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Review Article

Premalignant lesions of the oral cavity: current perspectives

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ABSTRACT

Premalignant lesions of the oral cavity are also called as potentially malignant disorders. The common premalignant lesions of the oral cavity include leukoplakia, oral submucous fibrosis (OSMF) and oral erythroplakia. These lesions have a very high malignant transformation rate. The exact etiological factors for development of the premalignant lesions of the oral cavity are not fully understood till date. Use of tobacco, alcohol drinking, chewing betel quid containing areca nut and solar rays are important etiological factors for resulting the premalignant lesions of the oral cavity. Early diagnosis is an important step for preventing the malignant transformations of these lesions and can be also life-saving. There are several treatment options including conservative to surgical for eliminating the premalignant lesions of the oral cavity. The aim of this study was to discuss the details of epidemiology, etiopathology, clinical presentations, diagnosis and current treatment of the premalignant lesions of the oral cavity.

Keywords: Premalignant lesions, Oral cavity, Leukoplakia, Erythroplakia

INTRODUCTION

Premalignant lesion of the oral cavity often presents as an abnormal area on the mucosal lining of the oral cavity and may result in significant anxiety of the patients. The premalignant lesions can be found in any part of the oral cavity and the anatomical landmark for oral cavity includes lips, the mucosal lining of the cheek, floor of the mouth, anterior two third of tongue, upper and lower gingiva (gums) and hard palate.[1] The exact etiology of the premalignant lesions of the oral cavity is often variable which may be associated with betel nut chewing, cigarette smoking and alcohol consumption. The premalignant lesions of the oral cavity are seen in association with and preceding oral squamous cell carcinoma.[1] According to the WHO, the premalignant lesions of the oral cavity which may undergo malignant transformation are called as potentially malignant disorders (PMD).[2] There are five types of lesions of the oral cavity described as potentially malignant disorders such as leukoplakia, erythroplakia, lichen planus, OSMF and actinic cheilitis.[3] Early diagnosis and prompt treatment of the premalignant lesions of the oral cavity is crucial for preventing the oral cavity squamous cell carcinoma.[4] The clinician often face difficulty for diagnosis of the premalignant lesions of the oral cavity on the basis of the clinical findings only as it may consists of disorderly mixture of the dysplastic and non-dysplastic cells. So, the clinicians should not underestimate this difficult situation and always suspect the threat of the malignancy in these benign looking lesions of the oral cavity. The objective of this review article is to discuss about epidemiology, etiopathology, clinical manifestations, diagnosis and current treatment of the premalignant lesions of the oral cavity.

METHODS

Research articles regarding premalignant lesions of the oral cavity were searched through a multiple approach. First, we conducted an online search of the pubmed,

scopus, google scholar and medline databases with word premalignant lesions of oral cavity, leukoplakia, erythroplakia, lichen planus and oral submucosal fibrosis. The abstracts of the published articles were identified by this search method and other articles were identified manually from citations. This manuscript reviews the epidemiology, etiopathology, clinical presentations, diagnosis and current treatment of the premalignant lesions of the oral cavity. This review article presents a baseline from where further prospective trials for premalignant lesions of the oral cavity could be designed and helps as a spur for further research in these potentially malignant disorders.

EPIDEMIOLOGY

Cancer of the oral cavity is 5th most common cancer in the world.[5] The annual incidence of the cancer of the oral cavity is approximately 29,370 cases in the United States.[5] Oral cancer was the fourth important cause for death among males and sixth among both sexes in all varieties of the cancers.[6] Leukoplakia is the most common premalignant lesions of the oral cavity.[7] The prevalence of the oral leukoplakia ranges between 1.1% to 11.7% with a mean value of 2.9%.[7] The prevalence of the erythroplakia is between 0.02% to 0.83%.[8] Oral submucous fibrosis (OSMF) is more commonly found in Southern Asia particularly Indians. The malignant transformation of OSMF is 7% to 30%. Chewing areca (betel) nut is a leading cause for leukoplakia, OSMF and oral cancer in region of Asia and the Pacific.[9] Betel nut which comes from the *Areca catchu* palm tree constitutes 10% to 20% of the world's population with highest prevalence in South and Southeastern Asia and Pacific. [9]

ETIOPATHOLOGY

There are multiple etiological factors associated with origin of the premalignant lesions of oral cavity. However, the exact etiology and pathogenesis of the premalignant lesions of the oral cavity are not fully understood. It is thought that majority of the premalignant lesions of the oral cavity are associated with chronic cigarette smoking, tobacco chewing and alcohol consumption.[10] The oral cavity leukoplakia is found six times more common among the individuals with smoking habits than non-smokers.[11] Chronic alcohol consumption is an important predisposing factor for causing leukoplakia and oral cancer. It is believed that for the carcinogenesis process, tobacco acts both in initiation and promotion stage; however, alcohol promotes the stage of carcinogenesis. The carcinogenic effects of these two factors usually do not add up but multiply.[12] Alcohol consumption increases the risk of oral leukoplakia by 1.5 folds, the risk of OSMFS by two folds and risk of erythroplakia by three folds.[13-15]

Leukoplakia may be seen in any age group but often found among the persons under the age of 40 years.[16] There are several factors have been proposed for etiology of the premalignant lesions include infectious agents (herpes simplex virus, epstein barr virus, cytomegalovirus, herpes virus, hepatitis-C virus, human papilloma virus, herpes virus-6, hepatitis-C virus and human papilloma virus), autoimmunity, food allergies, injuries, autoimmunity, immunodeficiency, stress, diabetes, hypertension, malignant neoplasm and bowel diseases.[17] The systemic predisposing factors like hormonal imbalance, excessive secretions of gastric juice, decreased salivation, plummer-vinson syndrome and vitamin deficiencies are associated with premalignant lesions of the oral cavity.[17] The risk factors associated with malignant transformation of the oral leukoplakia is given in Table 1.

Table 1: Risk factors associated with malignant transformation of the oral leukoplakia.

Risk factors
Female sex
Long standing leukoplakia
Leukoplakia in non-smokers
Leukoplakia found on the tongue and/or floor of the mouth
Size of the leukoplakia >200 mm^2
Non-homogenous type of leukoplakia
Leukoplakia with presence of epithelial dysplasia

The strongest risk factor for causing OSMF is the chewing of betel quid containing the areca nut. Betel nut chewing is an important etiology for development of the premalignant diseases of the oral cavity.[18] The important chemical constituents of the betel nut are polyphenols, tannins and alkaloids. Arecoline is the primary alkaloid present in the betel nut.[19] Long-standing chewing of the betel nut may induce chronic irritation and inflammation of the mucosal lining of the oral cavity. Other associated factors for the OSMF are immunologic disposition also play important role for development of the OSMF. The lesions of the OSMF are often related with chewing of the areca nut betel palms. Alkaloids of the areca nut affect the deposition and degradation of collagen which are crucial for pathogenesis of the OSMF. The malignant transformation of the OSMF is documented in 0.5% of the cases.[20] Actinic cheilitis is usually seen in elderly men with fair skin those are exposed to the ultraviolet radiation.[21] Human papilloma virus (HPV) may also play a role for etiopathogenesis of the premalignant lesions of the oral cavity.[22] One study reported that high prevalence of p53 mutations found in premalignant oral erythroplakia.[23]

The oral candidiasis or oral thrush is an opportunistic fungal infection of the oral cavity by candida species, the commonest being Candida albicans. This disorder is considered as a premalignant lesion of the oral cavity. There are three varieties of oral candidiasis such as acute candidiasis, chronic candidiasis and angular cheilitis. The risk factors for oral candidiasis include impaired salivary gland function, dentures, drugs, high carbohydrate diets, old age, smoking and diabetes mellitus.[24,25]

CLINICAL PRESENTATIONS

As per the WHO definition, the oral leukoplakia is defined as a white lesion of the oral cavity mucosa which cannot characterized as any other definable condition, constitutes a worldwide prevalence of around 2%.[26] Leukoplakia can be seen at any age group, however it often seen in individuals of young adults.[27] Clinically the leukoplakia may affect any part of the oral cavity and oropharynx. The leukoplakia (Figure 1) in the oral cavity is classified into two subtypes such as homogeneous and non-homogeneous types.[28]

Figure 1: Leukoplakia found on the tongue of the oral cavity.

Homogeneous variety of leukoplakia is characterized by uniformly flat, thin, uniformly white in appearance and shows a shallow crack on the surface of the whitish patch.[28] Non-homogeneous variety is defined as a white and red lesion called as erythroleukoplakia which often irregularly flat (speckled) or nodular. Verrucous leukoplakia is other types of non-homogeneous leukoplakia. Proliferative verrucous leukoplakia is a form of verrucous leukoplakia and characterized by multifocal presentations. It has high risk for malignant transformation and even resistant to treatment. The other type of the whitish lesions of oral cavity often confuse with lichen planus. These whitish lesions of the oral cavity are considered as the differential diagnosis which include hyperplastic candidiasis, chemical injury, aspirin burn, frictional lesions, stuff induced lesion, oral hairy leukoplakia, leukoderma, lupus erythematous, smoker's palate (nicotinic stomatitis), mucous patches in secondary syphilis, white sponge nevus and lichenoid reaction.[29]

Erythroplakia is a red fiery mucosal patch in the oral cavity which cannot be characterized pathologically or clinically as any other definable diseases of the oral cavity. The clinical appearance of the erythroplakia is characterized flat or even depressed erythematous alteration of the mucosa of the oral cavity without a patch lesion. It is well demarcated as red discs with smooth or granular surface. There may be concave changes seen and rarely nodular lesions are found. The soft palate, buccal mucosa and floor of the mouth are reported to be the common sites of the oral erythroplakia. Moderate to severe dysplasia are usually found in erythroplakia. Clinically, the typical erythroplakia lesion is less than 1.5 cm in size, but it is also less than 1 cm and larger than 4 cm.[30] Both white and red colour changes in the same lesion which can be called as erythroleukoplakia. The clinical symptoms of the premalignant lesions of the oral cavity are burning sensation and and/or intolerance to spicy food. The lesions often progress into fibrosis which may result in trismus. Oral erythroplakia often mimic to other red patches found in the oral cavity. These lesions are differential diagnosis of the erythroplakia such as pemphigus, oral histoplasmosis, hemangioma, telangiectasia, kaposi's sarcoma, early squamous cell carcinoma, atrophic oral lichen planus, oral candidiasis, amelanotic melanoma, drug reaction, mucositis and median rhomboid glossitis.[31]

Oral lichen planus is a premalignant lesion with characteristic lacy, white, reticular which classically seen in the buccal mucosa.[32] Lichen planus of the oral cavity may be found clinically as six different subtypes such as popular, reticular, plaque like, atrophic, erosive and bullous types.[32] The commonest variety of the oral lichen planus is reticular pattern which shows as fine white striae called as 'Wickham's striae'. Typically, these lesions are asymptomatic and may present bilaterally and symmetrically. The erosive variety is often seen as irregular erosion or ulceration covered by a fibrinous plaque or pseudo-membrane. Both erosive and atrophic types are usually associated with a burning sensation and pain which can be exacerbated by trauma/injury, spicy, hot or acidic diet. The atrophic and erosive types of the oral lichen planus have greater chance of malignant transformation in comparison to other varieties.

Predominantly, OSMF is found in second and third decade of life and both genders may be affected. It is rarely seen in pediatric age group. The earliest sign in OSMF is blanching of the oral mucosa imparting a mottled, marble like appearance. The mature lesions of the OSMF (Figure 2) show palpable fibrous bands which are essential for the diagnosis.

Figure 2: Patient with oral submucous fibrosis showing whitish bands in the oral cavity.

If the disease progresses, it leads to difficulties in mastication, speech and swallowing because of the

progressive fibrosis in the oral cavity. In OSMF, patients often present with burning sensation and/or intolerance to the spicy food. These are often seen in early stages of the OSMF. However, over time, it gradually progresses and develops fibrosis which affects the mouth opening and results in trismus.[33] The clinical and functional staging of OSMF is given in Table 2.[34]

Table 2: Clinical and functional staging of the OSMF.

Clinical stages	Functional stages
Faucial bands only	Mouth opening ≥20 mm
Faucial and buccal bands	Mouth opening 11-19 mm
Faucial, buccal and labial bands	Mouth opening ≤10 mm

Actinic cheilitis is a premalignant lesion which affect affect vermilion border of the lower lip.[35] In the early stage of the actinic cheilitis, redness and swelling of the lips are found along with desquamation of the epithelium. As the disease progresses, erosions and scrub covered ulcers may develop.

DIAGNOSIS

The diagnosis of the premalignant lesions of the oral cavity is usually done on the basis of the clinical findings and histopathological study. Brush cytology/biopsy is a minimally invasive technique, where a brush is used for obtaining a complete trans-epithelial specimen and not just exfoliated superficial cells. As this is a trans-epithelial technique which involves sampling the basal, intermediate and superficial layers of the lesions, it cannot be helpful to differentiate carcinoma in situ versus invasive carcinoma. This technique's sensitivity varies from 73% to 100% and specificity ranges from 32% to 94% respectively.[36] On the basis of the histopathological report, the leukoplakia may be found as dysplastic or non-dysplastic types. The diagnosis is confirmed by biopsy which also evaluates the degree of dysplasia. Histopathologically, erythroplakia shows moderate or severe dysplasia. In actinic cheilitis, histopathological findings show hyperplasia, acanthosis or atrophy of the epithelium, thickening of the keratin layer and/or mild to moderate dysplasia. In addition to these epithelial changes, basophilic degeneration of collagen fibers, called as solar elastosis is found in connective tissues.[37] In OSMF, the histopathological diagnosis shows chronic inflammatory cells with eosinophilic components infiltrating the sub-epithelial tissues. Long standing lesions show a reduced vascularity, decreased number of inflammatory cells and dense sheets of collagen deposited just beneath the epithelium.

The diffuse hyalinization of the sub-epithelial stroma often extends into the submucosal tissues which replace the fatty and fibrovascular tissues.[38] Currently narrow band imaging (NBI) shows high accuracy in detecting of premalignant and malignant lesions. NBI is helpful for diagnosis of the premalignant and early malignant disorders of the oral cavity as well as to assess the tumor invasion.[1]

TREATMENT

Timely diagnosis and treatment of the premalignant lesions of the oral cavity are helpful in the preventation of the development of the squamous cell carcinoma in the oral cavity.[39] If the leukoplakia is treated in its incipient stage, the chance of occurrence of the oral cancer can be reduced. Although there are several treatment options for leukoplakia, there is no specific and appropriate one for minimizing the malignant transformation of the leukoplakia. The choice of treatment options depends on the clinical stage of the leukoplakia. Presence or absence of dysplasia in histopathological study decides the treatment method. In early phase of the leukoplakia, the treatment procedure aims to eliminate the possible etiological factors such as cessation of the tobacco, alcohol and removal of mechanical and chemical injuries. A 2 to 4 weeks period is required for observation of the leukoplakia. In case of no improvement of the lesion during observation period with cessation of the etiological factors, the histopathological diagnosis should be done. The choice of the treatment depends on the presence or absence of the dysplasia in the leukoplakia of the oral cavity. In absence of any improvement or with presence of dysplasia need surgical treatment.

CONSERVATIVE TREATMENT

The conservative or nonsurgical or medical treatment of oral cavity leukoplakia include easy application, minimal or no toxicity or side effects and does not need treatment at a hospital set up and relatively low cost for the patients. The medical treatment of leukoplakia of the oral cavity is based on chemoprevention like vitamin A and retinoid, carotenoids, tea extract, bleomycin and vitamin C have been used although with inconclusive output.[3] The nonsurgical treatment overweighs because of its non-invasiveness, good cosmetic result, well tolerated by the patient without cumulative toxicity and used when the surgery is avoided or contraindicated.[3] There is another treatment option called, photodynamic therapy which helps to excise the premalignant lesions of the oral cavity as it can be used repeatedly without cumulative side effects and cause little or no scar formation.[40] Photodynamic therapy is one of the recent treatment options for oral leukoplakia. It causes cellular and tissue damage in an oxygen dependant method by the help of the non-toxic components such as light and photosensitizer.

This treatment technique is based on administration of an exogenous photosensitizer for making the sensitive of the tumor cells to light of a specific wavelength. The photo-sensitizers are usually inert and often selective affinity towards tumor cells.

In case of OSMF, the physical treatment includes physical exercise regimen, splints or different mouth opening devices and microwave diathermy. There are several medical treatments of OSMF which include steroids, interferon gamma, placental extracts, beta carotene, lycopene vitamins, immunized milk, collagenase, hyaluronidase, chymotrypsin and aloevera.[41] Different treatment options of lichen planus are given in Table 3.

Table 3: Treatment options available for lichen planus.

Topical treatment	Systemic treatment	Surgical treatment
Corticosteroids	Corticosteroids	Resection of the lesion Lasers Cryrotherapy
Cyclosporine	Azathioprine	
Tacrolimus	Basilximab	
Alo vera	Cyclosporine	
Retinoids	Dapsone	
Rapamycin	Levamisole	
Pimekrolimus	Interferon alpha	
Hyaluronic acid (0.2% gel)	Thalidomide	
	Tetracycline	
	Acitretin	

In recent years, oral candidiasis is recognized as an important factor in development of potentially malignant oral disorders. However, there is an enduring discussion whether oral candidiasis can be cause of oral malignancy or a superimposed infection in a pre-existing lesion. Thus, this candida infection of the oral cavity should be treated with great caution as it often shows a higher rate of malignant transformation. The management of the oral candidiasis involves appropriate antifungal drugs, maintaining good oral hygiene and treatment of the predisposing factors.[42] Oral candidiasis responds well to the antifungal medications and cessation of the smoking which may stop dysplasia.

SURGICAL TREATMENT

The gold standard treatment for clinically high-grade premalignant lesions of the oral cavity includes surgical excision/cold knife, laser ablation and coblation assisted excision.[43] However, the low-grade premalignant lesions may be treated with observation only. The traditional treatment of the premalignant lesions of the oral cavity such as leukoplakia, erythroplakia and erythroleukoplakia is total surgical excision which may cause a scar formation in case of large lesion.[7]

Despite advancement in the surgical techniques, the resection of the soft tissues of the oral cavity may cause negative impact on deglutition, speech and swallowing of the patient. Currently there are three treatment modalities for OSMF such as surgery, physical and medical. The surgical treatment is done to improve the mouth opening and movements.

PREVENTION

The important part for controlling the premalignant lesions of oral cavity is always advice the patient to stop the habits of betel nut chewing, gutkha chewing, cigarette smoking and alcohol consumption.[44] Mass screening of the oral cavity should be done for early detection of the premalignant lesions and prompt treatment. There should be an intensive public education for changing the life style for preventing such premalignant lesions of the oral cavity. The legislative measures like control on the production or banning and restriction on sale of tobacco products and alcohol should be strictly applied. Proper counselling by clinicians greatly helps to quit the addictions towards the tobacco. There is possibility of recurrence of the premalignant lesions of the oral cavity after its treatment, so monitoring of the patient should be needed.

CONCLUSION

The diagnosis of the premalignant lesions of the oral cavity is based on the clinical findings and histopathological report. Clinicians should do the oral cavity examination properly and alert for the patient's addiction to the smoking, alcohol consumption and betel nut chewing. The suspicious lesions in the oral cavity are usually biopsied to evaluate for dysplasia. The treatment of choice is the surgical excision and it should be initiated early for preventing into malignant transformation. Early diagnosis and prompt treatment are important steps for managing the premalignant lesions of the oral cavity as late stags may progress into severe dysplasia and even carcinoma in situ and/or squamous cell carcinoma in oral cavity.

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