*MINIREVIEWS*

# Precancerous lesions of oral mucosa

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## Abstract

Precancerous lesions of oral mucosa, known as potentially malignant disorders in recent years, are consists of a group of diseases, which should be diagnosed in the early stage. Oral leukoplakia, oral submucous fibrosis, and oral erythroplakia are the most common oral mucosal diseases that have a very high malignant transformation rate. Oral lichen planus is one of the potentially malignant disorders that may be seen in six different subtypes including papular, reticular, plaque-like, atrophic, erosive, and bullous type, clinically. Atrophic and erosive subtypes have the greater increased malignant transformation risk compared to another subtypes. Although there are various etiological studies, the etiology of almost all these diseases is not fully understood. Geographically, etiologic factors may vary. The most frequently reported possible factors are tobacco use, alcohol drinking, chewing of betel quid containing areca nut, and solar rays. Early diagnosis is very important and can be lifesaving, because in late stages, they may be progressed to severe dysplasia and even carcinoma *in situ* and/or squamous cell carcinoma. For most diseases, treatment results are not satisfactory in spite of miscellaneous therapies. While at the forefront of surgical intervention, topical and systemic treatment alternatives such as corticosteroids, calcineurin inhibitors, and retinoids are widely used.

**Key words:** Oral premalignant lesions; Leukoplakia; Erythroplakia; Submucous fibrosis; Lichen planus; Malignant transformation

**Core tip:** Precancerous lesions of oral mucosa are the diseases that have malignant transformation risk at different ratios. Clinically, these diseases may sometimes resemble each other. Thus, the diagnosis should be confirmed by biopsy. In early stages, histopathological findings are distinctive, but if malignant transformation occurs, identical histological features with oral carcinoma are seen. If these diseases left untreated, they can cause many problems, which may affect a patient's social and daily life.

## INTRODUCTION

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].

The most common oral precancerous lesions are oral leukoplakia, oral submucous fibrosis (OSMF), and oral erythroplakia. Actinic cheilitis, some miscellaneous inherited diseases such as xeroderma pigmentosum and Fanconi's anemia, and immunodeficiency are another potentially malignant disorders for oral carcinoma as well as these three diseases[1,2]. In a clinicopathological study

**Figure 1 White and red lesions known as erythroleukoplakia are seen.**

| Table 1 | Risk factors of malignant transformation |
|---|---|
| Female gender | |
| Long duration of leukoplakia | |
| Leukoplakia in non-smokers | |
| Location on the tongue and/or floor of the mouth | |
| Size > 200 mm$^2$ | |
| Non-homogenous type | |
| Presence of epithelial dysplasia | |

designed by Phookan *et al*[3], different oral premalignant lesions were observed in 70 of 320 patients with lower or middle socioeconomic group. Leukoplakia was the most common premalignant disorder (20.65% of patients), while percentages of lichen planus and OSMF were reported equally (0.62% of patients)[3].

The etiology of precancerous lesions of oral mucosa is not well-known[4]. 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, OSMF, 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. According to Thomas *et al*[2], while alcohol drinking and tobacco chewing may possibly be risk factors for multiple oral premalignant lesions, smoking was not associated with the risk of multiple oral premalignant lesions.

Various studies reported about etiopathogenesis of precancerous lesions of oral mucosa. Vlková *et al*[4] analyzed saliva markers of oxidative stress and reported that salivary thiobarbituric acid reacting substances and advanced glycation endproducts were significantly higher in patients than in control. They also reported that no significant differences were found in salivary advanced oxidation protein products, vascular endothelial growth factor, sialotransferase, and neuraminidase. Total antioxidant capacity and expression of superoxide dismutase were lower in patients than in age-matched controls. Nanda *et al*[5] investigated expression of CK8 and CK18 in potentially malignant disorders such as oral leukoplakia, OSMF, and oral squamous cell carcinoma and they reported that expression of CK8 and CK18 were statistically significant higher than controls. Feng *et al*[6] reported that expression of podoplanin and ABCG2 in oral erythroplakia correlate with oral cancer development. Qin *et al*[7] reported a high prevalence of p53 mutations in premalignant oral erythroplakia. Human papilloma virus (HPV) has been suggested to play a role in the etiopathogenesis of precancerous lesions of oral mucosa[8]. Punyani *et al*[9] reported that there was no statistically significant in salivary IL-8 concentrations among the precancer group and controls.

Early detection of premalignant lesions and oral cancer is very important. Therefore, 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[10].

We think that the following criteria should be taken into consideration in terms of the importance of early diagnosis: (1) symptomatic and/or non-symptomatic non-healing lesions of oral mucosa; (2) history of smoking, chewing tobacco, alcohol consumption, oral HPV infection, drug use, long-term exposure to sunlight; (3) advanced age; (4) the presence of immunodeficiency; (5) the presence of genetic disease; and (6) poor oral hygiene.

## ORAL LEUKOPLAKIA

Leukoplaki is defined as "A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"[1]. In studies reported in recent years, the prevalence of oral leukoplakia varies between 1.1% and 11.7%, with a mean value of 2.9%[11]. Although leukoplakia can occur at any age, it often occurs in individuals under the age of 40[12]. Leukoplakia is seen six times more among smokers than among non-smokers[1].

Clinically, leukoplakia may be affect any part of the oral and oropharyngeal cavity and can be divided into two subtypes including homogeneous and non-homogeneous types[1]. Homogenous lesions are characterized by uniformly flat, thin, uniformly white in colour and shows shallow cracks of the surface keratin[1,13]. Non-homogenous lesions have been defined as a white and red lesion (known as *erythroleukoplakia*) that may be either irregularly flat (speckled) or nodular (Figure 1). Verrucous leukoplakia is yet another type of non-homogenous leukoplakia[14].

Proliferative verrucous leukoplakia, which is a form of verrucous leukoplakia, was first described by Hansen *et al*[14,15] in 1985 and characterized by multifocal presentation. It has a strong potential for malignant transformation and is resistance to treatment.

Histopathologically, two distinct appearances may be seen as dysplastic or non-dysplastic leukoplakia. Risk factors of malignant transformation are shown in Table 1[14].

Oral leukoplakia should be distinguished from miscellaneous benign and/or potentially malignant disorders

that may be seen white or predominantly white diseases of the oral mucosa. The diseases should be considered in the differential diagnosis including aspirin burn, chemical injury, oral pseudomembranous and hyperplastic candidiasis, frictional lesions, oral hairy leukoplakia, leukoedema, linea alba, lupus erythematosus, morsicatio buccarum, papilloma and allied lesions, mucous patches in secondary syphilis, tobacco-induced lesions, smoker's palate (nicotinic stomatitis), stuff-induced lesion, white sponge nevus, oral lichen planus (OLP), and lichenoid reaction[1,13].

Oral leukoplakia should be confirmed by mucosal biopsy. But before biopsy, some staining methods may be used as a diagnostic aid. Chen *et al*[16] used methylene blue in fifty-eight patients with suspicious oral cavity lesions. They reported that the overall sensitivity of methylene blue uptake in cases with suspected lesions was 90%, specificity 69%, and accuracy 79%. They also reported that the positive predictive value was 74% and the negative predictive value 87%[16].

The most commonly preferred treatment options are surgical excision or $CO_2$ laser therapy. In widespread lesions, photodynamic therapy may be considered[14]. Cryotherapy is another preferred destructive method[17]. Non-surgical treatment modalities might be considered in selected patients. Carotenoids (β-carotene, lycopene), vitamins [L-ascorbic acid (vitamin C), α-tocoferol (vitamin E), retinoic acid (vitamin A), and fenretinide], and bleomycin may be used in patients with oral leukoplakia[18].

Surgical excision should be recommended in the presence of moderate and severe epithelial dysplasia. Reported recurrence ratios after surgery treatment have been varied between 10% and 35%[18]. Kawczyk-Krupka *et al*[19] compared to efficacy of cryotherapy and photodynamic treatment and reported that complete responses were obtained in 72.9% and 89.2% of patients in groups treated by photodynamic treatment and cryotherapy, respectively. Recurrence ratios were reported as 27.1% and 24.3% in groups treated by photodynamic treatment and cryotherapy, respectively[19]. Pietruska *et al*[20] reported significant reduction (on average by 53.8%) of leukoplakia lesions sizes after photodynamic therapy. Among patients treated by topical retinoic acid, while complete response ratio was reported between 10% and 27% of patients, partial response ratio was reported between 54% and 90% of patients. Recurrence of leukoplakia was reported as approximately 50% after withdrawing the topical retinoic acid[21].

## ORAL 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*". Prevalence of erythroplakia varies between 0.02% and 0.83%. It mainly occurs in the middle aged and the elderly. Male gender is most frequently affected. Mostly, a solitary le-

sion occurs over the surface of any part of the oral cavity. But the most commonly affected areas were reported as the soft palate, the floor of the mouth, and the buccal mucosa[14,22].

Etiopathogenesis is not known exactly[22]. Chewing tobacco and alcohol use are the possible etiologic factors for the development erythroplakia. Hashibe *et al*[23] reported that chewing tobacco and alcohol drinking are strong risk factors for erythroplakia in the Indian population. High prevalence of p53 mutations in premalignant oral erythroplakia was reported in a study designed by Qin *et al*[7].

Clinically, typical lesion of oral erythroplakia is less than 1.5 cm in diameter, but it also be less than 1 cm and larger than 4 cm[22]. Histopathologically, moderate or severe dysplasia was usually seen in lesion with erythroplakia. Malignant transformation rates is very high (vary from 14% to 50%), so it needs to be treated expeditiously[14,22].

Oral erythroplakia should be diminished from any disease which clinically appears red colour in oral cavity. Oral candidiasis, oral histoplasmosis, oral tuberculosis, atrophic OLP, lupus erythematosus, pemphigus, pemphigoids, amelanotic melanoma, haemangioma, telangiectasia, lingual varies, Kaposi's sarcoma, early squamous cell carcinoma, local irritation, mucositis, drug reaction, median rhomboid glossitis, and oral purpura may be confused with oral erythroplakia[22,24].

Owing to the high malignant transformation rate, early effective treatment is mandatory[22]. Surgery, either by cold knife or by laser, is the recommended therapy[1]. Surgical excision may be used in lesions with severe epithelial dysplasia or carcinoma *in situ*[22].

## OLP

Lichen planus was first described by Erasmus Wilson in 1869[25]. The disease is a chronic, autoimmune, inflammatory disease which may affect skin, oral mucosa, genital mucosa, scalp, and nails[26]. Prevalence of OLP varies from 0.5% to 3%[25]. It mainly occurs among female gender and the age of onset is usually between third and sixth decade[25,27].

Although it is believed that OLP is a T-cell mediated autoimmune disease, its cause is partially understood in most cases[28]. Several factors have been proposed for the etiology including genetic background, dental materials (amalgam, metals, gold, and composite restorations), drugs (especially antimalarials, cardiovascular agents, gold salts, non-steroidal anti-inflammatory drugs, hypoglisemics), infectious agents (herpes simplex virus, Epstein-Barr virus, cytomegalovirus, herpes virus-6, hepatitis-C virus, and human papilloma virus), autoimmunity, immunodeficiency, food allergies, stress, habits, trauma, diabetes and hypertension, malignant neoplasms, and bowel disease[26,29,30].

Even though OLP may affect any part of the oral mucosa, most commonly affected areas are dorsum of the tongue (Figure 2), buccal mucosa (Figure 3), and gin-

**Figure 2  Liken planus lesions on the dorsum of the tongue.**



**Figure 3  Reticular pattern lesions on the buccal mucosa.**

giva[26]. Clinically, OLP may be seen as six types including papular, reticular, plaque-like, atrophic, erosive, and bullous type[25]. The most common type is the reticular pattern which present as fine white striae known as "*Wickham's striae*". Typically, lesions present symmetrically and bilaterally, and usually asymptomatic. Atrophic pattern presents as a red lesion. Erosive pattern is usually seen as irregular erosion or ulceration covered with a fibrinous plaque or pseudomembrane. Both atrophic and erosive pattern are generally associated with a burning sensation and pain that exacerbated by trauma and hot, spicy or acidic foods. Plaque type clinically resembles leukoplakia because of its homogenous white nature. The dorsum of the tongue and buccal mucosa are the most affected areas in the oral cavity of patients with plaque type OLP. Multifocal plaque type lesions may be seen. This subtype is more common among tobacco smokers. The papular pattern, which is rarely seen, is characterized by small, white, raised papules with fine white striation at the periphery of the lesion. Bullous pattern is the least common type of OLP that characterized by bullae formation range from a few millimeters to several centimeters in diameter[26].

In 1906, Dubrell first described the histologic features of OLP, but within the next years, it has been revised. Diagnostic histologic features include liquefactive degeneration of the basal cells, colloid bodies (known as *Civatte* bodies), homogenous infiltrate of lymphocytes in a dense, band-like pattern along the epithelium-connective tissue interface in the superficial dermis, cytologically normal maturation of the epithelium, sawtooth rete ridges, and hyperkeratosis. In erosive lichen planus, ulceration may be seen in the surface epithelium[31].

The first case of OLP-related oral carcinoma was reported by François Henri Hallopeau in 1910. Malignant transformation ratio has been reported in 0% to 10% of patients, according to the sample's characteristics and study design, after mean follow-up of 1.5 to 10 years[25]. Increased malignant transformation risk occurs greater in erosive and atrophic forms and in cases of lesions of lateral border of the tongue[27].

If there are Wickham's striae typically, the diagnosis is easy and can be made clinically, especially reticular

pattern of OLP. But erosive or atrophic pattern need to be confirmed by biopsy in order to make the correct diagnosis[32]. Direct immunofluorescence may be useful to distinguish from some bullous diseases such as pemphigus vulgaris, benign mucous membrane pemphigoid, and linear immunoglobulin A (IgA) bullous dermatitis[31]. IgA, IgG, IgM or C3 deposition throughout the basement membrane and irregular fibrinogen deposition in the basement membrane are the diagnostic immunofluorescence findings in OLP and positivity rate is 65.8% of the patients with OLP[33]. Indirect immunofluorescence studies are not useful in terms of diagnosis[32].

Patients with reticular and other asymptomatic OLP can be followed without treatment. But if there are any symptoms and/or potential malignant risk, lesions should be treated. Both topical and systemic treatment modalities have been reported for OLP, shown in Table 2[31,34-36].

## ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis, was first described by Schwartz in 1952, is chronic and potentially malignant disorder characterized by juxtaepitelial fibrosis of the oral cavity. Fibroelastic change of the lamina propria and epithelial atrophy occur in consequence of juxta epitelial inflammatory reaction, and eventually, stiffness of oral mucosa, trismus and an inability to eat develops[37].

OSMF is usually seen in Asians population (particularly Indians) from the southern states and Taiwanese. Predominantly, it occurs in the second and third decade, and both sexes may be affected[37]. But in patients with pediatric age group were rarely seen[38-40]. Paymaster firstly described its premalignant nature in 1956. This malignant transformation rate was reported 7%-30%[37].

Its etiology is not well-known and thougt to be multifactorial[37]. The strongest risk factor for OSMF is the chewing of betel quid containing areca nut. Other factors like genetic and immunologic predisposition also play a role in OSMF because of reported in families whose members are not in the habit of chewing betel quid or areca nut[41]. Ranganathan *et al*[42] designed a case-control study consisting of 185 patients in Chennai, South India and reported strong association between areca nut

| Table 2 Miscellaneous treatment regimens for oral lichen planus | | |
|---|---|---|
| **Topical treatments** | **Systemic treatments** | **Surgery** |
| Corticosteroids | Corticosteroids | Resection |
| (triamcinolone, | Acitretin | Cryotherapy |
| fluocinolone acetonide, | Azathioprine | Lasers |
| fluocinonide, clobetasol, | Basiliximab | (CO₂, excimer laser) |
| fluticasone propionate, | Cyclosporin | |
| betamethasone sodium | Dapsone | |
| phosphate, mometasone | Eiconol | |
| furoate) | Enoxaparin | |
| Cyclosporin | Glycyrrhizin | |
| Tacrolimus | Hydroxychloroquine | |
| Pimekrolimus | Interferon alpha | |
| Rapamycin (sirolimus) | Levamisole | |
| Retinoids (tretinoin, | Mycophenolate mofetil | |
| isotretinoin) | Thalidomide | |
| Aloe vera | Tetracycline | |
| Hyaluronic acid 0.2% gel | Mesalazine | |
| | Phenytoin | |
| | Griseofulvin | |

| Table 3 Clinical and functional staging | |
|---|---|
| **Clinical stage** | **Functional stage** |
| Faucial bands only | Mouth opening $\geqslant$ 20 mm |
| Faucial and buccal bands | Mouth opening 11-19 mm |
| Faucial, buccal, and labial bands | Mouth opening $\leqslant$ 10 mm |

use and OSMF. Mehrotra *et al*[43] firstly investigated lipid profile in Indian patients with OMSF, and they observed a significant decrease in plasma total cholesterol, high-density lipoprotein cholesterol (HDL) cholesterol and Apo-A1 in patients with OSMF as compared to the controls. Similarly, Kumar *et al*[44] reported a statistically significant decrease in plasma total cholesterol, LDL and HDL cholesterol in patients with OSMF as compared to controls. Arakeri *et al*[45,46] observed that the mean concentration of copper in the home drinking water of patients with OSMF was significantly higher than in controls. Patients with OSMF also had a significantly higher copper concentration in serum and saliva, and serum ceruloplasmin than controls[45,46]. Aggarwal *et al*[47] reported that the serum beta carotene levels was significantly lower in patients with OMSF than in the controls. From these results, authors suggested that beta carotene plays an important role in the pathogenesis of OMSF and should be treated with a diet rich in beta carotene in order to reduce disease severity and progression towards malignancy[47]. Higher mast cell density as another possible pathogenic factor in patients with OSMF was suggested by Del Vecchio *et al*[48].

Symptoms such as burning sensation and/or intolerance to spicy food are the most common symptoms in the initial phase of the disease. Over time, it gradually progresses and fibrosis develops that can affect mouth opening[37]. Haider *et al*[49] proposed clinical and functional staging of OMSF, shown in Table 3.

Isaac *et al*[50] investigated histopathologic features of OSMF and observed some mucosal and submucosal changes. Mucosal changes such as atrophic changes, pigment incontinence, ulceration with granulation tissue, hyperplastic changes, dysplasia, and carcinoma were seen 74.3%, 62.8%, 40%, 25.7%, 8.6% and 0%, respectively. Submucosal changes such as fibrosis, diffuse chronic inflammatory infiltrate, atrophy of minor salivary glands, skeletal muscle atrophy, bandlike infiltrate, edema and congestion, and vesicle formation were observed 100%, 100%, 85.7%, 57.1%, 45.7%, 22.8%, and 2.8%, respectively[50].

Three current treatment modalities including surgical, physical, and medical are available for the management of OSMF. Surgical treatments may be used to improve mouth opening and movements. Physical treatment including physical exercise regimen, splints or other mouth opening devices, and microwave diathermy may be useful in some patients with OSMF. There are numerous medical therapy alternatives such as steroids, interferon gamma, placental extracts, immunized milk, pentoxifylline, buflomedil hydrochloride, nylidrin, isoxsuprine, β-carotene, lycopene, vitamins, micronutriens, collagenase, hyaluronidase, chymotrypsin, and aloe vera[37,51-57].

## ACTINIC CHEILITIS

Actinic cheilitis is a potentially malignant disease of the lip caused by exposure solar radiation. It is commonly seen the surface area of the lower lip due to the anatomic proximity. In addition to solar rays, tobacco use, lip irritation, poor oral hygiene, and ill-fitting dentures may play a role in the development of actinic cheilitis. The disease predominantly occurs in men compared to the women[58]. Martins-Filho *et al*[59] reported that the prevalence of actinic cheilitis in farmers in a semi-arid area of Brasil was 16.7%.

While actinic cheilitis shows erythema and edema in the early stages of the disease, diffuse scaling, thickened epithelium with small greyish-white plaques (known as *leukoplakia*), inflammatory areas (known as *erythroleukoplakia*), and linear fissures may present in the late stages of the disease[58]. Malignant transformation rate has been estimated ranging from 1.4% to 36% at an interval of 1 to 30 years[60]. Diagnosis should be confirmed by biopsy to evaluate the degree of dysplasia. Histopathologically, hyperplasia, acanthosis or atrophy of the epithelium, thickening of the keratin layer, and/or dysplasia, which may range from mild to severe, may be shown. In addition to these epithelial changes, in connective tissue, basophilic degeneration of collagen fibers, known as solar elastosis, is usually detected[61].

In treatment, 5-fluorouracil, scalpel vermillionectomy, chemical peel, electrosurgery, cryosurgery, CO₂ laser, imiquimod, photodynamic treatment, diclofenac 0.3% gel can be preferred[58,60,62].

## SOME INHERITED CANCER SYNDROMES

In patients with xeroderma pigmentosum and Fanconi's anemia, incidence of oral cancer has increased[1].

## IMMUNODEFICIENCY

In patients with prolonged use of immunosuppressive drugs after solid organ transplants, human immunodeficiency virus-patients, and chronic graft versus host disease after stem cell transplantation are the patients in risk group for oral cancer development[1].

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