Cancer Association of South Africa (CANSA)

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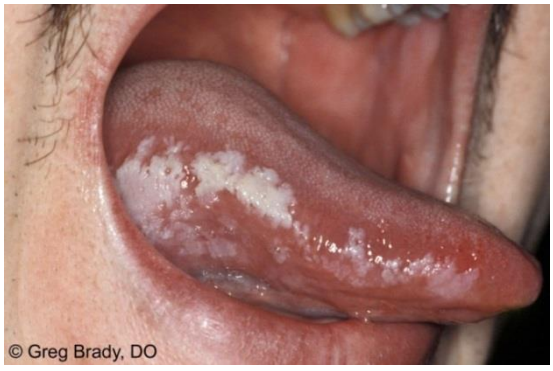
Fact Sheet
on
Leukoplakia

Introduction

Leukoplakia (also sometimes referred to as leucoplacia, leukokeratosis, leukoplasia, idiopathic leukoplakia, idiopathic keratosis, or idiopathic white patch), normally refers to a condition where areas of keratosis (a horny growth) appear as firmly attached white patches on the mucous membranes of the oral cavity, although the term is sometimes used for white patches of other mucosal sites in the gastrointestinal tract, or mucosal surfaces of the urinary tract and genitals.



[Picture Credit: Leukoplakia]

Leukoplakia

Leukoplakia is the mouth's reaction to chronic irritation of the mucous membranes of the mouth. Leukoplakia patches can also develop on the female genital area; however, the cause of this is unknown.

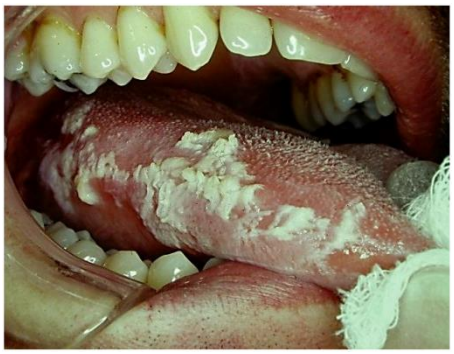
Leukoplakia patches can occur at any time in one's life, but it is most common in senior adults.

Mohammad, F., Arishiva, T. & Fairozekhan, T. 2020.

"Oral premalignancy is considered as an intermediate stage. It is classified into two broad straplines, premalignant lesions and premalignant conditions. The premalignant lesion is defined as "a morphologically reformed tissue in which oral cancer is more likely to occur than in its seemingly normal counterpart." An example is leukoplakia. A premalignant condition is defined as "a generalized state associated with a significantly increased risk of cancer." An example is oral submucous fibrosis. Recently the World Health Organization (WHO) considered premalignant lesions and conditions under a single group of disorders known as Potentially Malignant Disorders. Oral leukoplakia is a potentially malignant disorder affecting the oral mucosa. It is defined as "essentially an oral mucosal white lesion that cannot be considered as any other definable lesion." Oral

leukoplakia is a white patch or plaque that develops in the oral cavity and is strongly associated with smoking. Risk factors include all forms of tobacco use forms, including cigar, cigarette, beedi, and pipe. Other synergistic risk factors include alcohol consumption, chronic irritation, fungal infections such as candidiasis, oral galvanism due to restorations, bacterial infections, sexually transmitted lesions like syphilis, combined micronutrient deficiency, viral infections, hormonal disturbances, and ultraviolet exposure."

'Hairy' leukoplakia of the mouth is an unusual form of leukoplakia (caused by the Epstein-Barr virus) that is seen only in people who are infected with HIV, have Aids, or Aids-related complex. It consists of fuzzy, white patches on the tongue (hence, its name) and less frequently, elsewhere in the mouth. It may resemble thrush, an infection caused by the fungus *Candida* which, in adults, usually occurs if one's immune system is not working properly. Thrush in adults may often be one of the first signs of infection with the HIV virus.



[Picture Credit: Hairy Leukoplakia]

Complications of Leukoplakia

Leukoplakia usually does not cause permanent damage to tissues in one's mouth. However, oral cancer is a potentially serious complication of leukoplakia. Oral cancers often form near leukoplakia patches, and the patches themselves may show cancerous changes. Even after leukoplakia patches are removed, the risk of oral cancer remains.

'Hairy' leukoplakia is not painful and is not likely to lead to cancer. But it may indicate HIV infection or Aids.

Incidence of Leukoplakia in South Africa

Because Leukoplakia itself is not a cancerous condition, the National Cancer Registry (2017) does not provide information regarding its incidence.

Symptoms of Leukoplakia

Leukoplakia can have various appearances. Changes usually occur on the gums, the insides of the cheeks, the bottom of the mouth and, sometimes, the tongue.

Leukoplakia may appear:

- White or greyish in patches that cannot be wiped away
- Irregular or flat-textured
- Thickened or hardened in areas
- Along with raised, red lesions (erythroplakia), which are more likely to show precancerous changes

The type of leukoplakia called 'hairy' leukoplakia primarily affects people whose immune system have been weakened by medications or disease, especially HIV/Aids. Hairy leukoplakia causes fuzzy, white patches that resemble folds or ridges on the sides of the tongue. It is often mistaken for oral thrush - an infection marked by creamy white patches, which can be wiped away, on the area that extends from the back of the throat to the top of the oesophagus (pharynx) and the insides of the cheeks. Oral thrush is common in people with HIV/Aids.

When to see a doctor - sometimes mouth sores can be annoying or painful without being harmful, but in other cases, mouth problems can indicate a more serious condition.

One should see a dentist or doctor if any of the following are present:

- White plaques or sores in the mouth that do not heal on their own within two weeks
- Lumps or white, red or dark patches in the mouth
- Persistent changes in the tissues of the mouth

Diagnosis of Leukoplakia

Leukoplakia is generally diagnosed following an oral examination. Many patients mistake the condition for oral thrush. Thrush is a yeast infection of the mouth. The patches it causes are usually softer than leukoplakia patches and they may bleed more easily.

During a physical examination, the doctor or dentist can confirm if the patches are leukoplakia. Other tests may be needed to confirm the cause. With treatment, one may be able to prevent future patches from developing.

If a patch looks suspicious, the doctor or dentist will do a biopsy. A small tissue sample is sent to a pathologist for diagnosis. The goal is to rule out the possibility of oral cancer.

Vella, F.D., Pannone, G., Patano, A., Ninivaggi, R., Prete, R.D., Lauritano, D. & Petruzzi, M. 2020.

Aim: The aim of the present study was to evaluate the prevalence of HPV infection in oral leukoplakia, specifying the HPV genotypes eventually involved. We also compared the micro-biopsy and brushing HPV detecting efficacy.

Materials and methods: Consecutive patients with a presumptive diagnosis of oral leukoplakia were enrolled. Demographical, behavioral data (smoking, alcohol) and lesion features were recorded. Each patient underwent a brushing procedure, performed with a cytobrush rubbed on the lesion, and then a biopsy was performed. The brushing and micro-biopsy specimens were both analyzed with the HPV 28 Anyplex II Seegene RT-PCR. The prevalence of HPV infection was calculated considering the two methods' outcomes separately and then combining both. Cohen's k coefficient was used to assess the agreement between the two methods.

Results: Sixty-five patients were enrolled with a mean age of 60 years. The HPV infection prevalence was 17%, decreasing to 5% considering the brushing outcomes alone. The most frequently detected genotypes were 6 (12%), 11 (3%), 42 (3%), and 16 (3%). No statistically significant correlation was found between HPV infection and the variables analyzed, except for smoking and the type of mucosa ($p < 0.05$). The strength of agreement between cytobrush and micro-biopsy was "fair" ($k = 0.384$).

Conclusions: The present study showed a low prevalence of HPV infection in oral leukoplakia. The micro-biopsy appeared to be more reliable than brushing in detecting HPV DNA in oral leukoplakia, but the method invasiveness discourages its employ as a screening tool. The importance of HPV in the etiopathogenesis of oral potentially malignant lesions remains unclear; further studies are needed to establish the HPV role in oral leukoplakia.

Clinical relevance: HPV involvement in oral leukoplakia and an effective and appropriate detecting technique are still a debated issue. From this study, the restricted use of brushing did not appear sufficient to assess the presence of HPV infection with PCR techniques in samples obtained from oral leukoplakia.

Grochau, K.J., Safi, A.F., Drebber, U., Grandoch, A., Zöller, J.E. & Kreppel, M. 2018.
PURPOSE: The aim of this prospective work was to examine oral leukoplakia for their podoplanin expression to determine whether podoplanin expression is associated with the degree of dysplasia.
MATERIALS AND METHODS: We took biopsy samples from 50 patients with oral leukoplakia in 2013. The preparations studied by immunohistochemistry were analyzed in correlation with the degree of dysplasia and other clinicopathological variables.
RESULTS: The Chi-square test showed a significant correlation between podoplanin expression and the degree of dysplasia according to the squamous intraepithelial neoplasia (SIN) classification ($p = 0.033$). Also, a significant association between age grouping and podoplanin expression was found. We were able to show that the distribution is the same for both age groups in relation to the score of podoplanin expression ($p = 0.003$).
CONCLUSION: In a comparable retrospective work of our working group, it could be shown that podoplanin is a reliable predictive marker for the assessment of the risk of malignant transformation. The present work was able to substantiate the assumption that podoplanin not only plays an important role in the context of malignant degeneration but also exerts a major influence in advance.

Treatment of Leukoplakia
Surgical excision of oral leukoplakia (OL) may be considered. Frequent clinical observation accompanied by photographic records is recommended.

Because of the unpredictable behaviour of dysplastic lesions, it is recommended to immediately obtain a biopsy on any areas that are suggestive or that change in appearance.

Cryotherapy ablation and carbon dioxide laser ablation are also used. The area heals rapidly, and apparently healthy mucosa is left behind. However, uncertainty remains regarding the risk of invasive carcinomas subsequently arising in sites previously treated.

Stopping smoking - if smoking or using other tobacco products, the most effective form of treatment for leukoplakia is to stop. Avoiding tobacco can cause a leukoplakia patch to slowly disappear and may also significantly reduce any risk of developing mouth cancer.

Avoiding alcohol consumption - giving up alcohol usually assists to reduce the size of a leukoplakia patch or cause it to disappear entirely. As with stopping smoking, avoiding alcohol will reduce the risk of developing oral cancer.

Wetzel, S.L. & Wollenberg, J. 2020.
"Oral potentially malignant disorders (OPMDs) are precursor lesions that may undergo malignant transformation to oral cancer. These lesions most commonly present clinically as white patches (leukoplakia). However, they may also be red (erythroplakia), or red and white (erythroleukoplakia). There are many risk factors associated with the development of an OPMD, and with the risk of malignant transformation of the lesion. A biopsy with subsequent microscopic examination from the

lesional tissue is necessary in identification of OPMD. This article reviews the clinical appearance of OPMDs, associated risk factors, diagnosis and histologic appearance, and treatment."

Bewly, A.F. & Farwell, D.G. 2017.
"Benign lesions can be observed or treated with topical therapy, and dysplastic lesions should be excised. Some risk of malignant transformation remains even after treatment, and close follow-up is required. Oral cavity squamous cell carcinoma is an aggressive malignancy that can result from malignant conversion of oral leukoplakia or occur de novo. These tumors are primarily treated with surgical resection and adjuvant radiation or chemoradiation as dictated by histopathologic findings."

Li, Y., Wang, B., Zheng, S. & He, Y. 2018.
OBJECTIVE: The aim of the present study was to systematically review the efficacy of photodynamic therapy (PDT) in the management of oral leukoplakia (OLK).
METHODS: This systematic review aimed to address the following focused question: "Is photodynamic therapy effective in the management of oral leukoplakia?'' PubMed/Medline, EMBASE, ISI Web of Knowledge, OVID, CNKI, and WANFANG DATA were searched up to and including June 2018 using different combinations of the following keywords: photodynamic therapy, leukoplakia, oral dysplasia, oral precancers, and oral premalignant lesions.
RESULTS: Sixteen studies were included in the present study. A total of 352 patients was included in this review, with age ranging from 20 to 79 years. Photosensitizers used were aminolevulinic acid, Photofrin, methylene blue, and chlorine-e6. Laser wavelength, duration of irradiation, and power density were 420 to 660 nm, 60 to 1000 seconds, and 100 to 150 mW/cm^2, respectively. On the whole, the rates of complete response and partial response were 32.9% and 43.2%, and the sum was 76.1%. The follow-up period ranged from 1 month to 119 months. The recurrence rate of OLK was 0-60%.
CONCLUSION: PDT seems to be a useful therapeutic strategy in the management of oral leukoplakia as a non-surgical treatment. Further RCTs with long follow-up period, standardized PDT parameters, and comparing efficacy of PDT with various therapies are expected to acquire definite conclusions.

Arduino, P.G., Cafaro, A., Cabras, M., Gambino, A. & Broccoletti, R. 2018.
OBJECTIVE: The purpose of this prospective analysis was to evaluate the efficacy of erbium-substituted yttrium aluminum garnet (Er:YAG) laser compared with that of conventional surgery, regarding the long-term outcome of nondysplastic oralleukoplakias (OL).
BACKGROUND: To date, this comparison has never been performed.
METHODS: Patients were randomly allocated to two different groups: some underwent surgical excision with traditional scalpel (Group TrSc) and others underwent an ablative session with Er:YAG laser (Group Las), with these modalities: 1.5-W power, 150-mJ pulse energy, 10-Hz frequency, 500-µs pulse duration, and 0.9-mm spot size. During the follow-up period, the evolution of the OL was listed as (1) healing: if novel lesions did not appear in the same place of the surgery and (2) recurrence: if a new mucosal change has been detailed in the equivalent place of the primary disease.
RESULTS: One hundred seventeen lesions were treated. Fifty-eight lesions underwent surgery with traditional scalpel, whereas 59 underwent laser surgery. Follow-up ranged from 24 to 108 months (median of 58). Healing was detailed for 52.99% (n = 62) of the 117 OL, with no statistical differences between the two randomized groups.
CONCLUSIONS: It seems reasonable to consider the Er:YAG laser as effective as traditional scalpel in terms of healing for OL, with the same rate of recurrences in a period of almost 5 years.

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