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Keratotic Lesions of the Oral Cavity: Classification, Malignant Potential, Diagnosis and Treatment

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ABSTRACT

Background: The oral mucosa is lined by stratified squamous epithelium and has topographic differences that correlate with physical demands or a higher degree of specialization. The term 'white patch' is often used clinically to describe the appearance of lesions presenting as white areas on the oral mucosa, and as many such lesions are associated with abnormal or increased keratin production, they are often described as keratoses. Keratotic "White lesions" of the oral mucosa often present problems of differential diagnosis, which are of primary importance when assessing precancerous changes in the mouth. All these white lesions may be clearly identified, differentiated, and circumscribed as clinico-pathological disease-entities, by clinical, histopathological and ultra-structural methods, thus facilitating early diagnosis, treatment and prevention of possible malignancy. The process of diagnosis and treatment planning in the case of keratotic white lesions of oral cavity is of great concern to the patient as it determines the nature of future follow up care. Differentiation between early stage cancers, precancerous lesions and other benign keratotic lesions is often difficult because of the similar clinical presentations. Therefore, the early detection of a premalignant or cancerous oral lesion promises to improve the survival and the morbidity of patients suffering from these conditions. This review is aimed at discussing the malignant potential of keratotic lesions, the various advanced diagnostic methods and the treatment of such lesions to avoid the further malignant complications.

Keywords: Keratotic white lesions, potentially malignant lesions, leukoplakia, oral lichen planus.

INTRODUCTION

The oral mucosa is lined by stratified squamous epithelium and has topographic differences that correlate with physical demands or a higher degree of specialization. For example, the epithelium associated with the gingiva and hard palate, the dorsal surface of the tongue is keratinized to respond better to masticatory demands. The epithelium lining the floor of the mouth, the ventral side of the tongue, the buccal mucosa, and the soft palate is nonkeratinized.[1]

The color of normal oral mucosa depends on the interplay between four factors: vascularity, melanin pigmentation; epithelial thickness and keratinization. The term 'white patch' is often used clinically to describe the appearance of lesions presenting as white areas on the oral mucosa, and as many such lesions are associated with abnormal or increased keratin production, they are often described as keratoses.[2] Tissues that are not keratinized at one stage of development may keratinize at another. Similarly, tissues may be modulated from keratinized-parakeratinized and nonkeratinized variants in pathologic states. Although the terms "keratinized" and "parakeratinized" may be used interchangeably with the terms "parakeratosis" and "keratosis," the former terms refer to physiologic and the latter

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terms refer to pathologic stages. When keratinization occurs in a normally nonkeratinized tissue, it is referred to as keratosis. When normally keratinizing tissue such as the epidermis becomes parakeratinized, it is referred to as parakeratosis.[3] Oral keratosis appears white because the thickened or abnormal keratin becomes hydrated as a result of being bathed by saliva, and then evenly reflects light. A similar reaction is seen in areas of the skin, for example palms and soles, following prolonged soaking or bathing in water. Hyperkeratinization (excessive formation of tenaciously attached keratin) may be present in a variety of clinical conditions, including genetic, physiologic, inflammatory, immunologic, premalignant, and malignant conditions. The change may result from a local insult, including chemical, thermal, or physical irritants.

The keratotic lesions which appear white in color on clinical examination comprises of a group of conditions which can appear in Varity of clinical forms. It is described as an abnormal area of the oral mucosa that appears whiter than the surrounding tissue & is usually slightly raised, roughened, or otherwise of a different texture from adjacent normal tissue. This white appearing lesion may be smooth, folded, shaggy, elevated, lacy or annular. Each of these may be in turn fissured, ulcerated, eroded or inflamed & occur as solitary, multiple, focal or diffuse lesions.

Thus any condition that increases the thickness of the epithelium causes it to appear white by increasing the distance to the vascular bed. Lesions most often appear white because of a thickening of the keratin layer or hyperkeratosis. Other common causes of white appearance include acanthosis (a thickening of the spinous cell layer), an increase in the amount of edema fluid in the epithelium & reduced vascularity in the underlying lamina propria. Surface ulcerations covered by a fibrin cap can also appear white, as would collapse bullae.[4]

Keratins:

Keratins are a group of fibrous proteins resistant to autolysis and enzymic digestion. This property is probably the result of the disulphide (S-S) linkages between adjacent component polypeptide chains. These bonds are contained in the amino acid cystine, and it is the high content of cystine that is the most characteristic feature of the keratin molecule. The amount of cystine varies with the type of keratin, in addition to exhibiting regional and diurnal variation. Other types of cross-linkages are also important in joining the polypeptide chains of keratin. Hydrogen bonds provide links between two dipoles, one a hydrogen atom and the other either a nitrogen or oxygen atom: these hydrogen bonds are primarily responsible for the stability of the molecular configuration of keratin, with the polypeptide chains having a spiral configuration with the hydrogen bonds not only linking between adjacent chains, but also preventing extension. Salt 'linkages -also form a number of cross-linkages between polypeptide chains, but are weaker than disulfide bonds.

Keratins constitute the intermediate filament cytoskeleton of epithelial cells. About 20 keratins are known, and they have been numbered 1-20. In the oral squamous epithelium, a certain set of keratins is present under normal circumstances; like K5/K14 is present in the basal cell layer, whereas K4/K13 and K1/K10 are present in the spinous cell layer in non-cornified and cornified epithelium, respectively. However, during malignant development, changes in the type or distribution of keratins are seen. In general, the distribution of keratin mRNAs involves a higher number of epithelial cell layers than the corresponding proteins, indicating that these genes are under post-transcriptional control.[5]

Keratin genes - molecular biology:

Many mammalian genes occur in 'multiple families', having evolved by multiple rounds of gene duplication, whose individual members are differentially expressed in relation to distinct pathways of cellular differentiation and organ development. The genes coding for keratins represent one of such large multi-gene families, comprising at least 30 genes encoding keratin polypeptides (around 20 epithelial genes).

Hybridization studies have indicated that approximately 10 genes encode each class of keratin sequence. It is yet unclear whether genes within each class are identical or not. Some of the genes are also thought to be non- functional/ psuedo-genes. Type I and II keratins usually have nine exons and eight introns, with exception of K8,

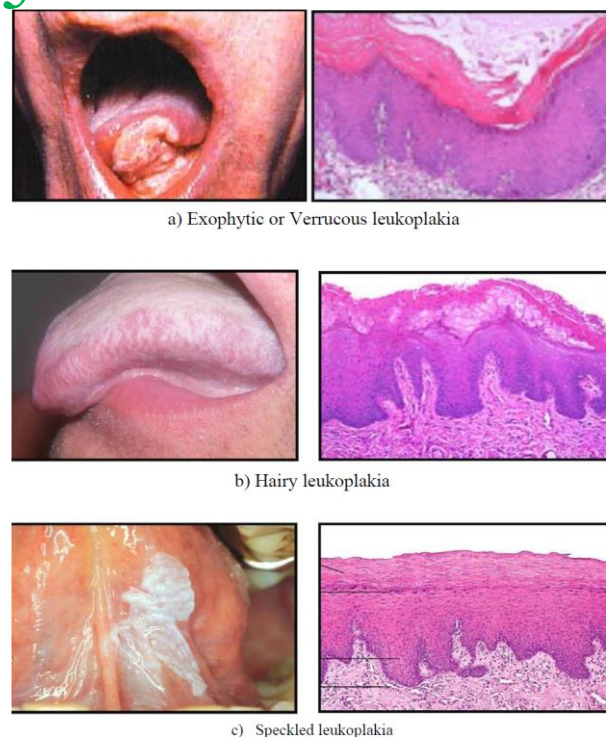

Fig 1: Different clinical types of Leukoplakia.

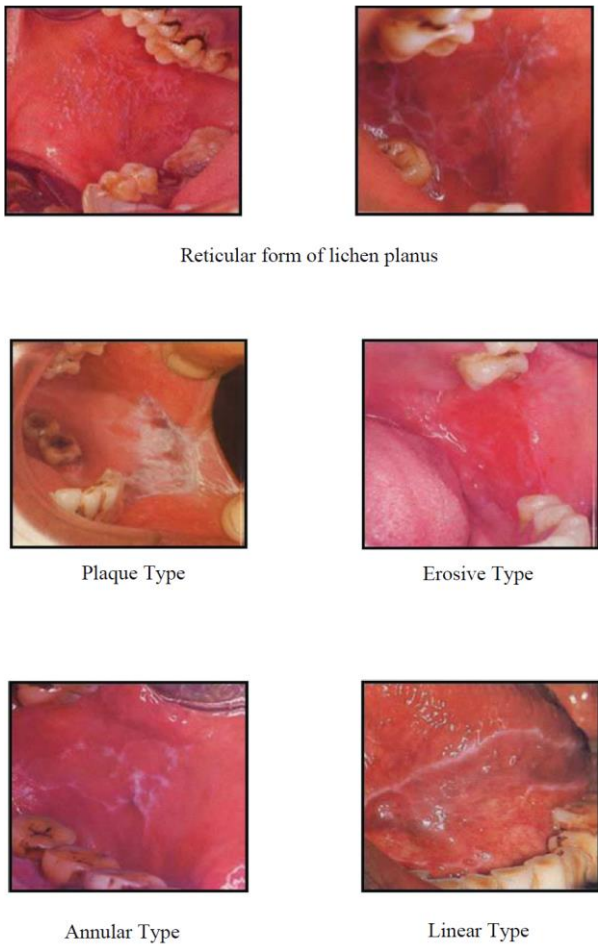

Fig 2: Oral Lichen Planus (OLP).

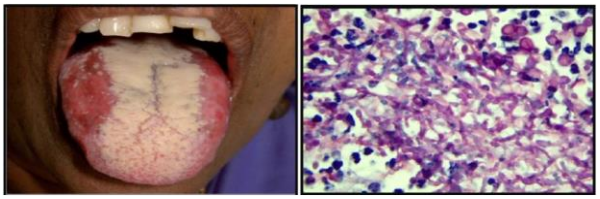

Fig 3: Chronic Hyperplastic Candidiasis.

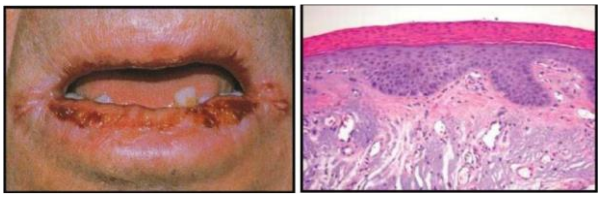

Fig 4: Actinic Cheilitis.

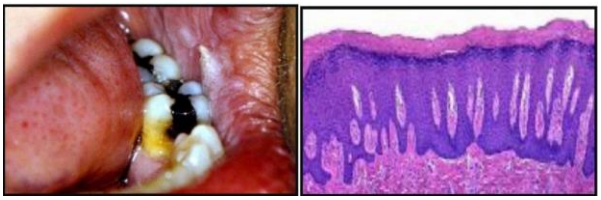

Fig 5: Actinic Cheilitis.

which is missing intron V. The number and position of intron sequences or lengths are generally well preserved. The locations of the introns in the keratin genes vary slightly. The smaller or acidic Type I keratins (K9-K20) are encoded on chromosome 17q, while the larger or more basic Type II keratins (K1-K8) are encoded on chromosome 12q.[6] Changes in color of the oral mucosa have been classically used to catalogue and classify the mucosal and soft tissue pathology of the oral cavity. Thus, most of the keratotic lesions have been catalogued clinically as white lesions due to one of the several reasons like a thickened surface layer of keratin, an acanthotic epithelium or oedematous epithelial cells; the reason for a lesion's white appearance can be determined clinically, but the final diagnosis relies on microscopic examination.

CLASSIFICATION: [7]

1. Hereditary/Developmental:

- Leukoedema

- White spongy nevus

- Hereditary benign intraepithelial dyskeratosis

- Pachyonychia Congenita

- Dyskeratosis Congenita

2. Reactive:

- Frictional keratosis

- Morsicatio buccarum

- Nicotine stomatitis

- Tobacco pouch keratosis

- Chemical burn

3. Immunologic:

- Lichen planus

- Lichenoid mucositis

- Discoid lupus erythematosus

- Graft-versus- host disease

4. Bacterial/Viral/Fungal:

- Candidiasis

- Mucous patches in secondary syphilis

- Oral hairy leukoplakia

5. Systemic disease:

- Uremic stomatitis

6. Potentially malignant disorders:

- Leukoplakia

- Actinic cheilitis

7. Neoplastic:

- Squamous cell carcinoma

Malignant potential of keratotic lesions:

The chances of a patient with a keratotic lesion developing a carcinoma are much higher than in patients without such lesions. Indeed, so-called leukoplakia is a much over-valued clinical sign of malignancy. In the classical study by **Waldron and Shafer** keratotic white lesions on the floor of the mouth had a **50%** probability of being either severe dysplasia or worse and the keratotic lesions of the lateral border of the tongue had approximately **37%** chance of being dysplastic. Apart from the site or location of the lesion, other important parameters to be considered include age of the patient, history of tobacco and alcohol use, presence/ absence of pain, clear demarcation from surrounding mucosa. Prevention and early detection of such potentially malignant disorders (PMDs) have the potential of not only decreasing the incidence but also in improving the survival of those who develop oral cancer.[8] Keratotic "White lesions" of the oral mucosa often present problems of differential diagnosis, which are of primary importance when assessing precancerous changes in the mouth. Epithelial dysplasia are frequently associated with candidiasis and discoid lupus erythematosus, but neither this, nor such other keratotic lesions as white sponge naevus or morsicatio buccarum, are considered to be preneoplastic. All these white lesions may be clearly identified, differentiated, and circumscribed as clinico-pathological disease-entities, by clinical, histopathological and ultra structural methods, thus facilitating early diagnosis, treatment and prevention of possible malignancy. All keratotic lesions from different categories are not having the malignant potential. Amongst those having the greater risk of malignant transformation in descending orders of frequencies are Leukoplakia, Lichen planus, Hyperplastic Candidiasis, Tobacco-associated keratotic lesions, Frictional keratosis, Actinic Cheilitis, Papilloma, Keratoacanthoma, Dyskeratosis Congenita, lupus erythematosus. The most common ones are discussed here.

Leukoplakia: (fig 1)

The precancerous character of oral leukoplakia is well established, and the "high-risk" type: erosive-dysplastic leukoplakia has a greater malignant potential. Multiple studies over the years have shown a malignant transformation rate of **3.6-17.5%,** while few Indian studies have shown a transformation rate as low as **0.3-0.5%**. However, dysplastic and carcinomatous changes are more common in **speckled leukoplakia (26%)** than in homogeneous leukoplakia.[9]

Oral lichen planus (OLP): (fig 2)

The malignant potential of OLP is a matter of serious controversy. Many studies regarding this

have shown that the rate of malignant transformation varied from 0-10%. The risk of malignant transformation is in OLP is real but not high. Erosive & Plaque type OLP in older patients with pain & who also have habits of tobacco & alcohol use is more likely to undergo malignant transformation. Therefore, during the diagnosis & treatment of OLP, much attention should be paid to potential malignant transformation of OLP to facilitate the early diagnosis of oral cancer, with an aim of reducing morbidity & mortality from OSCC arising in patients with OLP.[10]

Chronic hyper plastic candidiasis: (fig 3)

There are several reports of carcinomas developing in chronic hyperplastic candidiasis. Malignant change in chronic hyperplastic candidiasis was reported to be as high as 30%. These reports claimed that candidal infection was the direct cause of the malignant transformation. It was not clear whether the host cell proliferation, secondary to candidal invasion, leads to uncontrolled epithelial growth or whether these events, together with other as-yet-unidentified factors, initiate a neoplastic change. Many investigators from their studies concluded that nitrosamines produced by Candida appear to play a role in the causation of oral cancer.[11]

Actinic cheilitis: (fig 4)

It is an irreversible change and squamous cell carcinoma, almost always well-differentiated, develops in 6-10% of cases. Malignant transformation seldom occurs prior to 60 years of age and the resulting carcinoma typically enlarges so slowly and metastasizes so late that one population study found no deaths and minimal morbidity from the carcinomas.

Frictional keratosis: (Fig 5)

The mucosa abraded by a broken tooth, for instance, may become keratinized. Though this is traditionally regarded as a cause of cancer, experimental evidence suggests that mechanical injury alone is not carcinogenic. In any case the condition is readily dealt with and the mucosa will rapidly revert to normal if trauma is the sole cause.[9]

Diagnosis and treatment:

The process of diagnosis and treatment planning in the case of keratotic white lesions of oral cavity is of great concern to the patient as it determines the nature of future follow up care. Differentiation between early stage cancers, precancerous lesions and other benign keratotic lesions is often difficult because of the similar clinical presentations. Therefore the early detection of a premalignant or cancerous oral lesion promises to improve the survival and the morbidity of patients suffering from these conditions.

A variety of commercial diagnostic aids and adjunctive techniques are now available to assist in the screening of patients.

A. Clinical methods:

1. Vital staining:

a. Toluidine Blue: It is an acidophilic metachromatic dye of the thiazine group which selectively stains acidic tissue components (sulfates, carboxylates and phosphate radicals), thus staining DNA and RNA. It stains mitochondrial DNA, cells with greater than normal DNA content or altered DNA seen in dysplastic and malignant cells.

b. Lugol's iodine: It stains normal tissue brown, but proliferating epithelium is unstained or poorly stained. Lugol's iodine solution produces a brown-black stain by reaction of the iodine with glycogen. Glycogen, content is inversely related to the degree of keratosis. In the oral mucosa, the glycogen content varies with the keratinization of the area of mucosa.

2. Vizilite: It is a non toxic chemiluminescent light that is shined in the mouth. Normal epithelium absorbs Vizilite; appears dark. Abnormal epithelium reflects Vizilite; appears white. As a cell becomes more dysplastic the nucleus becomes larger compared to the rest of the cell. The enlarged nucleus reflects light and thus appears white.

B. Photodiagnosis:

1. S-Aminolevulinic Acid Mediated Digitized Fluorescence Endoscopic Imaging : The digitized 5-ALA mediated fluorescence imaging endoscopic system developed has the capability of requiring high quality on-line images and quantifying the fluorescence intensity of the diseased oral tissues.

2. Autofluorescence Spectroscopy: It is a promising tool for oral cancer detection; it is non-invasive and easily applicable for the detection of alterations in the structural and chemical compositions of cells, which may indicate the presence of diseased tissue.

3. Fluorescence Photography: It is non-invasive, rapid, simple, and reproducible. The system is a useful adjunct in the diagnosis of squamous cell carcinoma & potentially malignant disorders.

C. Histopathological methods:

1. Oral Exfoliative Cytology: It is the microscopic examination of shed cells from an epithelial surface. It is recommended as a diagnostic aid for studying the malignant potential especially of ulcerated and erythematous oral lesions. It is usually reported by the cytologist into five classes. Treatment procedure, however, cannot be instituted only based on exfoliative cytology; if any abnormalities are found on cytological examination, the diagnosis of malignancy should be confirmed by a biopsy.

2. Oral CDx Test: In this method each brush biopsy specimen is scanned by the Oral CDx computer. This consists of a neural-network-based, image-processing system, specifically designed to detect oral epithelial precancerous and cancerous cells.

3. Scalpel Biopsy: It is the gold standard amongst all diagnostic methods; but for differential diagnosis we have to utilize the advanced diagnostic aids. Following are the few special stains used for the keratotic lesions:

The Glenner-Lillie or by the Ayoub-Shklar modification of the Mallory connective tissue stain, which stains the keratin bright red & the pre-keratin orange. In the Glenner-Lillie technique, the keratin stains deep purple.

D. Molecular techniques:

1. The Flow Cytometer Analysis: It is an automated, precise, reproducible, reliable, and objective measuring device of cellular DNA content and cell cycle analysis. Flow cytometers with appropriate computer -software are able to detect DNA aneuploid populations in mild, moderate, and severe dysplasias of premalignant oral lesions.

2. Tumour markers: The various dysplastic changes can be detected with several markers including PCNA, Ki-67 (Mib-l) and Cyclin Dl & it has value in predicting lesion behaviour and could be used as surrogate end-point biomarkers in cancer prevention trials.

3. Micro Satellite Markers: Polymerase Chain-Based Microsatellite Analysis for Allelic Loss: This is one of the more sensitive techniques available for studying clonal changes in tumors and premalignant lesions. It requires only small quantities of DNA yet yields valuable data on the loss of chromosomal regions that contain putative suppressor genes. Hence we can obtain information on critical genetic events even before the identification of the actual suppressor gene.

Management of keratotic lesions:

Establishing the proper clinical diagnosis of keratotic lesions, followed by histopathological analysis, leads to consideration of the appropriate clinical management which should be designed according to the anticipated clinical or biologic behaviour. Balancing the lesional qualities with treatment modality and associated morbidity becomes the major clinical decision. With such considerations in mind, a wide choice of treatments has been used, ranging from those which are locally directed to others which are systemic.

A. Genokeratoses group:

Many of this group of Keratotic White lesions are harmless and do not require any treatment other than reassurance from the side of the clinician. Topical retinoids can be prescribed. Chemotherapy with bleomycin or cyclophosphamide is effective for treating leukoplakia associated with Dyskeratosis Congenita.

B. Preneoplastic and neoplastic lesions:

1. Leukoplakia:

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 & 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.[12]

2. Actinic chilities:

Patients should use lip balm with sunscreens in order to prevent further degeneration. In severe cases without malignancy, a lip shave procedure (vermilionectomy) can remove the vermilion mucosa and replace it with a portion of the intraoral labial mucosa.

3. Keratoacanthoma:

The lesion is usually treated by surgical excision. Other treatment modalities include cryosurgery, lasers, curettage and cauterization, radiotherapy, topical podophyllin and 5-flourouracil, intralesional bismuth, bleomycin, interferon alfa- 2a, mehtotrexate and triamcinolone.[13]

4. Squamous papilloma:

Conservative surgical excision including the base of the lesion is adequate treatment for squamous papilloma, and recurrence is unlikely. Other treatment modalities include electrocautery, cryosurgery, and intralesional injections of interferon.[14]

5. Verrucous carcinoma:

Surgery is considered the primary mode of treatment for verrucous carcinoma. Irradiation alone or in combination with surgery is rarely performed. Combined therapy can be useful when the tumor extends to the retromolar area. When surgery is not indicated, other treatment modalities such as cytostatic drugs may be preferred.[15]

6. Oral squamous cell carcinoma:

The treatment of oral squamous cell carcinoma is guided by the clinical staging & histological grading of the disease and consists of wide (radical) surgical excision; radiation therapy or a combination of surgery and radiation therapy. Location of tumor may influence the treatment plan. A variety of chemotherapeutic agents are used as adjunctive therapy. For the small intraoral carcinoma a single treatment modality is usually chosen.[16]

C. Immunologically-mediated diseases:

1. Lichen planus:

At present there is no cure, although various agents have been tried. Patients should be observed periodically. The non-surgical management of oral lichen planus includes use of corticosteroids, retinoids, griseofulvin, and cyclosporin. Photodynamic therapy, Cryosurgery and carbon-dioxide laser ablation have also been tried. Surgical treatment is more applicable to the plaque-like lesions, because the affected surface epithelium can be removed easily.[17]

2. Lupus erythematosus:

Therapy usually involves non steroidal anti inflammatory drugs (NSAIDs), corticosteroids, antimalarial agents, and immunosuppressive drugs. These drugs may be used alone or in combination.

D. Reactive lesions:

As these are the lesions caused by any stimulating factor; the first line of treatment in such cases is complete removal of the causative agents which may be in the form of biting, sucking, or chewing habits, and fractured or rough tooth surfaces or irregularly fitting dentures or other appliances in cases of frictional keratosis.

Tobacco habits cessation enhance most of the conditions like Nicotina stomatitis, Palatal erosions, Keratotic patches, Smokeless Tobacco Leukoplakia, Hairy Leukoplakia & Black Hairy Tongue (Scraping or brushing & sometimes trimming of the papillae required in extreme cases). Antifungal treatment- (Nystatin and Amphotericin B) is prescribed in chronic hyperplastic candidiasis in addition to removing of causative agents.

CONCLUSION

Keratotic White lesions of the oral cavity can range from genetic disorders like white spongy nevus to neoplastic lesions like oral squamous cell carcinoma. Differentiating these lesions histologically is extremely important as the treatment and prognosis is highly variable.

Schwimmer in 1877 suggested the term leukoplakia to describe white raised lesions involving the oral mucosa. Since that time the term leukoplakia was used for *all w*hite keratotic lesions of the mouth and the lesion has had more than 75 names applied to it, but with the advancement in research & diagnostic techniques, these lesions are differentiated & have been treated accordingly. After conferring the definitive diagnosis for the specific keratotic lesion the management can be in the form of a reassurance that the lesion need not be a concern or in the form of a follow up advice after eliminating all possible local irritants. In a few cases it should be an immediate biopsy followed by definite treatment.

The path to be taken or the strategy to be adopted depends on the judgment making capacity of the dental diagnostician. Clinical diagnostic skills and good judgment; forms the key to successful management of keratotic white lesions of the oral cavity. Under diagnosing followed by dismissal of suspicious early lesions or over diagnosing and instituting aggressive management strategies is deplorable and should be avoided in the interest of the patient community. A careful observant eye and sensible judgment can add to the diagnostic skills of the clinician and are considered important for proper patient care

A proper diagnosis & early detection of a premalignant or cancerous oral lesion promises to improve the survival and the morbidity of patients suffering from these conditions.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

REFERENCES

1. Catherine M F, Alfredo A, Jose L T. Oral Frictional Keratosis. Crit Rev Oral Biol Med 2006; 25: 32-40.

2. Somes J V, Southam J C. Keratosis & related disorders of oral mucosa. In Somes J V, Southam J C. Oral Pathology.4th ed. Oxford, 2006. p117.

3. Kumar G S. Oral mucous membrane. In orban's oral histology and Embryology. 12th ed. Elsevier, 2009. p226.

4. Bhattacharyya N, Cohen D M, Silverman S J. Red & White lesions of the oral mucosa. In Burket's Oral Medicine Diagnosis & treatment. 10th ed. Elsevier, 2008. p86.

5. Jesper R. Prognosis of oral premalignant lesions: significance of clinical, histopathological, and molecular biological characteristics. Crit Rev Oral Biol Med 2003; 14: 47-62.

6. Chu P G, Weiss L M. Review: keratin expression in human tissues and neoplasms. Jr of Histopathology 2002; 40: 403–439.

7. Jayanthi P A, Ranganathan K A. Review article: differential diagnosis of white lesions of oral mucosa. J Oro Fac Sci 2010; 2: 58-63.

8. Joshy V R, Hari S. White lesions of the oral cavity- diagnostic appraisal & management strategies. JOMFP 2011; 2: 1-7.

9. Cawson R A. Leukoplakia and Oral Cancer. Proc. Roy. Soc. Med. 1969; 62.

10. Fang M, Zanhg E. Malignant transformation of oral lichen planus: a retrospective study of 23 cases; Quintessence Int 2009; 40: 235-242.

11. Sitheeque M A, Samaranayake L P. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). Crit Rev Oral Biol Med 2003; 14:253-267.

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

13. Neville B W, Douglas D D. Epithelial pathology. In Neville's Oral and Maxillofacial Pathology, 2nd ed (2004), Saunders; p353-354.

14. Jaju P P, prashant V, Suvarna P, Desai R S. Squamous Papilloma: Case Report and Review of Literature. Int J Oral Sci 2010; 2: 222-225.

15. Alper A, Emel B Omer G Ozden B. Oral Verrucous Carcinoma: A Study of 12 Cases. Eur J Dent 2010; 4:202-207.

16. Scully C, Bagan J V. Review article Oral squamous cell carcinoma: overview of current

understanding of etiopathogenesis and clinical implications. Oral Diseases 2009; 15: 388-399.

17. Thornhill M H. The Current Understanding of the etiology of Oral Lichen Planus. Oral Diseases 2010; 16: 507-118.