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POTENTIALLY MALIGNANT DISORDERS AFFECTING ORAL CAVITY– A REVIEW

Dental Science

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ABSTRACT

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. Biopsy is essential to confirm the provisional clinical diagnosis, and timely referral to a specialist is indicated. Lack of awareness about the signs and symptoms of oral Potentially malignant disorders(PMDs) in the general population and even healthcare providers is believed to be responsible for the diagnostic delay of these entities. The aim of this article is to update and improve the knowledge of healthcare providers about oral PMDs.

KEYWORDS

oral cancer, potentially malignant disorder, precancerous conditions, precancerous lesion

Cancer is Latinized from Greek word 'Karkinos', meaning crab, indicating how carcinoma extends its claws like a crab into the adjacent tissues. Cancer is the second most leading cause of mortality in economically developed countries. It is the third most leading cause of death in developing countries. [1]Incidence of oral cancer has been rising in many countries in the world. The 5-year survival rate for oral cancer has not significantly improved in the past 30 years and remains at approximately 50 . Many oral squamous cell carcinomas are preceded by clinically evident oral

potentially malignant disorders (OPMDs). It isvery important to prevent malignant change in people diagnosed with OPMDs, but the hazard ratios of various OPMDs are not well known. The OPMDs include hyperk-eratosis or epithelial hyperplasia, epithelial dysplasia ,erythroplakia and oral submucous fibrosis (OSF).

Etiology[1-3]

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 – treponemapallidum.
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[3-8]

Schwimmer[4]first used this term in 1877 to describe a white plaque on the tongue. Since 1980, World Health Organization has changed the definition of leukoplakia as follows:[5]

1) A white patch or plaque that cannot be character-ized 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 ex-cluded (other) known disease or disorders that carry no increased risk for cancer.

This lesion is seen most often in middle-aged and older men.[7]Although leukoplakia is more common in males than in females, the latter has a higher risk of developing oral cancer.Approximately 70% of oral leukoplakias are seen on the buccal mucosa, lip vermilion and gingivae. However, lesions on the floor of the mouth (42.9%), tongue (24.2%) and lip vermilion (24%) account for more than 90% of those with dysplastic or malignant changes. Malignant potential of Leukoplakia is between 15.6% and 39.2%. Leukoplakia usually occurs about 5 years earlier than OSCC. 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. Thick leukoplakia undergoes malignant transformation in 1–7% of cases verruciform and speckled leukoplakia ranges from 4% to 15% and 18% to 47%, respectively. Leukoplakia exhibiting moderate to severe dysplasia needs complete removal by electrocautery, cryosurgery or laser ablation. Leukoplakia not exhibiting dysplasia usually is not excised, but clinical assessment every 6 months is recommended. [3-8]

ORAL SUBMUCOUS FIBROSIS

OSMF was first reported by Schwartz in 1952 while examining five Indian women from Kenya, which he called as "atrophicaidiopathica (tropica) mucosae oris". Later in 1953, Joshi from Mumbai renamed the condition as OSMF, due to mainyits histological nature. Its precancerous potential was first reported by Paymaster in 1956. Rao in 1962 suggested that OSMF is a localized condition of collagen disease. Pindborg in 1966 defined OSMF as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroblastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating. OSMF is regarded as a condition as it affects different regions of the oral cavity as well as pharynx. Prevalence of OSMF is 2.01% and malignant transformation rate of 2.3-7.6% has been reported in the literature.[9-14]

ETIOLOGY

Various possible etiological factors to date proposed are areca nut, capsaicin in chillies, micronutrient deficiencies of iron, zinc and essential vitamins. A possible autoimmune basis to the disease with demonstration of various auto-antibodies and genetic predisposition with specific human leukocyte antigen (HLA) has also been proposed. However, from the available scientific literature, it is clear that the

regular use of areca nut/betel nut is the major etiological factor.[9]

CLINICAL FEATURES[15-18]

OSMF is preceded by symptoms such as burning sensation of the oral mucosa, ulceration and pain. Main characteristic features of OSMF are loss of pigmentation of oral mucosa, blanching of oral mucosa, depapillation and reduced movement of tongue, progressive reduction of mouth opening and sunken cheeks.

- Blanching may be localized, caused by impairment of the local vascularity because of increasing fibrosis of the oral mucosa and results in a marble-like appearance. Blanching may be associated with small vesicles that rupture to form erosions.
- In the more advanced stage of the disease, restricting mouth opening and causing difficulty in mastication, speech, swallowing and maintaining oral hygienedue to fibrous bands.Fibrosis may extend posteriorly to involve the soft palate and uvula. The uvula may appear shrunken and in extreme cases, budlike. Fibrosis makes cheek thick and rigid and fibrosis of the tongue and the floor of the mouth interfere with tongue movement. Hard palate involvement includes extensively blanched mucosa.

STAGING

Most useful proposed classification is by More *et al*. in 2012.[17]

Clinical staging

- Stage 1: (S1) – Stomatitis and/or blanching of the oral mucosa
- Stage 2: (S2) – Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, with/without stomatitis
- Stage 3: (S3) – Presence of palpable fibrous bands in buccal mucosa and/or oropharynx and in any other parts of oral cavity, with/without stomatitis
- Stage 4: (S4) – (A) Any one of the above stage, along with other potentially malignant disorders, e.g. oral leukoplakia, oral erythroplakia, etc., (B) Any one of the above stage along with oral carcinoma.

Functional staging

M1: Inter-incisal mouth opening up to or >35 mm
M2: Inter-incisal mouth opening between 25 mm and 35 mm
M3: Inter-incisal mouth opening between 15 mm and 25 mm
M4: Inter-incisal mouth opening <15 mm

ORAL LICHEN PLANUS

Lichen planus is a comparatively common, mucocutaneous disorder that is mediated immunologically. It can also be autoimmune in pathogenesis. It is chronic in occurrence, with periods of exacerbations and remission. It was first described by British Physician Wilson Erasmus in 1869. Lichens are primitive plant that consists of symbiotic algae and fungi and the word planus in Latin means flat. Lichen planus has varied clinical manifestations affecting the skin, oral mucosa, nail, genital mucosa, nail, and scalp.This lesion has well-established clinical features and histological features that aid in the diagnosis.[19]

Etiology:[19]

1. **Stress**
2. **Genetics**
3. **Autoimmuned disease**
4. **Graft versus host disease**
5. **Chronic liver disease and hepatitis C virus**

Oral lichen planus is classically present as lesion with radiating whitish gray lines thread like papules, velvety appearance. It is usually present bilaterally. They can be lacy or reticular, annular, patches or strings. The occurrence and distribution of lesion in the oral mucosa is 80% in the buccal mucosa, 65% in the tongue, 20% lips, <10% seen in floor of mouth and palate. The disease manifests in the oral cavity several weeks before the skin lesions. About 15% of oral lichen planus patients have concurrent skin lesions.The reticular form has a better prognosis as 40% of cases has spontaneous remission, the erosive type being long standing and with frequent exacerbations and severe pain and complications.[20,21]

ERYTHROPLAKIA

It is an uncommon fiery red patch, which cannot be classified as any other condition clinically, and histopathologically.They present as flat to slightly raised red lesions with irregular borders clinically. TP53 mutation has been detected in 46% of oral erythroplakias. Lack of excess surface keratinization, some degree of dysplasia, and even carcinoma in situ or SCC are various histological presentations of erythroplakia.[22]

PALATAL CHANGES IN REVERSE SMOKERS

Reverse smoking, which is an unusual form of smoking in which the lighted end of a cigar, *chutta*(an Indian smoking product), or cigarette, is placed inside the mouth. This habit is common in parts of India, the Caribbean Islands, Colombia, Panama, Venezuela, Jamaica, Sardinia, and the Philippines. It causes various mucosal changes. The mucosal changes observed due to reverse *chutta*smokers includes thickened leukoplakic plaques of the palate, mucosal nodularity, excrescences around the orifices of the palatal (minor) mucosal glands, yellowish brown staining, erythema, and ulceration. Due to heat changes occur in most of the palatal surfaceFollow-up studies reported from Indiaclearly demonstrated the potentially malignant nature of this condition as 6 persons in a cohort of almost 3000 patients studied over 6 years developed palatal cancer. Reverse smokers' palatal lesions are moreresistant than leukokeratosisnicotinapalati lesions found in regular cigarette smokers (referred to earlier) and, compared with leukoplakia, have a higher risk of developing into malignancies.[23-25]

DISCOID LUPUS ERYTHEMATOSUS.

It is a chronic, scarring, immunological and mucocutaneous disease. It is characterized by white keratinized plaques with elevated borders, radiating white striae, andtelangiectasia . The prevalence of DLE is fewer than 5 per 10,000 individuals. It is more common in women than men . A female to male ratio of DLE is 1.8:1. DLE shows malignant transformation rarely.[26-28]

GRAFT-VERSUS-HOST DISEASE

It is a complication arising in recipients of allogenic hematopoietic stem cell or bone marrow transplants.GvHD is a systemic condition with a wide variety of signs and symptoms and affects many organ sites. One of most common affected site is oral cavity. This lesion can be widespread in the mouth. The primarysymptom relates to soreness at mealtimes. GvHD appear as keratotic striations, white plaques, or erosive and ulcerative areas of the oral cavity.It most commonly involve the buccal mucosa and the lateral tongue. The dorsum of the tongue may show papillary atrophy. GvHD may show clinical features likexerostomia (oral dryness), and patients may develop recurrent mucoceles on the labial and buccal mucosae, tongue, or soft palate. It shows malignant transformation in some cases too.[29]

DIAGNOSTIC AIDS IN DETECTION OF POTENTIALLY MALIGNANT DISORDERS[3,30,31]

There are many diagnostic aids which are developed 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 (201Tl) 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. ImmunoHistochemistry.
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.

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