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LEUKOPLAKIA- A COMPREHENSIVE CLINICO-PATHOLOGICAL REVIEW

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ABSTRACT

Leukoplakia, one of the most common potentially malignant disorder of the oral mucosa, usually presents whitish patch over the oral mucosa. The term 'Leukoplakia' is a clinical term only, when biopsy is taken the term leukoplakia should be replaced by the diagnosis obtained histopathologically. The malignant transformation rate varies in different parts of the world, as a result of differences in tobacco & dietary habit and genetic mutations. The management of oral leukoplakia depends on their types, varies from "wait and see" attitude and topical chemopreventive agents to complete surgical removal. In this article, we have reviewed the literature to provide comprehensive update on leukoplakia.

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INTRODUCTION

Precancerous lesion is defined by the World Health Organization (1978) as "a morphologically altered tissue in which cancer is more likely to occur than its normal counterpart"[1]. Oral precancerous lesions are relatively common, occurring in about 2.5% of the general population and are important target for cancer prevention[2]. At a workshop coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer in the UK: The term, "potentially malignant disorders' was recommended to refer to precancer as it conveys that not all disorders described under this term may transform into cancer[2].

Potentially malignant disorders include

- Leukoplakia
- Erythroplakia
- Oral Submucous Fibrosis
- Oral Lichen Planus.
- Palatal changes among reverse smokers.

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The most commonest potentially malignant disorder of the oral mucosa is Oral Leukoplakia (OL). Oral Leukoplakia was defined in 1997 by WHO as *"A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion"*[3]. Oral Leukoplakia usually affects individuals older than 40 years of age, especially males. Approximately 70% of all OL cases are found on buccal mucosa, gingiva, tongue, floor of the mouth and lip. This disease has varied clinical presentation ranging from slightly elevated gray-white plaques, with fissured, or wrinkled surface & sharply demarcated borders to grayish white plaques interspersed with erythematous areas [3].

The most common etiological factors associated with OL are

- Tobacco (smoke and smokeless)
- Alcohol
- Candida albicans
- Viral antigens (HPV strains 16, 18)
- Levels of Vit A, B12, C, beta-carotene, folic acid and syphilis are associated[4].

The incidence of this lesion varies from 1.3 to 2.1 per 1000 individuals in India but the prevalence of this lesion in India was found to be about 17 per 1000 tobacco users[4].

Microscopically Oral Leukoplakia is characterized by hyperkeratotic surface epithelium with or without thickened spinous layer (acanthosis). The striking feature is the presence of varying degrees of epithelial dysplasia characterized by both cellular and nuclear atypia. The sub epithelial fibro vascular connective tissue usually reveals varying degrees of nonspecific inflammatory changes[5]. Genetic mutations often produce early phenotypic changes that may present as clinically apparent, recognizable lesions. An oral premalignant lesion is an area of morphologically or genetically altered tissue that is more likely to develop cancer than normal one. The reported rates of malignant transformation of leukoplakia range from less than 1% to 18%[6]. Cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs.There are about 8.8 million people worldwide who died from cancer in 2015, that is nearly 1 in 6 of all global deaths[7]. Oral Squamous Cell Carcinoma (OSCC) is the most common malignancy affecting the oral cavity and oropharynx constituting approximately 95% of all oral malignancies[8]. Despite the variation in the incidence rate in various parts of the world, the highest incidence is in the Indian subcontinent[9]. The strongest risk factors for developing this form of cancer are tobacco use (including smoking or using chewing tobacco) and heavy alcohol consumption. In addition, studies have shown that infection with certain strains of human papillomavirus (HPV) is linked to the development of this disease process[10].

OSCC is predominant mostly after fourth decade of life and commonly affects the postero- lateral and ventral surface of the tongue, floor of the mouth, soft palate, gingiva, buccal mucosa[11]. It usually presents as an ulceroproliferative, exophytic or endophytic growth associated with rolled margin & indurated borders associated with the presence of surface granularity or nodularity. Regional lymph nodes are enlarged, often metastasize[5]. Microscopically, the degree of differentiation is evaluated on the basis of the extent of resemblance of the lesional cells to that of normal squamous epithelium and can be divided into well differentiated, moderately differentiated and poorly differentiated squamous cell carcinoma[12]. The prognosis of OSCC is assessed through biopsy followed by histopathological examinations. It is characterized by actively proliferating neoplastic epithelial cells which may invade into the sub-epithelial connective tissue. These cells show eosinophilic cytoplasm with large hyperchromatic nuclei and an increased nuclear to cytoplasmic ratio, varying degrees of cellular and nuclear pleomorphism and keratin pearl formation[12]. Oral Squamous Cell Carcinoma are thought to be initiated and progress through a series of genetic alterations and several cellular signaling pathways are dysregulated through genetic & epigenetic alteration, such as those involving TP53, CDK2NA, NOTCH1[13]. The most intensely involved gene in carcinogenesis is tumor suppressor gene called p53 and it is the most commonly mutated locus in human cancer, located on the short arm of chromosome 17[14]. Its biological role is to protect cells from DNA damage caused by Carcinogen, radiation or other mechanisms. P53 does this either by arresting the cell cycle so that DNA repair can occur or by inducing apoptosis[15]. It seems clear that mutation of the p53 gene is one of the most common abnormalities in Head & Neck Squamous Cell carcinoma (HNSCC) and frequency approximately 30-70%. Tumors with mutation of p53 gene grow faster and have a worse prognosis[16].

REVIEW OF LITERATURE: Literature was thoroughly reviewed in light of genetic mutations in OSCC and Oral Leukoplakia compared to normal oral mucosa along with the malignant potentiality of leukoplakic lesions.

NORMAL ORAL MUCOSA: The term mucous membrane" is used to describe the moist lining of the oral cavity, gastro-intestinal tract, nasal passages, pharynx and other body cavities that communicate with the exterior. In the oral cavity this lining is known as the „oral mucous membrane or oral mucosa" (Ten Cates oral histology 5th edition, 1998)[17]. The exterior of body has a dry covering, the skin, which is continuous with oral mucosa at the lips. Structurally, the oral mucosa resembles skin in some respect and similar to the mucous membrane of oesophagus, cervix, vagina but totally different from gastrointestinal tract. Despite these differences, skin and different types of mucosa all consists of two structurally different tissue components: a covering epithelium and underlying connective tissue (Christopher squier *et al* 2011)[18].

ORAL LEUKOPLAKIA: Precancerous lesion is defined by the World Health Organization (1978) as "a morphologically altered tissue in which cancer is more likely to occur than its normal counterpart" (Pindborg JJ *et al* 1978)[19]. Oral leukoplakia (OL) is the most frequent potentially malignant disorder of the oral mucosa. Although OL is mentioned in clinical reviews since 1969(Sugar L *et al* 1969)[20], the first international conference on OL (1984) Malmo, Sweden, described leukoplakia as "A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except the use of tobacco (E. B. Kayalvizhi *et al* 2016)[21].

In 2007 it was decided that the name of leukoplakia should be limited only to a clinical diagnosis, defined by exclusion of other white lesions such as oral lichen planus , white sponge nevus, nicotine stomatitis, leukoedema etc(Warnakulasuriya *et al*. 2007)[22]. In 2012 Van der Waals proposed a new definition which seems more opportune as it includes the histological confirmation "A predominantly white lesion or plaque of questionable behaviour having excluded clinically and histopathologically, any other definable white disease or disorder"(Brouns E *et al*. 2012)[23].

EPIDEMIOLOGY

The incidence and prevalence of oral leukoplakia is different in different countries depending on the ethinicity & tobacco habits. Petti S (2003) estimated the prevalence rate of oral leukoplakia in 2003 and observed that it varied between 1.7 to 2.7% in general population[24]. According to Shafer G. *et al*, 2006, the incidence of the lesion varied from 1.3 to 2.1 per 1000 individuals in different parts of India depending on the types of tobacco habits but the prevalence of the lesion in the country was found to be 17 per 1000 tobacco users(Shafer G *et al*. 2006)[25].

ETIO-PATHOGENESIS

The etiology of leukoplakia is considered by most investigators to be varied one. Factors most frequently blamed have been tobacco, alcohol, oral sepsis, local irritation, syphilis, vitamin

deficiency, endocrine disturbances, galvanism, actinic radiation and viral infection. According to review by Mehta *et al*.1961, pindborg *et al*.1967, Wahi *et al* 1970, Peterson *et al* 1972, Gupta *et al* 1980, Warnakulasuriya S *et al* in 2005, the etiology of Oral Leukoplakia is considered as multifactorial, but smoking is appreciated to be the most frequently involved factor. It is much more common among smokers than non smokers [26]. Axell T *et al* in 1994 conducted a study and reported alcohol is thought to be an independent risk factor but definitive data are still lacking (Axéll T *et al*, 1994)[27]. Trauma and chronic irritation have also been considered to be important in the etiology of leukoplakia (Shafer *et al* 2008)[28]. Many studies have reported the presence of Human Papilloma Virus (HPV) DNA in oral leukoplakias. However, there is not enough evidence to prove any casual association between HPV and the development of oral leukoplakia as published by Feller *et al* in 2012[29].

CLINICAL FEATURES

Study was conducted by Mehta *et al* in 1969, Peterson & Pindborg in 1973, Bhonsle *et al* in 1976, Bancozy *et al* in 1982, Salem *et al* in 1984, Murti *et al* in 1990, Rajendran R in 2004, and they stated that the onset of leukoplakia usually takes place after the age of 30years and resulting in a peak incidence above the age of 50 years[30]. The gender distribution varies, ranging from a strong male predominance in different parts in India, to almost 1: 1 in the western world (Mehta *et al*.1969, Roed-Peterson and Pindborg in 1973, Bhonsle *et al*.1976, Gupta *et al* 1980, Salem *et al*.1984, Rajendran R *et al*, 2004; Leu *et al*, 2010)[31].

Various authors like Hirayama *et al* in 1966, Murti *et al* in 1990, Warnakulasuraya *et al* in 2001, Kannan S *et al* in 2005 opined that leukoplakia is commonly seen on lips, buccal mucosa, tongue and gingiva. The site varies with the form of tobacco habit; like in beedi smokers the site is anterior buccal mucosa whereas in patients who chew tobacco the lesion is seen on the posterior buccal mucosa[32]. Clinical manifestations of oral leukoplakia can take different forms according to the clinical pattern (homogenous or nonhomogenous), distribution or spread of the lesion (focal or disseminated) and location within the oral cavity (Smith CJ *et al*, 2006)[33].

Clinical presentation

Various authors have reported that Oral Leukoplakia has a various clinical appearance which is given below.

- Homogenous Pattern- The homogenous pattern refers to lesions with a regular, smooth, whitish surface and well-defined edges (Figure-3.2). This clinical pattern shows a low risk of long-term malignant transformation (5%) (E. B. Kayalvizhi *et al*, 2016; WHO 1980)[34].
- Brouns *et al*. (2013) found that 52.7% had homogeneous leukoplakia and 47.27% cases had non-homogeneous leukoplakia.
- Non homogenous Pattern- The nonhomogenous pattern includes leukoplakias that are associated with an erythematous component (erythroleukoplakia)(Figure-3.3) or a nodular(Figure-3.4), erosive, ulcerated, or verrucous leukoplakia(Figure-3.5) (Silverman *et al*. 1984; Lind P *et al*. 1987;Gupta *et al*; 1989; Reibel J.*et al*. 2003)[35].

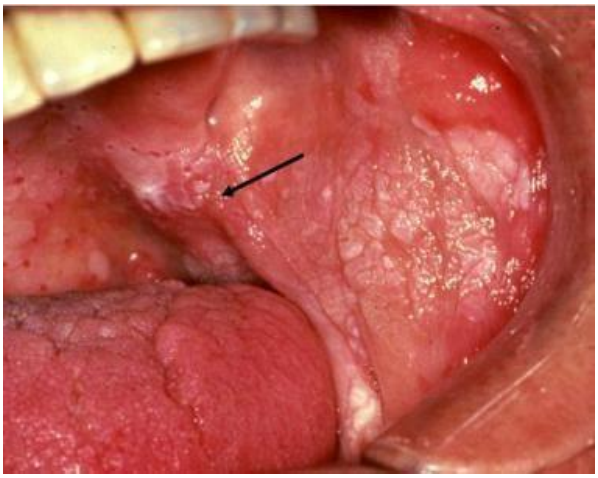

Figure2.1: Clinical photograph showing the presence of Erythro-Leukoplakia

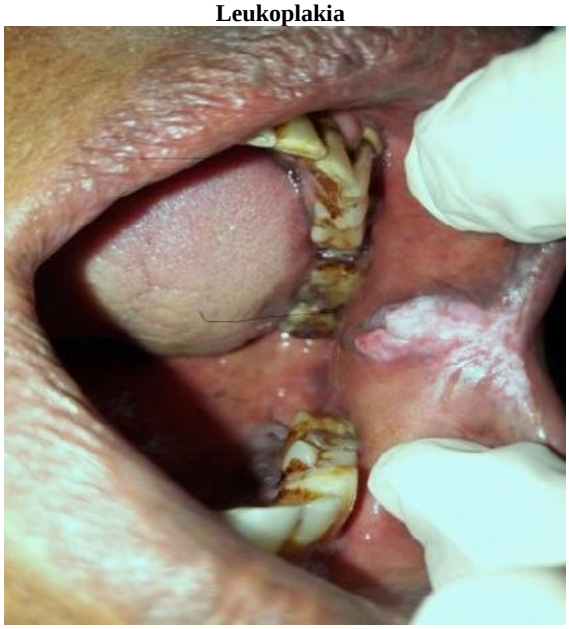

Figure 2.2: clinical photograph showing the presence of Nodular Leukoplakia

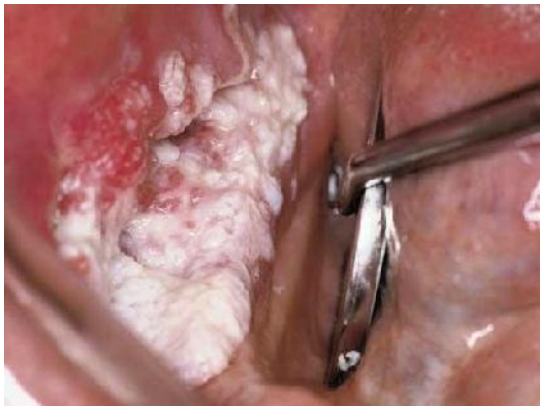

Figure 2.3: Clinical photograph showing the presence of Verrucous Leukoplakia

proliferative verrucous leukoplakia- It is currently considered as an independent entity from the set of leukoplakias which is associated with a higher risk of malignant transformation (Figure-3.6); as many as 80% may become malignant (Pindborg JJ *et al*.1989; Hansen LS *et al*. 1985)[36]. According to Slootweg and Müller *et al* (1983), the coexistence or subsequent development of squamous cell carcinoma or

epidermal dysplasia was detected in 63% of a series of 27 patients with proliferative verrucous leukoplakia. Those authors concluded that this variant of leukoplakia is a clear precursor of carcinoma[37].

Clinical classification: Others classification of leukoplakia includes[38]:

- Mehta *et al* 1971:Homogenous, Ulcerated and Nodular leukoplakia
- WHO in 1980: Homogeneous and Non Homogeneous
- Banoczyin1982: Leukoplakia-simplex, Leukoplakiaverrucosa, Leukoplakiaerosiva.
- WHO in 2002:

Phase I: thin, smooth leukoplakia – better prognosis. Phase II: thick, fissured leukoplakia. PhaseIII: Proliferative verrucous Leukoplakia(PVL)-higher malignant transformation rate.
Phase IV: Erythroleukoplakia- poor prognosis

HISTOPATHOLOGICAL FEATURES

Microscopically Oral leukoplakia(OL) is characterized by hyperkeratotic surface epithelium with or without thickened spinous cell layer (acanthosis). The most striking feature is the presence of varying degrees of epithelial dysplasia characterized by both cellular and nuclear atypia. The sub epithelial fibro vascular connective tissue usually reveals varying degrees of non-specific inflammatory changes. The combination of cellular and architectural changes observed in the gradual transition to malignancy is termed as „Epithelial Dysplasia"[39]

Individual cell alterations found in epithelial dysplasia include the following:

- Enlarged Prominent nucleoli
- Hyperchromatic nuclei (hyperchromasia)
- Nuclear pleomorphism
- Altered nuclear cytoplasmic ratio
- Increased mitotic activity
- Abnormal mitotic index
- Multinucleation of cells

Architectural alterations include combinations of the following.

- Formation of bulbous rete pegs
- Basilar hyperplasia
- Hypercellularity

Altered maturation pattern of keratinocytes (Martorell–calatayud *et al*, clinical dermatology, 2007).

Degree of severity of epithelial dysplasia can be graded into three types:

- Mild epithelial dysplasia -when the architectural disturbances is limited to the lower third of the epithelium with minimal cellular atypia.
- Moderate epithelial dysplasia–when the architectural disturbances extending into the middle third of the epithelium but does not extending upper third of the epithelium in association with marked cellular changes.
- Severe epithelial dysplasia – In severe degree dysplasia starts with greater than two-thirds the architectural disturbances of the epithelium associated with marked cellular atypia[40].

HISTOPATHOLOGICAL GRADING SYSTEMS

Various grading systems of dysplasia are as follows (Prabhu SR *et al*)[41]

- **Smith and Pindborg grading system (1969):** no dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia.
- Conventional grading system: mild dysplasia, moderate dysplasia, severe dysplasia and carcinoma in situ.
- Ljubljana grading system (Zoedner, 2003): simple hyperplasia, abnormal hyperplasia, atypical hyperplasia, carcinoma in situ.
- WHO system (2005): Mild, Moderate, Severe and carcinoma in situ.

CLINICAL STAGING

A proposal for a modified classification and staging system for oral leukoplakia (OL) was stated by Van der Waal *et al* 2000 in which the size of the leukoplakia and the presence or absence of epithelial dysplasia were taken into account. Altogether four stages are recognized[42.]

(L- Size of leukoplakia)
L1-size of leukoplakia is < 2cm L2 -size of leukoplakia is 2- 4 cm L3-size of leukoplakiais>4cm
Lx- size of leukoplakia is not specified.
(P -Pathology)
PO- No epithelial dysplasia
P1 –Distinct epithelial dysplasia
Px –Dysplasia not specified in pathology report

OLEP Staging System Stage I -L1 PO
Stage II -L2PO
Stage III -L3 PO or L1 L2 PI
Stage IV -L3 P 1

MALIGNANT TRANSFORMATION RATE: Various researches have reported that the rates of malignant transformation of oral leukoplakia range from 0.13 to 17.0% (Mitra S *et al*.2005)[43]. The estimated overall (mean) malignant transformation rate amounts to 3.5% with a wide range between 0.13%- 34.0% as reported by Warnakulasuriya S *et al*. in 2015[44].

Management: The main objective in oral leukoplakia's management of care is to detect and to prevent malignant transformation arising in the lesion.. At the first, the ceasing of the risk activities such as smoking is recommended or cessation of tobacco followed by observation of the lesion. Further, the histopathological evaluation is needed in case of advance lesion. The degree of dysplasia will guide the choice of the treatment. Oral leukoplakia presenting low malignant risk (no dysplasia or simple displasia) may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation[45]. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended[46].

The medical treatment uses local and systemic chemopreventive agents such as vitamin A and systemic beta carotene, lycopene (a carotenoid), local bleomycin, and a mixture of tea used both topically and systemically with a reduced benefit[47]. Other possible choice is an attitude of "wait and see" to keep oral leukoplakia under clinical and histological surveillance with frequent multiple visits and biopsy without other treatment. This follow-up can observe an early malignant transformation of the disease and subsequent specific treatment[48].

CONCLUSION

Most of the cancers develops from the potentially malignant disorders. It can be prevented if diagnosed at early stages. The role of dental surgeon, Oral Pathologist or general practitioner is important in the early diagnosis when leukoplakia is usually aymptomatic. The proper understanding, diagnosis & differentiating these lesion and thorough knowledge about the potentiality of malignant transformation of these lesion will ensure proper treatment & save a life of patient.

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