Review Article- Leukoplakia: A mysterious white patch.

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ABSTRACT:

Leukoplakia is one of the most common precancerous lesions occurring in the oral cavity and is associated with a high incidence of malignant transformation. The term leukoplakia simply means a “white patch” and it has been used in a general sense to describe any white lesion in the mouth. In this review article on Leukoplakia, early diagnosis is stressed upon for patient prognosis.

Keywords: Leukoplakia, White Patch, Tobacco, Alcohol

INTRODUCTION

More than 80% of patients with leukoplakia are being smokers. The development of leukoplakia in smokers depends on dose and on duration of use as evidenced by various prospective studies. Alcohol by itself has not been associated with leukoplakia.\textsuperscript{2} When chronically used as a recreation / in mouth rinses, in concentration greater than 25% alcohol is known to have a strong synergistic effect with tobacco relative to oral cancer and produce grayish buccal mucosal plaques.\textsuperscript{1} Persons using tooth paste / mouth rinses containing the herbal extract SANGUINARIA cause leukoplakia it is also known as Sanguinaria associated keratosis. Leukoplakia of lower lip vermilion is usually associated with actinic radiation.\textsuperscript{3} Leukoplakia is defined as a raised white patch of the oral mucosa measuring 5mm or more, which cannot be scraped off and which cannot be attributed to any other diagnosable disease.\textsuperscript{4} WHO, 1971

“A white patch or plaque that cannot be characterized clinically or pathologically, as any other disease”. – WHO 1978

“Leukoplakia is a whitish patch or plaque that cannot be characterized, clinically or pathologically, as any other disease and it is not associated with any physical or clinical causative agent except the use of tobacco”. (Axell et al 1983).

“Oral Leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion, some oral leukoplakias will transform into cancer” (Axell et al 1996).
A predominantly white lesion that cannot be characterized clinically or pathologically as any other definable lesion. Pindborg et al., 1997 (WHO).

**Mechanism of tobacco carcinogenesis:**
Carcinogenic agents act locally on keratinocyte stem cell, and are absorbed and act in many other tissue in the body. They produces DNA adducts, principally 0-6-methylguanaine, and these interfere with the accuracy of DNA replication, leading to mutation which thus contribute to the molecular chain of events leading to malignant transformation of a cell and its clonal derivatives. There is damage to all replicating cells, including those of the immune response.  

**Mechanism of alcohol in oral cancer**
Ethanol increases the permeability of the oral mucosa to water itself and to many water soluble molecules, probably including important carcinogenesis. It also implies a solvent action of ethanol on keratinocyte membrane with likely enhanced penetration of carcinogens into proliferating cells where they may exert a direct mutagenic action.

**CLASSIFICATION AND STAGING SYSTEM FOR ORAL LEUKOPLAKIA:**
The purpose of classification staging system is necessary for uniform reporting of lesions, communication, treatment plan and monitoring treatment during followup

1) **Pindborg J.J. et al and Schepman et al 1997.**
In this classification the size of the leukoplakia (L), the oral sub site (S) (high-risk sites vs. non-high-risk sites), clinical sub classification (C) (homogeneous vs. non-homogeneous) and degree of epithelial dysplasia (P) as assessed by histopathologic examination were taken into account.

L (Provisional): When on clinical examination, the lesion cannot be clearly diagnosed as any other disease of OMM with a white appearance.

L (Definitive): Is made as a result of the identification, and if possible elimination, of suspected etiologic factors and in the case of persistent lesion, histopathologic examination.

**Modified classification and staging system for leukoplakia:**

van der Waal et al 2000

It is a modification of the earlier classification. Apparently, there is room for improvement of this classification and staging system. For instance, the subdivision in sizes was not incorporated in the final staging of the leukoplakia. Furthermore, the subdivision in the classification system into high-risk and non-high-risk oral subsites seems somewhat questionable. In some parts of the world the floor of the mouth and borders of the tongue are considered high-risk sites, while in other parts, particularly in India, the cheek mucosa is more a risk. Finally, it is well recognized that clinically non-homogeneous leukoplakias in general
carry a greater risk of malignant transformation than the homogeneous one, which is largely due to the presence of epithelial dysplasia. If the assessment of the presence and degree of epithelial dysplasia is already incorporated in the staging system, the clinical sub typing is more or less redundant.

In view of the above, it seems possible to simplify the classification and staging system by applying only two categories, being: (1) size of the leukoplakia; and (2) pathology, focusing on the absence or presence of epithelial dysplasia.

The classification and staging system thus modified for oral leukoplakia (OLEP) is as follows;

**L - SIZE OF THE LEUKOPLAKIA**

- L1 - Size of single or multiple leukoplakias together < 2 cm
- L2 - Size of single or multiple leukoplakias together 2±4 cm
- L3 - Size of single or multiple leukoplakias together >4 cm
- Lx - Size not specified

**P - PATHOLOGY**

- P0 - No epithelial dysplasia
- P1 - Distinct epithelial dysplasia
- PX - epithelial dysplasia not specified in the Pathology report

**STAGING SYSTEM**

- Stage I - L1P0
- Stage II - L2P0
- Stage III - L3P0 or L1L2P1
- Stage IV - L3P1

Vander Wall, et al, 2000

**CLINICAL CLASSIFICATION**

**Homogenous leukoplakia:** a predominantly white lesion of uniform flat, thin appearance that may exhibit shallow cracks and has smooth, wrinkled or corrugated surface with a consistent texture throughout.

**Nonhomogenous leukoplakia:** a predominantly white or white and red lesion that may be irregularly flat, nodular or exophytic.

**Erythroplakia:** the term erythroplakia is used analogously to leukoplakia to designate lesions of oral mucosa that present as red areas and can not be diagnosed as any other definable lesion.

**Clinical features:** it is more common in males and usually affects person older than 40 years of age. 70% of lesions occur in the buccal mucosa followed by vermilion border of lower lip and gingiva. It is less...
common in palate, retro molar area, floor of the mouth, tongue 90% cases in floor of the mouth and tongue show dysplasia or carcinoma. On C.E., patches of leukoplakia vary from a non-palpable, faintly translucent white area to thick, fissured papillomatous indurated lesion. The surface of the lesion is often finely wrinkled / shrieveled in appearance and rough on palpation.

Sharp described 3 stages of leukoplakia

1st stage: Non palpable, faintly translucent white discoloration.

2nd stage: Localized / diffuse slightly elevated plaque of irregular outline which appear white and have a fine granular texture.

3rd stage: Thick white lesions with induration fissuring and ulceration.

CLINICAL SUBTYPES

Homogenous Leukoplakia

Non-Homogenous Leukoplakia

   Nodular / Speckled Leukoplakia
   Verrucous Leukoplakia

**Homogenous Leukoplakia**: Refers to a usually well-defined white patch, localized or extensive that is slightly elevated and has a fissured, wrinkled or corrugated surface which appear leathery to dry, or cracked mud like on plapation.

**Nodular or Speckled Leukoplakia**: It is a granular or non-homogenous patch in a mixed red and white appearance due to distribution of keratotic white nodules or patches over an atrophic erythematous background. It has higher malignant transformation rate

**Verrucous Leukoplakia**: It is characterized by the presence of thick white lesions with papillary surfaces in the oral cavity which are heavily keratinized and are most often seen in older adults in 6th to 8th decade of life. Some of these lesions may exhibit an exophytic growth pattern.

**Proliferative Verrucous Leukoplakia**: PVL is a very high risk precancerous lesion with a high mortality rate. This destructive form of oral Leukoplakia was first described and named as PVL by Hansen et al (1986) after a long term study of 30 patients with this disease.

It was named PVL since the case reviewed seemed;

To origin in flat, white keratotic patches, histologically simple hyperkeratosis without dysplasia - **Leukoplakia**

Because in all cases, over a period of time, warty, vesicle, exopytic, keratotic lesions develop in areas of leukoplakia - **Verrucous**.
Because the cases, although slow growing, were persistent, progressive, diffuse and multifocal - *Proliferative*.

**INVESTIGATIONS:**

**DIAGNOSIS:**

History and clinical examination

Chair side investigations

Conventional

Advanced

Laboratory investigations

Conventional

Advanced

**CHAIR SIDE INVESTIGATIONS:**

**Conventional**

1) **Intravital Staining** - Toludine blue and Lugol’s iodine

Toludine blue is an acidophilic metachromatic dye which selectively stains dysplastic and malignant lesions. It stains acid components in DNA and RNA which are more in dysplastic cells. It helps directing and selecting the site of biopsy.

**PROCEDURE:** 1% acetic acid is applied on the lesion for 2 second and is rinsed with water followed by 1% Toludine blue application for 10-20 seconds and decolorized with 2% acetic acid for 20-30 seconds.

A study was conducted on reliability of toludine blue application in detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinoma in 1993 sensitivity of the staining was 77%, the specificity 67%

A study was done over a period of 3 years. In this study sensitivity was found to be 97.29% and specificity was 62.5%.

**ADVANTAGES:**

Low cost

Simple technique

Non-invasive

Relatively accurate
DISADVANTAGES:
False positive results
It is known to induce Mutagenicity
The false positive results can be overcome by the use of Lugol’s Iodine with Toluidine blue. Lugol’s iodine binds to glycogen present in normal epithelium and produces a brown black stain whereas, toluidine blue stains dysplastic lesions.

2) Exfoliative Cytology:
It is an adjunct to Biopsy and Offers microscopic study of cells obtained from the surface of an organ or lesion after suitable stains. The neoplastic cells are less cohesive than normal cells and usually shed on the surface of lesion or into the section.

ADVANTAGES:
Quick, painless, simple and non-invasive.
Helps in screening large samples

ORAL BRUSH BIOPSY:
It makes use of a cytobrush with firm bristles that obtain individual cells from full thickness of the stratified squamous epithelium. It is significantly more accurate than other cytologic technique used in the oral cavity.

Treatment: Homogenous Leukoplakia
Patient education & motivation
Identification & removal of any predisposing factors.
Anti-fungal agents - 2 weeks may reduce lesion size.
Periodic observation.
Increase in lesion size / change in appearance indicates need for histological examination.
Dysplastic changes indicate surgical removal and long term follow-up.

Treatment: Speckled /Verrucous Leukoplakia
Patient education & motivation
Identification and removal of any predisposing factors.
Histological examination.
Dysplastic changes indicate surgical removal and long term follow-up.
Non-dysplastic lesions may be treated similar to homogenous variety.
PROGNOSIS:
Overall 4 to 5% of oral leukoplakias become S.C.C which varies from months to decades (5-20 years) which depends on various factors.\textsuperscript{10}

REFERENCES
1. Text book of oral pathology Shafer’s Hine Levy 5\textsuperscript{th} edition
2. Oral & maxillofacial pathology Neville Damm Allen Bouquot 2\textsuperscript{nd} edition.
5. Robbins Pathologic basis of diseases, Cortran, Kumar Robbins 5\textsuperscript{th}.
7. Advanced methods in the evaluation of premalinant lesions and carcinomas of oral mucosa, journal of oral pathology 1985: 14, 751-778