Management of Oral Leukoplakia: A Review

SMA SADAT[a], F TAJIN[b], NJ NISHI[c], N ISLAM[d]

Abstract:

Oral leukoplakia is a widely known white oral mucosal lesion which is encountered by dental practitioners specially by oral and maxillofacial surgeons in daily practice. The objective of this article is to update the reader on the concept of treatment algorithm for the management of leukoplakia. Articles were searched through PubMed, Google Scholar and the Cochrane Library (2017 to 2021), confining search to English language with the key words e.g., leukoplakia, white patch, precancerous lesion, premalignant lesion and oral potentially malignant disorders. After initial collection of abstracts of 78 articles, finally 24 papers have been selected for writing up the paper updating on clinico-pathologic characters, diagnosis, evaluation, risk of malignant transformation, management and prognosis of oral leukoplakia. Oral leukoplakia is a common oral potentially malignant disorder. Early diagnosis and screening for oral cancer can potentially subside the mortality and morbidity of disease. Incisional biopsy is mandatory for diagnosis, treatment planning and for checking the prognosis of the lesion. There are no universal modalities on the most appropriate treatment, and despite the treatment disease can recur and undergo malignant transformation in patients. For high-risk lesions, complete excision is recommended and clinician should closely follow up these patients for life. For low-risk lesions and successfully treated cases, routine check-up is recommended by dental practitioners. Health education, counselling the individual, and behavioral therapies are most essential methods of prevention at a primary level by every health care provider.

Key words: Oral Leukoplakia, Oral Potentially Malignant Disorders (OPMD), Precancerous lesion, Premalignant lesion, White patch

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Introduction:

Oral leukoplakia is a widely known white oral mucosal lesion which is encountered by dental practitioners specially by oral and maxillofacial surgeons in daily practice. In a meeting supported by the World Health Organization (WHO), oral leukoplakia has been defined as "a predominantly white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer".[1] Petti reported an estimated world leukoplakia prevalence of 2%[2] while for Van Der Wall a rate of 0.5% or lower is more realistic given the geographical variations.[3] The prevalence rate of leukoplakia increases with the advancing age. Oral leukoplakia is often investigated by biopsy to find out the presence of dysplastic changes. As leukoplakia has malignant potential, it should be diagnosed and managed accordingly and distinctively form other oral white lesions. There is also no consensus on management or best practice guidelines for treating dysplastic lesions, much less leukoplakia with or without dysplasia.[4]

The objective of this article is to update the reader on the concept of treatment algorithm for the management of leukoplakia with or without dysplasia.

Methodology:

We searched the articles through PubMed, Google Scholar and the Cochrane Library (2017 to 2021), confining our search to English language with the following key words: leukoplakia, white patch,

a. Dr. S. M. Anwar Sadat, Associate Professor, Dept of Oral & Maxillofacial Surgery, Dhaka Dental College, Dhaka, Bangladesh. Consultant, Square Hospitals Ltd. President, Oral Cancer Care and Research (OCCR)

b. Dr. Fariha Tajin, Dental Surgeon

c. Dr. Nowrin Jahan Nishi, Dental Surgeon

d. Dr. Naimul Islam, Registrar, Oral Maxillofacial and Head Neck Surgery, University Hospitals of Derby and Burton NHS Foundation Trust. Member, Oral Cancer Care and Research (OCCR)

Address of Correspondence: Dr. S. M. Anwar Sadat, Associate Professor, Dept of Oral & Maxillofacial Surgery, Dhaka Dental College, Dhaka, Bangladesh. Consultant, Square Hospitals Ltd. President, Oral Cancer Care and Research (OCCR). E-mail: an_sadat@yahoo.com, Mobile: +8801711156023

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precancerous lesion, premalignant lesion and oral potentially malignant disorders. The authors initially collected abstracts of 78 articles according to the relevance of the topic. After evaluation, 24 papers have been selected finally as key papers for writing the update on clinico-pathologic characters, diagnosis, evaluation, risk of malignant transformation, management and prognosis of oral leukoplakia.

Epidemiology:

Leukoplakia is the most common premalignant lesion of the oral cavity. The most common site is buccal mucosa and gum. It can also involve lips, tongue and rarely the floor of mouth.

The prevalence of leukoplakia shows high geographical and socio-demographical variance. In general population the prevalence varies from less than 1% to more than 5%.[5] In a systematic review the pooled global prevalence of oral leukoplakia was estimated to be between 1.49% and 4.27%.[2] But according to Van der Waal a rate of 0.5% or lower is more realistic.[3]

Oral leukoplakia is multifactorial disease, and the main causative factor behind this is use of tobacco. Most of the people with leukoplakia have a positive smoking history. So, in population where the use of tobacco is more common, there is a higher prevalence. In a study conducted in India the prevalence of leukoplakia was found to be 1.59%[6] and all of the respondents with leukoplakia were either tobacco smoker or chewer. In that study it was more prevalent in men than in women. Similar result was found in another study in India where males were the main sufferer as consumption of tobacco is higher among men.[7]

But an opposite scenario is seen in case of proliferative Leukoplakia. it affects mostly females and has a very weak association with smoking.[8] It occurs both in smokers as well as non-smokers. The etiology behind proliferative leukoplakia is still unclear but many studies showed viral and genetic association.[9] Proliferative leukoplakia has a very high chance of malignant transformation. Its overall malignant transformation rate is 70-100%.[8] In localized leukoplakia overall malignant transformation rate is 3-15%.[8] The annual malignant transformation rate of oral leukoplakia is 2-3%.[10] But proliferative leukoplakia has a higher annual malignant transformation rate of 10%.[8]

Clinical Types:

According to the macroscopic appearance, oral leukoplakia is classified into homogenous (Figure 1, 2) and non-homogeneous subtypes. The term homogenous leukoplakia is assigned to a leukoplakia which is typically uniformly white, relatively flat, superficial and with clear demarcated margins.[11] These lesions are typically free from interspersed areas pf fissuring, erythema and without a nodular, verrucous or otherwise irregular surface.[11] Nonhomogeneous plaques are predominantly white, or white and red (erosive leukoplakia, erythroleukoplakia) may be either irregularly flat, nodular (speckled), or verrucous.[1,12,13] Proliferative verrucous oral leukoplakia is a subtype of verrucous leukoplakia and is characterized by a multifocal presentation, resistance to treatment and high rate of malignant transformation.[12]

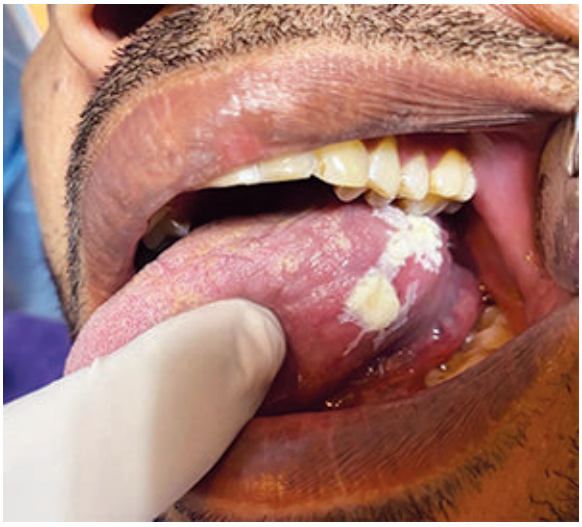

Fig.-1: *Homogenous Leukoplakia tongue*

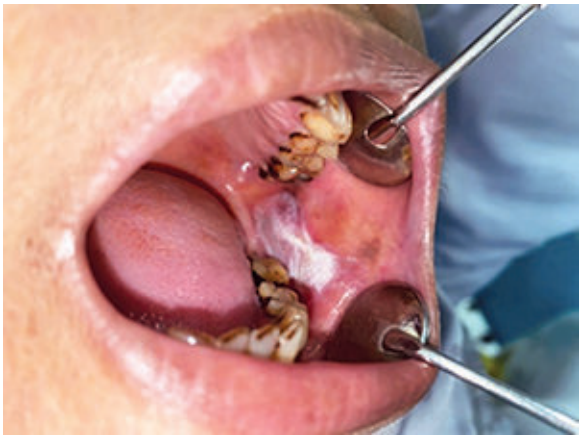

Fig.-2: *Oral Leukoplakia on Buccal Mucosa*

Etiology:

The majority of oral leukoplakia develops because of smoking tobacco, alcohol and betel quid use. Betel nut chewing habits is the main factor in South East Asia for the increased prevalence rate in this region. Oral Leukoplakias that arise in the absence of such identifiable risk factors are described as idiopathic leukoplakias and are considered to have an underlying genetic basis for development.[12,14]

Clinical Findings:

Leukoplakia is presented as a white patch which cannot be rubbed or wiped off the mucosa. Clinically, we can divide leukoplakias into homogenous and nonhomogeneous lesions.[15,16]

Homogenous lesions are usually uniformly white, flat, superficial and has clear demarcated margins. These lesions are free from interspersed areas of fissuring. Nonhomogeneous leukoplakia has speckled or Erythroplasia and nodular or verrucous (wart-like) surface. The margin of these lesions also tends to be less well demarcated.[1]

Verrucous leukoplakia type is non-homogeneous leukoplakia. This lesion usually has a uniform white appearance but its verrucous texture differentiates it from homogeneous leukoplakia.[12]

Proliferative verrucous leukoplakia (Figure 3) is yet another form of nonhomogeneous lesion. But it is far more aggressive in nature and poses a very high risk of malignant transformation.[9] It is considered as a sub type of verrucous leukoplakia. At primary stage Proliferative Verrucous Leukoplakia presents as unifocal, homogeneous, persistent lesion.[17] At this stage, it is extremely difficult to clinically differentiate it from oral leukoplakia. It slowly and persistently turns into multifocal lesion with exophytic, verrucous, or erythematous areas.[18]

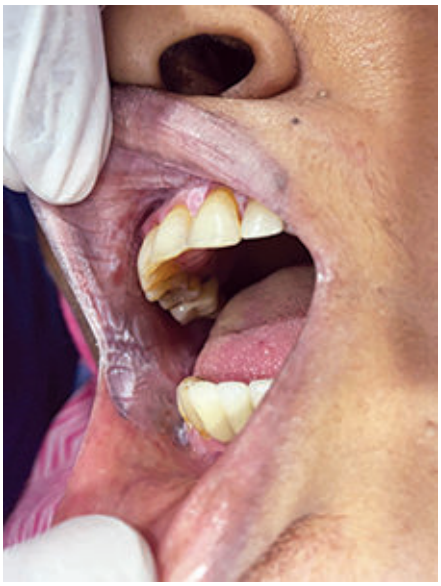

Fig.-3: *Proliferative Verrucous Leukoplakia*

Histological features:

Leukoplakia may present wide range of possible histologic features. It includes hyperkeratosis, acanthosis (thickening), atrophy (thinning) of oral epithelium, infiltration of inflammatory cell in the underlying lamina propria and dysplastic changes.[19]

Hyperkeratosis means an increase in the thickness of the keratin layer of the epithelium, or the presence of such a layer in a site where it is normally not expected. The keratin gives the lesion its white appearance. Hyperkeratosis shows variation in thickness throughout the lesion. It may be either of ortho- or para-keratotic type.[19] And the two types may alternate along the length of the sample.[20]

Oral leukoplakia can be both dysplastic and non-dysplastic although it is not very common in most leukoplakias.

Various degrees of epithelial dysplasia may also be noticed leukoplakic lesions.[21] It indicates a risk of malignant transformation.

The severity dysplastic leukoplakia can be assessed based on architectural changes of tissue and cytological atypia and treatment plan should be made accordingly.

In 2005 WHO proposed some criteria for the diagnosis of dysplasia.[22]

The criteria used for diagnosing dysplasia are Given bellow:

Architecture

Irregular epithelial stratification

Loss of polarity of basal cells

Drop-shaped rete ridges

Increased number of mitotic figures

Abnormal superficial mitoses

Premature keratinization in single cells (dyskeratosis)

Keratin pearls within rete pegs

Cytology

Abnormal variation in nuclear size (antinucleonic)

Abnormal variation in nuclear shape (nuclear pleomorphism)

Abnormal variation in cell size (anisocytosis)
Abnormal variation in cell shape (cellular pleomorphism)
Increased nuclear-cytoplasmic ratio
Increased nuclear size
Atypical mitotic figures
Increased number and size of nucleoli

Hyperchromatic

Based on these criteria WHO gave a classification that recognizes five histopathological stages in epithelial precursor lesions.[22]

Malignant Transformation:

The reported annual risk of malignant transformation of oral leukoplakia varies in the numerous studies on this subject and range from 2 to 3% or even much higher.[23] In general risk factors for oral leukoplakia are similar to the risk factors for oral cancer including smoking, alcohol consumption, areca nut chewing, old age etc. Still there are many predictive factors of malignant transformation of oral leukoplakia such as the size of the lesion, the clinical subtype, the oral subsite and the presence or absence of epithelial dysplasia, a history of cancer but these are not applicable for use in the

1	Squamoushyperplasia	This may be in the spinous layer (acanthosis) and/or inthe basal/parabasal cell layers (basal cell hyperplasia);the architecture shows regular stratification withoutcellular atypia
2	Mild dysplasia	The architectural disturbance is limited to the lowerthird of the epithelium accompanied by cytologicalatypia
3	Moderatedysplasia	The architectural disturbance extends into the middlethird of the epithelium; consideration of the degree ofcytological atypia may require upgrading
4	Severedysplasia	The architectural disturbance involves more than twothirds of the epithelium; architectural disturbance intothe middle third of the epithelium with sufficientcytologic atypia is upgraded from moderate to severedysplasia
5	Carcinomain situ	Full thickness or almost full thickness architecturaldisturbance in the viable cell layers accompanied bypronounced cytological atypia

Histopathological stages in epithelial precursor lesion

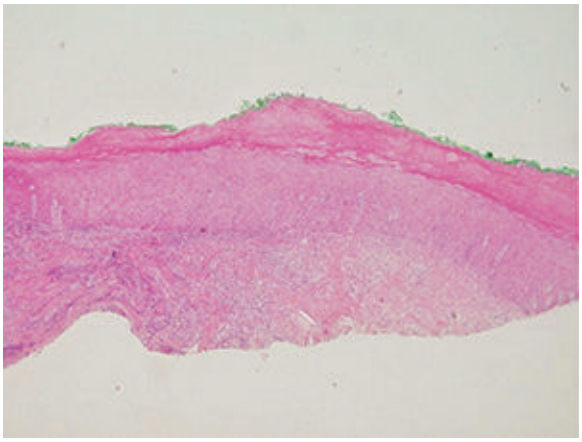

Fig.-4

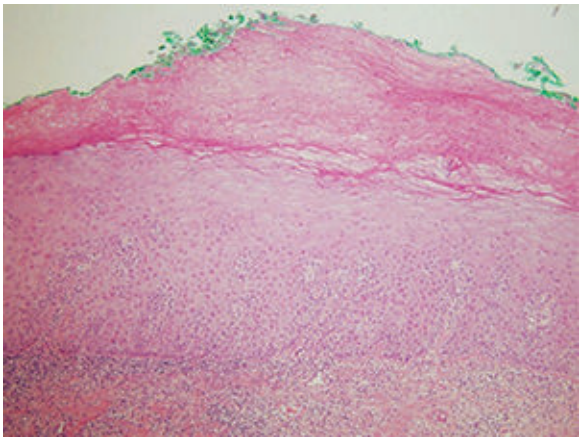

Fig.-5

Sections (Figure 4 & Figure 5) show hyperkeratosis, parakeratosis and acanthosis in the epithelial layer along with chronic inflammation in the subepithelial layer.

individual patient. The most common sites for malignant transformation are floor of the mouth, ventrolateral tongue and soft palate. Candidal infection is one of the risk factors for malignant transformation. The underlying theory centers on the ability of certain Candidal strains forming nitrosamines which are known carcinogens.[24] PVL is characterized not only by a high rate of recurrences after treatment but also by malignant transformation in nearly 74% of cases, with a tendency for several oral cancers to appear.[25] Cladeira et al. (2011) found a high-risk factor of leukoplakia for malignant transformation is the infection with human papilloma viruses as the expression of oncogenic proteins such as human papillomavirus-16L1 can promote carcinogenesis.[26] Factors outlined above such as site, grade of dysplasia, idiopathic nature and nonhomogeneous leukoplakia would result in patient-related specific risks that would need to be discussed with the patient concerned[27-30].

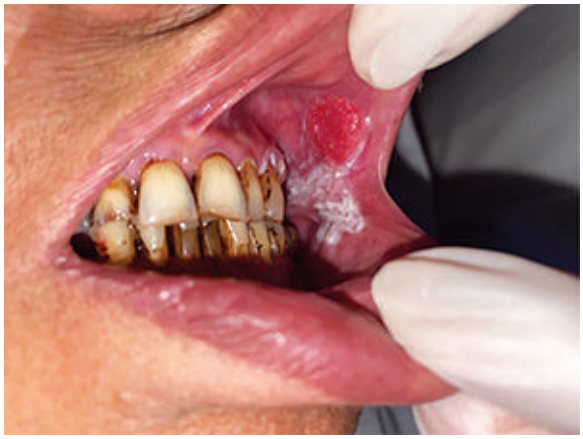

Fig.-6: *shows the evidence of malignant transformation (Squamous Cell Carcinoma) from leukoplakia in buccal mucosa*

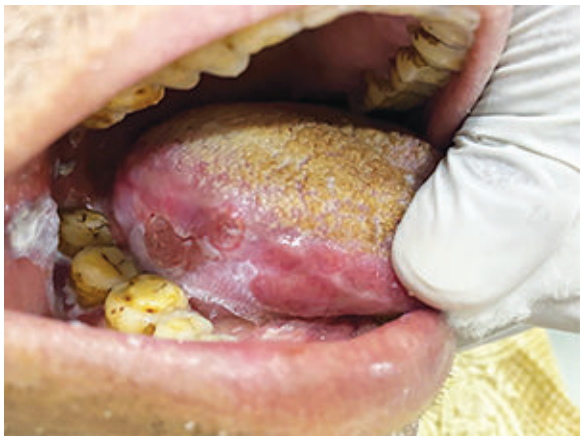

Fig.-7: *shows the evidence of malignant transformations (Squamous Cell Carcinoma) from leukoplakia in buccal mucosa and lateral border of tongue.*

Diagnosis:

Diagnosis of oral leukoplakia is made with the help of proper patient history, clinical presentation and histopathology. It is usually a diagnosis of exclusion.[166]

Other possible causes of the white patches are investigated at first. These could include trauma from teeth or denture and fungal infection, heat or chemical burn or any immunologic cause. If the lesion does not show any sign of healing within two weeks, it should be biopsied.

Biopsy followed by histopathology is considered the gold standard diagnosis and helps to rule out other keratotic lesions. Punch and brush biopsy both can be done but if there is a strong suspect of carcinoma then incisional biopsy is strongly indicated.[31] Besides more obvious white hyper keratinized areas, if there is any indurated, red, erosive, or ulcerated area that should be included in the sample as they are more likely to show any type of dysplastic change.[31] Immunohistochemistry can be done to see the association of HPV with the lesion.

Management:

Management of oral leukoplakia with dysplastic changes is treated by surgery. Other proposed treatment are topical medical agents, systemic medical treatment, removal of risk factors, combined treatment, or the "watchful waiting" approach.[32,33]

Non-surgical Management:

There is currently no high-quality evidence to support systematic treatment-based medication or indeed alternative medicinal drugs as an intervention for Oral Leukoplakia.[11,20-22] The use of carotenoids (beta-carotene, lycopene), vitamins A, C and K, fenretinide,[37] bleomycin and photodynamic therapy have been reported, but at this time randomized controlled trials for non-surgical treatment have not shown evidence that they effectively prevent malignant transformation and recurrence.[33] Wu et al concluded that patients with OL of tongue with epithelial dysplasia had much higher

risk of candidal infection (Figure 8). Antifungal therapy was further recommended to be the routine treatment.[38]

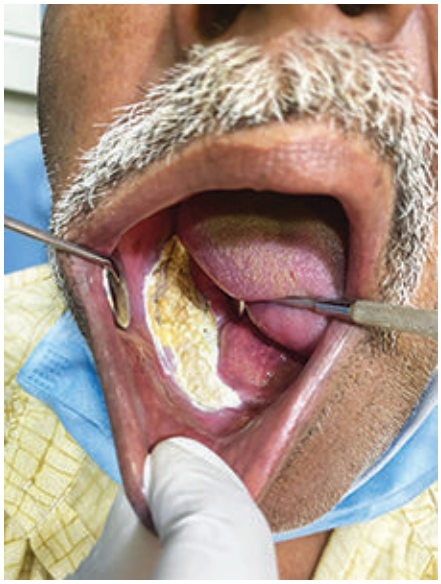

Fig.-8: *Candidal Leukoplakia*

Surgical Management:

White lesions with a histopathologic diagnosis of dysplasia or carcinoma in situ should be excised with clear margins, especially for cases of moderate or severe epithelial dysplasia.[39] Operation can include conventional surgery[33,40], electro cauterization, laser ablation[41,42], or cryosurgery.[33] Conventional surgery involves excision of the lesion with or without a skin graft or other dressing material, but often is not feasible for extensive lesions or those in certain anatomical locations.[43] Carbon di oxide, neodymium: yttrium-aluminium garnet (Nd: YAG), argon, and potassium-titanyl-phosphate (KTP) lasers are used in the management of oral leukoplakia.[41] The reported cure rates after LASER surgery vary between 33.9% and 82%, and recurrence between 7.7% and 66%.[44] The annual recurrence rate of OL following surgical excision is considered to be around 5-10% and hence patients considering this option need to be appraised of this risk.[25] However, this is a global estimate and the inherent risk of an OL can vary significantly which would hence need to be factored into the decision-making process.[45] Studies have shown that OLs, excised and histopathologically examined, have contained foci of oral squamous cell carcinoma in 7-12% of cases.[46,47] Patients with leukoplakias and a histopathologic diagnosis of SCC should be referred to the head and neck oncology team for further evaluation and management.[14] Treatment (surgery, radiation, or chemotherapy) is dependent on the stage.[48,49]

Ultimately, the clinician should guide and facilitate the decision-making process of the patient, helping them understand both the potential risks and benefits.

Modification of risk factors:

Patients should be encouraged to stop using tobacco and alcohol consumption as part of their clinical management. Cessation of smoking habits considerably reduces the risk of developing cancer after surgical treatment of oral potentially malignant lesions.[50] Similarly, patients using betel or areca nut should be encouraged to stop. Dental practitioners have an important role to play to spread the awareness as a health worker who often has regular contact with patients.

Conclusion:

Oral leukoplakia is a common premalignant condition. It is over all accepted that early diagnosis and screening for oral cancer can potentially subside the mortality and morbidity of disease. Incisional biopsy is considered mandatory for diagnosis, treatment planning and for checking the prognosis of the lesion. There are no universal modalities on the most appropriate treatment, and despite the treatment disease can recur and undergo malignant transformation in patients. For high-risk lesions, complete excision is recommended and clinician should closely follow up these patients for life. On the other hand, for low-risk lesions and successfully treated cases, routine check-up is recommended by dental practitioners. However, health education, counselling the individual, and behavioral therapies are most essential methods of prevention at a primary level.

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