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RESEARCH ARTICLE

THE WARNING SIGN OF PREMALIGNANCY LEUKOPLAKIA- A REVIEW.

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Abstract

The most commonly encountered and accepted precancerous lesions in the oral cavity are leukoplakia,OSMF,Lichen planus. Oral leukoplakia causes no great discomfort, and it is rarely disfiguring.It is undiagnosed by patient and neglected by many clinician.Investigation and treatment of leukoplakia helps to prevent the patient from turning into malignancy.

Introduction:-

The most commonly encountered and accepted precancerous lesions in the oral cavity are leukoplakia and erythroplakia.[1] Since the term leukoplakia was introduced by Schwimmer in 1877 it has been applied in many different ways. The most important variation is between those who use it in a clinical sense alone, and those who restrict the term to lesions that show, histologically, a significant degree of epithelial dysplasia: in other words, to lesions that presumably are more likely to become malignant[2] .Commonly, oral leukoplakia causes no great discomfort, and it is rarely disfiguring. Therefore, our main concern about this condition arises from the well-established observation that about 4% of patients with leukoplakia ultimately develop squamous cell carcinoma within the area of leukoplakia (Pindborg 1971), this progression often being on a very long time scale. However, this general figure conceals many variations, and special reference should be made to leukoplakia associated with the use of tobacco. [2]. The site of involvement may also have a marked influence on the risk of malignant change. Of all leukoplakias, those of the floor of the mouth and the ventral surface of the tongue, and especially leukoplakia confined to those areas, seem to carry a very high risk of malignant change.[2].

Defination:-

WHO (1978): "A white patch or plaque that cannot be characterized clinically or pathologically as any other disease".

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Warnakulasuriya et al.(1978): "Leukoplakia should be used to recognize white plagues of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer".

First International Conference on oral leukoplakia. Malmo, Sweden : " 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 use of tobacco".

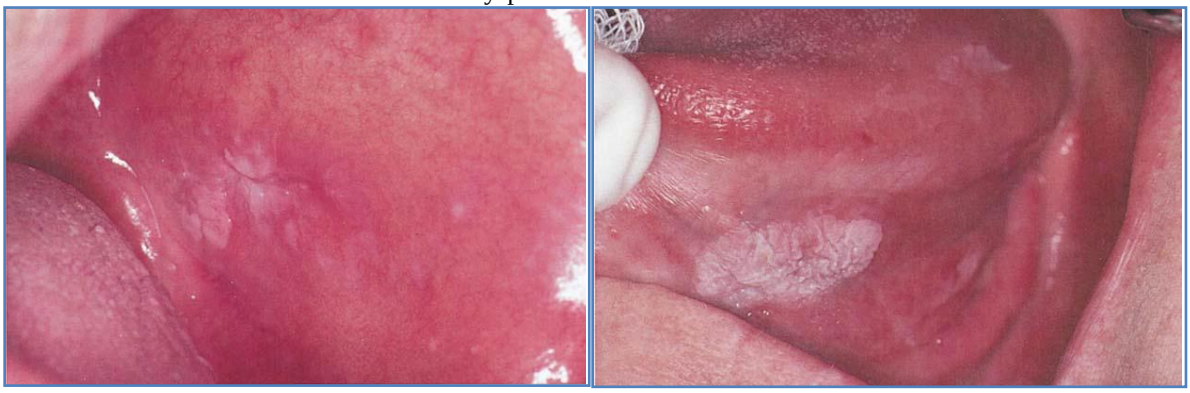
Etiology:-
A number of locally acting etiologic agents, includes: Tobacco**,** Alcohol**,** Candidiasis**,** Electrogalvanic reactions**,** Herpes simplex and Papillomaviruses, Sunlight (specifically, ultraviolet radiation).

These have been implicated as causative factors for leukoplakia. True leukoplakia is most often related to tobacco usage; more than 80% of patients with leukoplakia are smokers. The development of leukoplakia in smokers also depends on dose and on duration of use, as shown by heavier smokers' having a more frequent incidence of lesions than light smokers. Cessation of smoking often results in partial to total resolution of leukoplakic lesions.

Smokeless tobacco is also a well-established etiologic factor for the development of leukoplakia; however, the malignant transformation potential of smokeless tobacco–induced lesions is much lower than that of smoking-induced lesions.

Alcohol consumption alone is not associated with an increased risk of developing leukoplakia, but alcohol is thought to serve as a promoter that exhibits a strong synergistic effect with tobacco, relative to the development of leukoplakia and oral cancer. In addition to tobacco, several other etiologic agents are associated with leukoplakia. Sunlight (specifically, ultraviolet radiation) is well known to be an etiologic factor for the formation of leukoplakia of the vermilion border of the lower lip. *Candida albicans* is frequently found in histologic sections of leukoplakia and is consistently (60% of cases) identified in nodular leukoplakias but rarely (3%) in homogeneous leukoplakias. The terms "candidal leukoplakia" and "hyperplastic candidiasis" have been used to describe such lesions. Human papillomavirus (HPV), particularly subtypes HPV-16 and HPV-18, have been identified in some oral leukoplakias. there is evidence that HPV-16 may be associated with an increased risk of malignant transformation.[3]

Clinical features:-
The incidence of leukoplakia varies by geographic location and patients' associated habits. For example, in locations where smokeless tobacco is frequently used, leukoplakia appears with a higher prevalence . Leukoplakia is more frequently found in men, can occur on any mucosal surface, and infrequently causes discomfort or pain. Leukoplakia usually occurs in adults older than 50 years of age. Prevalence increases rapidly with age, especially for males, and 8% of men older than 70 years of age are affected. Approximately 70% of oral leukoplakia lesions are found on the buccal mucosa, vermilion border of the lower lip, and gingiva.[1] They are less common on the palate, maxillary mucosa, retromolar area, floor of the mouth, and tongue. However, lesions of the tongue and the floor of the mouth account for more than 90% of cases that show dysplasia or carcinoma.



Homogenous leukoplakia on left buccal mucosa & lateral border of tongue

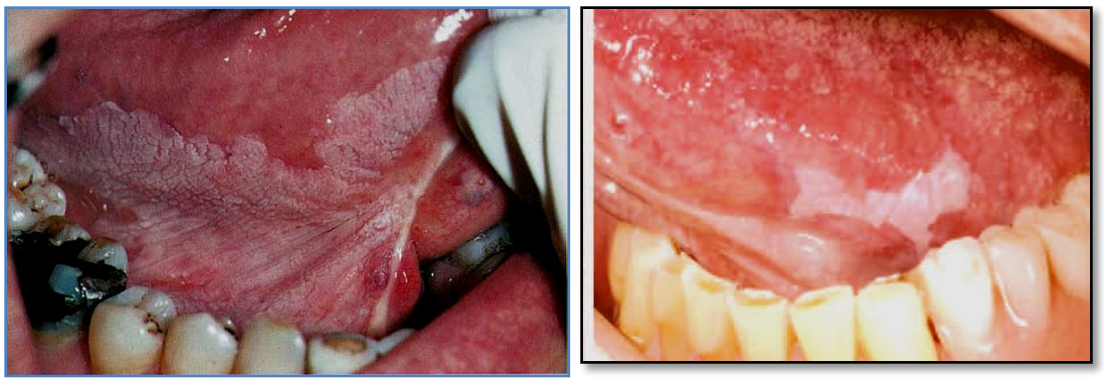


Figure:- Diffuse leukoplakia on floor of mouth and left lateral border of tongue

Clinical Subtypes:-
Many varieties of leukoplakia have been identified.
"Homogeneous leukoplakia" (or "thick leukoplakia") refers to a usually well-defined white patch, localized or extensive, that is slightly elevated and that has a fissured,wrinkled, or corrugated surface. On palpation, these lesions may feel leathery to "dry, or cracked mud-like."

Non homogenous varity includes:
Nodular (speckled) leukoplakia which is granular in nature. The name refers to a mixed red-and-white lesion in which keratotic white nodules or patches are distributed over an atrophic erythematous background. This type of leukoplakia is associated with a higher malignant transformation rate, with up to two-thirds of the cases in some series showing epithelial dysplasia or carcinoma.

"Verrucous leukoplakia" or "verruciform leukoplakia" is a term used to describe the presence of thick white lesions with papillary surfaces in the oral cavity. These lesions are usually heavily keratinized and are most often seen in older adults in the sixth to eighth decades of life. Some of these lesions may exhibit an exophytic growth pattern.

Proliferative verrucous leukoplakia (PVL) was first described in 1985. The lesions of this special type of leukoplakia have been described as extensive papillary or verrucoid white plaques that tend to slowly involve multiple mucosal sites in the oral cavity and to inevitably transform into squamous cell carcinomas over a period of many years. PVL has a very high risk for transformation to dysplasia, squamous cell carcinoma or verrucous carcinoma .Verrucous carcinoma is almost always a slow growing and well-differentiated lesion that seldom metastasizes.

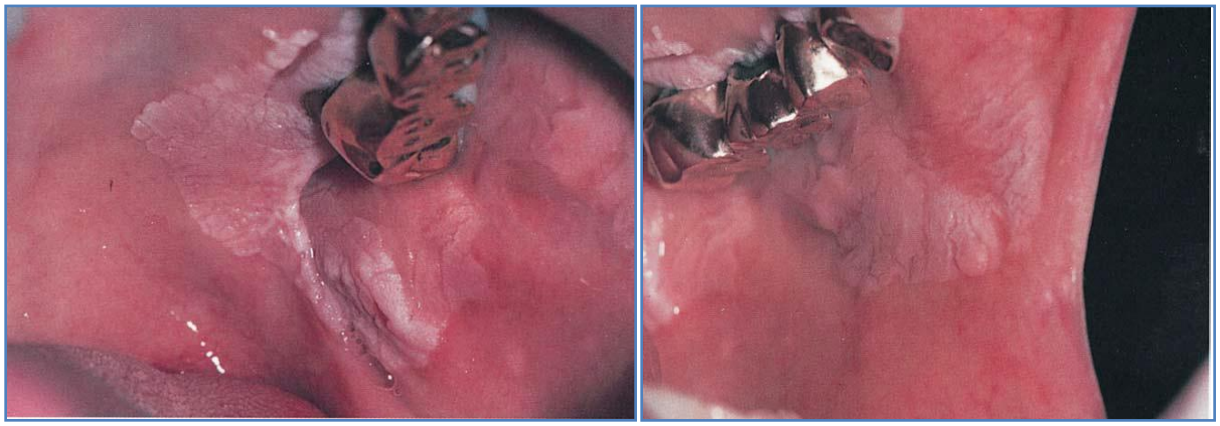


Figure:- Proliferative verrucous leukoplakia (PVL)

Leukoplakia begins as thin, gray, or gray white plaque that may appear some what fissured or wrinkled, & are typically soft & flat. They usually have sharply demarcated borders but occasionally blend gradually into normal mucosa.

This early stage is sometimes referred as '**preleukoplakia**' but preferable designated **'Mild or thin leukoplakia'**. Thin leukoplakia may disappear or continue unchanged but as time progress as many as two thirds of such plaques slowly extend laterally & acquire a distinctly white appearance from a thick keratinized layer. They may become leathery to palpation & fissures may deepen, but there should be only a few, if any, localized nodule or surface projections. At this stage the lesion is severe often called 'homogenous or thick leukoplakia'. [4,5]

L C P STAGING: (L - size C - Clinical P – Pathological:-
Recently the Leukoplakia was graded according to size, clinical and pathological stages it is known as LCP Stagging :
L x = Size not specified, L 1 = Less than 2cm, single/ multiple, L 2 = 2 to 4 cm, single/ multiple
L 3 = More than 4cm, single/ multiple, C 1 = Homogenous,C 2 = Non homogenous
P x = Not specified, P 0 = No epithelial dysplasia,P 1 = Distinct epithelial dysplasia

	Pathological	**Clinical**
STAGE 1	L1 P0	L1 C1
STAGE 2	L2 P0	L2 C1
STAGE 3	L3 P0	L3 C1
STAGE 4	L3 P1	L3 C

I**nvestigations:-**
The following investigation should be done to detect the lesion which includes biopsy, toluidine blue (tolonium chloride.), lugol's iodine solution, punch biopsy, exfoliative cytology, brush biopsy, chemiluminiscent illumination.

Histopathology:-
Specific microscopic characteristics of dysplasia include:
Drop-shaped epithelial ridges, Basal cell crowding, Irregular stratification, Increased and abnormal mitotic figure, Premature keratinization,Nuclear pleomorphism and hyperchromatism, and An increased nuclear cytoplasmic ratio. [4,5]

Treatment:-
Nonsurgical treatments (Medical management) options for oral leukoplakia :
Carotenoids:-
Beta-Carotene : The carotenoids are a group of extremely hydrophobic molecules with little or no solubility in water . Beta-carotene is a carotenoid commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges . Beta-carotene is a vitamin A precursor. The only known effect of excessive beta-carotene intake is a state in which the skin becomes strongly yellowish, the so-called carotenodermy, which disappears in a few weeks after the reduction of consumption. While some authors have demonstrated the absence of side effects in patients that have received beta-carotene treatment, in other studies, the supplement diet based on beta-carotene caused headaches and muscle pain in some of the patients. The use of beta-carotene has been recommended in order to prevent oral leukoplakia and possibly oral cancer[5]. The potential benefits and protective effects against cancer are possibly related to its antioxidizing action. This function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals [6].

Lycopene : Lycopene is a carotenoid without provitamin A action. This is a fat-soluble red pigment found in some fruit and vegetables. The greatest known source of licopene is tomatoes, which are widely employed in cooking. There is a positive relationship between lycopene consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardiovascular diseases. Lycopene has the uncommon feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological Antioxidizing agent. [7]. In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to be an anticancer mechanism. Lycopene is better absorbed

in oil resin capsules and in tomato juice than in the form of raw tomatoes. No systemic significant toxical effect of lycopene has been observed and there is no evidence of side effects from the treatment with lycopene. Lycopene is a promising candidate in reducing cancer and chronic diseases in human beings; however, further research is needed to clarify its potential function in human health, according to the following criteria.

Vitamins:-

L-Ascorbic Acid (Vitamin C):-

L-ascorbic acid (L-AA), the so-called vitamin C, is found in citrous fruits such as kiwi, strawberries, papaya, and mango. The current US recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults. It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of the L-AA concentration in serum leukocytes.[8]. L-AA has antioxidizing properties and reacts with superoxide produced as a result of the cells' normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. L-AA toxicity does not occur, since vitamin is water-soluble and a decrease in absorption efficiency occurs when consumption exceeds 180 mg/day.[9]

Retinoic Acid (Vitamin A):-

The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. Vitamin A exists in the human body as various interconvertible compounds, notably retinal (essential for vision) and retinol, which is the most potent analogue and the main form of storage and transportation. Retinoic acid is obtained from carotene and animal products such as meat, milk, and eggs, which, while in the intestine, are converted, respectively, into retinal and retinol[10]. In the systemic use with dosage of 300.000 IU of retinoic acid (Vitamin A), a clinical resolution of the 50% has been demonstrated. In topical use with dosage range from 0.05% to 1% a clinical resolution from 10% to 27% has been obtained [11].

Bleomycin:-

Bleomycin, a cytotoxic antibiotic, was first used for the treatment of neoplasms of the penis and scrotum, but has also been employed for squamous cell carcinoma of the head and neck region, oesophagus, and skin. The most commonly adverse effects are mucocutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin. The use of topical 1% bleomycin in DMSO was evaluated for the treatment of dysplastic OL. [12,13]

Photodynamic Therapy:-

Photodynamic therapy (PDT) is a noninvasive method for the treatment of premalignant lesions and head and neck cancers. The principle of PDT is a non thermal photochemical reaction, which requires the simultaneous presence of a photosensitising drug (photosensitiser), oxygen, and visible light. After a period to allow the photosensitiser to collect in the target tissue, the photosensitiser is activated by exposure to low-power visible light of a drug-specific wavelength. Illumination of the tumour by light at the activating wavelength results in the destruction of cells by a non free radical oxidative process. These reactive oxygen species may damage crucial cell components, such as structural proteins, enzymes, DNA, and phospholipids. PDT is a cold photochemical reaction, and the photosensitizing agents are of inherently low systemic toxicity. PDT damage heals mainly by regeneration rather than scarring. Due to the organ preserving principle of PDT, important structures are maintained with good functional and cosmetic outcome. Several photosensitisers have been developed during the past. Haematoporphyrin and haematoporphyrin derivatives were the first photosensitisers.[14]

Surgical treatment:-

A consensus considered that surgery is the 1st choice in the management of oral leukoplakia, but it has not been demonstrated that totally removing the lesion will exclude the malignant transformation.

The surgical treatment is a diagnostic tool which is used also in the evolution of oral leukoplakia as part of its surveillance. there are different surgical techniques: laser, scalpel, electrocauterisation and cryosurgery.

The **laser surgery** has been reported as most appreciated in the last 30 years . There are two main benefits of the laser: the haemostatic effect and the limited scars post treatment. This can be performed for extensive lesions. It also has reduced post operative discomfort but the main disadvantage is that the histological diagnosis of the excised area will be missing. Furthermore comparing different laser techniques, CO2 laser, neodymium: yttrium aluminum

garnet (NdYAG) laser, and potassium-titanyl-phosphate (KTP) there are differences in recurrence rates (34.2%, 28.9%, and 17 %) [15].

Electrocoagulation can be used alone or as an adjuvant to scalpel surgery. It induces thermal damage in the surrounding tissues thus causing postoperative pain and edema and tissue scarring.

Cryotherapy:-
It is a method which permits the destruction of lesion tissue by freezing. It is carried out by either an "open" or a "closed" system . The open-system cryotherapy is the direct application of cryogen on the lesion using a cotton swab or by an open spray. The closed system of cryotherapy brings a greater degree of control with more complex and delicate apparatus. The main advantages of cryotherapy are the bloodless intervention, reduced risk of post-operative infection, and the lack of scarring [16,17].

Conclusion:-

It is estimated that most of all cancers and cancer mortality worldwide are preventable through early detection, as it provides a greater chance of initiating early and successful treatment. Only sure way to avoid cancer is not to be born, but we can reduce our chances for cancer by a balanced approach to cancer prevention, early detection and effective early treatment. The main objective of secondary prevention is early detection of PMDs when they can be treated most effectively. PMDs are often undiagnosed due to lack of public awareness and due to lack of knowledge among medical professionals. Clinical appearance and diagnosis of a lesion is not adequate to determine its premalignant nature, as not all white lesions turn malignant. Diagnostic biopsy and histopathological examination should be considered for any mucosal lesion that persists for more than 14 days after obvious irritants have been removed.

Prognosis and patient survival is directly related to stage and grade of cancer at initial diagnosis.

Dentists and other health care professionals need to understand and play an important role in the early detection and diagnosis of oral cancer and potential malignant disorders as it can prevent the development of severe dysplasia of potential malignant disorders or provide a better prognosis for patients affected by oral cancer through an immediate treatment.

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