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Historical perspective and nomenclature of potentially malignant or potentially premalignant oral epithelial lesions with emphasis on leukoplakia—some suggestions for modifications

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Of the potentially (pre)maligant oral epithelial lesions, leukoplakia is the most common. A brief overview of the various definitions of leukoplakia that have been used in the past is presented here. A proposal has been made to modify the current definition. Clinically, for decades, leukoplakias have been divided into homogeneous and nonhomogeneous leukoplakias and further into different subtypes. A proposal has been made to slightly rearrange these subtypes. Furthermore, attention has been paid to a number of keratotic lesions that have been reported in the literature. It is expected that the increasing knowledge on carcinogenesis, including various genetic aspects, will be reflected in the definition of oral potentially (pre)malignant lesions in the near future. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:577–581)

Of the potentially (pre)malignant oral epithelial lesions, leukoplakia, being a predominantly white lesion, is the most common one. The term *leukoplakia* was introduced in 1877 by Schwimmer, a Hungarian dermatologist.[1] Entirely red lesions, *erythroplakias*, are much less common than leukoplakias but carry a much higher risk of malignant transformation. The discussion on whether or not oral lichen planus is a potentially (pre)malignant disorder is ongoing. Therefore, this entity will not be discussed here.

For a long time, the adjectives premalignant and precancerous have been used to designate an increased risk of malignant transformation of leukoplakias. A *precancerous lesion* has been defined as a morphologically altered tissue in which cancer is more likely to occur compared with its apparently normal counterpart, whereas a *precancerous condition* has been defined as a generalized state associated with a significantly increased risk of cancer.[2] However, no odds ratios that would define "more likely" and "significantly increased" have been provided by previous studies. Currently, preference is given to the term *potentially (pre)malignant* instead of the terms *premalignant* and *precancerous*. At present, this qualification is also used for fields of epithelial cells in the mucosa that are not visible clinically, harboring one or more cancer-associated genetic alterations, such as loss of 17 p (*TP53*) or 9 p (*CDKN2 A* encoding $p^{16\ Ink4\ A}$).[3,4]

Several attempts have been made in the past to provide a definition of leukoplakia, partly for scientific purposes and partly for use in the everyday practice. In 1968, Pindborg et al. defined *oral leukoplakia* as a white patch or plaque, not less than 5 mm in diameter, which could not be removed by rubbing and which could not be classified as any other diagnosable disease.[5] It was noted that the use of the term *leukoplakia* does not carry any histologic connotation. In 1978, the term was redefined by the World Health Organization (WHO) as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.[6] The reasons for excluding the criteria of size and whether or not the lesion could be removed by rubbing have not been made explicit.

At an international seminar held in 1983, the 1978 WHO definition of leukoplakia was slightly modified by the additional description that leukoplakia is not associated with any physical or chemical causative agent except the use of tobacco.[7] As a result, 2 types of leukoplakia were introduced: tobacco-associated leukoplakia and non–tobacco-associated (idiopathic or cryptogenic) leukoplakia. At yet another symposium, held in 1994, the 1978 WHO definition was left more or less unchanged.[8] However, a proposal was made to apply a *provisional* clinical diagnosis of leukoplakia in case of only a single oral examination and that a *definitive* diagnosis of leukoplakia should be based on the result of elimination of suspected etiologic factors, if any—and, in case of a persistent or an idiopathic lesion, as revealed on histopathologic examination.

Statement of Clinical Relevance

Oral leukoplakia is an important potentially (pre)malignant lesion. Proper use of the definition and terminology related to leukoplakia and leukoplakia-like lesions is of great importance for both clinical and research purposes.

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PRESENT DEFINITION AND CLASSIFICATION OF ORAL LEUKOPLAKIA AND ERYTHROPLAKIA

Definition

In 2005, in another WHO-guided conference on the definition and terminology related to leukoplakia and leukoplakia-like (leukoplakic) lesions, the 1978 WHO definition was amended as follows: "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."[9] It was added that *leukoplakia* is primarily a clinical term and has no specific histology. In Table I, a series of well-defined, known lesions or disorders that should be differentiated from leukoplakia is presented.

The definition of *erythroplakia*, that is, a fiery red patch that can not be characterized as any other definable disease, has remained unchanged over the years.[9]

Clinical classification of leukoplakia

In the 1960s, a 3-tier clinical classification of leukoplakia was proposed: (1) simple leukoplakia, (2) verrucous leukoplakia, and (3) erosive leukoplakia.[10] In the 1978 WHO classification a 2-tier clinical classification was recommended—homogeneous and nonhomogeneous leukoplakia.[6] The distinction between homogeneous and nonhomogeneous leukoplakia has been shown in most studies to be of statistical significance with regard to the prediction of malignant transformation, which is higher for the nonhomogeneous type.

Homogeneous leukoplakia. Some apply the term *homogeneous leukoplakia* only for leukoplakias that are thin and flat,[8] whereas others also recognize a thick type of homogeneous leukoplakia. In addition, subvariants of homogeneous leukoplakia have been reported, such as velvet-like and pumice stone–like types.

Table I. Well-defined predominantly white lesions or diseases that should be excluded from leukoplakia

Lesion or disease	*Main diagnostic criteria*
Aspirin burn (including other types of chemical burns)	History of prolonged application of aspirin tablets or other chemical agents.
Candidiasis, hyperplastic	Somewhat questionable entity; some refer to this lesion as candida-associated leukoplakia.
Cinnamon-induced contact stomatitis	Identification of the frequent use of chewing gums and also of some toothpastes that contain a high concentrate of cinnamon; a biopsy may be helpful.
Glassblower's white patch	Mainly located in the buccal mucosa; disappears within a few weeks after cessation of glassblowing.
Hairy leukoplakia	Usually bilateral on the borders of the tongue; histopathology is important, including the immunohistochemical demonstration of the presence of Epstein-Barr virus.
Keratotic lesions (include reversed smoking keratosis, sublingual keratosis, alveolar ridge keratosis, frictional keratosis, sanguinaria-associated keratosis, tobacco pouch keratosis, and keratosis of unknown significance)	Different etiologies and various clinical presentations; in many cases, biopsy is indicated. Some of the keratotic lesions carry an increased risk of malignant transformation.
Lesion caused by prolonged, direct contact of the oral mucosa with an amalgam restoration or other dental restorations; often listed as a lichenoid lesion	Disappearance of the lesion within an arbitrarily chosen period of 2 to 4 weeks after removal of the restoration; pretreatment biopsy is recommended.
Leukodema	Clinical diagnosis of a veil-like aspect of the buccal mucosa, bilaterally; tends to disappear when stretched. Occurs almost exclusively in dark-skinned people.
Lichen planus and lichenoid lesion	Often a clinical diagnosis; occasionally difficult to distinguish from leukoplakia. A biopsy may be helpful.
Linea alba	Clinical diagnosis; almost always bilateral on the line of occlusion.
Lupus erythematosus	Often a clinical diagnosis; almost always cutaneous involvement as well. Histopathology and direct immunofluorescence may be helpful.
Morsicatio	History of habitual chewing or biting. Clinical aspect of irregular whitish-yellowish flakes. Often bilateral.
Papilloma and allied lesions (e.g., condyloma acuminatum, multifocal epithelial hyperplasia and verruca vulgaris)	Clinical aspect; medical history. A biopsy, including human papillomavirus typing, may be helpful.
Reversed smoking–induced palatal lesion	May mimic leukoplakia or erythroplakia; carries a high risk of malignant transformation.
Skin graft (e.g., after vestibuloplasty)	History of a previous graft.
Smoker's palate ("stomatitis nicotina")	Usually a clinical diagnosis. Rarely becomes malignant. Regresses after cessation of the smoking habit.
Snuff dipper's lesion	See keratotic lesions (tobacco pouch keratosis).
Syphilis, secondary ("mucous patches")	Medical history; clinical aspect. Demonstration of *Treponema pallidum*; serology.
White sponge nevus	Young age; often family history. The clinical aspect is more or less diagnostic. Occasionally a biopsy may be helpful.

Slightly modified from Warnakulasuriya et al.[9]