Clinico-Pathologic Evaluation & Medical Treatment of Oral Leukoplakia

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ABSTRACT: Leukoplakia is defined as a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion. Histopathological diagnosis is needed to evaluate prognosis of this lesion. Chewing tobacco and smoking are distinct risk factors particularly among males in certain countries; however it has been noted that females or non-smokers may be at risk of malignant transformation. HPV has been detected in oral dysplasia lesions and cancer in non-smokers. Malignant transformation rates of oral leukoplakia (OL) range from 0.13 to 17.5%, while the rates of five year cumulative malignant transformation range from 1.2 to 14.5%. Although the administration of retinoic acid and beta-carotene has some efficacy to resolve OL, the role of photodynamic therapy (PDT) is believed to play an important therapeutic role in these patients. This article emphasizes need of uniform classification methods to evaluate the malignant potential of leukoplakia, and new treatment avenues in its resolution.

KEYWORDS: Epithelial dysplasia, Histopathology, Oral leukoplakia, Malignant transformation, Photosensitisers, White lesions.

I. INTRODUCTION

According to WHO definition (1978)¹, premalignant lesion is defined as “a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart. Examples: leukoplakia, erythroplakia, palatal keratosis associated with reverse smoking. WHO (1978) defined an oral precancerous condition as “a generalized pathological state of oral mucosa associated with a significantly increased risk of cancer.” Examples: OSMF, lichen planus, DLE, epidermolysis bullosa. Warnakulasuriya² et al have recommended abandoning the distinction between the terms “potentially malignant lesions” and “potentially malignant conditions” and to use the term “potentially malignant disorders” instead. According to them, the term “potentially malignant disorders” means that not all abnormalities may transform into cancer, but some may have an increased potential for malignant transformation.

Leukoplakia is most common premalignant, potentially malignant or precancerous lesion of the oral mucosa. The word leukoplakia is derived from two words, leuko meaning white and plakia meaning patch. Leukoplakia is usually found in between fourth to seventh decade of life, but has been found to occur in initial decades of life also. Males have been found to be more affected than females. According to Petti¹² et al (2003), oral pre-malignant diseases affect males at least three times as often as females. Clinically leukoplakia exhibits varying features.²⁰, ⁴⁵ The surface can be smooth or wrinkled, sometimes smooth surfaced lesions may be traversed by small cracks or fissures. The lesions may be white, whitish yellow or gray. The surface may be homogenous, ulcerated, or speckled. The homogenous varieties are uniformly flat and thin having shallow cracks of surface keratin giving an appearance likened to cracked mud. The non-homogenous varieties, like nodular and verrucous have irregular surfaces.

II. FEATURES OF ORAL LEUKOPLAKIA

Leukoplakia is generally defined by exclusion of other diseases, particularly white lesions.²⁷ W.H.O. defines it as “A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any other physical or chemical causative agent except use of tobacco.” According to Warnakulasuriya³ et al., in 2007, “Leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known disease or disorders that carry no increased risk for cancer.” Leukoplakia is caused by cumulative effect of various risk factors.²⁹, ³⁰ Wynder⁴ et al (1957) applied the terms ‘intrinsic’ and ‘extrinsic’ to group factors which act together to produce a premalignant state. Exogenous or “extrinsic” factors in leukoplakia include tobacco, alcohol and mechanical trauma. The endogenous or “intrinsic” factors include systemic or generalized states such as malnutrition or iron deficiency anemia and genetic factors. Tobacco has been considered as an important causative agent.³¹, ³⁴, ³⁵, and ³⁶ The role of human papilloma virus (HPV) in the etiology of premalignant and malignant lesions has been studied extensively. In a
study done by Nielsen et al, HPV was mentioned as a likely causative agent. Meta analysis by Miller and Johnstone (2001), reported that the likelihood of detecting HPV was 2-3 times higher in precancerous oral mucosa. HPV genotypes 16 and 18 have been detected in many cases of leukoplakia. Mehtta et al (1971) classified leukoplakia in three categories: 1) *Homogenous leukoplakia*: Characterized by a raised plaque formation consisting of a plaque or groups of plaques varying in size with irregular edges. The lesions are predominantly white but can be grayish white or yellow. 2) *Ulcerated leukoplakia*: Characterized by a red area at times with yellowish area of fibrin, giving the appearance of ulceration. 3) *Nodular (speckled) leukoplakia*: Characterized by white patches on an erythematous base. Banoczy et al in 1982, categorised leukoplakia in three types: Type I or *Leukoplakia simplex*: Keratinized mucosa with flat or very slightly elevated white lesions. *Type II or Leukoplakia verrucosa*: Verrucous proliferation raised above the mucosal surface. *Type III or Leukoplakia erosive*: White lesion with erythematous area or erosion, and fissures. In an International seminar on Oral leukoplakia, Malmo, Axell et al (1984) classified leukoplakia as: *Homogenous leukoplakia (simplex)*: A uniform whitish lesion with a smooth or corrugated surface. *Erythro-leukoplakia (erosive leukoplakia)*: A whitish lesion that includes red areas. *Nodular leukoplakia*: A lesion with slightly raised, rounded, red and whitish excrescences that may be described as granules or nodules. *Verrucous leukoplakia*: An exophytic lesion with irregular sharp or blunt projections.

In some prospective study on large samples from India, carried out in several geographic areas with various kinds of tobacco usage, the annual age-adjusted incidence rates of leukoplakia varies per 1000 population per year. The annual screening program reported from Japan showed that the age-adjusted incidence rate for leukoplakia was high in male than in female per 100, 000 persons. The age-adjusted incidence rate for tobacco-associated leukoplakia in males was almost 12 times as compared to females. The reported incidence of oral leukoplakia in Japanese population was somewhat higher to those reported from India. The prevalence of oral leukoplakia varied from 1.1% to 11.7%. Axell et al, studied the prevalence in Swedish community. According to Petti (2003), the global prevalence was about 2.6%. A study done by Gupta et al (1980) showed the annual incidence of 1.1 to 2.4 percent among men and 0.2 to 0.03 percent among women.

### III. MICROSCOPIC FEATURES OF LEUKOPLAKIA

Leukoplakia can present as benign hyperkeratosis, mild dysplasia, moderate dysplasia, severe dysplasia or invasive carcinomas microscopically. *Mild dysplasia* histologically shows hyperplasia of cells of the basal layers, cytological atypia with mild pleomorphism of cells and nuclei, and minimal architectural changes. Moderate dysplasia histologically shows proliferation of atypical cells seen upto one-thirds of epithelium with prominent cytological changes. Hyperchromatism and cellular pleomorphism are seen. Architectural changes are seen in form of loss of polarity of basal cells. In *severe dysplasia*, abnormal proliferation of cells is seen from basal layer to upper third of epithelium. There is marked pleomorphism of cells with changes in nuclear-cytoplasmic ratio. Architectural changes are severe, with loss of stratification. In *carcinoma-in-situ*, the cytological and architectural changes are clearly evident throughout whole epithelium.

The 14th International Cancer Congress in Hungary suggested the following microscopic changes for the diagnosis of oral epithelial dysplasia: Drop-shaped rete processes, Disturbed nuclear polarity, Basal cell hyperplasia, Disturbed epithelial maturation, Pleomorphic cells, Anisocytosis, Hyperchromatic nuclei, Prominent nucleoli, Increased nuclear - cytoplasmic ratio, Cell crowding, Increased number of mitoses, Abnormal mitoses & Reduced cellular cohesion.

Pindborg in 1997 proposed the following criteria for epithelial dysplasia: Loss of polarity of basal cells, Presence of more than one layer of cells having basaloid appearance, Increased N/C ratio, Drop shaped rete-ridges, Irregular epithelial stratification, Increased number of mitotic figures, Mitotic figures that are abnormal in form, Presence of mitotic figures in the superficial half of the epithelium, Cellular and nuclear pleomorphism, Nuclear hyperchromatism, Enlarged nuclei, Loss of intercellular adherence & Keratinization of single cells or cell groups in prickle cell layer.

WHO classification of head and neck tumors gave cellular and architectural changes for grading leukoplakia. (Table: 1)
Table 1: Microscopic Features of Leukoplakia

<table>
<thead>
<tr>
<th>Cellular changes</th>
<th>Architectural (tissue) changes</th>
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<tr>
<td>Abnormal variation in nuclear size (anisonucleosis)</td>
<td>Loss of polarity</td>
</tr>
<tr>
<td>Abnormal variation in cell size (anisocytosis)</td>
<td>Disordered maturation from basal to squamous cells</td>
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<tr>
<td>Increased nuclear/cytoplasmic ratio</td>
<td>Increased cellular density</td>
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<tr>
<td>Enlarged nuclei and cells</td>
<td>Basal cell hyperplasia</td>
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<tr>
<td>Hyperchromatic nuclei</td>
<td>Dyskeratosis (premature keratinization and keratin pearls deep in epithelium)</td>
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<tr>
<td>Increased mitotic figures</td>
<td>Bulbous drop-shaped rete pegs</td>
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<tr>
<td>Abnormal mitotic figures (abnormal in shape or location)</td>
<td>Secondary extensions (nodules) on rete tips</td>
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<tr>
<td>Nuclear and cellular pleomorphism</td>
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<td>Increased number and size of nucleoli</td>
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IV. DISPARITY IN DIAGNOSIS OF VARIOUS GRADES OF LEUKOPLAKIA

The progression rates from oral epithelial dysplasia are varied. Several studies have shown greater inter and intra - observer variability study in the assessment of various grades of dysplasia. Although generally moderate or severe dysplasias (in-situ carcinomas) show a greater disposition for malignant transformation than mild or non-dysplastic cases, carcinomatous transformation may also take place in non dysplastic cases. Very small lesions have been found to exhibit dysplastic changes. The WHO Collaborating Centre for Oral Pre-cancerous Lesions, established in Copenhagen in 1967, recognized three major problems that were attached to the importance of epithelial dysplasia in predicting malignant development: (i) the final diagnosis was essentially subjective. (ii) Not all lesions showing dysplasia would eventually become malignant, and some even regressed. (iii) Carcinoma developed from lesions in which epithelial dysplasia had not been diagnosed in previous biopsies. Nowadays the role of biomarkers is considered to be helpful in evaluation of oral leukoplakia.

V. MALIGNANT POTENTIAL OF LEUKOPLAKIA

According to Amagasa et al., (2006), the percentage of leukoplakia that progresses to invasive squamous cell carcinomas ranges from 0.13 to 17.5 percent, and the rates of five year cumulative malignant transformation ranges from 1.2 to 14.5 percent. Gangadharan et al., (1971), in the study of 626 leukoplaikas found malignant transformation rate to be 10 percent over a mean period of 8-9 months. Mehta et al., (1972) in a 10 year follow-up study of 117 leukoplakias found mean transformation rates of 0.9 percent only. Gupta et al., (1980) observed malignant transformation rate higher among women than men, and more in persons chewing tobacco. In their study they also found that patients with oral leukoplakia carry a five-fold higher risk of developing oral cancer than controls. Burkhardt et al., (1985) reported that mild, moderate and severe dysplasia has malignant potential of about 3%, 4% and 43% respectively. Zhang et al., in 2001 analyzed 71 epithelial dysplasia cases from the floor of the mouth, ventro-lateral tongue, and soft palate, designated as high-risk sites and 56 epithelial dysplasia cases from other sites of the oral cavity, designated as low-risk sites. The results were not influenced by gender or smoking. They found that epithelial dysplasias from high-risk sites had a higher frequency of loss of heterozygosity and a pattern of loss associated with an increased risk of progression to malignancy. Bouquot et al., (2006) reported that severe dysplasia has an overall malignant transformation rate of about 16% with 7-50% range. Speight et al., (2007) reported that moderate dysplasys have malignant transformation potential of 3-15%, whereas mild epithelial dysplasia show a very low risk (<5%). Silverman et al. (1976) in a study found that 11% of lesions altered clinically and exhibited increased tendency towards. Banoczy et al., found 13% of lesions undergoing malignant transformation. studies by silverman et al. (1984), Holmstrup et al., Lind (1987), Schepman et al., (2.9%) and shiu et al., found malignant transformation rates 17.5%, 20%, 7%, 2.9% and 2.6% respectively.

VI. TREATMENT OF ORAL LEUKOPLAKIA

6.1 BETA-CAROTENES:

The use of beta-carotene has been recommended in order to prevent OL and possibly oral cancer. The potential benefits and protective effects against cancer are possibly related to its antioxidizing action. 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. According to Liede et al., a diet...
supplemented with beta-carotene can prevent changes in the oral mucosa, especially in smoker patients, who present low serum levels of vitamin C and beta-carotene when compared to non-smokers. It has also been shown that beta-carotene has a better therapeutic clinic response in the prevention of oral leukoplakia lesions, and in smoker patients than in the non-smoker ones.\textsuperscript{55}

6.2 LYCOPENE:

Lycopene is a carotenoid without provitamin A action. Lycopene is considered one of most efficient biological antioxidants.\textsuperscript{56} 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 cardiovascular diseases.\textsuperscript{57} Due to this property, studies have been done to find out whether or not it could be an alternative to protect patients against the damaging effects of free radicals. Lycopene is believed to modify intercellular exchange junctions, and so effective in potentially malignant disorders.\textsuperscript{56}

6.3 RETINOIDS:

At the cellular-level, retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus by various proteins. Retinoids affect diverse processes, such as keratin production, the expression of growth factors and kinases, oncogenesis, apoptosis, production of the collagen matrix, immunologic and inflammatory response, cellular differentiation, embryonic morphogenesis and carcinogenesis.\textsuperscript{58} 13-cRA is the retinoid recommended for OL treatment. The use of 13-cRA has been shown to be effective in resolving OL.\textsuperscript{53,54} However, the high recurrence rates after short periods of discontinuance, together with its side effects, are limiting factors.\textsuperscript{55,58} Various studies have evaluated the therapeutic effectiveness of vitamin A derivatives in the treatment of OL. In one study, patients received a fixed dose of 13-cRA (10 mg/day) plus an escalating dose (beginning at 800 IU/day, until 2000 IU/day) for 4 months. Seventy-one percent of OL patients had complete clinical responses.\textsuperscript{59}

6.4 PHOTOSENSITISERS:

Among various photosensitisers, 5-Aminolaevulinic acid (ALA) has been used for treatment of oral leukoplakia. 5-Aminolaevulinic acid (ALA) was also approved in several countries for the treatment of skin cancer. The ALA is a naturally occurring compound in the haem biosynthetic pathway, which is metabolised to a photosensitive product, protoporphyrin IX (PpIX). The major advantage of ALA when compared to synthetic photosensitisers is the rapid metabolism, which significantly reduces the period of cutaneous photosensitivity. For very superficial skin lesions or premalignant lesions of the oral mucosa, the ALA can be applied topically. For all other indications intravenous application is mandatory.\textsuperscript{60} Zakrzewska et al.\textsuperscript{61} reported effective role of it than surgery & carbon dioxide laser in treatment of proliferative verrucous leukoplakia.

VII. CONCLUSION

Disparity in evaluating oral leukoplakia can be minimised by uniform classification systems. Research is going on to evaluate role of specific biological markers in diagnosing and predicting the prognosis of premalignant disorders. The role of photosensitisers has shown promising results in its regression.

VIII. ACKNOWLEDGEMENTS

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