Oral Leukoplakia: An Insight

Gigi Roy¹, Anu Vijayan¹, Shamji Shajahan¹, Anuja S³, Rashmi Elizabeth Mathen⁵

¹,3,4,5-Post Graduate, Department of Oral Medicine and Radiology, Mar Baselios Dental College, Kothamangalam, Ernakulam(Dist), Kerala, India. 2-Senior Lecturer, Department of Oral Medicine and Radiology, Mar Baselios Dental College, Kothamangalam, Ernakulam(Dist), Kerala, India.

Correspondence to:
Dr. Gigi Roy, Department of Oral Medicine and Radiology, Mar Baselios Dental College, Kothamangalam, Kerala, India
Contact Us: www.ijohmr.com

ABSTRACT

Leukoplakia is the most common oral white lesion that is classified under potentially malignant disorder affecting oral mucosa. It is significant as it has a high risk of malignant transformation. This article reviews the epidemiology, etiology and pathogenesis, clinical features and clinical variants, diagnosis, differential diagnosis, malignant potential, histopathological features, and treatment.

KEYWORDS: Potentially Malignant Disorder, Smoking, Malignant, Dysplasia, Leukoplakia, Oral Cancer

INTRODUCTION

Earlier clinical presentations of the oral cavity that are recognized as precancerous were classified into two broad groups like lesions and conditions¹, with the following definitions: a precancerous lesion is a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart, and a precancerous condition is a generalized state associated with a significantly increased risk of cancer. But now all clinical presentations that carry a risk of cancer come under the term ‘potentially malignant disorders’ to reflect their widespread anatomical distribution.²

Leukoplakia (leukos meaning white; plakia meaning patch) is the most common potentially malignant disorder affecting the oral mucosa. The term leukoplakia was coined by Schwimmer in 1877. It has been defined as “a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion, not associated with any physical or chemical causative agent except the use of tobacco”³.⁴

Warnakulasuriya et al.in 2007 defined Leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer⁵. According to Warnakulasuriya et al., the new concept of OL shall acknowledge white lesions with a questionable risk of being an OL, being excluded any other pathologies or known disorders which do not present potential malignant risks such as candidiasis, lupus erythematosus, lichen planus, hairy leukoplakia, frictional keratosis, nicotine stomatitis, and leukoedema.⁴

EPIEMIOLOGY

Global prevalence of oral leukoplakia range from 0.5% to 3.46%, and of the rates of carcinomatous transformation of oral leukoplakia from 0.7% to 2.9%.⁵ Oral leukoplakia is more prevalent in India where persons smoke and practice the habit of tobacco and areca nut chewing more than elsewhere⁶. Prevalence in India is 0.2-4.9 percent.⁵,⁷ Oral leukoplakia is usually seen in middle aged people, and its prevalence is higher with age. About 90% of oral leukoplakias are associated with the use of tobacco/areca nut and remaining 10% are idiopathic. Males are more often affected than females probably owing to the greater prevalence of tobacco use by males. The buccal mucosa is affected in 25% of cases, the mandibular gingiva in 20%, the tongue in 10%, the floor of the mouth in 10%, and other oral sites account for the remainder.⁶

ETIOLOGY AND PATHOGENESIS

Tobacco: The etiology of OL is considered multifactorial, but smoking is appreciated to be a frequently involved factor. It is much more common among smokers than among nonsmokers⁸. Either in smoke or smokeless (chew) form is the main etiologic factor. Smoke/ Smokeless form release carcinogens that either bind to epithelial DNAs and cause damage to DNA causing mutation and resulting in dysplasia or malignant transformation of a cell or highly reactive radicals are formed which damage cell membrane, DNA fragmentation, tissue damage and alter cellular antioxidant defense system and causes keratinocyte stimulation resulting in hyperkeratinization. Heat from smoke and frictional irritation from chew form cause keratinocyte stimulation as a protective response causing hyperkeratinization⁹.

Alcohol- Individuals with leukoplakia generally consume alcohol and tobacco together. Consuming alcohol alone was not associated with development of leukoplakia. But it was found to have some synergistic effect with tobacco in the development of both leukoplakia and oral cancer⁹.

Mechanical trauma- Continuous trauma in the form of chronic cheek biting, ill-fitting dentures, etc. have also found to be causative factors for leukoplakia.⁹

Sanguinaria- Herbal extract sanguinaria which is used in mouthwashes and toothpastes was found to develop

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leukoplakia (Sanguinaria-associated keratosis). Even after stopping usage of this product, the lesion did not subside. The commonest site was maxillary vestibule and alveolar mucosa.3

**Candida causing leukoplakia**- Candida releases nitrosamine specific proto-oncogene and also efficiently converts ethanol into carcinogenic acetaldehyde in alcohol drinker. This has a synergistic effect with tobacco which increases dysplasia or leukoplakia. Studies show that even after elimination of surface mycosis after administration of antifungals, the leukoplakia persisted. Malignant transformation of candida infected leukoplakias was high, suggesting candida association as a significant risk factor for oncogenesis.9

**Papilloma virus**- The role of Human Papilloma Virus (HPV) in the etiology as well as oncogenesis of oral leukoplakia have been under extensive molecular biology and virology studies. HPV type 16 was isolated in oral leukoplakias and carcinomas. In Proliferative Verrucous leukoplakia (PVL), HPV 16 and 18 were demonstrated.3

**Epstein barr virus (EBV)**- The role of EBV in oral leukoplakias was not found in any of the studies even though it was found to be associated with etiology of oral squamous cell carcinomas. If there is any role of EBV in oral leukoplakias studies carrying out on a larger sample may help us.3

### CLINICAL FEATURES

Leukoplakia is seen in middle age and older age with a peak incidence in fifth to seventh decades. It is more prevalent in males than females. Generally, it is seen as gray, white or yellowish white in color. OL present on the floor of the mouth, soft palate, and tongue are considered as high-risk lesions, while, they may be considered as low malignant risk when occurs in other areas5. Common sites are buccal mucosa and commissures, followed by lips, tongue, palate, alveolar ridge, floor of mouth, soft palate and gingiva.7

### CLINICAL VARIANTS

**Axell et al.,1984**9

1. Etiological
   - Tobacco-associated leukoplakia
   - Idiopathic leukoplakia

2. Clinically
   - Homogenous
   - Non homogenous ✓
   ✓ Erosive
   ✓ Nodular
   ✓ Verrucous

**Bouquot Je & Whitaker**10

**Phase 4-** Erythroleukoplakia/ Speckled/ Non homogenous leukoplakia

**Pindborg**11
- Homogeneous leukoplakia
- Non homogeneous leukoplakia

**Bailoor and Nagesh**12
- Speckled leukoplakia and non speckled leukoplakia
- Homogenous, Ulcerative, Speckled
- Reversible / irreversible

**WHO (1980)**11
- Homogeneous leukoplakia
  ✓ Smooth
  ✓ Furrowed(Fissured)
  ✓ Ulcerated
- Non Homogeneous
- Nodulospeckled

**Preleukoplakia** usually begins as thin, grey or greyish white plaque that may appear somewhat translucent.9,10

**Homogenous leukoplakia** is thick smooth whitish with cracked mud appearance and leathery consistency. These are asymptomatic with a very low risk of malignancy.9,10

**Granular/ Nodular/ Verruciform/ Rough leukoplakia** are more severe form with surface irregularities like nodular or granular or pointed papillary projections.9,10

**Non- homogenous leukoplakia** consists of erythematous area seen on the whitish plaque. It is suggestive of further progression of lesion towards malignancy. Patients complain of pain, itching and discomfort.9,10

**Proliferative verrucous leukoplakia** is a subtype of verrucous leukoplakia characterized by an aggressive evolution, a multifocal appearance, resistance to treatment, higher degree of recurrence and a high rate of malignant transformation.5 Hansen et al. (1985) first described PVL as a distinct clinical form of OL. WHO described the high rate of malignant transformation of PVL. It is multifocal progressive lesions, commonly seen in women. The most affected area was the lower gingival, tongue, buccal mucosa, and alveolar ridge.3,13

There are four stages that have been described in the development of PVL, initially as a simple hyperkeratosis without epithelial dysplasia, followed by verrucous hyperplasia, verrucous carcinoma, and finally conventional carcinoma.14,15,16 Ghazali et al.,17 suggested the following criteria for the diagnosis of PVL:

1. The lesion should start as homogeneous leukoplakia with histopathological findings of dysplasia
2. Later in it should show verrucous areas
3. From single lesion, it should progress to multiple lesions at the same or different site
4. It should progress later into different histological stages.
5. It should show recurrence after treatment

Table 1 shows comparison of proliferative verrucous leukoplakia and leukoplakia.18
Oral hairy leukoplakia (OHL): OHL is a white lesion related to Epstein-Barr virus (EBV). It is usually associated with AIDS. OHL is seen on lateral border of the tongue, rarely on the buccal mucosa, with slightly raised and corrugated hairy surface. These lesions are also white in colour, cannot be scraped off and asymptomatic like leukoplakias. As its etiological factor is EBV, OHL must not be considered as a variant of leukoplakia. Typically unilateral or bilateral, adherent, slightly elevated whitish or gray patches. Principally located mainly on lateral margins, dorsum, or ventrum of the tongue Occasionally observed over the floor of the mouth, palate, or oropharynx. Usually asymptomatic.

Idiopathic leukoplakia: It is a rare potentially malignant lesion with an increased risk of malignant transformation as compared to the tobacco associated form. It is usually found on the tongue. It can also develop on the gingiva. Van der Waal et al., reported that idiopathic leukoplakia have an incidence of 36%.

**DIAGNOSIS**

On the basis of history and clinical examination, a diagnosis of leukoplakia is made. To confirm the diagnosis, a biopsy is done, so that proper treatment can be planned. An incisional biopsy should be performed in large lesions including some adjacent normal tissue and an excisional biopsy should be performed in small lesions. The main significance of incisional biopsy in large lesions is to detect the dysplasia, grade of dysplasia if present, as dysplasia, carcinoma in situ or invasive carcinoma cannot be predicted clinically. Incisional biopsy is done if the lesion is large in size, inaccessible sites, multiple sites, and if the lesion is non homogenous. It also helps in excluding other definable white lesions. The site of the biopsy should be from symptomatic area of the lesion. It should be taken from red or indurated areas if the lesion is asymptomatic.

**Table 1 shows comparison of proliferative verrucous leukoplakia and leukoplakia**

**Table 2 shows Disorders that need exclusion to diagnose leukoplakia**

**Fig 1. A schematic diagram to assist recognition of oral leukoplakia by eliminating other mucosal disorders**

**Fig 2. A schematic diagram showing diagnosis and management of leukoplakia**

**Differential Diagnosis:** Differential diagnosis of leukoplakia includes lichen planus, leukoedema, white sponge nevus, syphilitic mucous patch, discoid lupus erythematosus, verruca vulgaris, chemical burn, and chronic cheek bite. Table 1 shows comparison of proliferative verrucous leukoplakia and leukoplakia.
MALIGNANT POTENTIAL

Warnakulasuriya et al. were listed as a risk for malignant transformation in PMD.\(^{2,2}\)

1. Female gender
2. Long duration of leukoplakia
3. Leukoplakia in non-smokers (idiopathic leukoplakia)
4. Location on the tongue and/or floor of the mouth
5. Size >200 mm\(^2\)
6. Non-homogeneous type
7. Presence of Candida albicans
8. Presence of epithelial dysplasia.

Fig 3 Clinical presentations of leukoplakia, progressing from a low-risk malignant transformation potential on the left to a high-risk potential on the right.\(^{11}\) Malignant transformation of oral leukopakias has been reported in the range of 1%-20% over 1-30 years.\(^{23}\)

Conservative treatment includes\(^{3,9,24}\)
- Elimination of habit
- Advise to take green tea
- Enameloplasty to smoothen sharp teeth and replacement of faulty restorations to avoid trauma
- Nystatin therapy in case of candidal leukoplakia
- Carotenoids and retinoids
- Lycopene
- Topical bleomycin
- Photodynamic therapy
- Gene therapy - Newer treatment in which synthetic antisense oligonucleotides complementary to the start codons of human papilloma virus type 18E6 and E7 genes can significantly inhibit growth invitro of oral carcinoma cell lines.

Surgical treatment includes\(^{3,9,24}\)
- Scalpel surgery is the treatment of choice and mostly performed procedure. Scar formation is the main disadvantage.
- Cryosurgery - Application of extreme cold with liquid nitrogen has been successfully used in treatment of leukoplakia.

HISTOPATHOLOGICAL FEATURES

In some lesions epithelial dysplasia may be seen and may range from mild to severe, based on its presence leukoplakia is of two types dysplastic and non-dysplastic. Sublingual keratosis are bilateral and possess a parallel corrugated wrinkled surface texture. This is called Ebbing tide.

Table 3 shows histological changes in leukoplakia. Table 4 shows Van der Waal et al., (2000) OLEP Classification and Staging System. Table 5 shows Leukoplakia classification (WHO 1980).

Table 3 shows histological changes in leukoplakia.

<table>
<thead>
<tr>
<th>Histological changes</th>
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<tbody>
<tr>
<td>1. Loss of polarity of basal cells</td>
</tr>
<tr>
<td>2. More than one layer of cell with basaleoid appearance</td>
</tr>
<tr>
<td>3. Drop-shaped rete-ridges</td>
</tr>
<tr>
<td>4. Increased nuclear-cytoplasmic ratio</td>
</tr>
<tr>
<td>5. Nuclear hyperchromatism</td>
</tr>
<tr>
<td>6. Enlarged nuclei</td>
</tr>
<tr>
<td>7. Increased number of mitosis</td>
</tr>
<tr>
<td>8. Abnormal form of mitosis</td>
</tr>
<tr>
<td>9. The presence of mitotic cells in the superficial epithelium</td>
</tr>
<tr>
<td>10. Cellular and nuclear pleomorphism</td>
</tr>
<tr>
<td>11. Irregular epithelial stratification</td>
</tr>
<tr>
<td>12. Loss of intercellular adherence</td>
</tr>
<tr>
<td>13. Keratinization of single cells or cell groups in the prickle cell layer</td>
</tr>
</tbody>
</table>

Table 4 Van der Waal et al., (2000) OLEP Classification and Staging System\(^3\)

<table>
<thead>
<tr>
<th>SIZE OF THE LESION</th>
<th>CLINICAL</th>
<th>PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 size not specified</td>
<td>C1 - Homogenous</td>
<td>P1 - Not specified</td>
</tr>
<tr>
<td>L1 2 to 4 cm, single/multiple</td>
<td>C2 - Non-homogenous</td>
<td>P0 - No epithelial dysplasia</td>
</tr>
<tr>
<td>L3 more than 4cm, single/multiple</td>
<td>C3 - Non-homogenous</td>
<td>P1 - Distinct epithelial dysplasia</td>
</tr>
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</table>

Table 5 shows Leukoplakia classification (WHO 1980).\(^3\)

<table>
<thead>
<tr>
<th>SIZE OF THE LESION</th>
<th>CLINICAL</th>
<th>PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE 1</td>
<td>L1 P0</td>
<td>L1 C1</td>
</tr>
<tr>
<td>STAGE 2</td>
<td>L2 P0</td>
<td>L2 C1</td>
</tr>
<tr>
<td>STAGE 3</td>
<td>L3 P0</td>
<td>L3 C1</td>
</tr>
<tr>
<td>STAGE 4</td>
<td>L3 P1</td>
<td>L3 C2</td>
</tr>
</tbody>
</table>

MANAGEMENT

Conservative treatment includes\(^3,9,24\)
- Elimination of habit
- Advise to take green tea
- Enameloplasty to smoothen sharp teeth and replacement of faulty restorations to avoid trauma
- Nystatin therapy in case of candidal leukoplakia
- Carotenoids and retinoids
- Lycopene
- Topical bleomycin
- Photodynamic therapy
- Gene therapy - Newer treatment in which synthetic antisense oligonucleotides complementary to the start codons of human papilloma virus type 18E6 and E7 genes can significantly inhibit growth invitro of oral carcinoma cell lines.
• Laser surgery - The main advantage of CO₂ laser therapy are excellent healing, lack of postoperative complications like bleeding and low recurrence rates which is superior to other forms of treatment.

**CONCLUSION**

Oral leukoplakia is the most common potentially malignant disorder. It is important in the early diagnosis of leukoplakia when it is usually asymptomatic and it is simple to remove possible factors involved in its etiology -smoking, thus reducing the rate of malignant transformation.

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