
Preeti Sharma, Pooja Aggarwal, and Vandana Reddy

Department of Oral Pathology & Microbiology, Subharti Dental College, India

Abstract

Leukoplakia is the most common potentially malignant lesion of the oral mucosa. Studies on the risk factors of oral leukoplakia (OL) are relatively scarce. The present study was planned to assess the clinical risk factors of OL in our institution, which represents a sample of the Western UP population, based on the clinical status of OL patients spanning a period of eight years. The clinical and pathological data (age, sex, lesion location and presence/absence of dysplasia) were analyzed in these patients. Possible relationships between habitual tobacco use and lesion location were explored. The data obtained showed that habitual bidi smoking was prevalent among elderly males, while buccal mucosa was the most affected site by this lesion. Applying the Z-test for double sample proportions, a significant difference was observed for the buccal mucosa, labial mucosa, tongue and habitual smoking (1% level of significance, p<0.01) between the two age groups. A significant difference was observed between habitual tobacco use and various degrees of dysplasia (Fisher’s exact test = 0.00008, p<0.05). The present study underlines the role of habitual tobacco use in the etiology of OL in the Western UP population of India. Rigorous anti-smoking measures need to be taken in this region in order to prevent transformation into oral cancer.

Introduction

Oral leukoplakia (OL), as defined by WHO in 1978, is a white patch or plaque that cannot be characterized clinically or pathologically as any other disease(1). An international working group comprising specialists in the fields of epidemiology, oral medicine and pathology and molecular biology, amended the original 1978 WHO definition to stand as: ”The term 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” (2). In this WHO workshop coordinated by the Collaborating Centre for Oral Cancer and Precancer, held in 2007, it was decided to use the term “potentially malignant disorders”, as it conveys that not all disorders described under this term may transform to cancer (2). The WHO monograph on Head and Neck Tumors (2005) uses the term ‘epithelial precursor lesions’ and did not define leukoplakia stating that no distinction is made from other white patches (3). Precursor lesions are defined as altered epithelium with an increased likelihood for progression to squamous cell carcinoma (SCC). The principal oral and oropharyngeal lesions which may be precursor lesions are white patches (leukoplakia) and red patches (erythroplakia) or mixed red and white lesions. The majority of leukoplakias will not show dysplasia and correspond to the hyperplasia category. Squamous cell hyperplasia describes increased cell numbers. This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (progenitor compartment), termed basal cell hyperplasia. The architecture shows regular stratification without cellular atypia (3). The major risk factors of oral leukoplakia (OL) are generally believed to correspond to those of oral squamous cell carcinoma (OSCC): tobacco, alcohol, chewing of areca nut and dietary factors (4). Several studies have shown that risk of OL is 4–6 times higher in smokers than in nonsmokers (5, 6). It has also been suggested that OL lesions in smokers occur preferentially in particular
locations in the oral cavity (7). In some parts of Asia and Africa, chewing of areca nut or use of additional tobacco preparations such as kiraiku or nass are common. The risks of OL for these habits have been described as higher when compared with alcohol and, for areca nut chewing, when compared with tobacco (8–11). However, studies on the risk factors of OL are relatively scarce. Therefore, a study was planned to assess the clinical risk factors of OL in a representative Western Uttar Pradesh population of India and to analyze the incidence and trends of OLs in this population belt. Quoted malignant transformation rates for OLs, for example, vary from less than 1 to greater than 40% (4). The significance of the current study lies in assessing the geographic variation seen in the trends of OLs, which can help us further in planning treatment modalities. Study of the risk factors of OL is important as invasive OSCCs are often preceded by clinically detectable premalignant lesions such as leukoplakia or erythroleukoplakia.

**Materials and Methods**

A retrospective study was performed based on analysis of clinical records of 143 patients diagnosed with OL and seen at the Oral Medicine Department of our institution over a period of 8 y (from 2004 to 2012). OL had in all cases been diagnosed by the criteria of Axell et al., (12); predominantly white oral lesions not diagnosable as any other well-defined lesion type and characterized as either homogeneous or non-homogeneous. Clinically, a distinction was made between a homogeneous and a non-homogeneous leukoplakia; the latter includes erythroleukoplakias, nodular, exophytic and proliferative verrucous types. On the basis of clinical records, for each patient, we recorded age, gender, tobacco (both smoking as well as chewing) and alcohol consumption, and lesion site at the moment of diagnosis. Pan-chewing, pan-tobacco-chewing, bidi or cigarette smoking, and alcohol consumption were the habits assessed, in terms of daily frequency, total duration in years and the age of initiating the habit. Pan used for chewing consists of fresh betel leaf smeared with aqueous lime and sliced clay/fresh arecanut. The mixture used for pan-tobacco-chewing, in addition, has locally cured tobacco leaves/ stem or both. A bidi is a local cigarette manufactured by wrapping coarse tobacco dust in a dried tembuni leaf. In all these patients, biopsies had been taken for histopathologic study. Biopsy location was based on clinical judgment and on manifestations including reddish or verrucous components, ulceration or hardness on palpation. According to histopathologic findings, lesions were classified as hyperkeratotic lesions and hyperkeratotic lesions with various degrees of dysplasia. Tables were prepared listing age, sex, site, habits and histopathologic findings of one hundred forty three OL patients. Comprehensive analysis was performed on the data collected and the results were formulated.

**Results**

Of the 143 OL patients, men represented a higher proportion (89%) of OL cases than women (11%). Patients were broadly or arbitrarily classified into a younger age group (≤ 40 years) and an older age group (≥ 41 years). A greater proportion of cases were seen in the older age group (64%). Overall, buccal mucosa was the most common site involved (71%), while the floor of the mouth showed the lowest incidence of OL in this population belt (one case only). The present study also revealed that bidi or cigarette smoking was more prevalent (64%) than smokeless tobacco use (14%), while 28 patients (20%) had both smoking and smokeless tobacco habits (gutkha chewing, pan chewing, etc.). Overall, 4 patients did not report any tobacco habit, and three of these were women.

Histopathologically, 94 lesions were hyperkeratotic with no obvious features of dysplasia, while 33 lesions showed mild dysplasia, 5 lesions showed moderate dysplasia, and severe dysplasia was observed in only 5 lesions of the 143 lesions Eight lesions proved to be histopathologically well-differentiated squamous cell carcinoma, out of which six lesions were seen on multiple oral sites and were provisionally diagnosed as proliferative verrucous leukoplakia (PVL). Four patients with PVL showed habitual bidi smoking as well as areca nut chewing, while two patients were chronic bidi smokers. Out of the remaining two lesions, one was homogeneous (on the dorsolateral surface of the tongue) and the other was non-homogeneous leukoplakia (involving bilateral buccal mucosa with commissural area).

Statistically, of 143 OL patients, 47 males (33%) and 4 (3%) females below 40 years of age, and 80 (56%) males and 12 (8%) females above 40 years of age were analyzed for OL features. In the two age groups, different sites and tobacco habits were analyzed. Z-test for double sample proportions was used to find the significant differences in the oral sites and habits between the two age groups. Significant differences were seen for the buccal mucosa, labial mucosa, tongue and smoking habit at the 1% level.
between the two age groups (Table 1).

Fisher's exact test showed a significant association between smoking status and different degrees of epithelial dysplasia for 41 patients at the 5% level (p = 0.00008), (p < 0.05). Of 41 epithelial dysplasia patients, 81% showed mild dysplasia, 12% showed moderate dysplasia and 7% showed severe dysplasia. A significant difference was observed between tobacco use and degree of dysplasia (Fisher's exact test = 0.00008, p < 0.05) (Table 2).

**Discussion**

Different levels of tobacco and alcohol exposure, diet, socioeconomic circumstances, age, gender and sites are causative factors in the differences seen in the incidence rates of OL in various populations globally.

Tobacco usage is the most important known etiological factor in the development of oral leukoplakia. Patients who smoke have a six-fold increased risk of developing leukoplakia of the oral mucosa when compared with non-smokers. The influence of smoking on oral leukoplakia risk has been clearly demonstrated in longitudinal studies (13, 14). In a study by Gupta et al, chewing habits were practiced by very few individuals; therefore almost all leukoplakias were associated with either bidi smoking, clay pipe smoking or a combination of the two (in Bhavnagar district, Gujarat) (15).

In the present analysis, we found tobacco smoking to be the single most important etiological factor of OL, with bidi smoking being a more prevalent habit in this region. Several studies support our results; for example, Hogewind and Van der Waal (6) found tobacco smoking to be the more prevalent habit in a prevalence study of OL in a Dutch population. A study in India found that keeping chewing tobacco in the cheek overnight was a risk factor for oral leukoplakia (15). Based on the OL incidence rates in subjects with different tobacco habits, chewing tobacco was considered a stronger risk factor than smoking (17, 18), in contrast with the current study.

Although alcohol is a risk factor for oral cancer (19), it is not an established risk factor for OL (4, 10). The clinical records used for patient characterization in the current study did not contain consistent information on alcohol use; thus, we were unable to evaluate the possible importance of this factor for our patients. Under reporting of alcohol consumption may have occurred due to social expectations, particularly among women. Although alcohol can be considered an independent risk factor, fifteen cases reported to be regular alcohol drinkers, while ten cases were occasional drinkers. Some studies have reported a higher prevalence of OL among alcohol users in each age group, as well as in each tobacco habit category (15, 19), but alcohol consumption showed no independent association with OL in other research publications (4, 10).
The results of the present study suggest that the influence of tobacco on the development of OL varies by anatomical subsite. This finding is more or less in accordance with that of a study suggesting the influence of tobacco on the development of OL varying by anatomical site (7). Some research publications have concluded that leukoplakias in the FOM appeared to be statistically significantly more often present in smokers than in non-smokers, as compared to all other oral sites. In contrast, leukoplakias on the borders of the tongue were more common among non-smokers than smokers, as compared to all other sites (6, 7). However, in the current analysis of lesion site, buccal mucosa and palate were the most frequently involved sites (71% & 10% respectively), while FOM was the least commonly involved site consistent with some other studies (20-23). These differences may be attributed to different tobacco habits and a higher prevalence of OL in men in our study. Similarly, lesions in the BM were significantly more frequent among male smokers than among male non-smokers. The apparent preferential localization of smokers’ lesions in the BM may be attributable to accumulation of tobacco smoke toxins in saliva. In addition, spatial variations in the degree of keratinization and permeability of the oral mucosa may modulate the local effects of tobacco-smoke toxins (24).

Several investigators have analyzed whether the structure of the clinically healthy oral mucosa shows any alteration in smokers. It was found that smoking affected keratinocytes differently in different regions, depending on the extent of direct exposure to smoke. The initial changes were more marked in nonkeratinized regions than in keratinized regions and, interestingly, showed less differentiated cell types, leading to oral epithelial dysplasia (OED) (25). Geographic variations in site distribution are evident, as Hogewind and Van der Waal (1988) demonstrated that the lateral border of the tongue was the most frequently involved site in the Netherlands (6).

The susceptible age for leukoplakia lesions ranged from 40 to 70 years in a study from the Netherlands. In most age categories in this study, the number of women was larger than or equal to the number of men in the leukoplakia group (6). The present study showed a small female preponderance and largely affected elderly males, which is similar to the results of several other studies (4, 5, 7, 20). Of a total of 143 patients in the present study, 56% were men in the older age group, in line with most previous studies that have found a higher prevalence in men (5, 20).

Interestingly, 3% of the patients were not associated with tobacco smoking or chewing in our study, and OL may be attributed to other etiological factors such as low consumption of fruits and vegetables, genetic predisposition and diabetes mellitus. The vast majority of the tobacco users were bidi or cigarette smokers consuming more than ten bids/cigarettes per day. In addition, 20% of patients had mixed habits. With regard to the clinical appearance of leukoplakia, the results of this study also show that homogeneous leukoplakias are much more prevalent than non-homogeneous leukoplakias.

The current study also revealed that 66% of our patients did not show obvious features of epithelial dysplasia, which is similar to previous studies (20, 24). In addition, mild dysplasia was detected in 23% of smoking patients, while no dysplasia was associated with smokeless tobacco habits. These observations are of particular interest given that tobacco smoking is the most important etiologic factor of SCC of the oral cavity.

Jaber et al. (26) assessed the importance of tobacco and alcohol consumption on the development of oral epithelial dysplasia (OED) in a large group of European patients. Their study concluded that, while tobacco and alcohol synergistically influence the development of oral epithelial dysplasia, exclusive tobacco consumption is more likely than exclusive alcohol consumption to give rise to OED. In another research study, the authors observed a dysplastic lesion in only 5% of the smoker group patients while in never-smoker group, dysplastic lesions were observed in 38% of patients (24).

Conclusion

OL is an important disease, as it is the most common oral premalignant lesion and there is a high incidence of oral cancer in India. A useful clinicopathologic profile on the trends of OLs was much needed in the Western UP population of India. Thus, this retrospective study was undertaken to present comprehensive data on the risk factors of OL in this population belt. The present study underlines the role of tobacco smoking in the etiology of OL in the Western UP population. Most other risk factors, including alcohol, demonstrated a considerably lower strength of association.

Determining the risk factors for oral leukoplakia may allow for better directed prevention efforts against oral
leukoplakia and oral cancer. For patients who already have oral leukoplakia, cessation or limitation of tobacco smoking and chewing habits can be advised to prevent the progression to oral cancer.

References


