**Oral and Maxillofacial surgery/Fifth year**

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**Potentially malignant disorders of oral mucosa**

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ral carcinogenesis involves a complex, multistage process of cumulative sequence of cellular (atypia) and tissue (dysplasia) changes resulting from multiple genetic alterations during a protracted period, some of these changes may be reversible, but when the overall effect of these changes surpasses the inherent reparative ability of the cells, they will be transformed ultimately into invasive malignant cells.

In the course of this process, many physical and morphological alterations of the oral tissues that are of diagnostic and prognostic relevance occur; these changes are termed **premalignant or precancerous changes**.

**Terminology**

The terms (pre-cancer), (precursor lesions), (premalignant), (intra epithelial neoplasia), and (potentially malignant) have been used in the international literature to broadly describe clinical presentations that may have a potential to become cancer.

The term “premalignant” conveys the idea that all the lesions subsumed under this heading will, necessarily, transform into malignancy, which is not true. This is why; recently, the term “potentially malignant” is preferred by many as a more accurate term for these lesions.

**Risk factors**

* Inherent susceptibility; genetic predisposition, age (usually older than 45 years), ethnicity, and socioeconomic status.
* Tobacco use; smoking and smokeless.
* Betel quid (pan) use; betel nut, slaked lime, tobacco and spices wrapped in betel leaf.
* Alcohol use.
* Diet and nutrition; nutritional deficiency, high intake of processed meat products
* Poor oral health and dental hygiene
* Infective agents; human papillomavirus 16, candida, syphilis.
* Immunodeficiency; congenital, immunosuppression, HIV infection and AIDS.
* Ultraviolet irradiation.

**Diagnostic method**

**Patient history**

A detailed history is obtained from the patient with emphasis on identification of risk factors and recognition of medical conditions predisposing to premalignant lesions or conditions.

**Clinical examination**

Careful and thorough inspection of the mucosal surfaces by a trained clinician in a good light remains the standard method for identifying suspicious oral lesions. Any detected lesion should be palpated by a gloved finger to determine its texture. Leukoplakic lesions should be wiped away by careful use of a damp swab, in which case the diagnosis may well be that of an acute pseudomembranous candidiasis. All findings must be recorded, clinical photographs of the lesions may be helpful during follow up visits.

**Investigations**

These may include blood investigations, oral swab for microbiological assessment, and incisional or excisional biopsy for histopathological examination and diagnosis. In case of incisional biopsy, it is important to select a specific site for biopsy that includes the most representative and/or clinically severe-looking region, together with the lesion margin and adjacent normal-looking tissue.

**Diagnostic aids for clinical detection of oral premalignant lesions**

**Vital tissue staining**

It is based upon the principle that neoplastic and dysplastic tissue may preferentially take up an applied chemical dye which results in staining and thus identification of abnormal mucosa compared with adjacent normal tissue. Vital stains include: Toluidine blue, Lugol’s iodine, and 5-aminolevulenic acid, the latter is visualized by subsequent fluorescence imaging.

**Light-based detection**

These systems act as visualization aids to facilitate accurate localization of dysplastic or neoplastic mucosa.

**Brush biopsy and exfoliative cytology**

It is based on the analysis and interpretation of the characteristics of cells shed from mucosal surfaces.

**Salivary analysis**

It consists of analysis of salivary composition and the shed oral epithelial cells.

**Classification**

In 1978 the WHO proposed that clinical presentations of the potentially malignant disorders of the oral cavity to be classified into two broad groups; lesions and conditions.

**Premalignant lesions** were defined as morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart. Examples: leukoplakia;erythroplakia; Palatal changes associated with reverse smoking

**Premalignant conditions** were defined as generalized state or condition associated with significantly increased risk for cancer development. Examples:oral submucous fibrosis;lichen planus; discoid lupus erythematosus; actinic keratosis.

**Potentially malignant disorders**

**Leukoplakia**

It is the most common of all potentially malignant lesions (60%-70%). It is defined as a white patch or plaque which cannot be wiped off and cannot be characterized clinically or pathologically as any other disease. This definition is, therefore, a **diagnosis of exclusion** and only a clinical descriptive term and has no diagnostic or prognostic implication.

Oral leukoplakia has a reported prevalence of 2–4% worldwide and is significantly more common in males although, females are also affected. leukoplakias are usually seen in middle-aged or elderly patients (between 5th and 7th decade of life), however, there is a significant increase in the number of younger patients presenting with leukoplakic lesions. It is six times more common among smokers than non-smokers and can affect any part of the oral cavity and oropharynx, although the most common sites include buccal mucosa, gingiva, alveolar mucosa, and lower lip.

**Clinical appearance**

Based on clinical appearance (surface color and morphological or thickness characteristics), leukoplakia can be described as:

* Early, mild or thin; it is flat or slightly elevated, gray or white plaque, which may be somewhat translucent, fissured, or wrinkled.
* Thick (homogenous); it is thickened, leathery, distinctly white plaque with deepened fissures.
* Granular (nodular); it has increased surface irregularities.
* Verrucous; with sharp or blunt, wart-like projections.
* Speckled; it demonstrate scattered patches of redness where epithelial cells are so immature or atrophic that they can no longer produce keratin, this type is also called **erythroleukoplakia** which frequently exhibit high degree of dysplasia.
* Proliferative verrucous leukoplakia (PVL) is characterized by the development of multiple, slowly spreading, keratotic plaques with rough surface projections. It is a high risk type and its relation with the verrucous leukoplakia is uncertain.

Some lesions may exhibit a mixture of these subtypes. Lesions may disappear, remain indefinitely in one stage or change and progress over time.

**Histological features**

Leukoplakia is characterized by a thickened keratin layer of the surface epithelium **(hyperkeratosis),** with or without a thickened spinous layer **(acanthosis).** Some leukoplakias demonstrate surface hyperkeratosis but show atrophy or thinning of the underlying epithelium. Frequently, variable numbers of chronic inflammatory cells are noted within the subjacent connective tissue.

**Malignant transformation**

The rate of dysplasia or malignant transformation in leukoplakia is reported to range from 0.5% to 39%. Risk factors for malignant transformation include:

* The site of leukoplakia; leukoplakia of the floor of mouth had the highest risk of malignant transformation followed by the tongue and lip.
* Type of leukoplakia; speckled leukoplakia has the highest malignant potential among all subtypes with a rate of about 44% and a dysplasia rate of 51%, PVL also has a high risk of dysplasia/malignancy.
* Thickness of leukoplakia; the probability of dysplasia or malignancy increases as the lesion increases in thickness.
* Long duration of leukoplakia.
* Leukoplakia in non-smokers.
* Female patients.
* Presence of Candida albicans within the lesion.

**Differential diagnosis**

* White sponge nevus.
* Frictional keratosis.
* Morsicatio buccarum.
* Chemical injury.
* Acute pseudomembranous candidiasis.
* Leukoedema.
* Lichen planus.
* Lichenoid reaction.
* Discoid lupus erythematosus.
* Hairy leukoplakia.
* Skin graft.

**Diagnosis**

* Elimination of other white lesions (differential diagnosis).
* Biopsy; regardless of the subtype or location, all leukoplakias should be considered at risk for malignant transformation and biopsy should be obtained after diagnosis and elimination of other white lesions. Biopsies should be taken from areas of a lesion most likely to harbor dysplasia or carcinoma (e.g., red atrophic areas in speckled leukoplakia).

Following biopsy, if no other disorder is confirmed, the lesion is further characterized as leukoplakia with or without dysplasia.

The grade of epithelial dysplasia refers to its severity or intensity:

1. **Mild epithelial dysplasia** refers to alterations limited principally to the basal and parabasal layers.
2. **Moderate epithelial dysplasia** demonstrates involvement from the basal layer to the midportion of the spinous layer.
3. **Severe epithelial dysplasia** demonstrates alterations from the basal layer to a level above the midpoint of the epithelium.
4. **Carcinoma in situ**is defined as dysplasia involving the entire thickness of the epithelium.

**Treatment**

After establishing the diagnosis and identifying and quantifying epithelial dysplasia, the management is as follows:

* **No dysplasia or mild dysplasia**; the decision to observe versus definitively treat the lesion may be influenced by the site and clinical subtype of leukoplakia.
* **Moderate to severe dysplasia, and mild dysplasia in high-risk sites**; treatment is indicated with variable treatment options.
* **Carcinoma in situ or early invasive SCC**; excision with free margins

**Options of treatment**

* **Observation**

This is reserved for mild lesions with no dysplasia, any possible cause should be removed and patients are instructed to discontinue detrimental habits.

* **Surgical excision**

Using a scalpel, this may or may not involve removing clinically uninvolved margins. It is the traditional method of treatment indicated for smaller, localized lesions.

Possible disadvantages:

* Inability to excise widespread or diffuse lesions without causing significant morbidity.
* Scarring of the residual tissue bed.
* Excessive bleeding especially in the floor of mouth and tongue.
* The defect may require reconstruction.
* **Cryosurgery**

This modality essentially ablates soft tissue by therapeutic freezing, it is easy to perform.

Disadvantages:

* Lack of depth control in the freezing process.
* Lack of specimen availability because of the ablative process.
* Pain and swelling.

* **CO2 Laser**

It can be used either to ablate the entire lesion without obtaining tissue for biopsy or to excise a lesion and provide a tissue sample.

Advantages:

* Decreased morbidity.
* Adequate hemostasis.
* Healing is by secondary intention (no need for reconstruction).
* Decreased tissue distortion.
* **Non-surgical treatment**

This may include vitamin A, retinoids, beta-carotene, vitamin E, bleomycin, and alpha tocopherol used topically or systemically.

**Erythroplakia**

It is defined as a red patch that cannot be characterized clinically or pathologically as any other definable disease.

It is uncommon lesion with a reported prevalence of 0.02% to 5.7%. It occurs in middle-aged or older adults. The floor of mouth, buccal mucosa, soft palate and tongue are the most commonly involved sites. The lesions appear as well-demarcated, erythematous patches or plaques with soft, velvety texture.

The epithelium is atrophic and lacks keratin production allowing the underlying microvasculature to show through and produce a red appearance. The underlying connective tissue frequently demonstrates chronic inflammation.

It has the highest risk for malignant transformation compared with all other premalignant and potentially malignant oral mucosal lesions and 90% of erythroplakic lesions histopathologically represent severe epithelial dysplasia, carcinoma in situ, or superficially invasive squamous cell carcinoma. Malignant transformation rate ranges from 14% to 50%.

**Differential diagnosis**

* Infections (Mycotic infections e.g., erythematous candidiasis, histoplasmosis or Bacterial infections e.g., Tuberculosis).
* Mucosal diseases (e.g., atrophic oral lichen planus, systemic lupus erythematosis, pemphigus, pemphigoid).
* Hamartomas and neoplasms (e.g., hemangioma, vascular malformations Kaposi sarcoma).
* Others (e.g., telangiectasias, lingual varices, oral purpura).

**Diagnosis and Treatment**

Any source of irritation identified is removed, if the lesion does not regress after 2 weeks then biopsy is indicated and subsequent treatment is guided by the histopathological diagnosis. Because of the high incidence of significant epithelial dysplasia, carcinoma in situ, or early invasive squamous cell carcinoma at diagnosis, surgical intervention is necessary. Complete excision of the lesion with clear margins down to the submucosal level provides a specimen that can be assessed adequately for margin control and may reduce the risk for local recurrence significantly.

**Palatal changes associated with reverse smoking**

This disorder (lesion) is specific to populations who smoke with the lighted end of the cigar or cigarette inside the mouth, resulting in red, white or mixed lesions of the palate. There are no difficulties in diagnosing this lesion once this particular habit is noted. The reported malignant transformation rate is 0.3%.

**Treatment**

The treatment consists of discontinuation of habit and follow-up of the patient. If suspicious red areas, ulcerations, patches persist, then biopsy should be carried out. Subsequent treatment is guided by histopathological diagnosis. Surgical excision is indicated for dysplastic lesions.

**Oral submucous fibrosis**

It is a chronic disorder characterized by fibrosis of the lining mucosa of the upper digestive tract involving the oral cavity, oropharynx and frequently the upper third of the esophagus. It is seen primarily in the India with a prevalence rate of 0.2% to 0.5%, and other regions like Southeast Asia, Taiwan, and southern China.

The etiology is linked to chewing of betel quid (paan); other factors have been implicated like excessive consumption of spices, deficiencies of iron, vitamin B, and protein and genetic susceptibility.

Histologically there is submucosal deposition of densely collagenized, hypovascular connective tissue with variable numbers of chronic inflammatory cells. Epithelial changes include hyperkeratosis, atrophy, epithelial dysplasia in 10%-15% and carcinoma in 6% of the cases.

**Treatment**

Oral submucous fibrosis does not regress with habit cessation, and treatment depends on the severity of the condition. Treatment options are:

* **Nutritional**; vitamins and minerals; antioxidants (e.g., lycopene, B complex).
* **Physiotherapy**; forceful mouth opening and heat therapy.
* **Intralesional injections**; of corticosteroids, interferon gamma, or proteolytics (e.g., collagenase, hyaluronidase, chymotrypsin, and human placental extract). These are used to prevent or suppress inflammatory reaction, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen.
* **Surgical**; for moderate to severe cases may require surgical splitting or excision of the fibrous bands with or without grafting by skin graft, or using flaps followed by lifelong physiotherapy.

**Actinic cheilitis (cheilosis)**

It is a common potentially malignant alteration of the lower lip vermilion that results from long term or excessive exposure to the ultraviolet component of sunlight, other risk factors are fair complexion, old age, immunosuppression, arsenic exposure, certain genetic abnormalities and HPV. There is a similar cutaneous condition termed actinic keratosis.

Clinically it usually occur in individuals older than 40 years with male predilection, early clinical changes include atrophy of the lower lip vermilion border, blurring of margin between the vermilion zone and cutaneous portion of lip is seen. As the lesion progresses, rough scaly areas develop on the vermilion, these areas thicken and may appear as leukoplakic lesions. Chronic focal ulceration may develop which often suggest progression to early squamous cell carcinoma. Malignant transformation to SCC occurs in 6%-10% of actinic cheilitis cases.

**Treatment**

* Instruction of patients to avoid direct exposure to sun and using sunscreens.
* Areas of indurations, thickening, ulceration should be submitted for biopsy to rule out carcinoma.
* Lip shave (vermilionectomy) should be performed in cases of dysplasia. The vermilion mucosa is excised and the labial mucosa is advanced to reconstruct the vermilion.
* Alternative treatments include laser ablation, electrodesiccation, cryotherapy, 5-fluorouracil, topical imiquimod, and photodynamic therapy. Long-term follow-up is recommended.
* If a squamous cell carcinoma is identified, then the involved lip is treated accordingly.

**Lichen planus**

It is a chronic mucocutaneous disease that can affect the skin or mucosa. The cause is suggested to be an immunologically induced degeneration of the basal cell layer of the mucosa is the cause.

The prevalence of oral lichen planus is between 0.1% and 2.2%. It occurs in middle-aged adults with female predilection. Buccal mucosa, gingiva, and lateral tongue are the most commonly involved sites. Two main types of oral lichen planus have been described; reticular and erosive, but other types of oral lichen planus were described in the literature; papular, plaque-like, atrophic (erythematous), and bullous.

Reticular; most common type, usually arises in the buccal mucosa bilaterally and characteristically has fine, radiating white striae known as Wickham striae, which may be surrounded by a definite erythematous border. It is usually asymptomatic and usually can be diagnosed by its clinical features.

Erosive; it appears as irregularly shaped which may be covered with a fibrinous plaque or pseudomembrane over the erosion. This type is symptomatic and has a greater potential to undergo malignant change.

The skin lesions of lichen planus have been classically described as purple, pruritic, polygonal papules usually affecting the flexor surfaces of the extremities.

**Malignant transformation**

Although it is considered to be a controversial issue, the malignant transformation rate has been reported to range from 0.3% to 3%. The two types with an increased potential to undergo malignant transformation are the erosive and atrophic forms.

**Treatment**

Topical or systemic corticosteroid therapy is the mainstay in management of symptomatic oral lichen planus. Other agents have been used such as; cyclosporine, tacrolimus, griseofulvin, dapsone, azathioprine, and levamisole.