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REVIEW ARTICLE

A SNIPPET ON ORAL LEUKOPLAKIA

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ABSTRACT

Leukoplakia is the most common pre-cancerous lesion of the oral cavity with high incidence of malignant transformation. Several risk factors including tobacco usage and alcohol consumption leads to formation of leukoplakia and cytogenetically altered keratinocytes, arising from pre-cancerous oral epithelium results in its malignant transformation. Surgical excision and antioxidant therapy are the preferred line of treatment of oral leukoplakia. This review attempts to highlight various aspects of leukoplakia from its formation to diagnosis and treatment with the aid of various recent literatures available.

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INTRODUCTION

The word leukoplakia could be split into two, where "*leuko*" means white and "*plakia*" refers to a patch therefore the term leukoplakia literally means a white patch (Kardam *et al*., 2015). Leukoplakia and erythroplakia are most common premalignant lesions in the oral cavity. The transformation of oral leukoplakia to oral squamous cell carcinoma (OSCC) depends on several factors, *viz.* gender, size of the lesion and presence and absence of dysplasia (Diana and Messadi, 2013). According to van der Wall (2012), leukoplakia could be defined as a predominantly white lesion or plaque of questionable behaviour having excluded clinically and histopathologically any other definable white disease or disorder (Brouns *et al*., 2012).

Aetiology

Leukoplakia occurs usually after the age of 30 years; with a peak incidence above the age of 50 years (Brad *et al*., 2002).

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Gender distribution varies according to studies conducted, ranging from male predominance in various parts of India, to almost 1: 1 in the western world (Shafer *et al*., 2012). The aetiology of leukoplakia is multi-factorial, of which usage of tobacco, remains a major factor (Ioanina Parlatescu, 2014). Intake of alcohol has synergistic effect with smoking (Nitin Kumar Nigam *et al*., 2013). Tumour suppressor gene p53 usually shows mutations in cells from the area of leukoplakia, especially in patients those who smoke and drink heavily (https://en.wikipedia.org/wiki/Leukoplakia.). Leukoplakia of lower lip along with actinic chelosis is seen in patients subjected to ultraviolet radiation. Leukoplakia tends to develop in areas of epithelial atrophy, *viz*. in conditions of syphilis, iron deficiencies, oral sub mucous fibrosis, and sideropenic dysphagia. Leukoplakia may also develop in patients who use toothpastes and mouth rinses containing ***sanguinaria*** which is an herbal extract (http://www.ncbi.nlm.nih.gov/pubmed/10620468).

Clinical appearance

Oral leukoplakia lesions are usually observed on lip vermillion, buccal mucosa, gingiva and floor of the mouth, varying in size from few millimetres to several centimetres. Dysplastic

changes are accounted in about 90 % of lesions in tongue, lip vermillion and oral floor. Solitary leukoplastic lesions shows varied clinical appearance, that tends to change with time. Early mild lesions are slightly elevated, grey/white plaques, that are translucent, fissured and are typically soft and flat. They usually have well distinct borders but sometimes blend gradually into normal mucosa (Yadav Monu *et al*., 2014; Ioanina Parlatescu *et al*., 2014). Oral hairy leukoplakia is an irregular cheesy white corrugated lesion with a hairy surface affecting the sides of tongue, caused by Epstein Barr virus infection which may be associated with immunodeficiency virus (HIV) infection, and pseudomonas candidiasis. (https://en.wikipedia.org/wiki/Leukoplakia).

Classification of leukoplakia

Oral leukoplakia is classified into two types clinically i) homogeneous and ii) non homogenous. Homogenous leukoplakia mostly appears as a uniform white lesion, with a relatively smooth surface and has a consistent texture throughout. A non-homogenous leukoplakia usually has an irregular and corrugated surface, and might show intermingled white and red areas (erythroplakia) (Ioanina Parlatescu, 2014; Yadav Monu, 2014). Non homogenous leukoplakia is further classified into:

- Nodular/Speckled leukoplakia – It's a non-homogenous granular white and red lesion predominantly with white areas wherein keratotic white nodules are distributed on a background of atrophic erythematous area (Yadav Monu *et al.,* 2014).
- Verrucous leukoplakia – It is often encountered in 6^{th} to 8^{th} decade of life. Its surface appears as elevated, proliferative or corrugated. The lesion often shows presence of thick white lesions with papillary surfaces, which are heavily keratinized (Yadav Monu *et al*., 2014).

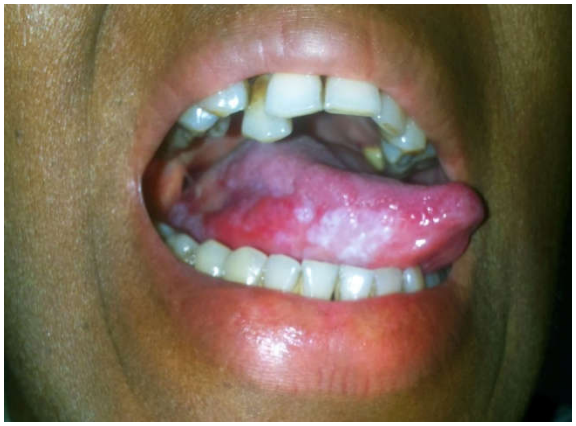

Fig. 1. Homogenous leukoplakia extending from the lateral to ventral surface of tongue

Proliferative verrucous leukoplakia

It is a precancerous lesion with greater frequency of mortality due to high rate of malignant transformation. It was first described by Hansen *et al.* (1986) and is a subtype of verrucous leukoplakia with an aggressive behaviour, multifocal appearance, high rate of recurrence and resistant to treatment (Ioanina Parlatescu *et al*., 2014; Yadav Monu *et al*., 2014).

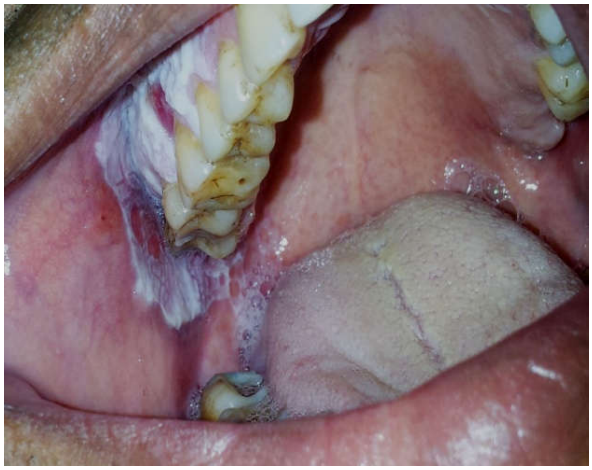

Fig. 2. Speckled Leukoplakia extending from right posterior maxillary gingiva to the buccal mucosa

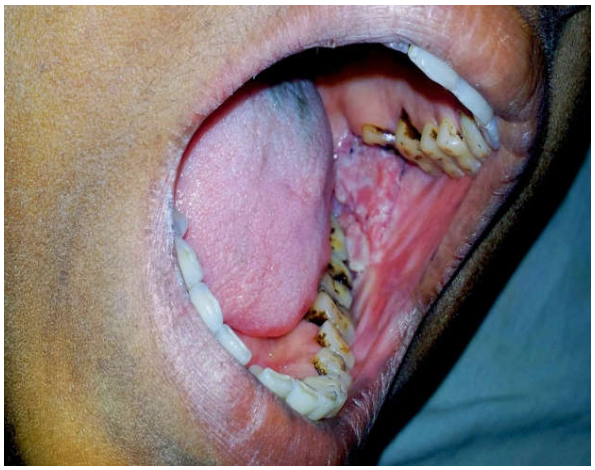

Fig. 3. Nodular leukoplakia near the left retro-molar pad area

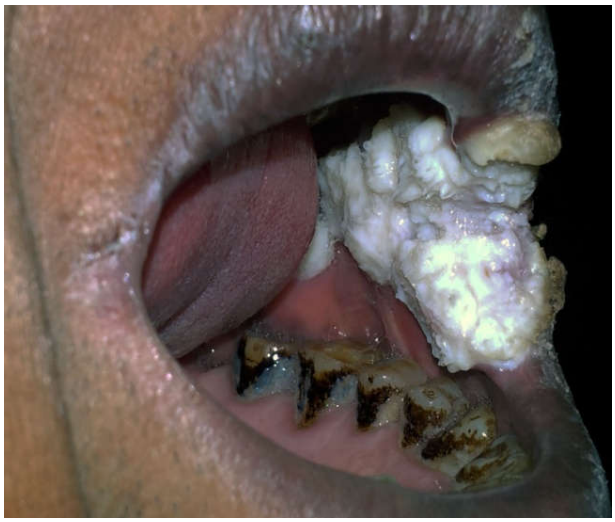

Fig. 5: Proliferative Verrucous leukoplakia extending from left labial commissure into the buccal mucosa

Classification and staging system of oral leukoplakia (Mirian Aparecida Onofre, 2001)

Van der Waal *et al.* (2000) proposed a modified classification and staging system for leukoplakia on the basis of two basic criteria *viz*. i) size of leukoplakia ii) pathology – presence or absence of dysplasia.

Size of leukoplakia <2 cm
L2 - Size of leukoplakia 2-4 cm
L3 - Size of leukoplakia >4 cm
Lx - Size not specified

Pathology
P0 - No epithelial dysplasia
P1 - Distinct epithelial dysplasia
Px - Dysplasia not specified in pathology report.

Stage I — L1 P0
State II — L2 P0
Stage III — L3 P0 or LI L2 P1
Stage IV — L3 P1

Histology

Microscopically oral leukoplakia varies in appearance between appearance of dysplasia and carcinoma. Lesions are usually classified as dysplastic (mild, moderate or severe) and non-dysplastic (Ioanina Parlatescu, 2014). Degree of dysplastic changes is often used for predicting the risk of malignant transformation (Feller *et al*., 2012). Classically leukoplakia shows hyperkeratosis of the surface epithelium with or without acanthosis. Some leukoplakia show hyperkeratosis of the surface epithelium but shows atrophy (thinning) of the underlying epithelium too. Also chronic inflammatory cells are observed in the adjacent connective tissue (Nevielle, 2002).

Malignant conversion

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies encountered today. Progression of oral leukoplakia to OSCC is less frequent with an average risk of 2% annually (Feller, 2012). The risk of transformation of oral leukoplakia to OSCC is related to habits like smoking and alcohol intake (Partridge *et al*., 2000). The frequency of idiopathic leukoplakia transformation to carcinogenic form is much higher (Feller, 2012). Vicious habits of tobacco usage gives rise to OSCC from pre-existing lesions of leukoplakia, but sometimes OSCC develop even in absence of these deleterious habits, from normal looking epithelium and are indeed more aggressive with less favourable diagnosis (Feller, 2012; Suarez, 1998). Large leukoplakia greater than 5 mm at sites *viz.* ventral surface of tongue, floor of mouth, soft palate and retro molar pad area tend to develop into carcinoma more frequently than leukoplakia which develops from other sites or which are smaller in size (Feller, 2012). Napier and Speight (2008) conducted a study and concluded that transformation of precancerous lesion into malignancy varies in different populations, *e.g.* in Italians, pre malignant lesions of tongue tend to develop into malignancy more frequently than in buccal mucosa, whereas in Indians leukoplakia of buccal mucosa shows more malignant transformation (Ioanina Parlatescu, 2014; Napier, 2008). Degree of dysplasia is not the only factor on which malignant transformation of leukoplakia occurs from high risk sites, several other unknown factors are present. Silverman *et al.* states that 36% of dysplastic lesions and 16% of non-dysplastic lesions progress into leukoplakia (Ioanina Parlatescu *et al*., 2014). Several studies have shown that some leukoplakia arise from keratinocytes of pre-cancerized oral epithelium which are cytogenetically altered. In such cases keratinocytes exhibit alteration in p53 gene and there is loss of heterozygosity and aberrations in DNA content thereby demonstrating malignant transformation. But in some cases cytogenetic changes of keratinocytes could not be illustrated and even then there is malignant transformation. Therefore the challenge is to distinguish between the two; as both, one that undergo malignant transformation and the other which do not, cannot be differentiated clinically (Feller, 2012).

Investigation

Visual examination is the conventional method to examine oral mucosa, but non-invasive techniques are required to determine the stage and risk level of a pre-cancerous lesion (Ioanina Parlatescu, 2014). Intravital staining – Toludine blue stains nucleic acids and abnormal tissue selectively. It stains acid components of DNA and RNA present in dysplastic cells, thereby aiding in determining the site of biopsy (Yadav Monu *et al*., 2014). Oral brush biopsy – It's a non-invasive procedure that collects basal layer cells of stratified squamous epithelium using a cytobrush. This eliminates the need of surgical intervention in doubtful lesion (Ioanina Parlatescu, 2014; Yadav Monu *et al*., 2014).

Narrowband Imaging (NBI): Flexible fibre optic endoscope along with NBI provides excellent images of the surface mucosa along with its vessels, aiding in diagnosis of precancerous lesions. NBI works on the concept of narrowing the band width of transmitted light by optical filters, absorbing all bands of light barring two. One band highlights sub mucosal capillaries, which usually appears brown, whereas the other band passes along the sub mucosal layer and determines the vessels as cyan in colour. Inflamed tissues as well as highly vascular tissues appear dark, as they absorb more light. Similarly oral cancers and tissues showing dysplasia also appear dark. Leukoplakia, *i.e.* tissue with dysplasia and keratinisation shows increased fluorescence along with loss of fluorescence at its periphery. Also traumatic, viral and apthous lesions are detected by NBI and show loss of fluorescence. The main aim of NBI is to aid the clinician in determining oral lesion including premalignant lesion that would otherwise have escaped detection. VelScope is a NBI device commonly used in routine dental practice for screening of patients. Mucosal abnormalities detected by NBI also helps in guiding excisional biopsies, by determining doubtful areas with superficial vascularity (Shih-Wei Yang *et al*., 2015; Neil *et al*., 2012; Edmond *et al*., 2011)

Treatment

The main aim towards treatment and management of oral leukoplakia is to arrest its malignant transformation. Cessation of deleterious habits of the patient *viz*. smoking is the first and foremost criteria. Degree of dysplasia usually determines the treatment of choice of leukoplakia (Ioanina Parlatescu *et al*., 2014).

Surgical management

Oral leukoplakia, without any significant dysplasia (low malignant risk) could be excised surgically or be left alone depending on location and size of the lesion. Nonhomogeneous and idiopathic leukoplakia with high risk of malignant transformation showing moderate or severe dysplasia are treated aggressively by surgery. Cryosurgery and laser surgery are usually recommended in multiple and large lesion where traditional surgery could result in disability or deformity (Ioanina Parlatescu *et al*., 2014; Feller *et al*., 2012).

Medical management

It includes several local and systemic chemo preventive agents. Retinoid along with antioxidant combination of Vitamin A, Vitamin C (ascorbic acid) and Vitamin E (alpha tocopherol) are quite effective clinically and aids in deceleration of dysplasia (97.5%).0.18% of topical isoterin with a clinical resolution of 85% and 4mg systemic lycopene with 80% clinical resolution are reported to be most effective against leukoplakia. Topical antioxidants are usually more effective than systemic antioxidants (Uma Maheswari, 2013). Adverse effects pertaining to both topical and systemic antioxidants are quite rare, with a few cases of lichenoid reactions and sensitivity being reported on using topical tretinoin cream. Mild side effects are reported with systemic 13 cis retinoic acid, beta carotene and isotretinoin. But patients administered with 4 HPR produced major side effects including haematological, cutaneous and gastro toxicity. Recurrence is quite common on discontinuation of antioxidant therapy (Uma Maheswari, 2013).

Conclusion

Leukoplakia is the commonest pre malignant lesion of the oral cavity. It sometimes remains stable, regresses on its own, or undergoes malignant transformation. The role of the clinician revolves around early diagnosis of the symptom and removing the possible etiological factors (smoking), which aids in reducing the rate of malignant transformation. Although lycopene and other antioxidants have proved to be effective in treatment of leukoplakia further studies and clinical trials are necessary both on topical and systemic antioxidant therapy. On current evidence, surgical intervention with regular follow-up of the patient is the treatment of choice. Dysplastic changes should be monitored and patient must be counselled against tobacco usage and alcohol consumption.

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