

Review Article

Potentially Malignant Disorders- An Update

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ABSTRACT:

The word cancer means crab, denoting how carcinoma extends its claws like a crab into the adjacent tissues. Oral cancer is the 12th most common cancer in women and the 6th in men. Many oral squamous cell carcinomas develop from potentially malignant disorders (PMDs). Lack of public awareness about the signs, symptoms and risk factors, along with the absence of knowledge for early detection by general dental practitioners and are believed to be responsible for this diagnostic delay and treatment initiation. This article aims to update and improve the knowledge of general dental practitioners and healthcare providers in order to prevent delay in diagnosis which could help in reducing mortality from cancer.

Keywords: Precancerous lesions, precancerous conditions, Leukoplakia, Lichen planus.

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Introduction

Cancer is Latinized from Greek word 'Karkinos', meaning crab, denoting how carcinoma extends its claws like a crab into the adjacent tissues.¹ It has been well established by researchers that virtually all oral cancer are preceded by visible clinical changes in the oral mucosa usually in the form of white or red patch (two-step process of cancer development).²

Thus, it is noteworthy that many oral squamous cell carcinomas develop from potentially malignant disorders (PMDs).^{3,4} In the Indian subcontinent the prevalence of oral cancer is the highest among all cancers in men even though it is only the sixth most common cancer worldwide.⁵ It's estimated that more than one million new cases are being detected annually in the Indian subcontinent. 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. Lack of public awareness about the signs, symptoms and risk factors, along with the absence of knowledge for early detection by health-care providers are believed to be responsible for the diagnostic delay in identifying the PMDs.⁶ This article aims to update and improve the knowledge of general dental practitioners and healthcare providers in order to prevent delay in diagnosis which could help in reducing mortality from cancer.

Potentially Malignant Disorders

In a World Health Organization (WHO) Workshop, held in 2005, the terminology, definitions and classification of oral lesions

with a predisposition to malignant transformation have been discussed. The term “potentially malignant” was preferred above “pre-malignant” or “precancerous”.⁷ Potentially Malignant Disorders is defined by WHO 2005 as the risk of malignancy being present in a lesion or condition either at time of initial diagnosis or at a future date.⁸

Precancerous Lesion can be defined as a benign lesion with morphologically altered clinical or histopathological tissue which has greater than normal risk of containing microscopic focus of cancer or of transforming into malignant lesion after diagnosis at a later date.

Precancerous Condition can be defined as a disease or patient habit which does not necessarily alter the clinical appearance of local tissue but is known to have a greater than normal risk of precancerous lesion or cancer development.^{2,9}

Table 1: Potentially malignant disorders¹⁰

Premalignant lesions	Premalignant conditions
Erythroplakia	Lichen planus
Proliferative verrucous leukoplakia(PVL)	Discoid lupus erythematosus
Viadent leukoplakia	Epidermolysis bullosa
Candida leukoplakia	Verruciform xanthoma
Reverse-smokings' palate	Graft-versus-host-disease
Dyskeratosis congenita	Cheilitis glandularis
Actinic cheilosis	Xeroderma pigmentosum
Oral submucous fibrosis	Syphilis (third stage)
	Plummer-Vinson syndrome

Etiology^{8,9,11}

No single factor has been identified as the causative factor for potentially malignant disorders. But a number of high risk factors

has been put forwarded which has greater than normal risk of malignancy at a future date.

A. Extrinsic Factors

1. Tobacco in any form (smoking or chewing) is the single most major extrinsic cause (people who smoke more than 80 cigarettes per day have 17-23 times greater risk).
2. Alcohol regardless of beverage type and drinking pattern – synergistic action along with tobacco (risk of smokers who are also heavy drinkers is 6-15 times than that of abstainers).
3. Virus infection – HPV, EBV, HBV, HIV, HSV.
4. Bacterial infection – Treponema pallidum.
5. Fungal infection – Candidiasis.
6. Electro-galvanic reaction between unlike restorative metals.
7. Ultraviolet radiation from sunlight – associated with lip lesions.
8. Chronic inflammation or irritation from sharp teeth or chronic cheek-bite (tissue modifiers rather than true carcinogens).

B. Intrinsic Factors

1. Genetic (5% are hereditary).
2. Immunosuppression – organ transplant, HIV.
3. Malnutrition – iron (anemia), vitamin A, B, C deficiency.

Leukoplakia

Schwimmer first used this term in 1877 to describe a white plaque on the tongue.¹² Since 1980, World Health Organization has changed the definition of leukoplakia as follows.

- 1) A white patch or plaque that cannot be characterized clinically or histologically as any other disease.
- 2) A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion.
- 3) A white plaque of questionable risk having excluded (other) known disease or disorders that carry no increased risk for cancer.^{10,13} There are 4 subdivisions of leukoplakia: early or thin,

homogenous or thick, granular or verruciform and speckled or erythroleukoplakia. Each subdivision has a different malignant transformation potential. For example, thin leukoplakia often becomes malignant without clinical changes. Thick leukoplakia undergoes malignant transformation in 1–7% of cases. The frequency of malignant changes in verruciform and speckled leukoplakia ranges from 4% to 15% and 18% to 47%, respectively.¹⁴ Leukoplakia is purely a clinical terminology and histopathologically it is reported as epithelial dysplasia. WHO in 2005 proposed five grades of epithelial dysplasia based on architectural disturbances and cytological atypia.

1. Squamous Hyperplasia – benign lesion.
2. Mild Dysplasia – better prognosis.
3. Moderate Dysplasia.
4. Severe Dysplasia.
5. Carcinoma In-situ – poor prognosis.⁸

It has been recently proposed to modify the above 5-tier system into a binary system of ‘high risk’ and ‘low risk’ lesions to improve clinical management of these lesions.¹⁰

Table 2: Criteria used for diagnosing epithelial dysplasia¹⁵

Architecture
Irregular epithelial stratification
Loss of polarity of basal cells
Drop-shaped rete ridges
Increased number of mitotic figures
Abnormal superficial mitoses
Premature keratinization in single cells (dyskeratosis)
Keratin pearls within rete pegs
Cytology
Abnormal variation in nuclear size (anisonucleosis)
Abnormal variation in nuclear shape (nuclear pleomorphism)
Abnormal variation in cell size (anisocytosis)
Abnormal variation in cell shape (cellular pleomorphism)
Increased nuclear-cytoplasmic ratio
Increased nuclear size
Atypical mitotic figures
Increased number and size of nucleoli
Hyperchromasia

Erythroplakia

Erythroplakia is defined as “A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease”.¹⁶ The clinical appearance may be flat or even depressed with a smooth or granular surface. In case of a mixture of red and white changes such lesion is usually

categorized as non-homogeneous leukoplakia (“erythroleukoplakia”). Tobacco and alcohol use are considered important etiologic factors. The possible role of *C. albicans* is at present still unclear.¹⁷ Shear classified erythroplakia into three variants

1. Homogeneous erythroplakia – lesion that appeared flat, velvety, with uniformly red appearance.
2. Granular erythroplakia – red lesions with granular surface.
3. Speckled erythroplakia / erythroleukoplakia – predominantly red lesion speckled with white spots.⁸

Histopathologically, erythroplakia commonly shows at least some degree of dysplasia and often even carcinoma in situ or invasive carcinoma.¹⁸ According to Shafer and Waldron, 51% of erythroplakias transformed into SCC, 40% were carcinoma in situ and 9% showed mild to moderate dysplasia. Because of 90% malignant transformation rate, early detection and immediate surgical excision are recommended.¹⁸

Oral Submucous Fibrosis

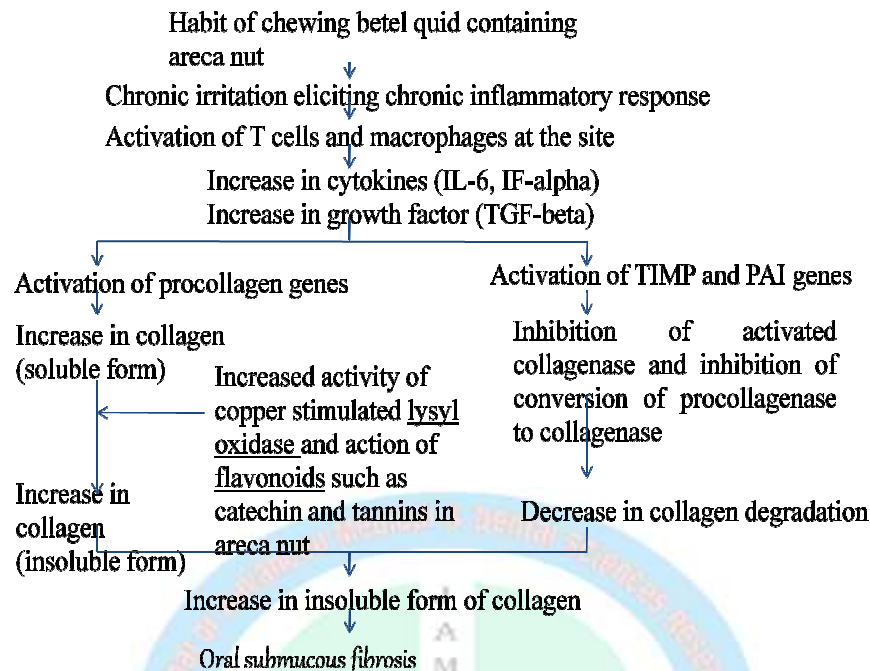
Oral Submucous Fibrosis is an insidious, chronic disease affecting any part of oral cavity and sometimes pharynx although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroblastic changes in lamina propria, with epithelial atrophy leading to stiffness of oral mucosa and causing trismus and inability to eat.¹⁹

Pathogenesis of oral submucous fibrosis¹⁹

Clinically, OSF is characterized by a burning sensation, blanching and stiffening of the oral mucosa and oropharynx, and trismus. In advanced stages vertical fibrous bands appear in the cheeks, faucial pillars, and encircle the lips. Through an as yet unknown process, fibrosis and hyalinization occur in the lamina propria, which results in atrophy of the overlying epithelium. The atrophic epithelium apparently predisposes

to the development of a squamous cell carcinoma in the presence of carcinogens.²⁰ Has a malignant transformation rate of about 0.5-6%.⁸

Pathogenesis of oral submucous fibrosis¹⁹



Oral Lichen Planus

Lichen planus (LP) is a common chronic, immuno-nologically mediated mucocutaneous disease, which was first described in 1869. Most patients with lichen planus are middle-aged (over 40), and it is rare in children. Females account for at least 65% of patients. Cutaneous lichen planus is seen in 1% and oral lichen planus (OLP) affects 0.1 -2.2% of the population. Clinical variations of OLP are reticular, erosive, atrophic, bullous, ulcerative, papular and plaque like. The most commonly affected site in the oral cavity is posterior buccal mucosa, followed by tongue, (lateral and dorsal), gingivae, palate and vermilion border. The risk of malignant change in OLP has been controversial for a long time and reported to be between 0.4% and 3.7%. Patients often experience this complication after 10 years.^{14,21}

Diagnostic aids in detection of potentially malignant disorders

Development and use of diagnostic aids that would help the oral health care professionals to readily identify persistent oral lesions of uncertain biologic

significance are essential to improve their ability to detect relevant PMDs at their most incipient stage. A variety of commercial diagnostic aids and adjunctive techniques are now available to assist us in the screening of healthy patients.

1. Clinical Methods

- Conventional Oral Examination (COE).
- Vital Staining.

2. Optical Methods

- Vizilite®.
- MicroLux DL®.
- VELscope®.
- Fluorescence Spectroscopy.

3. Imaging Methods

- Computed Tomography (CT).
- Magnetic Resonance Imaging (MRI).
- Positron Emission Tomography (PET).
- Thallium-201 (201Tl) Scintigraphy.
- Photoactive Imaging.
- Optical Coherence Tomography (OCT).
- Narrow Band Imaging (NBI).
- Nano Diagnostic Methods.

4. Histopathological Methods

- a. Scalpel Biopsy.
- b. OralCDx Brush Test®.
- c. Cytology.
- d. Laser Capture Micro Dissection.

5. Molecular Methods

- a. Immuno Histochemistry.
- b. Flow Cytometry.
- c. Polymerase Chain Reaction (PCR).
- d. Blotting Techniques.
- e. Spectral Karyotyping.
- f. AgNOR.
- g. Fluorescent In-situ Hybridization (FISH).
- h. DNA Microarray.
- i. Comparative Genomic Hybridization.

6. Salivary Diagnostic Methods

- a. Protein Electrophoresis.
- b. Sialochemistry.^{8,22,23}

Conclusion

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.⁸ 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.^{1,8}

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