Oral Leukoplakia Etiology, Risk Factors, Molecular Pathogenesis, Prevention and Treatment: A Review

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ABSTRACT

Oral leukoplakia is defined chiefly as a white colored affected area of the mucosa of the oral cavity that is difficult to distinguish from any other clear-cut or precise lesion; and moreover the affected area must be biopsied and confirmed on histopathology which also help in differentiating borderline ors malignant transformation of this particular lesion. Leukoplakia is noticed customarily in males after 35 years of age. The occurrence and distribution of leukoplakia of the oral mucosa varies globally depending on the race, ethnicity and habits. In general the documented and reported prevalence is between 0.2% and 5%, with exceptional differences in various regions of the world: India (0.2-4.9%), Sweden (3.6%), Germany (1.6%), and Holland (1.4%).

Keywords: Oral Leukoplakia, Pre-Malignant, Malignant, Dysplasia, Oral Mucosa, Dentistry.

INTRODUCTION

The oral mucosa of the humans have a varying colors of pink and red, like light pinkish-red in gingiva , dark red in vestibular region and pink-red in the palatal region , base of the tongue.

This pinkish red natural color occurs due to the reflectance of the passing light through the translucent superficial layers of the mucosa covering stratified squamous epithelium of the oral cavity and other areas of the oral cavity, striking the capillary bed.[1]

Any epithelial changes like keratosis, hyperkeratosis, acanthosis, edema between the cells or infiltration of hyphae of candid albicans may result in lesion which appears white owing to reflection of light on superficial keratin layer, debris of the keratin and dead and de-squamated epithelial cells. Therefore, a clear and valid differentiation of these white lesions of oral mucosa is significant to the clinician to give appropriate information for collating and contrasting different lesions affecting oral mucosa which have a routine clinical look, as the white patch can also be caused by a easy injury related to a particular infectious disease or the primary unknown or unseen cause.[1-3]

These white patches are classified into either clinically or histo-pathologically. Clinically, into 1) lesions that cannot be scrapped off or wiped away by tongue blade which denote for keratotic lesions of oral mucosa, 2) those affected areas which can be easily sweeped off or cleaned away by the tongue, which denote that these lesions were resulted from sloughing, piling up of necrotic tissue which forms a pseudo membrane or due the retention of dead and desquamated epithelial cells.

Apart from the above classification, other simple classification includes genetic white patches present since birth and runs in families, frictional keratosis occurs due to the constant rubbing of the epithelium by the defective teeth or dentures, white patches which occurs due to infections mainly by fungus, idiopathic white patches, dermatological white patches and neoplastic white patches.[1-3]

In contrast to clinical basis, histopathologically, the classification of white patches depends on the microscopic hallmark points of epithelial dyasplasia where the lesion may show.[1,2]

1. Mild dysplastic areas focally localized to the lower one third of the epithelial covering.
2. Moderate dysplastic areas focally localized to the lower two third of the epithelial covering.
3. Sever dysplastic areas involving entire thickness of the epithelium but without breaching the basement layer of the epithelium which is commonly termed as carcinoma in situ (CIN).
4. Those lesions that are infiltrating squamous cell carcinoma.
5. Those lesions that are histopathological features of other diseases and conditions other than the above 4 changes.

NOMENCLATURE AND DEFINITION

Leukoplakia is a word derived from the greek literature- Leucos means white and Plakia means patch- White Patch. This term was used in the second half of the 19th century by the Hungarian dermatologist, Schwimmer in 1877.[4,5]

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World Health Organization (WHO) in the year 1978 defined it as white patch or plaque which cannot be distinguished as any other disease by clinical examination or pathological examination.[6] International attempts to define or re-define the WHO definition of oral leukoplakia are: First International Conference on Oral Leukoplakia Malmo, Sweden in 1983-A white patch or plaque that cannot be characterized by clinical examination or pathologically into any other disease and its occurrence or origin is not associated with any physical or chemical causation except the tobacco use.[7]

International Symposium, Uppsala, Sweden in 1996 defined leukoplakia as- A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable disease.[8]

Warnakulasuriya et al narrated that the word Leukoplakia should be used to identify white plaques of doubtful risk after excluding other known diseases or disorders that carry no risk for cancer formation.[5]

EPIDEMIOLOGY

Leukoplakia is the best-known and highly potential pre-malignant disorder of the oral cavity, and its epidemiology is finely documented globally. The prevalence of leukoplakia is variable among various scientific studies, various ethnicities and races. It has a comprehensive global review point at a prevalence of 2.65% and malignancy conversion rate ranging from 0.12% to 17.51%. The statistical analysis from several Indian studies shown the prevalence of leukoplakia ranges between 0.21% and 5.22% and the malignant transformation ranges of 0.13% to 10%. This steep increase in the prevalence of leukoplakia particularly in India could be predominantly due to its cultural, ethnic and geographic factors.[9]

Downer and Petti reported that the annual malignant conversion incidence rate of leukoplakia was found to between 6.2 and 29.1 cases per 100,000 people. In other study by the authors, Martorell-Calatayud et al determined the prevalence of leukoplakia to be in the range of 0.4% to 0.7%, whereas Feller et al. estimated the prevalence towards higher range of 0.5% to 3.46%.[9] Furthermore, the same study concluded that the malignant transformation rate of leukoplakia ranged from 0.7% to 2.9%. In one more study by Brouns et al showed the prevalence and annual malignant transformation is 2% and 1% respectively.[9] The prevalence increases with increasing age.[9] In general the reported prevalence ranges between 0.2 % and 5%, with exceptional differences in various regions of the globe: India (0.2-4.9%), Sweden (3.6%), Germany (1.6%), and Holland (1.4%).[10]

ETIOLOGY AND RISK FACTORS OF ORAL LEUKOPLAKIA

The causes of oral leukoplakia is multifactorial, some well-known and identified such as tobacco, ill-fitted dentures , bacterial infections, Epstein Barr virus (EBV) and Candida species and some extracts of herbal plants.

Genetic Causes

These are extremely rare cause and all have distinctive histopathological hallmark features which are specific to that particular lesion.Hereditary benign intraepithelial dyskeratosis presents as bilateral thick white plaques of the oral mucosa and as gelatinous plaques of the conjunctiva without involvement of the skin.[11,12] Pachyonychia congenita also results in oral plaques but always with the presence of thickened skin lesions, and dyskeratosis congenita causes leukoplakia and oral cancer at a young age.[13,14]

Local Injury

Leukoedema occurs in up to 90% of the population and can occur after exposure to mildly irritating substances such as constant use of mouthwash, excess use of toothpaste, and tobacco or marijuana smoke.[15,16] It presents as delicate gray white lacy lines on the buccal mucosa or ventral tongue that disappear with stretching of the mucosa and histopathology shows only edema of epithelial cells.

Tobacco Smoking

Tobacco usage is practiced across the globe in various forms and it is the most common cause of leukoplakia of the mucosa of the oral cavity. Many authors have proved that the chemical carcinogens in the tobacco lead to various oral lesions. It is estimated that above 80% of patients presented clinically with leukoplakia are attributable to smoking.[17] Both reverse and normal smoking attributes to the development of the oral leukoplakia.

Fungal Etiology

Candida albicans is a normal inhabitant in the oral cavity, throat, large bowel and vagina, and the infection rate increases in pregnancy, tobacco smoking, denture wearers and presence of any medical conditions or immunoosupression. Oral cavity mucosa near to the commissure of the lips is the most frequently affected site in which the shape of the lesion and usually appears as triangular tapering and customarily it is associated with angular chelitis.[17]

Epstein Barr Virus

Hairy Leukoplakia (HL) is a separate disease entity which has strong link with HIV infection, although it can also occur in non-HIV infected patients who are on immuno-suppressive therapy. Epstein Barr Virus (EBV) cause oral leukoplakia and presents clinically as a thick white patch with folds, corrugated or hairy surface. The lesion may be seen on other parts of oral mucosa and the surface of the lesion may be smooth.[17]

Bacteria

Syphilis is a venereal disease caused by a delicate spirochete named treponema pallidum. Major route of transmission of the syphilis is by sexual transmission but may be transmitted by blood transfusion and direct contact with the infected. Once the organisms gain entry into the skin, it enters the blood stream and spreads within hours and becomes disseminated long before any local manifestation appears.

Vitamin A, B complex, C, E and Beta-carotene

Nutritional deficiency of the important vitamins, minerals and trace elements may form risk factors for the occurrence of leukoplakia.

Sanguinaria

This type of leukoplakia is known as sanguinaria-associated keratosis and is commonly occurs in the vestibule or on the alveolar mucosa of the maxilla. This is caused by an herbal extract used in the toothpaste and mouth rinse.

Alcohol

It seems to have a strong colloborative effect with tobacco relative to oral cancer production, has not been associated with leukoplakia. People who excessively use alcohol based mouth rinses with a concentration greater than 25% develops grayish buccal mucosal plaques, but these are pseudoleukoplakia. Alcohol causes dehydration of the oral mucosa and increases the ambient temperature of the oral cavity thereby making the oral mucosa more vulnerable to the carcinogenic effects of tobacco. Alcohol by itself contains known hydrocarbons and nitrosamines.

When a cell is exposed to various carcinogens, the cell tries to adapt to the changes caused by the carcinogen which increases cell proliferation, shrinking of the cytoplasm and the allied organelle load. In this process of proliferation of oral epithelium, a hastened growth occurs and results in hyperplasia, which is the earlier sequelae, and when the irritant persists further, the epithelium shows features of cellular degeneration, a well-characterized feature of adaptation (atrophy). When the stage of adaptation and revocable cell damage ends, the cells gradually reach a stage of irrevocable cell damage, manifesting as either apoptosis or malignant transformation. As an adaptative response, the hastened pace of cell division noted at the earlier stages of transformation facilitates further genetic damage, thereby forcefully pushing the cells further along the path to malignant transformation.

MOLECULAR EVENTS

In a review by the author Smith et al. (2009), p53, Ki-67, and Proliferating Cell Nuclear Antigen (PCNA) are the markers which were most frequently investigated, but loss of heterozygosity (LOH), survivin, matrix metalloproteinase, and altered DNA content were pointed as potential markers for progression of oral leukoplakia. According to the literature published by the authors Napier and Speight, 2008; Warnakulasuriya et al., 2008; Van der Waal, 2009 et al, the presence and degree of epithelial dysplasia in oral leukoplakia are regarded as the most relevant indicator of progression and prognosis, influencing the management of the patients.[18]

Kodani et al showed that oral leukoplakia presented lower

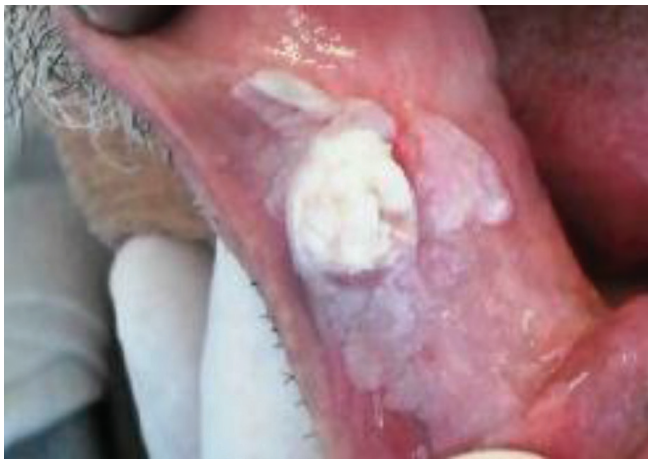

Figure-1: Leukoplakia on the right buccal mucosa in 56 year old male patient

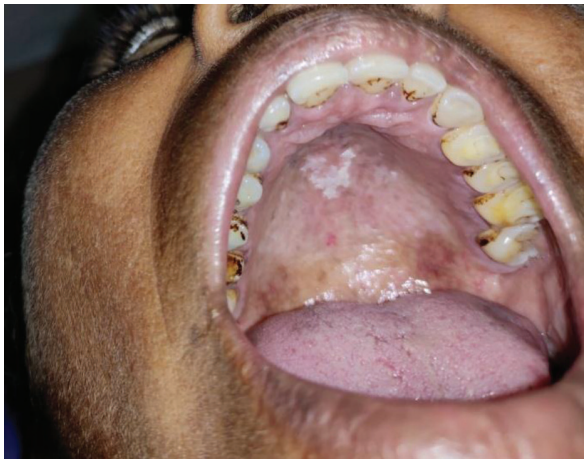

Figure-3: Leukoplakia on the palate in a female of age 43 years

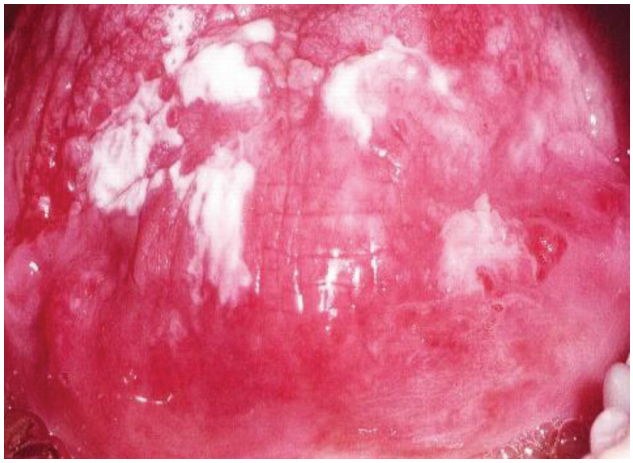

Figure-2: Multiple Leukoplakia patches on the tongue in a 49 year old tobacco and gutkha chewer.

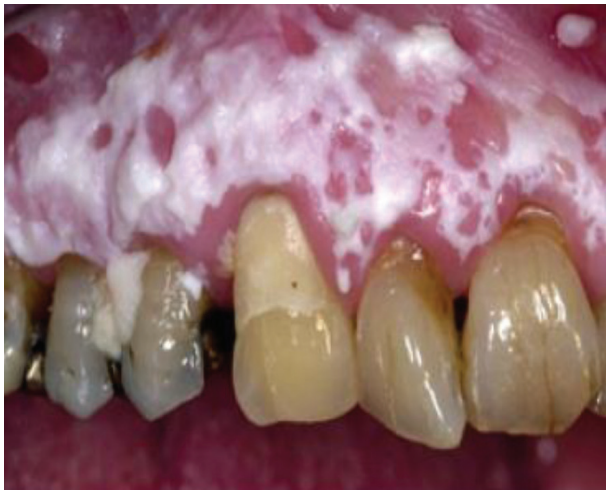

Figure-4: Leukoplakia on the upper Gingiva

indexes of Ki-67 than oral squamous cell carcinoma. Also, Zhao et al demonstrated that oral leukoplakia with mild form of dysplasia showing low levels of Ki-67, while severe form of dysplasia shows a significantly higher expression than oral normal mucosa and mild dysplasia.[19]

p53 alterations: The p53 protein induces DNA repair, cell cycle arrest, cell death or senescence, plays a important role in tumor avoidance . Its manipulation is a routine finding in human cancers. Likewise, p53 immuno-positive cells were identified in oral leukoplakia with mild dysplasia, with increasing indexes from hyperplasia, to dysplastic lesions and to oral squamous cell carcinoma, with immuno-positivity found in superficial layers of moderate and severe dysplasias.

Loss of heterozygosity (LOH): describes the removal of genetic loci containing tumor suppressor genes. In oral leukoplakia, LOH of the chromosome arms 3p and 9p seem to be related to a higher risk of malignant transformation. Fifty percent of oral leukoplakia contains allelic loss of either the 3p or 9p chromosome arms.

Microsatellite instability (MSI) and the mammalian mismatch repair system (MMR):
Microsatellites are regions of DNA with multiple repeated sequences of nucleotides . These regions are prone to the occurrence of mismatched DNA, developing the MSI phenotype. MSI was detected in many oral leukoplakia and there is a trend toward an increased prevalence of MSI in more aggressive histological oral leukoplakia lesions. The immuno-expression of hMLH1 - one of the main MMR protein - was shown to decrease in oral leukoplakia with more severe grades of dysplasia. Taken together, these results strongly suggest that the disturbed function of MMR and the occurrence of MSI could be early events in the carcinogenic process.

Methylation / hypermethylation: is an epigenetic aberration which inactivates various genes. In oral leukoplaia, it was described to occur in RAR-b2, p16, hMLH1 and hMLH2.

AgNOR number: AgNOR staining method is used to check cellular proliferation, and normal oral epithelium showed decreased AgNOR number than dysplastic oral leukoplakia, which in turn presents lower indexes than oral squamous cell carcinoma. It was suggested that mean AgNOR number would be useful in distinguishing oral leukoplakia with mild and moderate dysplasia.[20]

Telomerase activity: these are the enzymes that degrade telomeric ends of the chromosomes. The telomerase activity was detected in oral leukoplakia.

CLINICAL PRESENTATION

Leukoplakia predominantly affects males over 40 years and the incidence is directly proportional thereafter. Leukoplakia can occur at any location in the oral cavity but more prevalent over the buccal mucosa, gingiva and vermilion border of the lip. Leukoplakia can be either solitary or multiple. Initial leukoplakia appears as a mild elevated grayish-white plaque that is either well-defined or gradually mix into the surrounding normal mucosa. In the later stages of progression, it becomes thicker and whiter, and sometimes develops a leathery appearance with surface fissures. Some leukoplakias develop irregularities over the surface and are referred to as granular or nodular leukoplakias. Other lesions develop a papillary surface and are known as verrucous or verruciform leukoplakia.

DIAGNOSIS OF LEUKOPLAKIA

A diagnosis of leukoplakia is made when a predominantly white lesion at clinical examination cannot be clearly diagnosed as any other disease or disorder of the oral mucosa and in this situation a tissue biopsy from the lesion site proves to be very valuable.

Clinical Staining Methods

Toluidine Blue Method: Toluidine blue is an acidophilic meta-chromatic dye which specifically stains acidic components of a tissue. Applying a 1% aqueous solution of toluidine blue to the lesion, rinsing with1% solution of acetic acid, rinsing with water and then observe for any binding.[21] The accuracy has been found to be more than 90%. The mechanism is the rapport or binding of toluidine blue with nucleic acid and sulfated muco-polysaccharides.[21]

Lugol's Iodine Method: Richart used lugol's iodine to identify the malignant change. The normal mucosal tissue is stained brown color and proliferating or transforming epithelium doesn't take the stained or stains poorly. This color development is due to the reaction of iodine with glycogen of the tissues.

Photodiagnosis Methods

5-Aminolevulinic Acid mediated Fluorescence Endoscopic Imaging
After oral administration or topical application of aminolevulinic acid and the synthesis of protoporphyrin within the dysplastic cells, these cells can be simply detected by the fluorescence of protoporphyrin.

5-Aminolevulinic Acid Mediated Digitized Fluorescence Endoscopic Imaging
This developed technique has the capability of acquiring high quality online images and quantifying the fluorescence intensity of diseased oral tissues. It can be a useful to support diagnosis, for directing biopsies and assessing resection margins for oral cavity lesions.

Autofluorescence Spectroscopy
It is applicable for the detection of disturbances in the structural composition of cells which indicate the presence of diseased tissue. It is due to several endogenous fluorophores and can be useful in guiding the optimal location of biopsy.

Histopathological and Cytological Methods

Exfoliative Cytology
It is the process of staining and examining the dead and shed cells from the epithelium but the pitfalls of it are due to the

false negative results in many pre-malignant conditions and this is because many lesions have a thick keratinized surface layer and mimics dysplasia.

Biopsy

Biopsy is the surgical excision of an abnormal tissue from a living person for microscopic examination to confirm or to establish the diagnosis of a disease. It can be excisional biopsy, incisional biopsy or punch biopsy. Keyes biopsy punches are the type recommended for use on oral mucosal lesions. Most important in the diagnosis of oral leukoplakia is the determination of cellular dysplasia by microscopy. Benign forms are characterized by hyperkeratosis, chronic inflammatory cell infiltration in corium. Dysplasia is characterized by abnormal orientation of epithelial cells, cellular pleomorphism, and cellular atypia suggestive of early malignancy.

TREATMENT

Treatment Options

a. Cessation of tobacco use and observation
b. Antifungal agents (Candida-associated leukoplakia)
c. Chemoprevention- Retinoids; Vitamins (A, C, E); Carotenoids
d. Topical therapy- Bleomycin; Vitamin A
e. Photodynamic therapy
f. Surgical excision with or without grafting
g. Electrocoagulation
h. Cryosurgery
i. Laser surgery

CONCLUSION

Proper knowledge about biological and histological behavior of leukoplakia should be lnown for early detection and accurate diagnosis of the leukoplakia is most important for successful treatment. Leukoplakia should be removed totally and Patients should be regularly monitored for any relevant mucosal change and instructed to avoid the major risk factors of oral epithelial dysplasia, especially tobacco usage and alcohol consumption .

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