LEUKOPLAKIA

Definition

Leukoplakia is the most common premalignant or "potentially malignant" lesion of the oral mucosa.
Leukoplakia is a predominantly white lesion of the oral mucosa than cannot be clinicopathologically characterized as any other definable lesion.
The term leukoplakia is a clinical descriptor only and should not be used once histological information is available. On the other hand, the terms keratosis and dyskeratosis are histological features and should not be used as clinical terms.
Based on clinical examinations a provisional diagnosis of leukoplakia is made when the lesion cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance. A definitive diagnosis is made as a result of the identification, and if possible elimination, of suspected etiological factors and, in the case of persistent lesions, histopathological examination confirm the diagnosis.

Epidemiology

The incidence and prevalence of leukoplakia vary in different parts of the world.
In general the reported prevalence ranges from 0.2 to 5%, with remarkable regional differences: India (0.2-4.9%), Sweden (3.6%), Germany (1.6%), Holland (1.4%).
Leukoplakia is seen most frequently in middle-aged and older men.
Gender distribution is also variable. Men are more affected in some countries, while this is not the case in the Western world.

Clinical presentation

Leukoplakia can be either solitary or multiple.
Leukoplakia may appear on any site of the oral cavity, the most common sites being: buccal mucosa, alveolar mucosa, floor of the mouth, tongue, lips and palate.
Classically two clinical types of leukoplakia are recognised: homogeneous and non-homogeneous, which can co-exist.

- Homogeneous leukoplakia is defined as a predominantly white lesion of uniform flat and thin appearance that may exhibit shallow cracks and that has a smooth, wrinkled or corrugated surface with a consistent texture throughout. This type is usually asymptomatic.
- Non-homogeneous leukoplakia has been defined as a predominant white or white-and-red lesion ("eritroleukoplakia") that may be either irregularly flat, nodular ("speckled leukoplakia) or exophytic ("exophytic or verrucous

leukoplakia"). These types of leukoplakia are often associated with mild complaints of localised pain or discomfort.

Proliferative verrucous leukoplakia is an aggressive type of leukoplakia that almost invariably develops into malignancy. This type is characterised by widespread and multifocal appearance, often in patients without known risk factors.

In general, non-homogeneous leukoplakia has a higher malignant transformation risk, but oral carcinoma may develop from any leukoplakia.

Aetiopathogenesis

The aetiology of leukoplakia is still unclear. Although, tobacco seems to be the major inductor factor, its association cannot be determined in all cases.

A variety of smokeless tobacco habits have been reported as leukoplakia inductors: e.g. snuff, chewing. These lesions have shown to have a low malignant transformation risk.

A higher malignant transformation rate has been reported in *Candida*-infected leukoplakias. However, there is not an agreement of how this lesion should be named "*Candida*-leukoplakia" or "hyperplastic candidosis", and whether *Candida* infection is the cause of leukoplakia or is an infection superimposed in a pre-existing lesion.

The possible implication of human papillomavirus (HPV) and others virus has been studied. High risk HPV (16 and 18) have been associated with oral cancer.

Other factors such as alcohol, inadequate diet, vitamin deficiency (e.g. vitamin A and C), areca nut (betel), different mouthwashes, chronic traumatic irritation, poor oral hygiene, poor socio-economic status, galvanism, and even genetic factors have considered and studied in leukoplakia.

Diagnosis

Leukoplakia diagnosis has clinical and histopathological approaches.

- Provisional Clinical Diagnosis: clinical evidence from a single visit, using inspection and palpation as the only diagnostic means.
- Definitive Clinical Diagnosis: clinical evidence obtained by lack of changes after eliminating suspected etiologic factors during a follow-up period of 2-4 weeks (In some cases the time may be longer).
- Histopathologically Proven Diagnosis: definitive clinical diagnosis complemented by biopsy in which, histopathologically, no other definable lesion is observed.

Differential diagnosis includes lichen planus, lupus, leukoedema, candidosis, white sponge naevus, frictional lesions, *morsicatio* lesions, contact lesions, and smoker's palate.

Histopathological study of leukoplakia allows the clinician: 1.- to exclude any other definable lesions; and 2.- to establish the degree of epithelial dysplasia, if present.
It may be hazardous to just observe a white lesion without having taken a biopsy. It is important to biopsy the clinically most suspicious areas, especially the non-homogeneous zones or any associated red areas.
Other diagnostic methods such toluidine blue staining or Lugol's iodine, mycological culture and cytology might be helpful, but they do not replace the biopsy.

Treatment

There are different treatments for leukoplakia, which have shown different results. However, the risk of malignant transformation is not completely eliminated by any of the current therapies.
Initial treatment of a white oral lesion is the elimination of the possible aetiological factors: e.g. trauma, *Candida*, tobacco use etc. Complete and definitive cessation of tobacco is obligatory in patients with leukoplakia.
Presence of epithelial dysplasia in persistent lesions is a crucial aspect to consider, although measurement of DNA ploidy may be more reliable.
Complete surgical removal (leaving free-lesion borders) is recommended in cases with epithelial dysplasia. In cases without epithelial dysplasia the decision concerning further treatment or not, is influenced by the extent and location of the lesion as well as the patient 's medical condition.
Apart from surgical excision, other treatment modalities available include cryosurgery, laser surgery, retinoids, beta-carotene, bleomycin, calcipotriol, photodynamic therapy, etc.
The major drawbacks for most current agents are the frequency of adverse effects and the recurrence of lesions when treatment is discontinued.

Prognosis and complication

The malignant transformation rate of oral leukoplakia varies from 0 to 33%. Overall, 3 to 8% of leukoplakias develop malignant transformation in a average follow-up period of five years.
Any leukoplakia could transform into a carcinoma, even those which did not show epithelial dysplasia initially (or in which dysplasia happened to be absent from the biopsy taken). The main problem is that the malignant transformation cannot be reliably predicted yet. Nonetheless, some data could help identifying the possible risk. Leukoplakias show a high transformation risk when they: 1.- affect women; 2.- persist for long periods; 3.- appear in non smokers, 4.- are located on the floor of the mouth or tongue; 5.- are seen in patients with a previous head and neck carcinoma; 6.- are non-

homogenous; 7.- are infected by *Candida*; 8.- show epithelial dysplasia, 9.- show DNA aneuploidy. Of all these factors the presence of epithelial dysplasia still seems to be the most important indicator of malignant potential but ploidy may soon be more useful. Some leukoplakias show an increased recurrence rate (proliferative verrucous leukoplakia; PVL). On the other hand, some leukoplakias disappear spontaneously without any specific therapy.
Regular check-up of these patients is essential, probably every 3, 6 and then 12 months, both in treated and untreated patients.

Prevention

There is no known therapy to prevent development of oral leukoplakia and there is no known therapy to prevent oral squamous cell carcinoma developing from oral leukoplakia;.
It has been demonstrated that a healthy life style and the abstinence of tobacco are the best way to prevent both.
Fresh fruits and vegetables may have a protective effect in the primary prevention of oral cancer and precancer.
Early diagnosis and treatment of leukoplakia, can reduce the high rates of oral cancer morbidity and mortality in many countries.
Screening programs for oral cancer and precancer may be indicated in individuals at risk, such as predetermined age (40-70 years), gender (males in some countries), risk habits (tobacco/alcohol users) and in certain geographic areas with a high incidence of oral cancer.

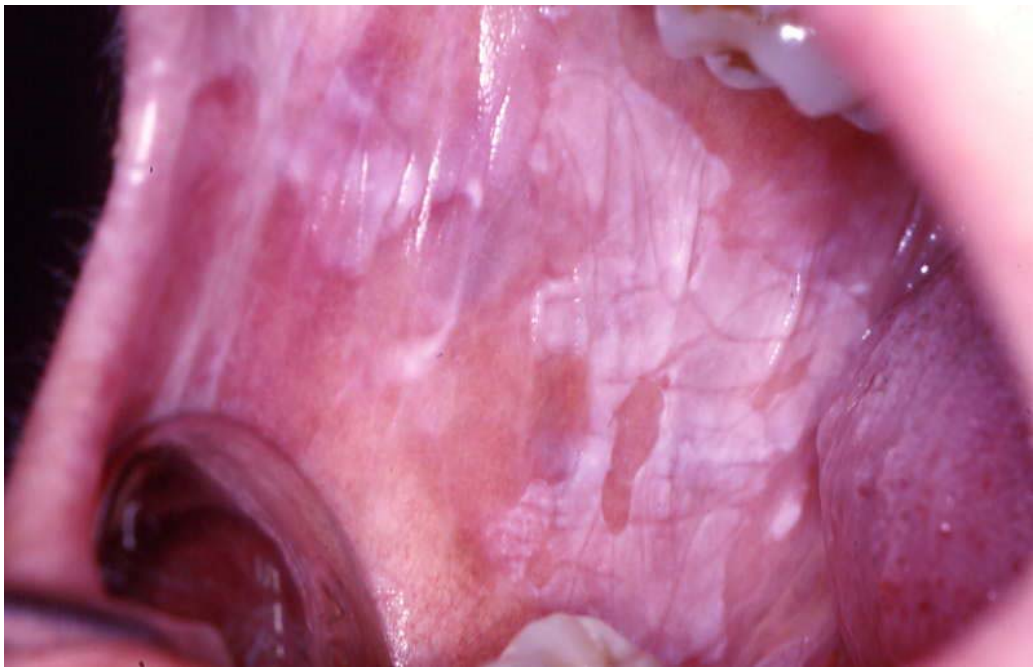

Figure 1. Leukoplakia of the buccal mucosa

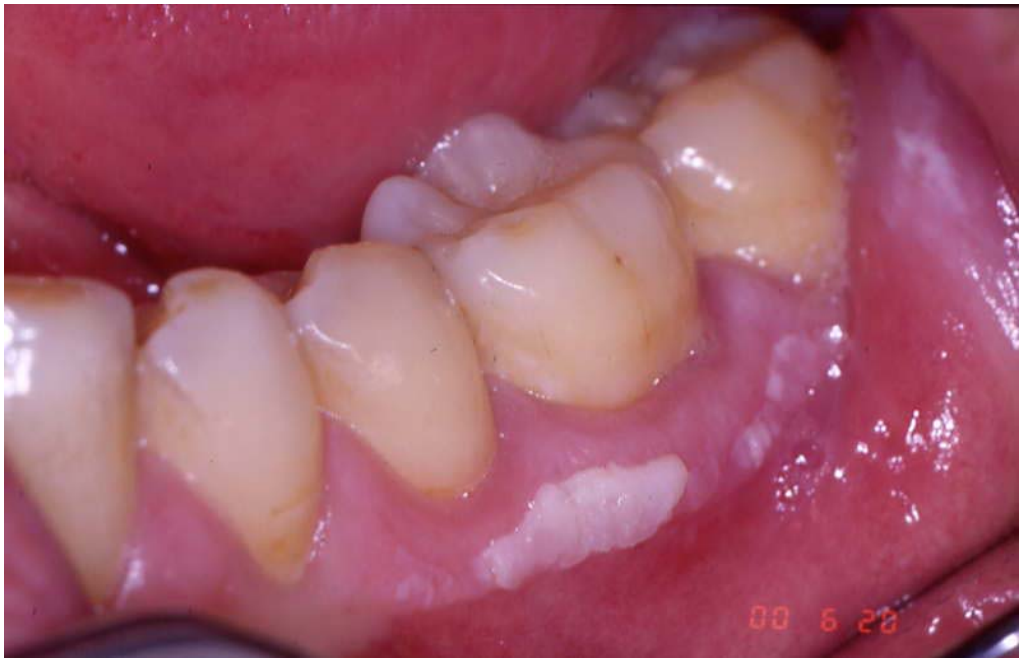

Figure 2. Leukoplakia of the gengiva

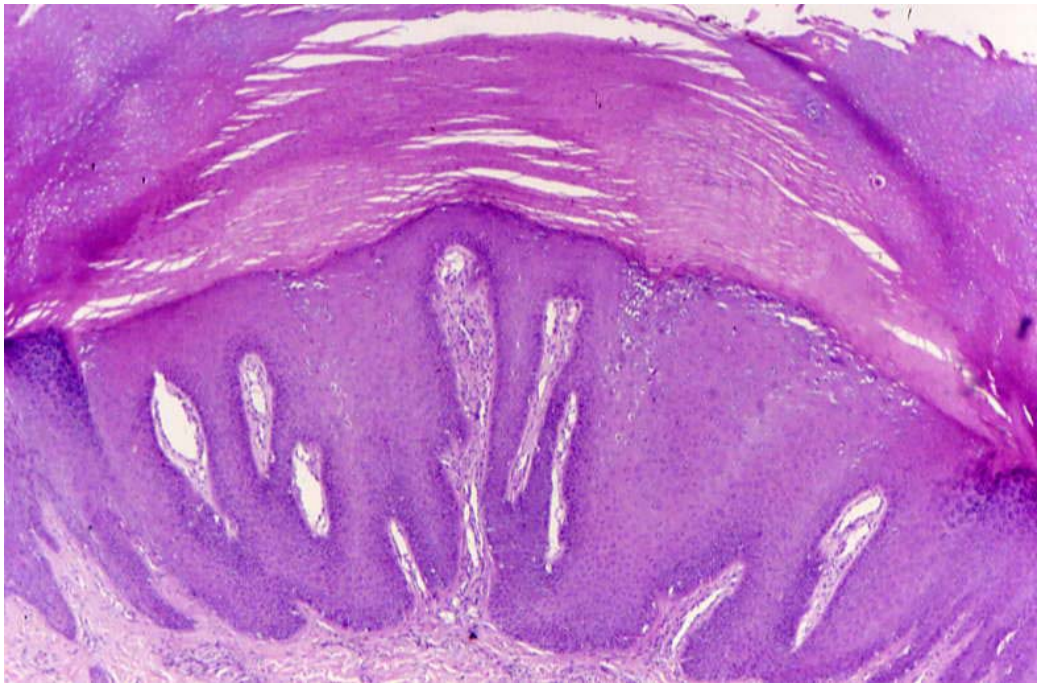

Figure 3. Leukoplakia, histological aspect

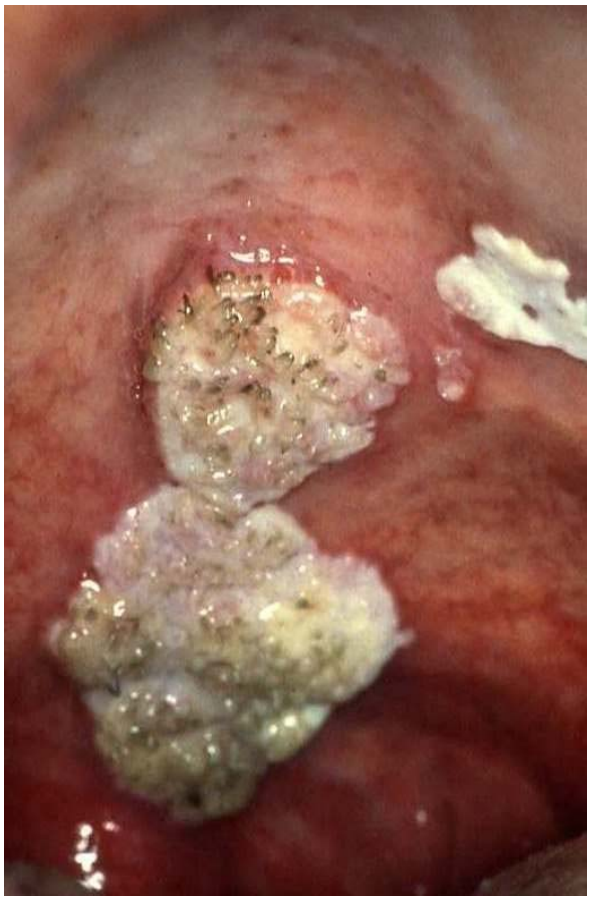

Figure 4. Leukoplakia, verrucous variant

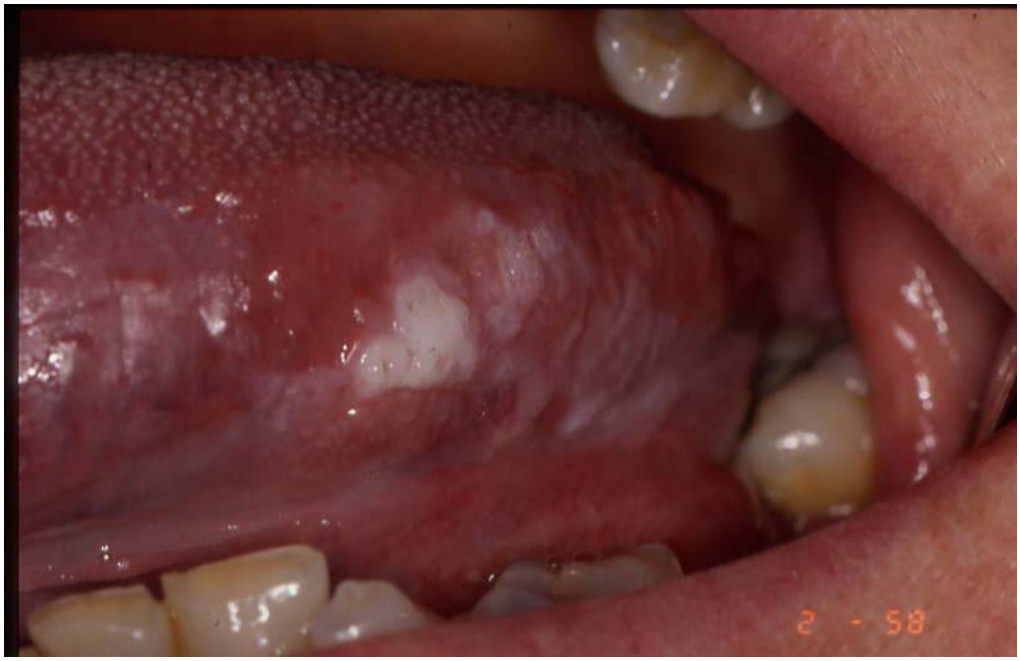

Figure 5. Leukoplakia of the lateral tongue

Further reading

1 van der Waal I, Schepman KP, van der Meij EH, Smeele LE. Oral leukoplakia: a clinicopathological review. Oral Oncol 1997; 33: 291-301.

2 Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001; 344: 1270-1278.

3 Neville BW. Oral cancer and precancerous lesions. CA Cancer J Clin 2002; 52: 195-215.

4 Lodi G, Sardella A, Bez C, Demarosi F, Carassi A. Interventions for treating oral leukoplakia (Cochrane review). In: Cochrane Database Syst Rev. 2004;(3):CD001829.

5 Reibel J. Prognosis of oral pre-malignant lesions: significance of clinical, histopathological and molecular biological characteristics. Crit Rev Oral Biol Med 2003; 14: 47-62.

Links

www.update-software.com/cochrane

www.emedicine.com/derm/topic227.htm

www.maxillofacialcenter.com/precancer.html