Review Article

Premalignant Lesions of the Oral Cavity: An Update

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ABSTRACT

Pre-malignant lesions or precancerous lesions are diseases that should be diagnosed at an early stage. Leukoplakia, erythroplakia, oral submucous fibrosis and lichen planus are the most common premalignant lesions. These lesions should be diagnosed at an early stage to prevent the risk of malignant transformation if left untreated, in which treatment would be difficult. The most common etiology includes smoking, alcohol, and areca nut chewing. A wide variety of treatment modalities are available including topical and systemic corticosteroids, retinoids, and surgical intervention.

Key words: *Premalignant Lesions, Precancerous Lesions, Leukoplakia, Erythroplakia, Oral Submucous Fibrosis, Lichen Planus.*

In a World Health Organization workshop held in 2005, the terminology, definitions and classifications of oral lesions with a predisposition to malignant transformation have been discussed and recommended to use the term "potentially malignant disorders" to eliminate terminological confusion [1]. A recent definition of OPML is a group of oral mucosal lesions with an increased risk of malignant transformation [2]. Oral premalignant lesions (OPMLs) are relatively common, occurring in about 2.5% of the general population and are an important target for cancer prevention [3]. The etiology of precancerous lesions of oral mucosa is not well-known. Some risk factors such as tobacco chewing, tobacco smoking, and alcohol play an important role in development of potentially malignant oral conditions. While tobacco chewing is a major risk factor for oral leukoplakia, oral submucous fibrosis, and erythroplakia, tobacco smoking may be a risk factor for oral leukoplakia. Alcohol drinking may increase the risk by 1.5-fold for oral leukoplakia, by 2-fold for OSMF, and 3-fold for erythroplakia [4]. Therefore, early detection of premalignant lesions and oral cancer is very important. Miscellaneous modalities such as oral cavity examination, supravital staining, oral cytology and optical technologies including spectroscopy, fluorescence spectroscopy, elastic scattering (reflectance) spectroscopy, Raman spectroscopy, fluorescence imaging, optical coherence tomography, narrow-band imaging, and multimodal optical imaging may be used [5].

LEUKOPLAKIA

The World Health Organization (WHO) group has defined leukoplakia as "a white patch or plaque that cannot be characterized, clinically or pathologically, as any other disease". These lesions are potentially premalignant and vary in size, shape, and consistency, and macroscopically said to be homogenous and nodular [6]. The nomenclature of the term was initially used by Schwimmer in 1877 [7,8]. Clinically, leukoplakia may be affecting any part of the oral and oropharyngeal cavity and can be divided into two subtypes including homogeneous and non-homogeneous presentations. Homogeneous lesions are characterized by

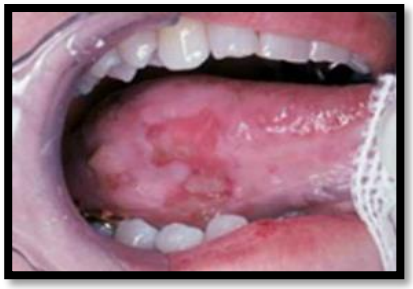

Fig. 1: Leukoplakia seen on ventral surface of the tongue

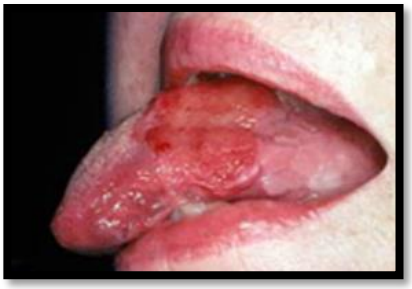

Fig. 2: Erythroplakia seen on side of the tongue

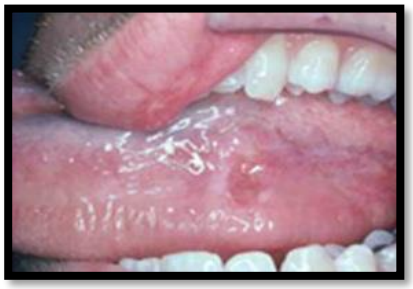

Figure 3: Oral Lichen Planus

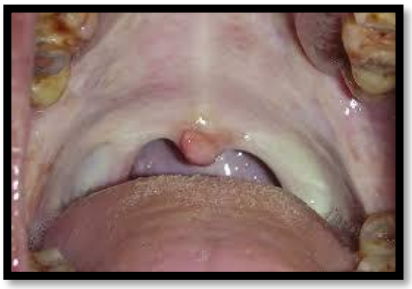

Fig. 4: OSMF seen on dorsal side of the tongue

uniformly flat, thin, uniformly white in color and show shallow cracks of the surface keratin. Non-homogenous lesions have been defined as a white and red lesion (known as erythroleukoplakia) that may be either irregularly flat (speckled) or nodular [1,9] . Leukoplakia can be observed at multiple sites in the oral cavity, most commonly of which is over the buccal mucosa, gingiva, and lip vermillion border [10]. Previous studies have reported ranges between 0.4-1.59% prevalence rate of leukoplakia, with higher rates seen in older males [11,12]. A less frequent variant of leukoplakia is the proliferative verrucous leukoplakia, categorized under the non-homogenous denomination [13]. This lesion was first described by Hansen et al. in 1985 and was seen to exhibit highly persistent and slow growing features, ultimately manifesting as a wart-like lesion with a high risk of malignant transformation [14]. This form of leukoplakia is more commonly seen in women, typically older in age [15,16].

The cause of oral leukoplakia is multifactorial, and many of which are idiopathic [17]. Some previously identified risk factors include tobacco in both the smoked or smokeless form, local injury, and Epstein Barr virus [9,18]. Major emphasis has been placed onto the use of tobacco as a paramount etiological agent for leukoplakia development with estimates of over 80% of the population with leukoplakia attributed to smoking [19]. Histologically, tobacco alters the epithelium of the oral mucosa and may lead to thickening of the epithelium and increase in pigmentation [20]. Variations in the nuclear-to-cytoplasmic ratio have been observed with exposure to carcinogenic agents such as tobacco [21]. Roed-Petersenis presented a resolution of 58.3% of oral leukoplakia cases with the elimination of smoking for at least 1 year [22]. Leukoedema may also appear in the oral cavity as faint white or gray lines on the buccal mucosa or ventral tongue in the presence of irritating substances causing local injury with use of excessive mouthwash, toothpaste, tobacco, or marijuana [23, 24]. In addition, Epstein Barr Virus has been associated with leukoplakia in the form of a thick white appearance with a folded or hairy surface. This manifestation of hairy leukoplakia is most commonly present with patients with HIV or non-HIV patients on immunosuppressive medication.

ERYTHROPLAKIA

Erythroplakia is defined as “A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease”. Clinical appearance is characterized by flat or even depressed erythematous change of the mucosa without a patch lesion. Both red and white changes in the same lesion refer to as “*erythroleukoplakia*” [13,25]. Erythroplakia lesions are most commonly observed in the floor of the mouth, the soft palate, and the ventral tongue.

They may present with a burning sensation or soreness although most cases are asymptomatic [26]. Erythroplakia is not as common as leukoplakia and has an incidence reported between 0.02% and 0.83% [10]. However, the potential for malignant transformation of erythroplakic lesions is amongst the highest for all precancerous oral lesions. Severe dysplasia or carcinoma has been observed in 80-90% of cases. An indurated lesion suggests the development of an invasive carcinoma, otherwise lesions are soft on palpation [25,27]. The etiology and pathogenesis of oral erythroplakia are poorly understood. Chewing tobacco and alcohol use are the possible etiologic factors for the development of erythroplakia. Hashibe et al [28] reported that chewing tobacco and alcohol drinking are strong risk factors for erythroplakia in the Indian population where betel-nut, paan and tobacco-chewing are highly prevalent. Human papillomavirus (HPV) and *Candida albicans* and their potential roles in the pathogenesis of oral erythroplakia have also been studied, but no definitive conclusions have been drawn [29,30]. Oral erythroplakia is commonly observed in middle aged adults and the elderly and may occur mostly in men, although more studies are required to support any significant gender predilection [31].

ORAL LICHEN PLANUS (OLP)

OLP is a chronic, autoimmune, inflammatory disease which may affect skin, oral mucosa, genital mucosa, scalp, and nails [32]. Cell death in keratinocytes triggers an uncontrolled immune response which causes an accumulation of CD8+ T cells in the basal membrane [33]. Although it is believed that OLP is a T-cell mediated autoimmune disease, its cause is partially understood in most cases and is likely multifactorial [34].

Several factors have been proposed for the etiology including genetic background, dental materials, drugs, infectious agents, autoimmunity, immunodeficiency, food allergies, stress habits, trauma, diabetes and hypertension, malignant neoplasms, and bowel disease [35]. There is a higher incidence of OLP in Indian, Arabian, and African-Americans [36]. OLP is associated with contact allergies to various dental materials such as amalgam, metal, gold, and composite restorations. However, clearance of OLP lesions results after removal of the sensitizing material [37]. Many drugs are associated with the development of OLP, especially antimalarials, cardiovascular agents, gold salts, non-steroidal anti-inflammatory drugs and hypoglycemics; however, recurrence is rare following re-administration of the drug. Infectious agents such as herpes simplex virus, Epstein-Barr virus, cytomegalovirus, herpes virus-6, hepatitis-C virus, and human papilloma virus, are associated with OLP. In particular, there is a strong association between the development of OLP and hepatitis C virus, as OLP patients are five times as likely to test positive for HCV compared to healthy adults. The virus has the ability to replicate in oral mucosal cells and attracts HCV-specific T cells [38]. Most commonly affected areas are dorsum of the tongue, buccal mucosa and gingiva. More than half of patients with OLP have mucosal involvement. Clinically, OLP may be seen as six types including papular, reticular, plaque-like, atrophic, erosive, and bullous type. The most common type is the reticular pattern, which present as a bilaterally symmetrical lesion with asymptomatic fine white lacy striae known as "*Wickham's striae*" [39]. The symptomatic erosive and atrophic forms of OLP presents with a burning sensation, mostly caused by eating hot and spicy foods. In regards to histopathology, OLP presents as hyperkeratosis, acanthosis, sawtooth shaped rete ridges, band-like T cell infiltrates in the connective tissue near the epithelium [37].

There are many conditions which mimics OLP, such as lupus erythematosus, chronic ulcerative stomatitis, proliferative verrucous leukoplakia and oral cancer. Therefore, biopsy is important if malignancy is suspected. Malignant transformation of OLP is suggested to occur due to fundamental changes in proteins of oral epithelial cells signaled by inflammatory mediatory mediators [40]. Risk factors of malignant transformation of OLP include: erosive or atrophic type, tobacco and alcohol consumption, hepatitis C infection, tongue site, and female sex. In a cohort study of women in Finland with OLP, association between OLP and the development of cancer of the lips, tongue, oral cavity, esophagus and larynx was found [41].

ORAL SUBMUCOUS FIBROSIS (OSMF)

It is a chronic and potentially malignant disorder characterized by juxta-epithelial fibrosis of the oral cavity. Fibroelastic change of the lamina propria and epithelial atrophy occur in consequence of juxta-epithelial inflammatory reaction, and eventually, stiffness of oral mucosa, leading to the development of trismus [42]. Trismus can cause difficulties in oral hygiene, speech, mastication and swallowing [43]. A burning sensation and/or intolerance to spicy food are the most common

symptoms in the initial phase of the disease as mouth opening is restricted [44,43]. Traditionally, OSMF was confined to the Indian subcontinent and parts of Asia. Due to the migration of Asian families to other areas of the world such as Europe and USA, OSMF is becoming a global issue [45]. Predominantly, it occurs in the second and third decade, and both sexes may be affected. Its etiology is not well-known and thought to be multifactorial [41]. Reported contributory risk factors include nutritional deficiencies, toxic levels of copper, chilies, genetic predisposition and immunological predisposition [46]. The strongest risk factor for OSMF, however, is the chewing of betel quid containing areca nut [42,47]. A dose-dependent relationship between the frequency and duration of chewing areca nut and the development of OSMF was observed [48]. The main hypotheses for the pathogenesis of OSMF are the defective collagen homeostasis theory, the genetic theory and the autoimmunity theory [49,50]. An abnormality in either an increase in collagen synthesis or reduction in collagen degradation is reasonable to hypothesize as the basic mechanism in the development of OSMF. Alkaloids found in areca nuts are known to stimulate fibroblasts to produce collagen. The genetic theory proposes a genetic predisposition of individuals to the effects of toxic substances found in betel quid. Finally, from an autoimmune perspective, raised autoantibodies and immune complexes have been observed in a few studies in OSMF patients, suggesting an underlying autoimmune basis for the disease [48].

TREATMENT

All leukoplakic lesions should undergo biopsy, if there is a strong suspicion of malignancy or when they do not respond to conservative therapy. Pharmacological management of Leukoplakia includes usage of antioxidants like Beta-Carotene, Lycopene, Vitamin A, Fenretinide, Bleomycin, L-Ascorbic Acid (Vitamin C), and Beta-Tocoferol (Vitamin E). Photodynamic therapy (PDT) and Carbon dioxide Laser could be used as alternative options to surgery and based on clinical evaluation. Surgical management options include for small areas of leukoplakia is excisional biopsy. For small areas of leukoplakia, excisional biopsy is usually appropriate. For larger lesions, incisional biopsy is generally preferable and it is important to obtain an adequate-size biopsy specimen, in that varying degree of hyperplasia and dysplasia may occur within the same specimen. Lesions characterized by dysplasia and CIS should be completely excised to clear margins when possible [6]. Herbal treatment includes usage of the blue green microalgae Spirulina. These are used in daily diets by natives of Africa and America, have been found to be a rich natural source of proteins, carotenoids, and other micronutrients. Green tea and its major polyphenol constituents have shown to have many health benefits including cancer prevention. Tea catechins and Tea catechin metabolites/ catabolites are bio-available in the systemic circulation after oral intake of green tea or green tea catechins.

Erythroplakia is managed in much the same fashion as leukoplakia. Non-surgical interventions include vitamin A, retinoids and bleomycin. Surgical interventions like laser surgery can be options considered for treatment. Complete surgical excision is indicated if either a premalignancy or malignancy is suspected and confirmed with a close follow-up [51]. Mixed tea and beta can be used as alternate herbal treatment options.

The treatment of patients with OSMF depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with OSMF present with moderate-to-severe disease, which is irreversible. Medical treatment is symptomatic and aimed at improving mouth movements and includes administration of steroids, placental extracts, hyaluronidase, and IFN-gamma [52]. Surgical modalities that have been used include simple excision of the fibrous bands, split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy, and nasolabial flaps and lingual pedicle flaps [53].

Because the cause of OLP is commonly unknown, treatment of OLP is dependent on its clinical presentation and whether it presents symptoms. Patients with reticular and other asymptomatic OLP can be followed without treatment. For symptomatic erosive OLP, treatment involves topical or systemic corticosteroids (ex. prednisone 30 to 60 mg) over 2 to 6 weeks or intralesional injections (triamcinolone 5 to 10 mg/mL) [37,54]. If OLP is drug induced, cessation of the drug will allow for gradual healing.

CONCLUSION

A thorough clinical and histopathological examination is required to diagnose and treat these lesions at an early stage thereby preventing the chances for malignancy.

Patient education is critical in the prevention and management of these life-altering oral diseases. The prevalence rates of Leukoplakia vary from 0.2%-5.2%, 0.02%-0.6% for Erythroplakia, 0.03%-3.2% for OSMF, 0.1%-1.5% for Lichen planus in Indian population. The global prevalence rate for Leukoplakia is between 1-2 % in all age groups, erythroplakia at 4.47%, OSMF at 4.96 % and Lichen planus at 2.0%. Future non-invasive treatment for pre-malignant leisons could be focused on traditional and herbal medicine. This is a research area with vast potential to even derive a preventive therapy for pre-malignant leisons.

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