POTENTIALLY MALIGNANT DISORDERS OF ORAL CAVITY

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Abstract

Even though rapid advances have been made in the field of medicine and surgery, cancer is the leading cause for human mortality. It is estimated that more than one million new oral cancer cases are being detected annually in the Indian subcontinent, of which 90% are oral squamous cell carcinomas (OSCC). 60-70% of the Indian patients presented for treatment only in the advanced stage of oral cancer leading to the high mortality rate. 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 this diagnostic delay and treatment initiation. It has been established by researchers that virtually all OSCC's are preceded by visible clinical changes in the oral mucosa, usually in the form of white or red patch. This article makes an attempt to provide and update the knowledge about the potentially malignant disorders to health-care providers in order to help in early detection and treatment, thus reducing the mortality of oral cancer.

Keywords: potentially malignant disorder, precancerous lesion, precancerous condition, oral cancer, erythroplakia, leukoplakia, oral submucous fibrosis, lichen planus, classification, diagnostic aids.

Introduction

Cancer is Latinized from Greek word 'Karkinos', meaning crab, denoting how carcinoma extends its claws like a crab into the adjacent tissues. The global burden of cancer continues to increase over the centuries as childhood mortality and deaths from infectious diseases decline, and people live longer.[1] Cancer is the second most leading cause of mortality in economically developed countries (following heart diseases) and the third most leading cause of death in developing countries (following heart diseases and diarrhoeal diseases).[1] It is estimated that there will be more than 12 million new cancer cases in 2007 worldwide, 6.7 million will occur in economically developing countries, of which 4.7 million will result in death.[1] On an average about 8-8.5% men and 4-8.1% women could develop oral cancer in their lifetime in developing countries.[1,2]

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.[3] It's estimated that more than one million new cases are being detected annually in the Indian subcontinent. 92-95% of all oral malignancies are oral squamous cell carcinomas (OSCC).[2] Five-year survival for cancer is directly related to the stage at which the initial diagnosis is made.[1] Surgical treatment of oral cancer is considered among the most debilitating and disfiguring of all cancers. It produces dysfunction and distortions in speech, difficulty in mastication and swallowing, and affects the patient's ability to interact socially.[4]

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).[5] 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.[4] 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. This article makes an attempt to update the knowledge of health-care providers about the high-risk PMDs, so as to help in

identification of these lesions at its early stage and thus reduce the mortality from oral cancer.

Terminology and Definitions [5-7]

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. Confusion prevailed between these two terminologies, and many opinioned that the prefix 'pre' qunotes that all precancerous lesions will eventually become cancer, whereas studies found this to be untrue. Hence it was recommended in WHO workshop of 2005 to abandon the distinctions between precancerous lesions & precancerous conditions and to use instead the term "potentially malignant disorders" incorporating both the terminologies. *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.

Etiology [1-3,5-10]

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.

Epidemiology [1-3,5-9]

Anyone can develop cancer, however the risk of being diagnosed with cancer increases with age. Longer people live the more likely it is for a sporadic mutation to occur in their genome, leading to genetic alterations that may lead to a malignant phenotype. Among the genders, PMDs have traditionally shown a predilection for males. But recent studies show a 1:1 male to female ratio. This could be due to the increased habitual use of tobacco and alcohol among women.

Average age of population affected with PMDs is 50-69yrs, occurring about five years earlier than oral cancer. However recent studies show that 1-5% of PMDs affect the younger age group of 30 years. This may be due to the fact that various extrinsic and intrinsic etiological factors are now more prelevant in today's younger population.

Most common sites for PMDs in India are buccal mucosa followed by tongue, palate and floor of the mouth. Location of PMDs differs from distribution of OSCC, for which the tongue, alveolar ridge and floor of mouth are the most common sites.

Classification of Oral Potentially Malignant Disorders

As far as we know no attempt has been made to classify oral PMDs till date, a possible classification could be

1. High Risk
   - 1.1. Erythroplakia.
   - 1.2. Leukoplakia.
   - 1.3. Oral Submucous Fibrosis (OSF).
   - 1.4. Erosive Lichen Planus.
2. Life-style Related
   - 2.1. Smokeless Tobacco Keratosis.
   - 2.2. Reverse Smoker's Palate.
   - 2.3. Actinic Cheilitis.

3. Infections
   3.1. Hyperplastic Candidiasis.
   3.2. Viral (HPV, HIV, EBV, HBV, HSV).
   3.3. Tertiary Syphilis.
4. Immunodeficiency
   4.1. Solid Organ Transplantation.
   4.2. Graft Versus Host Disease.
   4.3. Chronic Cutaneous Lupus Erythematous.
5. Inherited Disorders
   5.1. Xeroderma Pigmentosum.
   5.2. Dyskeratosis Congenita.
   5.3. Epidermolysis Bullosa.
   5.4. Bloom Syndrome.
   5.5. Fanconi's Anemia.

Erythroplakia [3,5-11]

Predominantly a well demarcated red lesion with flat, macular, velvety appearance, that may be speckled with white spots, which cannot be clinically or pathologically diagnosed as any other condition, most of which (90%) will transform into cancer at a future date. The red patch needs to be excluded from inflammatory conditions (mucositis), vascular lesions, psoriasis and fungal infections, that may mimic erythroplakia due to their red clinical appearance. 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.

Most of the clinically diagnosed erythroplakia represented severe dysplasia or carcinoma after biopsy and histopathological examination – 51% were well differentiated (grade I) OSCC, 40% were carcinoma in-situ or severe epithelial dysplasia, and 9% were mild to moderate epithelial dysplasia. Because of the 90% malignant transformation rate, early and immediate wide surgical excision of erythroplakic lesions are recommended.

Leukoplakia [2,3,6-11]

Leukoplakia has suffered from an excess of diagnostic terms and definitions, with at least 75 definitions been used so far in the literature. WHO in 1994 defined leukoplakia as "a predominantly white lesion of oral mucosa that cannot be characterized as any other definable lesion clinically or pathologically, often associated with tobacco products, some of which will transform into cancer". Later in 2005 WHO defined it as "a white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk of cancer". 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%.

Over the years WHO has made various attempts at classifications of leukoplakia. In 1980 the variants of leukoplakia were classified as

1. Homogeneous leukoplakia – lesion that was uniformly white and unscrapable.
2. Non Homogeneous leukoplakia – lesion predominantly white and speckled with red.

In 1998 WHO subdivision of leukoplakia were

1. Thin, smooth leukoplakia (preleukoplakia older terminology) – translucent thin gray soft flat plaques usually with sharply demarcated borders.
2. Thick, fissured leukoplakia – 2/3 of white plaques has distinctly white appearance (from thickening of keratin layer), fissured and are leathery to palpation.
3. Granular, verruciform leukoplakia – lesions have surface irregularities of nodular or granular nature with verrucous appearance.
4. Erythroleukoplakia – lesion showing intermixed red and white areas, because the epithelial cells are so immature that they no longer are able to produce keratin.

In 2002 WHO reclassified the above variants depending on the probability of a malignant change and prognosis of these lesions as

1. Phase I: thin, smooth leukoplakia – better prognosis.
2. Phase II: thick, fissured leukoplakia.
3. Phase III: proliferative verrucous leukoplakia (PVL) – higher malignant transformation rate.
4. Phase IV: erythroleukoplakia – poor prognosis.

A clinical staging system for oral leukoplakia (OL-system) on the lines of TNM staging was recommended by WHO in 2005 taking into account the size (L) and the histopathological features (P) of the lesion.

Lx: Size not specified. L1: Single or multiple lesions together <2 cm. L2: Single or multiple lesions together 2-4 cm. L3: Single or multiple lesions together >4 cm.
Px: Epithelial dysplasia not specified. P0: No epithelial dysplasia. P1: Mild to moderate epithelial dysplasia. P2: Severe epithelial dysplasia.
Stage I: L1 P0. *Stage II*: L2 P0. *Stage III*: L3 P0 or L1/ L2 P1. *Stage IV*: L3 P1 or any L P2.

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.

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.

Oral Submucous Fibrosis (OSF) [6-8,12-14]

The disease of Southeast Asia and Indian subcontinent with few cases reported from South Africa, Greece and United Kingdom. It is a chronic debilitating disease of oral cavity associated with arecanut (betel-nut) chewing, affecting all parts of oral mucosa and oro-nasopharynx. Has a malignant transformation rate of about 0.5-6%. Clinical symptoms are

- Progressive inability to open mouth (normal inter-incisal distance is +35mm or three fingers of the same individual can be inserted between the incisal edges of his/her anterior teeth).
- Vesicles, ulcerations, or blanched oral mucosa.
- Burning sensation on consumption of spicy foodstuffs.
- Petechiae – more common on palate.
- Increased salivation in early stages followed by xerostomia, change in taste sensation and dysphagia.
- Impaired jaw movements - eating, whistling, blowing, sucking becomes difficult.
- Hearing loss due to stenosis of Eustachian tubes with or without referred pain to ear.
- Nasal tone to speech due to fibrosis of naso-pharynx.

Ranganathan K et al[12] in 2001 clinically grouped OSF into 4 groups based on mouth opening parameters

1. Group I: Only clinical symptoms present with mucosal changes but no restriction of mouth opening (more than 35mm).
2. Group II: Restricted mouth opening (between 20 to 35mm).
3. Group III: Limited mouth opening (less than 20mm).
4. Group IV: Nil mouth opening with precancerous or cancerous changes in oral mucosa.

Utsunomiya H et al[14] in 2005 histopathologically divided OSF into 3 stages

1. *Early stage:* Juxta-epithelial area of hyalinization. Dilated and congested blood vessels with large number of lymphocytes, eosinophils and occasional plasma cells in sub-epithelial zone along with myxo-edematous changes.
2. *Intermediate stage:* Hyalinization of sub-epithelial zone with compression of blood vessels, reduced inflammatory cell infiltrate, and granulation tissue changes close to muscle bundles.
3. *Advanced stage:* Number of blood vessels reduced, obliterated, or narrowed in sub-epithelial zone with no inflammatory cell infiltrate. Marked fibrosis and hyalinization extending from sub-epithelial to superficial muscle layers with atrophic degenerative changes of muscle fibers.

Lichen Planus [6-8,15]

Oral Lichen Planus (OLP) is an immunologically mediated muco-cutaneous disease. Commonly occurs on skin of genitalia, flexor surfaces of forearm, thigh, scalp, lips, oral mucosa (buccal mucosa, tongue). Clinically appear as flat-topped, pearly, pinkish-purple, pruritic, polygonal papules with peripheral fine milky white lace-like reticular pattern, which are termed as Wickham's striae. Usually appear bilaterally unlike leukoplakia, and are often superimposed with candidial infection. Clinical variants of OLP are

1. Reticular Lichen Planus.
2. Erosive or atrophic Lichen Planus.
3. Papular or Bullous Lichen Planus.
4. Plaque-like Lichen Planus.

OLP is commonly managed with topical & systemic corticosteroids. On healing they usually cause hyperpigmentation of the mucosa. There is an ongoing debate on the malignant risk of OLP, as not all forms of lichen planus are potentially malignant. Mainly erosive and bullous variants have only shown malignant transformation. Malignant transformation rate of erosive lichen planus is reported to be less than 0.4-3.7%.

Factors associated with increased risk of malignant transformation [5,8,16]

Studies show that only a small fraction and not all PMDs turn malignant, and the challenge has been to identify the high-risk lesions that could turn malignant. Researchers found that greater than normal risk for malignant phenotype are associated with

- Red and white intermixed lesions, or presence of multiple lesions.
- Proliferative verrucous surface appearance, or presence of nodule, erosion, ulceration, or presence of candidiasis.
- Non-smoker (passive smokers have greater risk), or those with no habits (idiopathic leukoplakia).
- Lesion not regressed after habit cessation, or after the causative initiating factor is removed, or continuation of habit after initial diagnosis.
- Duration of the lesion before initial diagnosis (long duration poor prognosis).
- Lesion size greater than 200mm^2.
- High-risk anatomic site – floor of mouth, lateral posterior border tongue, lip.
- Young age at diagnosis (30-35yrs).
- Female gender (for unknown reason 47% of women show malignant transformation).

It is not within the scope of the present review to describe the rapidly evolving biological and molecular aspect of cancer development, but the most common genomic markers of PMDs include DNA ploidy, chromosome aberrations (allelic loss or gain) resulting in loss of heterozygosity (LOH), and changes in expression of oncogenes and tumor suppressor genes (p53).

Diagnostic aids in detection of potentially malignant disorders [17,18]

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
   a. Conventional Oral Examination (COE).
   b. Vital Staining.
2. Optical Methods
   a. Vizilite®.
   b. MicroLux DL®.
   c. VELscope®.
   d. Fluorescence Spectroscopy.
3. Imaging Methods
   a. Computed Tomography (CT).
   b. Magnetic Resonance Imaging (MRI).
   c. Positron Emission Tomography (PET).
   d. Thalium-201 (^{201}Tl) Scintigraphy.
   e. Photoactive Imaging.
   f. Optical Coherence Tomography (OCT).
   g. Narrow Band Imaging (NBI).
   h. 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.

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.[1] 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.[1] The main objective of secondary

prevention is early detection of PMDs when they can be treated most effectively.[1] 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.[16] 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]

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