REVIEW ARTICLE

Oral leukoplakia: A review and its update

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Abstract

Oral leukoplakia (OL) is the most common potentially malignant disorder of the oral mucosa. The etiological role of Candida in leukoplakia has been a subject of debate in recent years. Candida invasion has been suggested to be a significant risk factor for malignant transformation of OL and also it may be associated with certain clinical characteristics such as lesion type, size, and site, dysplasia, and tobacco use. Several studies showed that the greater risk of malignant change in women than men. Finally, the management of this common condition remains a variable and includes local, topical, and systemic therapies such as anti-oxidants, carotenoids, and antifungal therapies.

Keywords:
Candida, leukoplakia, oral mucosa, smoking

Introduction

Oral leukoplakia (OL) is one among important potentially malignant disorder (PMD) of the oral mucosa. It has been defined as “a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion.”[1] Leukoplakia is being recognized by two forms: Homogeneous and the non-homogeneous type. Homogeneous leukoplakia has predominantly white lesion of uniform flat, thin appearance, smooth, wrinkled or corrugated surface throughout the lesion, whereas non-homogeneous leukoplakia has been a mixture of white-and-red lesion that may be either irregularly flat, nodular, or verrucous.[2] Leukoplakia shows characteristic histologic findings such as epithelial hyperplasia, and/or hyperkeratosis, with or without epithelial dysplasia or carcinoma.[3] The pooled estimate of the annual rate of OL malignant transformation is 1.36% (0.69-2.03%).[4] Increased malignant potential may be associated with certain clinical characteristics such as lesion type, size, and site, dysplasia, and tobacco use.

Terminology and Definitions of OL

International attempts to define/refine WHO definition of OL are as follows: Kramer (1978) had recognized the malignant potential of leukokeratosis and smokers patch and its relationship to pipe smoking.[5] Paget (1860) recognized an association between a white keratotic oral lesion and lingual carcinoma.[5] Kramer (1978) suggested the term leukoplakia define white raised lesion involving oral mucosa. It was also called as leukoma, smokers patch, leukokeratosis, and ichthyosis.[5] Butlin (1885) related these lesions to smoking and considered smokers patch to be an early stage of a more advanced white raised lesion that he called as leukoma. Axéll (1996) states leukoplakia as a white patch measuring 5 mm or more which cannot be scrapped off and cannot be attributed to any other diagnostic disease.[6]

The First International Conference on OL (1984) Malmo, Sweden: Described leukoplakia as “A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except the use of tobacco.”[6]

In a conference of Uppsala (1994), it was established that it would be the “predominantly white lesion of the oral mucosa which could not be clinically or pathologically characterized as another specific entity.”[6] As per the International Symposium, Uppsala, Sweden (1996): It is “a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable disease.”[6]

The WHO (1997) described leukoplakia as “a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion.”[7] According to Warnakulasuriya et al. (2007), leukoplakia should be used to recognize...
white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer.[1] Warnakulasuriya et al. (2007) defined this lesion as "a white plaque with an increasing questionable oral cancer risk after excluding other known diseases and disorders that do not increase the risk."[1]

Incidence and prevalence

In the year 1992, Gupta et al. found a wide range of leukoplakia prevalence in various populations. In India, leukoplakia was found in 0.2% and 4.9% of the population present over 15 years of age.[1] Báñóczy (1983) found that the adult population prevalence varied between 0.6% and 3.6%.[9] Downer and Petti found an annual oral cancer incidence rate attributable to leukoplakia between 6.2 and 29.1 cases per 100,000 people.[10]

Martorell-Calatayud et al. found the prevalence of OL ranges from 0.4% to 0.7% of the population.[11] Feller and Lemmer estimated the prevalence of OL ranged from 0.5% to 3.46%, and also found the malignant transformation of OL from 0.7% to 2.9%.[5]

Brouns et al. found the prevalence of OL is approximately 2% with an annual malignant transformation of approximately 1%.[12]

Age and gender

Báñóczy (1977) estimated that the incidence of malignant transformation as 5.8% in women and 2.1% in men, and the incidence was higher in patients who were habitual smokers or drinker.[13] Báñóczy (1977) found that the increased risk of malignant change in women than men.[13] Báñóczy revealed the prevalence of leukoplakia in the age-group of 51-60 years and sex distribution showed a male:female ratio of 3.2:1.[13]

Espinoza (2003) reported the higher prevalence present in men after 50 years of age.[14] Espinoza et al. reported leukoplakia in all age groups with increased prevalence in the old population, ranging from 0.35% to 18.6%.[14] Downer and Petti found leukoplakia to be significantly more prevalent in males (prevalence ratio 3.22).[10]

Liu et al. conducted study on 218 patients and he found that peak incidence was the fifth decade of life (33.0%), and the gender ratio was equal.[14] Brzak et al. in his study between 1998 and 2007, including 12,508 patients found that women were found as predominantly affected.[15] Brouns et al. found the mean age of 57 years among 275 patients consisted of 112 men and 163 women.[12]

Site specificity

Axell et al. (1996) found that leukoplakia was commonly present in buccal mucosa (76%), alveolar sulcus (19%), and tongue (5%).[6] On the contrary, Schepman’s (1998) conducted a follow-up study in 166 patients on hospital-based population and found that the most frequent location of leukoplakia to be the vestibular mucosa.

Martorell-Calatayud et al. found that leukoplakia usually located on the floor of the mouth and in the ventrolateral region of the tongue with a greater risk of malignant transformation with an average rate of transformation of 43%. This is attributed to the fact that these areas are more exposed to carcinogens in salivary secretions and that the epithelium is more permeable in this area.[11]

Liu et al. conducted a study on 218 patients and found that tongue was affected in 51.4% patients with OL and 32.6% in buccal mucosa. A few lesions on the floor of mouth (FOM) and lip were probably due to the different ethnic population studied, nature of habit, and placement of the quid.[4]

Brouns et al. found the location of the OL specified according to eight subsites: Tongue, FOM, lower lip, hard palate, buccal mucosa, upper alveolus and gingiva, lower alveolus, and gingiva and finally in multiples sites.[12]

Clinical diagnosis

Leukoplakia usually present as a single or multiple lesion, localized change of the oral mucosa. The site distribution shows world-wide differences that are partly related to gender and tobacco habits. In fact, any oral site may be affected. Two clinical variants of leukoplakia such as homogeneous and the non-homogeneous type.[5] Daftary et al. (1972) conducted a study among leukoplakia patients and observed that 32% had nodular leukoplakia, 16% had ulcerated leukoplakia, and 52% had homogeneous leukoplakia.

Brouns et al. (2013) found that 52.7% had homogeneous leukoplakia and 47.27% cases had non-homogeneous leukoplakia. The reasons for the higher incidence of homogeneous leukoplakia in the present study are difficult to explain as they are multifactorial. It could be due to variation in the availability of tobacco products, consumption of tobacco with or without slaked lime, duration and frequency of tobacco products combined with alcohol usage in the Indian population.[33]

Etiopathogenesis

Roed-Petersen et al. (1972) and Daftary et al. (1972) found that according to the recent reports etiological role of Candida infection to be more important. Although Candida infection was present only in 13.5%, of the total leukoplakia group. The role of Candida in correlation with the clinical types and histological dysplasias has been evaluated positively in the literature.[16]

Báñóczy said that Candida albicans infection and the simultaneous existence seemed to play a role in malignant transformation among the etiological factors, and leukoplakia found the highest risk of developing into cancer (25.9%).[14] Krogh et al. have found that higher nitrosation potentials of candidal organisms can be isolated from non-homogeneous leukoplakias than homogeneous forms.[17]

Báñóczy (1977) observed statistically significant decrease in serum levels of Vitamin A, B12, C, beta carotene, and folic acid in patients with OL compared to controls.[33] Soames and Southam reported that the changes of developing leukoplakia were more in the areas of epithelial atrophy and the conditions associated with mucosal atrophy included iron deficiency, some vitamin
deficiencies, and oral submucous fibrosis. Soames and Southam reported mutations of p53 in the cells from dysplastic areas of some leukoplakias who smoke and drink heavily.[14] Schepman et al. found that smokers have 6 times higher risk of developing leukoplakia than non-smokers, despite lesions of non-smokers having a greater probability to evolve into cancer.[19]

Morse et al. observed that alcohol consumption was more strongly associated with oral carcinoma than with epithelial dysplasia, particularly where drinks such as beer and spirits and high consumption levels were concerned.[20]

Caldeira 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. Brzak et al. conducted study including 12,508 patients between 1998 and 2007 and found the highest frequency of leukoplakia in smokers.[15]

Various Forms of Leukoplakia

1. Proliferative verrucous leukoplakia (PVL): Hansen et al. (1985) first described PVL is a distinct clinical form of OL. PVL has a high rate of malignant transformation which was described by the WHO. It is multifocal progressive lesions, found in women. Most frequently affected area was the lower gingival, tongue, buccal mucosa, and alveolar ridge.[1]
2. Oral erythroleukoplakia (OEL) is a non-homogeneous lesion of mixed white and red components. It is defined as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease’. OEL shows a higher malignant transformation potential than homogeneous leukoplakia.[1]
3. Sublingual keratosis: It is a soft white plaque in the sublingual region with a wrinkled surface, an irregular but well-defined outline and sometimes a butterfly shape.[21]
4. Candidal leukoplakia (CL) is a chronic, discrete elevated lesions that are palpable, translucent, whitish areas to large, dense, opaque plaques, hard and rough to the touch.[22]
5. Oral hairy leukoplakia (OHL) otherwise known as Greenspan lesion. In 1984, Greenspan et al. first described OHL characterized by whitish patches with a corrugated or hairy surface and most commonly present on the lateral borders of the tongue. It is caused by the reactivation of a previous Epstein-Barr virus infection.[23]

Overall Risk Factors for Malignant Transformation in Leukoplakia

Warnakulasuriya et al. were listed as a risk for malignant transformation in PMD.[1]
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 mm²
6. Non-homogeneous type
7. Presence of C. albicans
8. Presence of epithelial dysplasia.

Treatment

Cawson (1996) reported that leukoplakia showed improvement and disappearance of a significant number of their cases with polynye-nystatin (tablets) dissolved slowly in the mouth.[24]

Ramanathan et al. suggested that the candida-associated leukoplakia (speckled leukoplakia) may respond to topical antifungal agents including imidazoles[25]

Lamie et al. (1994) reported an OL with epithelial dysplasia that resolved within 11 days of systemic treatment with fluconazole antifungal agent.[26]

Garber found that the anti-candidal treatment strategy was helpful in ruling out a possible fungal etiology for lesions. In immuno-compromised persons, candidal lesions may require the use of more toxic drugs such as amphotericin B.[27]

van der Waal and Axell stated if the patient had a white lesion in oral mucosa, the clinician would first try to rule out any of the definable white lesions before accepting a distinct clinical diagnosis of leukoplakia. For instance, in the case of a non-homogeneous white and red lesion, the result of antifungal treatment may be awaited for a period of 2-4 week. A 2-4 weeks interval to observe the possible regression or disappearance of a white lesion after elimination of possible causative factors, including smoking habits, seems a fully acceptable period of time for the general practitioner before taking a biopsy or before referring the patient to a specialist for further advice.[2]

Lodi and Porter showed in a review of various treatments for leukoplakias that carbon dioxide (CO₂) LASER vaporization showed maximal while CO₂ LASER evaporation showed minimal recurrence of leukoplakia. However, cryosurgery and conventional blade surgery showed up to 22% and 13% recurrence rates, respectively.[22]

Blaggana et al. suggested that beta-carotene, a therapeutic dose of 75,000 to 300,000 IU for a period of 3-month is advised, and also suggested that 13-cis-retinoic acid a synthetic analog of Vitamin A, given in doses of 1.5-2 mg/kg body weight for 3 months.[28]

Blaggana (2011) found in his 3 months follow-up study lycopene appeared to be a promising agent in the management of OL.[29]

Nystatin therapy is given in CL. 500,000 IU twice daily with 20% borax glycerol or 1% gentian violet or mouth rinses with chlorogen solution showed a favorable response. Along with Vitamin B-complex is given as a supplement in cases of lesion seen in commissural and lingual areas.[29]

Wu et al. concluded that patients with OL of the tongue with epithelial dysplasia had much higher risk of candidal infection. Antifungal therapy was further recommended to be the routine treatment.[3]
Treatment Guidelines for OL - Longshore and Camisa

1. Eliminate all contributing factors
2. Absence of dysplasia or presence of mild dysplasia - surgical excision/laser surgery of the lesions on the ventral/lateral tongue, floor of the mouth, soft palate, and oropharynx. Close observation and follow-up for all other anatomic locations
3. Presence of moderate or severe dysplasia - surgical excision or laser therapy is preferred treatments
4. Red lesions (erythroplakia or leukoerythroplakia) - Surgical removal is best
5. Proliferative verrucous leukoplakia - Complete surgical excision/laser surgery if possible
6. Follow-up for all lesions.

Conclusion

A thorough knowledge on various aspects of these pre-cancerous entities shall render a clinician to make appropriate diagnosis or plan treatment. In an Indian scenario, mostly leukoplakia are habit associated, tobacco usage over several years remains an important etiologic factor, in particular, smoking tobacco including chewing and other forms of tobacco are proven etiologic causes of mucosal alterations as well. So, health education, counseling the individual, and behavioral therapies are most essential methods of prevention at a primary level. Understanding the determinants of malignant transformation will help us better to estimate the cumulative risk at which a specific individual is with a leukoplakia. Thus, a complete knowledge from etiology of the disorder to diagnosis and provision of appropriate treatment is all in the benefit of preventing a leukoplakia from becoming malignant.

References
