

2.2. LEUKOPLAKIA

Introduction

Leukoplakia is the most common precancerous lesion. The term Leukoplakia simply means a “white patch”, and it has been used in a sense to describe any white lesion in the mouth. This non-specific usage led to confusion among physician, surgeons and researchers who attributed a precancerous nature to many innocuous lesions. Some investigators tried, although unsuccessfully, to restrict this term only to those white lesions that histologically indicated epithelial dysplasia. Since the mid-1960s there has been a considerable understanding and clarification in the concept of leukoplakia, and now leukoplakia is recognized as a specific entity.

The prevalence of leukoplakia in India varies from 0.2% to 4.9%. Men are affected more frequently than women, and a vast majority of leukoplakia occur in the age range of 35-45 years. Tobacco use is the most important etiologic factor for leukoplakia. Other factors such as alcohol, nutrition, and viral agents, namely HPV, may play a contributory role. Less than 1.3% of leukoplakias in India are idiopathic, i.e., with no discernible causative agent. The etiologic role of tobacco in leukoplakia is so strong that at

an International Seminar at Malmo in 1984, the definition of leukoplakia was modified as: “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease and which is not associated with any physical or chemical agent except the use of tobacco”. Thus, according to this definition, only those white lesions that are either idiopathic or associated with tobacco use should be termed as leukoplakia.

Definition

At a WHO-Meeting of Investigators on Oral Precancerous conditions at Copenhagen in 1967, leukoplakia is defined as: “a raised white patch of the oral mucosa measuring 5 mm or more, which cannot be scraped off and which cannot be attributed to any other diagnosable diseases; this definition does not carry any histologic connotation” (Fig. 1). In 1978 this definition was modified by the WHO Collaborating Centre for oral precancerous Lesions as: “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease; this definition does not carry any histologic connotation”. The current accepted practice worldwide is to use the WHO definition.

The definition of leukoplakia is a negative one. It merely excludes known

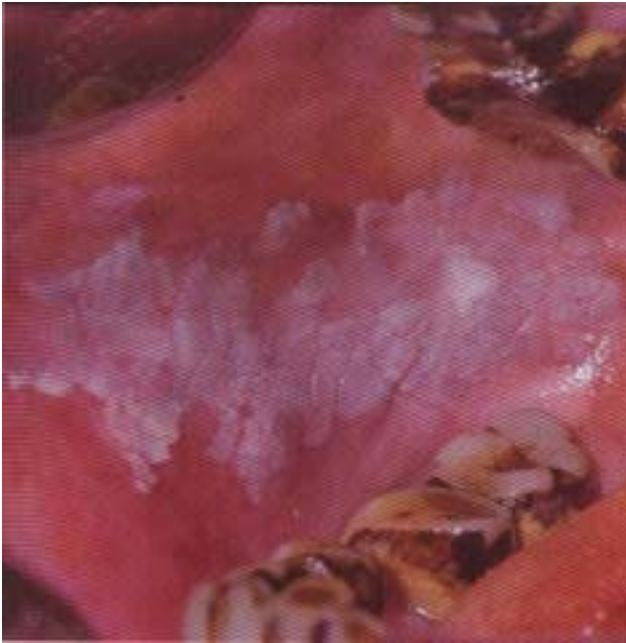


Fig. 1. An extensive leukoplakia in the right buccal mucosa of a betel-quid chewer.

entities which are white, such as white sponge nevus, candidiasis, etc. Although negative, the definition was found to be useful and

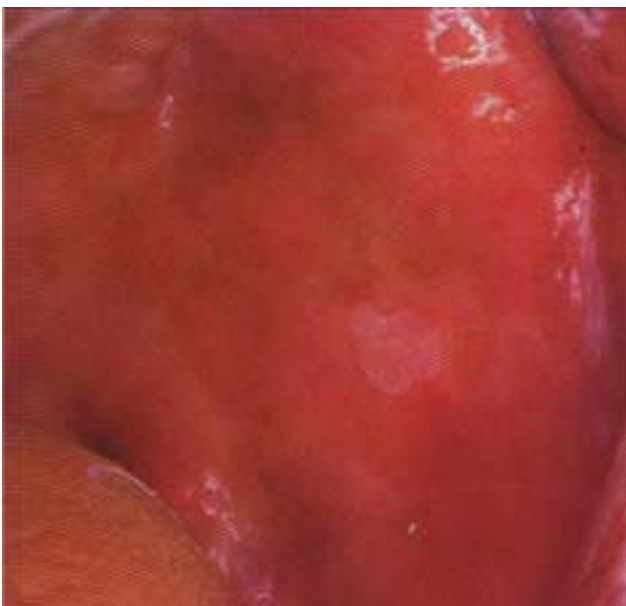


Fig. 2. A leukoplakia of about 1 cm in size in the left buccal mucosa of a betel-quid.

satisfactory. Subsequently, minor changes in the definition were made, with exclusion of the criteria “raised” and that “5 mm” be the minimum size. In our opinion, adherence to the criterion of minimum size is desirable to avoid over-diagnosis, especially in field studies (Fig. 2).

Clinical types of leukoplakia

Homogeneous leukoplakia: leukoplakias are classified into homogeneous, ulcerated, and nodular leukoplakias. This classification essentially takes into consideration the clinical appearance and the natural history, i.e., the long-term behavior of each type. Homogeneous leukoplakia is characterized by raised plaque formation consisting of a plaque or groups of plaque varying in size with irregular edges (Fig. 1) or yellow. About 84% of the leukoplakias are of the homogeneous type.



Fig. 3. A homogeneous leukoplakia in the right commissure and the buccal mucosa of a male who chewed betel quid and smoked *bidis*. Note separate plaques.

Ulcerated leukoplakia: Ulcerated leukoplakia is characterized by a red area which at times exhibits yellowish areas of fibrin. White patches are generally present on the periphery (Fig. 4). Ulcerated leukoplakia accounts for up to 13% of leukoplakias. It may appear as a small red area, with or without pigmentation on the periphery, or as a narrow rectangular ulceration consisting of a few whitish areas.

Nodular leukoplakia : Nodular leukoplakia (also called speckled leukoplakia) is characterized by small white specks or nodules on an erythematous base (Fig. 5); the nodules may be very fine (Speckled), pinhead sized or even larger. About 3% of leukoplakias are of the nodular type.

Leukoplakia at different intraoral locations

Like oral cancers, leukoplakia also involves all intraoral sites, and there is a site



Fig. 4. Ulcerated leukoplakia in the right commissure and the buccal mucosa of a *bidi* smoker. Note the peripheral keratinization.

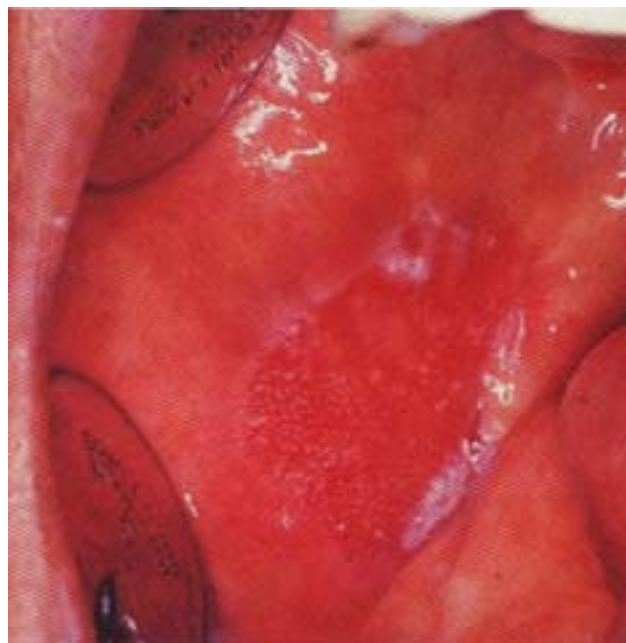


Fig. 5. A nodular leukoplakia in the right buccal mucosa of a betel-quid chewer. It is marked by numerous small white nodules anteriorly and few larger ones posteriorly on an erythematous base. Note a white patch in the lower part of the lesion.

and tobacco habit relationship. Correspondingly, the location distribution of leukoplakia varies in different geographic areas.

Leukoplakia on the labial mucosa: Apart from the type of tobacco use, the method of its use also plays a part in the occurrence of leukoplakia at a specific location. For example, those persons who smoke until only the small “butt” remains, tend to develop leukoplakia at the site (Fig. 6) where the *bidi* or cigarette is customarily held. This finding indicates that perhaps heat also plays a contributory role in the occurrence of leukoplakia.

Hookli associated leukoplakia: *Hookli* is a claypipe popularly used in Bhavnagar District of Gujarat for smoking (see Appendix I). Some 23% of the 173 leukoplakias in this

Fig. 6. A leukoplakia, about 5 mm in size, in the lower labial mucosa of an individual who smoked *bidi* and cigarettes to the small "butt". The patient was a chronic alcoholic.



area occurred among *hookli* smokers, with nearly half of the lesions in the lower (Fig. 7) and upper labial mucosa. The stem of the *hookli* becomes hot when smoked perhaps contributing to the pathogenesis of

leukoplakia. *Hookli* associated leukoplakia exhibits a delicate keratinized appearance. Over a 10-year observation period, none of these leukoplakias progressed to cancer.



Fig. 7. A homogeneous leukoplakia showing a delicate white keratinized pattern in the lower labial mucosa of a *hookli* smoker.

***Mishri* associated leukoplakia:** Various smokeless tobacco preparations used in noncombustible form, (see Appendix I) are associated with leukoplakia and these lesions also show a characteristic habit *versus* site relationship. *Mishri* is a roasted, powdered tobacco, popularly used for application over teeth and gingiva by women in Maharashtra, Goa, Gujarat, and some other areas of the country (see Appendix I). Among individuals with this habit, leukoplakia occur more often in the labial mucosa and on the gingiva (Fig. 8), location that product. For example, in Maharashtra, 26% of the 164 leukoplakias among women occurred among *mishri* users, most of them on the gingival and the labial mucosa. *Mishri* associated leukoplakias may be thick and extensive, or faint and small.



Fig. 8. A thick homogeneous leukoplakia in the upper labial mucosa, labial groove and the alveolar ridge associated with *mishri* use in a Maharashtrian woman.



Fig. 9. A homogeneous leukoplakia with a typical cracked mud appearance in left commissure of a *bidi* smoker.

Interestingly, short-term experimental studies showed that *mishri* is genotoxic and carcinogenic.

Homogeneous leukoplakia on the labial commissure: The labial commissure is the most favored location for leukoplakia, especially among *bidismokers* (Fig. 9). About 7-35% of the leukoplakias, most of them in *bidi* smokers, occur in the commissures.

Ulcerated leukoplakia on the labial commissure: while homogeneous leukoplakias may occur in any intraoral location, ulcerated leukoplakias occur almost exclusively in the commissures and the anterior part of the buccal mucosa. Sometimes they manifest just as ulceration with minimal keratinization (Fig. 10).

Ulcerated leukoplakia with pigmentation: Not uncommonly ulcerated leukoplakias are characterized by pigmentation of varying intensity, usually on the periphery of the



Fig. 10. An ulcerated leukoplakia in the left commissure of a *bidi* smoker from Goa. Note faint Keratinization.



Fig. 11. An ulcerated leukoplakia associated with pigmentation in the right commissure of a *bidi* smoker.

lesion (Fig. 11). Perhaps the heat produced during the smoking also contributes to the occurrence of pigmentation. This pigmentation may be a protective mechanism against the pyrolytic products of tobacco; it is not known to predispose to a melanoma.

Occasionally, especially in *bidi* smokers, an ulceration occurs along the occlusal plane which is superimposed by keratotic areas (Fig. 12).

Two different clinical types of leukoplakias may occur together at the same site (Fig. 13). Classification of such lesions should depend on the predominant appearance of a particular type.

Bilateral commissural leukoplakia: Leukoplakia can affect multiple locations. Most common, however, is the bilateral commissural involvement (Fig. 14) among

bidi smokers; some 12-23% of the leukoplakias in India show bilateral

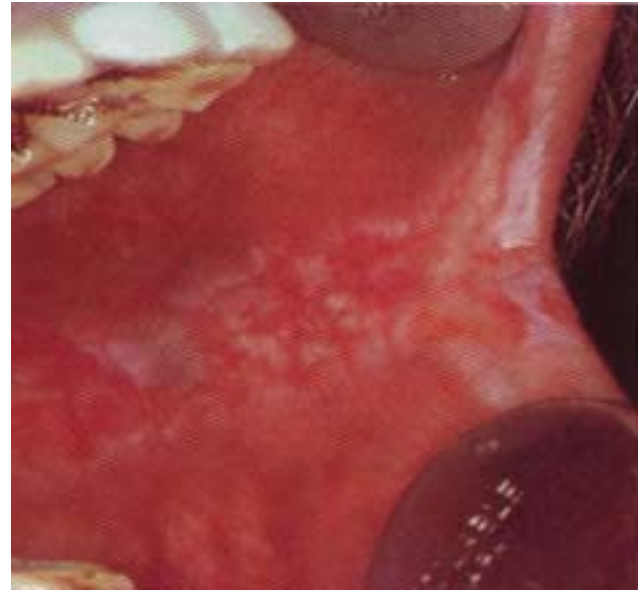


Fig. 12. An ulcerated leukoplakia in the left commissure and the buccal mucosa of *bidi* smoker.

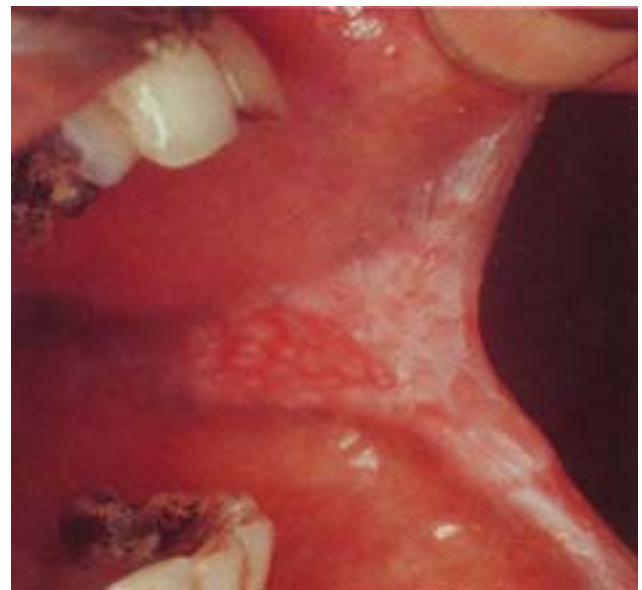


Fig. 13. A homogeneous and a nodular leukoplakia in a *bidi* smoker in the left commissure. Both clinical types are nearly of the same size and contiguous. Because nodular leukoplakia is a high-risk lesion, it was classified as such with a remark that a part of the lesion has a homogeneous appearance.



Fig. 14. A bilateral commissural leukoplakia in a *bidi* smoker.

commissural involvement. Bilateral commissural leukoplakias are often present in association with other *bidi* smoking-related lesions such as palatal erythema and central papillary atrophy of the tongue (see section 3).



Fig. 15. A homogeneous leukoplakia in the labial and buccal mucosa of a Maharashtrian male *khaini* user. He also had an exophytic adjacent to the leukoplakia.

***Khaini* associated leukoplakia on the buccal mucosa:** *khaini* use is widespread among men in some regions of the country (see Appendix I). In Maharashtra, this product is generally kept in the premolar-canine region of the mandibular groove, and in other geographic regions, elsewhere in the mouth. Usually, leukoplakia occurs at the site of placement of *khaini* (Fig. 15). For example, in Maharashtra, 58% of the 521 leukoplakias among men occurred among *khaini* users. Most of the *khaini* associated leukoplakias occur in the premolar region of the buccal mucosa. These leukoplakias may be thin and white with a characteristic cracked-mud appearance (Fig. 16), or thick and keratotic (Fig. 17); they may be extensive (Fig. 18) or small. Care should be exercised to distinguish leukoplakia in *khaini* users from the “tobacco-lime user’s lesion” (see section 3), which is not categorized as a precancerous lesion.

Leukoplakia associated with betel-quid chewing: Betel-quid is almost always held in the mandibular groove closely in contact

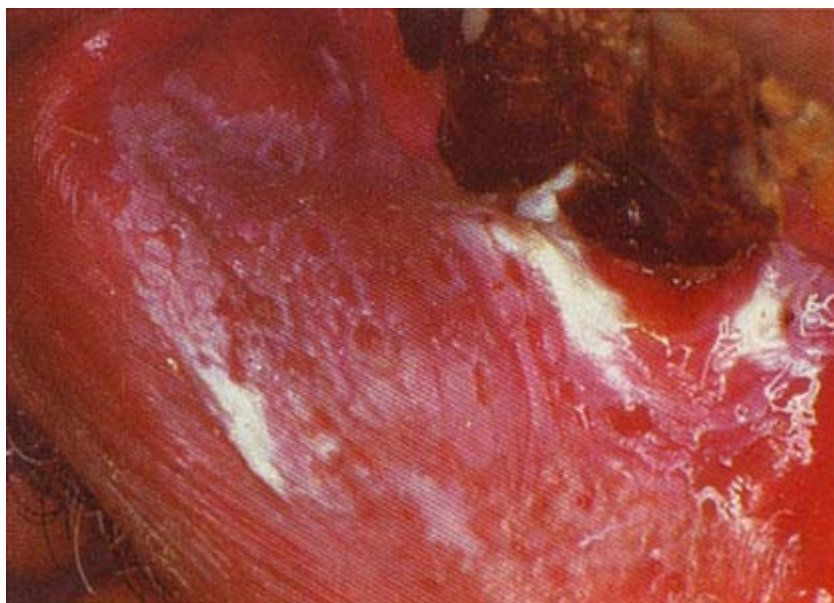


Fig. 16. An extensive leukoplakia in the right buccal and labial mucosa of a *khaini* user. Note areas of thick keratin.

With the buccal mucosa. About 44-64% of leukoplakias occur on the buccal mucosa; most are in betel-quin chewers and almost all are either homogeneous (Fig. 19) or nodular type (Fig. 20).



Fig. 17 A thick leukoplakia with cracked-mud appearance in premolar region of the right buccal mucosa in a *khaini* user.

Nodular leukoplakia: Nodular leukoplakia is an important lesion because of a very high risk for malignant transformation. It also shows a higher frequency of epithelial dysplasia, i.e., microscopic features which indicate the malignant potential, superimposed candidal infection and a high rate of malignant transformation. Epithelial dysplasia was observed in 59% of the nodular leukoplakias. Dysplastic nodular leukoplakias are at a risk that is seven times higher for cancer development than dysplastic homogeneous leukoplakia. Sometimes microscopically, a leukoplakia (Fig. 21.). Conversely, verrucous hyperplasias may start from leukoplakias.

Role of *Candida albicans*: About 32% of the nodular leukoplakias are infected by *Candida albicans* organism as compared to 18% of the homogeneous and 5% of the

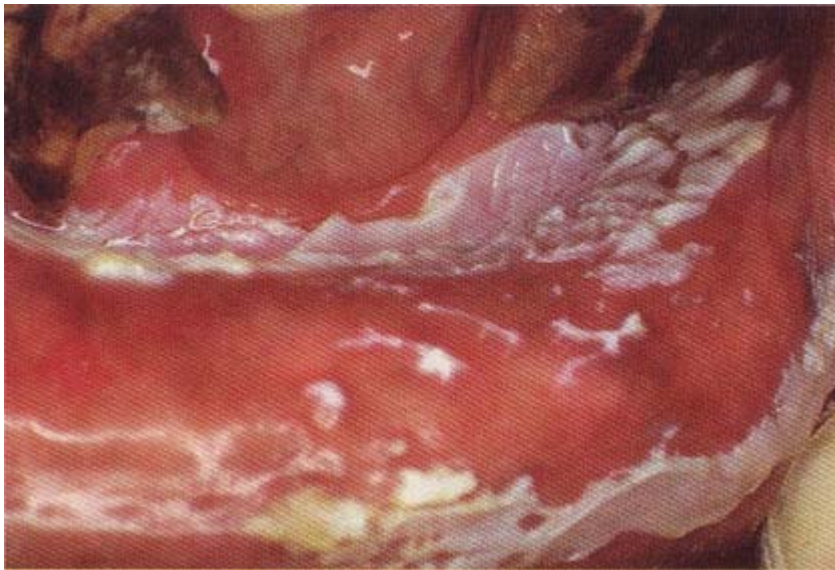


Fig. 18. An extensive and thick leukoplakia involving the vermilion border, lower labial groove, labial mucosa, alveolar ridge and the buccal mucosa of a *khaini* user.

ulcerated leukoplakias. Most of the *Candida* infected nodular leukoplakias were observed to be dysplastic as well (Fig. 22). The extract relationship between the presence of candidal hyphae on epithelial dysplasia and the natural

history of leukoplakia, is not clearly understood. Application of 1% gentian violet solution to nodular leukoplakia may result in its transformation into the homogeneous type (Fig. 23).

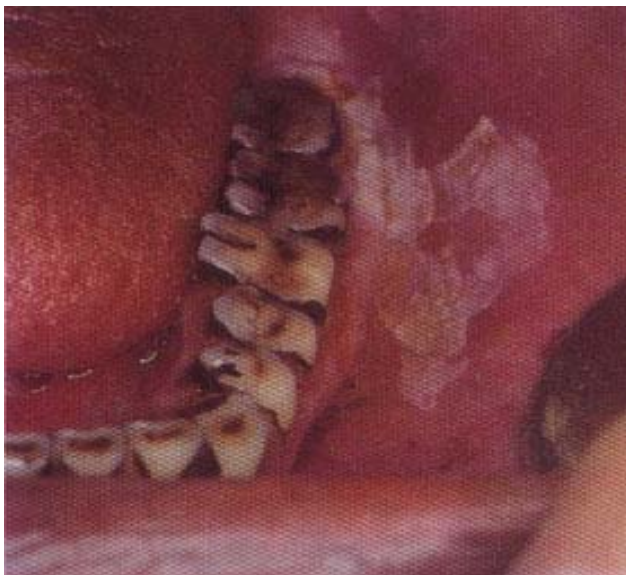


Fig. 19. A homogeneous leukoplakia in the left mandibular groove extending on to the gingival and the buccal mucosa of a betel-quid chewer.



Fig. 20. An extensive nodular leukoplakia in the right commissure and the buccal mucosa of a betel-quid chewer.



Fig. 21. A well-circumscribed nodular leukoplakia in the right buccal mucosa of a betel-quid chewer. Microscopically, it showed verrucous hyperplasia and epithelial dysplasia.



Fig. 22. A nodular leukoplakia in the left buccal mucosa of a betel-quid chewer. Microscopically, it showed epithelial dysplasia and was superimposed by candidal hyphae.

Leukoplakia on the lateral border of the tongue: Overall, up to 13% of leukoplakias occur on the tongue. The lateral border (Fig. 24) followed by the dorsum of the tongue (Figs. 25 & 26) are more frequently involved than the ventral surface.

Leukoplakia on the dorsum of the tongue: Although the dorsum of the tongue is less commonly affected by leukoplakia than the lateral border, the exceptions occur among submucous fibrosis patients (Fig. 25), *khaini* user of Singhbhum, Bihar (Fig. 26) and reverse smoker in Andhra Pradesh (See section 2.3). In Singhbhum District of Bihar, *Khaini* is usually kept on the dorsum of the tongue. In this area 13% of the leukoplakias occurred on the dorsum of the tongue.



Fig. 23 Eight weeks following antifungal treatment by application of 1% gentian violet solution to the lesion, it changed into a homogeneous leukoplakia. Microscopically, white it resulted in the disappearance of candidal hyphae, the epithelial dysplasia persisted. This observation perhaps indicates that candidal hyphae are secondary invaders.



Fig 24. A homogeneous leukoplakia in the left margin of the tongue in a betel-quin chewer.



Fig. 26. A homogeneous leukoplakia on the dorsum of the tongue in Singhbhum, Bihar.



Fig. 25. A homogeneous leukoplakia on the dorsum of the tongue in a betel-quin chewer who also has submucous fibrosis. Note the partial bald tongue due to the loss of lingual papillae.



Fig. 27. A leukoplakia in the floor of the mouth extending on to the ventral surface in a *bidi* smoker.

Leukoplakia on the floor of the mouth/ventral surface: In western countries, leukoplakias on the floor of the mouth and



Fig. 28. A Palatal leukoplakia in a *bidi* smoker.

the ventral surface of the tongue are regarded as high risk lesions. There is no evidence from India that these locations (Fig. 27) are



Fig. 29. A homogeneous leukoplakia in the posterior aspect of the upper and lower right buccal gingivae and the alveolar mucosa of a betel-quid chewer.

at higher for malignst transformation. Futhermore, in India, the floor of the mouth is an uncommon location accounting for less than 3% of leukoplakias.

Leukoplakia on the palate: The palate is also an uncommon location for leukoplakia. In addition to *chutta* smokers, palatal leukoplakias occur among *bidi* smokers as well (Fig. 28).

Leukoplakia on the gingival: Gingiva is another uncommon location for leukoplakia in most areas of India; it accounted for less than 1% of leukoplakias in five regions of India. Gingiva was most frequently (7%) involved in Darbhanga, Bihar. In betel-quid chewers leukoplakia occurs in the posterior aspect of the buccal gingival (Fig. 29). In edentulous individuals, leukoplakia may ridge; but such leukoplakias are not common in India.

Certain lesions that resemble leukoplakia

A wide range of oral mucosal lesions appear white. As mentioned previously, the definition of leukoplakia excludes all other clinical entries. This stresses the importance of obtaining a proper clinical history. Certain examples that can be mistaken for a leukoplakia are given below.

Acute pseudomembranous candidiasis: This is an infection caused by a fungus of the species *Candida*, the most important of which is *Candida albicans*. The organism occurs in nonpathogenic yeast form in the mouth of healthy individuals. Several factors predispose to a variety of clinical manifestation by this organism. Acute pseudomembranous

candidiasis can occur in any part of the oral mucosa; it consists of creamy, pearly-white patches (Fig. 30) that can be scraped off, leaving an erythematous base. Microscopically, these patches show desquamated epithelium, keratin, fibrin, necrotic tissue, food debris, and inflammatory cells with candidal hyphae on the surface. Among people with HIV infection the frequency of candidal infection is especially high.

Aspirin burn: Some individuals keep an aspirin tablet on the oral mucosa opposite a painful tooth to get quick relief from toothache. This act, however, causes chemical burn at the site of placement of aspirin wherein the muosa appears white, soggy (Fig. 31), and is often painful. The lesion consists of a slough that is produced by the coagulation



Fig. 30. A creamy white patch on the dorsum of the tongue in a male who did not use tobacco. Note the red area denoting the denuded patch.



Fig. 31. A soggy white lesion due to aspirin burn in the left commissure and the buccal mucosa in an individual who tried to relieve toothache by keeping aspirin tablets in that area.

Of protein in the superficial epithelial cells at an acidic pH of 3.5. Shorter exposure of the mucosa to aspirin causes a white wrinkled lesion, white and swollen lesion.

White lesion in a wind instrument player: *Kombu*, Literally meaning a “horn” in Malayalam (spoken in the state of Kerala), is a long, curved wind instrument (Fig. 32) played during the temple festivals of Kerala. In other regions similar instrument may be known by other names. The busy festive season in Kerala lasts for about six months (November to April) a year. An exponent usually plays the instrument for about 5 hours a day, four days a week. A whitish and spongy among *kombu* players during the season is a common occurrence (Fig. 33). Playing this instrument results in high intraoral pressure which is probably responsible for this lesion. The lesion



Fig. 32. The curved wind instrument (*kombu*).



Fig. 33. A white lesion in the posterior part of the left buccal mucosa in a *kombu* player. Its appearance corresponds to the playing of this instrument during the



Fig. 34. Six weeks following the stoppage of playing of the instrument, the lesion shown in Fig. 33 regressed considerably, and in another three weeks, completely.

regresses after the person discontinues playing the instrument, (Fig. 34) and therefore is rarely observed in the off-season.



Fig. 35. Fordyce's condition in the left buccal mucosa of a betel-quid chewer. This requires no treatment.



Fig. 36. A white lesion in the right buccal mucosa corresponding to an amalgam restoration (arrows). It should not be termed as leukoplakia.

Fordyce's condition: Fordyce's condition represents ectopic inclusion of sebaceous glands in the oral mucosa. It consists of well defined, slightly elevated, yellowish-white granules (Fig. 35). The granules may be isolated or extensive. Sometimes, especially in betel-quid chewers, Fordyce's condition can be mistaken for a nodular leukoplakia or even as a popular form of lichen planus. Fordyce's condition is innocuous and requires no treatment.

Lesion related to dental restoration: Occasionally, a lesion consisting of white patches (Fig. 36), sometimes with a lichenoid appearance, may occur in the oral mucosa corresponding to a dental restoration. It may be caused by contact allergy to mercury or some other material used for the restoration. Replacing the restoration with an inert one results in resolution of the lesion.

White sponge nevus: White sponge nevus consists of a white, thickened, folded and spongy lesion of the oral mucosa (Fig. 37). It exhibits an autosomal dominant mode of inheritance. Therefore, proper history should be elicited regarding the presence of similar lesions in other members of the family and, if possible, they should be examined. The diagnosis should be confirmed microscopically. This lesion does not require any treatment.

Natural history

The term "natural history" is used to describe the long – term behavior of a lesion in the absence of any intervention. Leukoplakia may be persistent, regress spontaneously, recur, or progress to cancer.



Fig. 37. A white sponge nevus in the left buccal mucosa of a 28-year old female who did not use tobacco in any form. She had a similar lesion on the right buccal mucosa and the clinical diagnosis was supported by the microscopic examination. Some 42 members who were related to this patients were examined and among them nine exhibited similar lesions.



Fig. 38. A homogeneous leukoplakia in the left buccal mucosa of a betel-quid chewer.

Regression of leukoplakia: leukoplakia (Fig.38) can regress spontaneously (Fig. 39), i.e. without any intervention in the habit or by other means in about 40% of the cases; however, significantly higher rates of regression are observed when tobacco habits are discontinued.

One year later the lesion shown in Fig. 38 regressed (Fig. 39). Leukoplakias associated with tobacco betel quid chewing regress more than those associated with smoking. Of the spontaneously regressed leukoplakias, 2.8-5.2% per year recur.

Malignant transformation: The term “malignant transformation” is used to denote the development of oral cancer from a preexisting leukoplakia. Such an observation confirmed by statistical tests validates the precancerous nature of leukoplakia (or any)

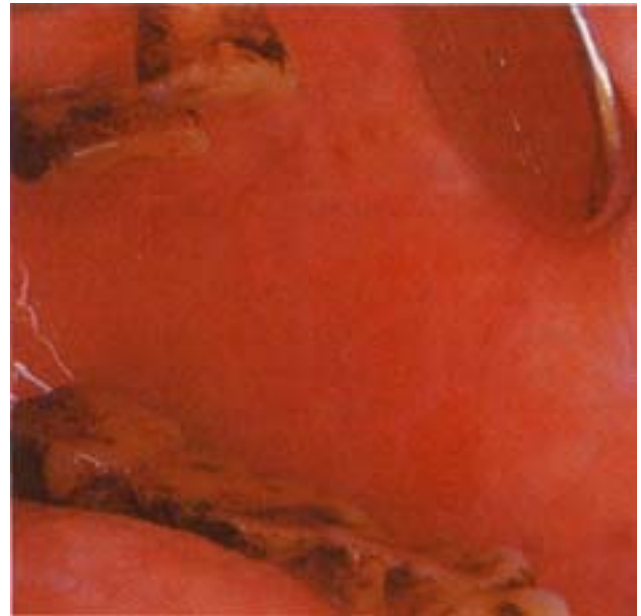


Fig. 39. Regression of the homogeneous leukoplakia shown in Fig. 38.

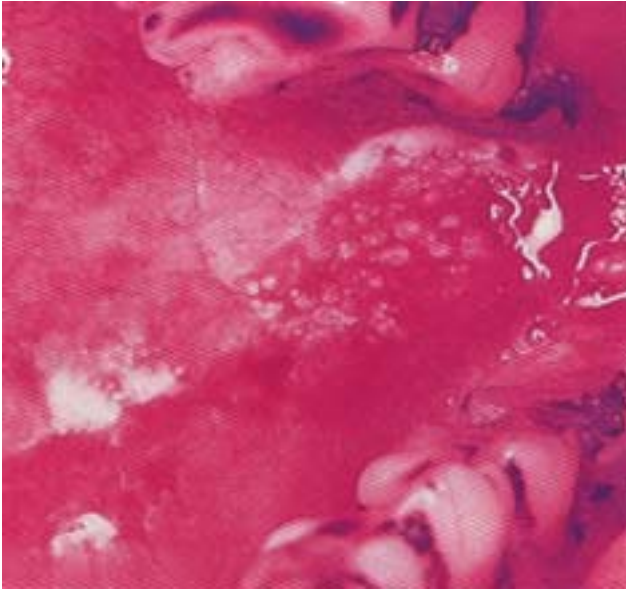


Fig. 40. A nodular leukoplakia in the right buccal mucosa of a 49-year old male betel-quid chewer.

lesion). Globally, 3-6% leukoplakias progress to cancer. In Ernakulam District, about 2.2% of leukoplakias progressed to oral cancer in mean observation period of 7.5 years forming a source for 69% of the oral cancers that developed during the 10-year observation period. Among the three clinical types of leukoplakia, about 20% of the nodular leukoplakias (Fig. 40) progressed to cancer (Fig. 41) as compared to 0.5% to 1.7% of the homogenous leukoplakias.

Nodular leukoplakias are high risk lesions because they show the highest relative risk (in one study it was 3243.2) for malignant transformation. Malignant transformation in a leukoplakia may occur in the form of a growth (Fig. 41) or other clinical changes.

Clinical aspects of malignant transformation

It is essential to follow-up all leukoplakias at intervals ranging from three months to one year for a possible progression

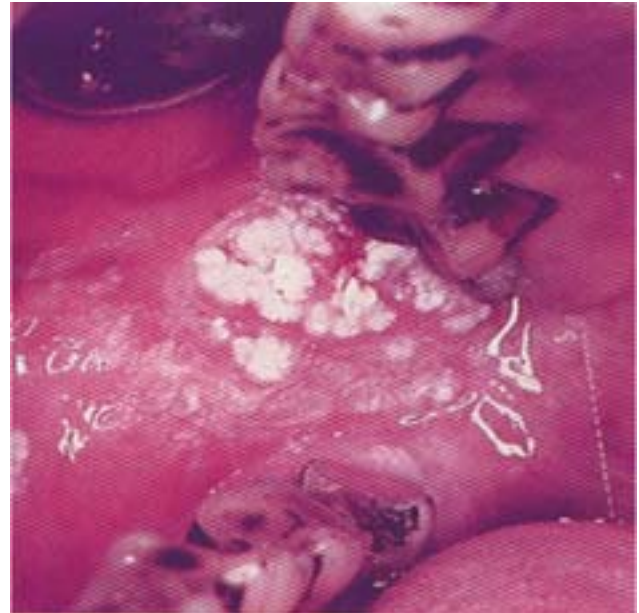


Fig. 41. Two years later, an exophytic growth, microscopically, a squamous cell carcinoma, developed from the nodular leukoplakia shown in Fig. 40.



Fig. 42. A nodular leukoplakia in the right commissure of a *bidi* smoker. Within six months following initial diagnosis, the nodules in the posterior part of the lesion increased in size. A biopsy from this area revealed a squamous cell carcinoma.



Fig. 43. A nodular leukoplakia in the right buccal mucosa with a fibrin-covered ulceration (arrow). The patient was a betel-quid chewer. Biopsy from the ulceration revealed a squamous cell carcinoma.

to oral cancer. During the follow-up, the lesion must be evaluated for the development of thickness/nodular areas (Fig. 42), ulceration (Fig. 43), rolled margins (Fig. 44), growths (Fig. 45) or indurated areas (Fig. 46), since these changes may represent early oral cancers.

Conclusions

Although a number of surgical and medicinal approaches of leukoplakia, there does not appear to be any universally adopted, successful treatment. In recent times treatment with a range of newer retinoids (vitamin A analogues) is being tried; the preliminary results in terms of remission of lesion are encouraging. The practical method of managing leukoplakia is based method of managing leukoplakia is based on clinical and microscopic appearance of the lesion. It



Fig. 44. A nodular leukoplakia in the right buccal mucosa of a betel-quid chewer. Note the rolled margin in the posterior aspect (arrow). A biopsy from this area showed a squamous cell carcinoma.

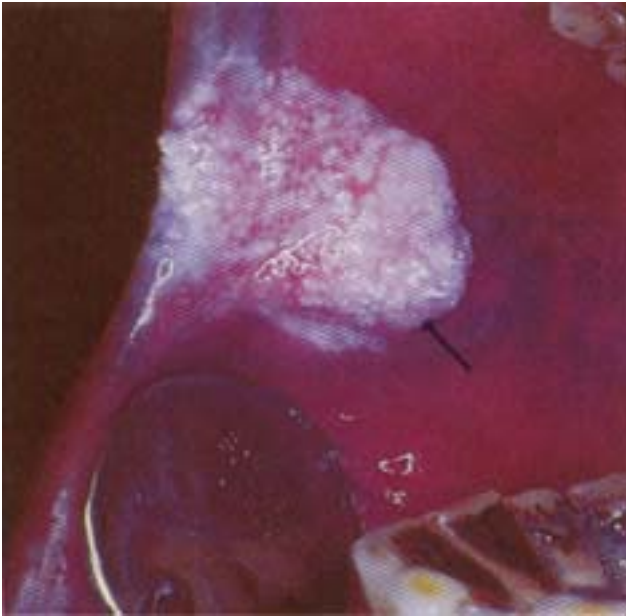


Fig. 45. A nodular leukoplakia in the right commissure of a *bidi* smoker. The patient developed an exophytic growth (arrow), which was confirmed as a squamous cell carcinoma microscopically.



Fig. 46. A homogeneous leukoplakia in the left buccal mucosa of a betel-quid chewer. An indurated ulceration developed in the center of the lesion. A biopsy from this area showed as a squamous cell carcinoma, microscopically.

is, therefore, advisable to biopsy all leukoplakias and, certainly, all nodular leukoplakias. Leukoplakias showing severe epithelial dysplasia must be excised and subjected to further histopathologic examination. Non-dysplastic leukoplakias or those showing mild dysplasia should be

Regularly followed-up. If these develop any changes indicative of oral cancer, a repeat biopsy is warranted. All individuals with leukoplakia, and those who were treated for it, should be educated to quit using tobacco use, and followed-up regularly.

