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Review

Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management

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SUMMARY

In a recently held WHO workshop it has been recommended to abandon the distinction between potentially malignant lesions and potentially malignant conditions and to use the term potentially malignant disorders instead. Of these disorders, leukoplakia and erythroplakia are the most common ones. These diagnoses are still defined by exclusion of other known white or red lesions. In spite of tremendous progress in the field of molecular biology there is yet no single marker that reliably enables to predict malignant transformation in an individual patient. The general advice is to excise or laser any oral of oropharyngeal leukoplakia/erythroplakia, if feasible, irrespective of the presence or absence of dysplasia. Nevertheless, it is actually unknown whether such removal truly prevents the possible development of a squamous cell carcinoma.

At present, oral lichen planus seems to be accepted in the literature as being a potentially malignant disorder, although the risk of malignant transformation is lower than in leukoplakia. There are no means to prevent such event. The efficacy of follow-up of oral lichen planus is questionable. Finally, brief attention has been paid to oral submucous fibrosis, actinic cheilitis, some inherited cancer syndromes and immunodeficiency in relation to cancer predisposition.

Introduction

In a World Health Organization (WHO) Workshop, held in 2005, the terminology, definitions and classification of oral lesions with a predisposition to malignant transformation have been discussed. The term "potentially malignant" was preferred above "premalignant" or "precancerous";[1] furthermore, it has been recommended to abandon the traditional distinction between potentially malignant lesions and potentially malignant conditions and to use the term "potentially malignant disorders" instead.

In this treatise, attention will be mainly paid to leukoplakia and erythroplakia. Furthermore, lichen planus and submucous fibrosis will be discussed, as well as a number of miscellaneous potentially malignant disorders.

Leukoplakia

Definition and terminology

Leukoplakia is at present defined as "A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer".[1] Examples of white or predominantly white diseases of the oral mucosa that carry no increased risk for cancer development are shown in Table 1.

The term leukoplakia can be used at different levels of certainty (C-factor) as a clinical term only (C_1 or C_2) or as a clinicopathological term (C_3 or C_4), as shown in Table 2.

Epidemiology and etiology

The estimated reported prevalence of oral leukoplakia, worldwide, is approximately 2%.[2] However, when viewed in relation to an annual malignant transformation rate of 1%, this prevalence figure would result in development of oral cancer in 20 per 100,000 populations per year. Obviously, this cancer incidence figure, based on malignant transformation of oral leukoplakia alone is much too high. Probably, the prevalence of oral leukoplakia has to be set at a more realistic figure of less than 0.5%. There are some geographical differences with regard to the gender distribution.

Leukoplakia is six times more common among smokers than among non-smokers.[3] Alcohol is an independent risk factor, regardless of beverage type or drinking pattern.[4] There are conflicting results of studies related to the possible role of human papillomavirus infection.[5–7]

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Table 1
The most common white or predominantly white benign diseases of the oral mucosa and their main diagnostic criteria

Lesion	Main diagnostic criteria
Aspirin burn	History of local application of aspirin tablets
Candidiasis, pseudomembranous	Clinical aspect (pseudomembranes, often symmetrical pattern)
Candidiasis, hyperplastic[a]	
Frictional lesion	Presence of mechanical irritation (e.g. habit of vigorous toothbrushing)
Hairy leukoplakia	Clinical aspect (incl. bilateral localization on the tongue); histopathology (incl. EBV)
Leukoedema	Clinical aspect (incl. symmetrical pattern)
Linea alba	Clinical aspect (incl. location on the line of occlusion in the cheek mucosa)
Lupus erythematosus	History of skin lesions; clinical appearance (incl. bilateral pattern); histopathology
Morsicatio (habitual chewing or biting of the cheek, tongue, lips)	History of habitual chewing or biting; clinical aspects
Papilloma and allied lesions	Clinical aspect; histopathology
Syphilis, secondary (“mucous patches”)	Clinical aspect; demonstration of T. pallidum; serology
Tobacco-induced lesions[b]	
Smoker’s palate (nicotinic stomatitis)	Clinical aspect; history of smoking
Snuff induced lesion	Clinical aspect; site were snuff is placed
White sponge nevus	Family history; clinical aspect (often symmetrical pattern)

[a] There is no consensus in the literature as whether to recognize a hyperplastic subtype of oral candidiasis: some prefer to refer to these lesions as Candida-associated leukoplakia.
[b] Palatal lesions in reverse smokers are considered potential malignant disorders.

Table 2
Certainty (C)-factor of a diagnosis of oral leukoplakia

C_1	Evidence from a single visit, applying inspection and palpation as the only diagnostic means (provisional clinical diagnosis)
C_2	Evidence obtained by a negative result of elimination of suspected etiologic factors, e.g. mechanical irritation, during a follow-up period of 2–4 weeks or in the absence of any suspected etiological factors (definitive clinical diagnosis)
C_3	As C_2, but complemented by incisional biopsy (provisional histopathological diagnosis)
C_4	Evidence following excision and pathological examination of the resected specimen (definitive histopathological diagnosis)

Clinical aspects

Leukoplakia may affect any site of the oral and oropharyngeal cavity. Clinically, leukoplakia can be subdivided in a homogeneous type (flat, thin, uniform white in colour) and a non-homogeneous type. The non-homogeneous type has been defined as a white-and-red lesion (“erythroleukoplakia”), that may be either irregularly flat (speckled) or nodular. Verrucous leukoplakia is yet another type of non-homogeneous leukoplakia. Although verrucous leukoplakia usually has a uniform white appearance, its verrucous texture is the distinguishing feature from homogeneous (flat) leukoplakia. Verrucous leukoplakia is clinically indistinguishable from the clinical aspect of verrucous carcinoma. Proliferative verrucous leukoplakia (PVL) is a subtype of verrucous leukoplakia,[8] being characterized by multifocal presentation, resistance to treatment and a high rate of malignant transformation.[9,10] PVL seems more prevalent among elderly women. There may or may not be a history of tobacco use.

Histopathological aspects

Histopathologically, a distinction can be made between dysplastic and non-dysplastic leukoplakia. The assessment and severity of dysplasia is based on architectural disturbance accompanied by cytological atypia. The WHO 2005 classification recognizes five histopathological stages in epithelial precursor lesions (Table 3).[11] The criteria used for diagnosing dysplasia are shown in Table 4. It should be emphasized that dysplasia is a spectrum and that no criteria exist to precisely divide this spectrum into mild, moderate and severe categories. Furthermore, there may be a substantial interobserver and intraobserver variation in the histopathological assessment of the presence and severity of epithelial dysplasia.[12–14] Perhaps a better consensus can be reached by modifying the WHO five tier system into a binary one, recognizing “low-risk” versus “high-risk” lesions.[15] It has been suggested that an AgNOR cut-point may be helpful to distinguish mild and moderate dysplasia.[16] In Table 5 two other grading systems – the Squamous Intraepithelial Neoplasia (SIN) system and the Ljubljana classification of Squamous Intraepithelial Lesions (SIL) – are shown. Occasionally, koilocytic changes in dysplastic lesions (“koilocytic dysplasia”) can be observed, apparently related to the presence of intermediate and high-risk human papillomavirus; the clinical significance and potential for malignant transformation is as yet unclear.[7] Yet another subtype of dysplasia is “lichenoid dysplasia” (see discussion on lichen planus).

Occasionally, a diagnosis of verrucous carcinoma, carcinoma in situ or invasive squamous cell carcinoma is made in the clinical presentation of leukoplakia; in such event the histopathological diagnosis replaces the clinical diagnosis of leukoplakia. It is well

Table 3
Histopathological stages in epithelial precursor lesions[11]

1	Squamous hyperplasia	This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (basal cell hyperplasia); the architecture shows regular stratification without cellular atypia
2	Mild dysplasia	The architectural disturbance is limited to the lower third of the epithelium accompanied by cytological atypia
3	Moderate dysplasia	The architectural disturbance extends into the middle third of the epithelium; consideration of the degree of cytological atypia may require upgrading
4	Severe dysplasia	The architectural disturbance involves more than two thirds of the epithelium; architectural disturbance into the middle third of the epithelium with sufficient cytologic atypia is upgraded from moderate to severe dysplasia
5	Carcinoma in situ	Full thickness or almost full thickness architectural disturbance in the viable cell layers accompanied by pronounced cytological atypia

Table 4
Criteria used for diagnosing dysplasia[11]

Architecture
Irregular epithelial stratification
Loss of polarity of basal cells
Drop-shaped rete ridges
Increased number of mitotic figures
Abnormal superficial mitoses
Premature keratinization in single cells (dyskeratosis)
Keratin pearls within rete pegs
Cytology
Abnormal variation in nuclear size (anisonucleosis)
Abnormal variation in nuclear shape (nuclear pleomorphism)
Abnormal variation in cell size (anisocytosis)
Abnormal variation in cell shape (cellular pleomorphism)
Increased nuclear-cytoplasmic ratio
Increased nuclear size
Atypical mitotic figures
Increased number and size of nucleoli
Hyperchromasia