamic therapy).
- Combined treatment.

Control
- Placebo.
- No treatment.

The degree of epithelial dysplasia plays a pivotal role while deciding onto the nature of treatment to be dispensed for the patient. Martorell-Calatayud\(^16\) defined two risk groups and the subsequent treatment options as:

1. Group with low risk of malignisation, comprising:
   a) Those leukoplakias lacking dysplasia, and b) those that show mild dysplasia located in low-risk areas or those with a thickness of less than 200 mm or that present clinically as homogenous leukoplakia. A range of therapeutic approaches can be taken in this group:
      - Regular patient follow-up. The interval between follow-up visits should not exceed 12 months in order to detect any change, suggestive of malignant transformation.
      - Treatment of lesions with topical or oral retinoids. Experience in the use of this therapeutic option is rather unsatisfactory as
lesions are not eradicated in the vast majority of patients.
- Treatments using nonsurgical ablative techniques, such as cryotherapy and carbon dioxide laser ablation.
Of these options, the use of laser light has shown better results in terms of controlling the lesions, and so it is considered the treatment of choice in this low-risk group.

2. Group of high-risk of malignant transformation, which comprises:
   a) Those leukoplakias with mild dysplasia located in high-risk areas measuring more than 200 mm, or those associated with a nonhomogeneous clinical form;
   b) Leukoplakias with moderate or severe dysplasia; and
   c) Verrucous leukoplakias.
In this group, there is justification for aggressive surgical treatment, consisting of excision of the entire thickness of the mucosa at the site of the leukoplakia.
Among the many therapeutic options available, however, eliminating risk factors (smoking, alcohol) and identified etiological factors (sharp broken down teeth, faulty metal restorations and metal bridges, etc.) is a preventive measure applicable to all patients with these lesions [17].
Emphasizing upon the efficacy of a conservative approach various authors [18,19,20] have advocated it for the restitution of oral health and prevent the possible recurrence.

- Carotenoids have a protective effect on the epithelium owing to their antioxidant properties. Beta (β) Carotene is a known Vitamin A precursor, thereby promoting epithelial turn over in the face of injury. It has also been shown that β-carotene has a better therapeutic clinical response in the prevention of oral leukoplakia lesions in smoker patients than in the nonsmokers [21]. A therapeutic dose of 75,000 to 300,000 IU for 3 months is advocated. Vitamin A may be used topically after painting the lesion with podophyllin solution (it inhibits mitosis). Vitamin A with vitamin E therapy is given to inhibit metabolic degradation. 13-Cis-Retinoic Acid a synthetic analogue of vitamin A, usually given in high doses of 1.5 to 2 mg/kg body weight for 3 months.
- Oral lycopene (a carotenoid without provitamin A action) has the uncommon feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent [22]. 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 [22]. Singh et al [23] in his 3 months follow-up study found lycopene to be a promising agent in the treatment and management of oral leukoplakia.
- Low-dose fenretinide, a synthetic retinoid, has recently been found to be clinically active in a 3 month trial in patients with resistance or relapse with natural retinoids by triggering a small increase in apoptosis. Data on antioxidant therapy shows that β-carotene supplementation can be beneficial for treatment of oral leukoplakia.
- Nystatin therapy is given in candidal leukoplakia. 500,000 IU twice daily plus 20 percent borax glycerol or 1 percent gentian violet or mouth rinses with chlorogen solution has revealed a favorable response.
- Vitamin B-complex is given as a supplement in cases of commissural and lingual lesions.
- Antimycotic preparations like canesten and pimafucin have also been found to be effective.
- Panthenol lingual tablet and oral spray may be used against glossitis and glossodynia, in case of tongue lesion.
- Topical chemotherapy by topical application of anticancer chemotherapeutic agents such as bleomycin and human fibroblast interferon has been used with success in limited cases of dysplastic leukoplakia.
- Photodynamic therapy (PDT) is a noninvasive method for the treatment of premalignant lesions and head and neck
cases. 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. Illumination of the tumor by light at the activating wavelength results in the destruction of cells by a non-free radical oxidative process. 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.

- Supportive administration of estrogen can be helpful in some cases.

**Conclusion:**

Some dysplastic lesions may have a worse prognosis than isolated carcinomas without leukoplakia owing to their unpredictable behavior. However, employment of apposite knowledge can allow for spontaneous remission with negligible recurrence.

**References:**


