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EVALUATION OF FACTORS RESPONSIBLE FOR THE OCCURRENCE OF ORAL SUBMUCOUS FIBROSIS IN PATIENTS REFERRED TO DARBHANGA MEDICAL COLLEGE AND HOSPITAL

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Abstract

Oral submucous fibrosis (OSF) is a chronic progressive and irreversible disease affecting the oral, oropharyngeal, and sometimes the esophageal mucous. OSF is a disease that causes changes similar to those of systemic sclerosis (scleroderma) but limited to oral tissues. The disease is seen in those from the Indian subcontinent and from many parts of South-East Asia. It causes significant morbidity (in terms of loss of mouth function as tissues become rigid and mouth opening becomes difficult) and mortality (when transformation into squamous cell carcinoma occurs). The introduction of chewing tobacco containing areca nut into the market has been associated with a sharp increase in the frequency of OSF. Hence based on above findings the present study was planned for Evaluation of Factors Responsible for the Occurrence of Oral Submucous Fibrosis in Patients Referred to Darbhanga Medical College and Hospital.

The present study was carried out in the Department of Dentistry, Darbhanga Medical College and Hospital Laheriasarai, Darbhanga Bihar. In the present study 30 cases of the oral submucous fibrosis were enrolled.

Oral submucous fibrosis (OSMF) is a chronic insidious disease affecting any part of the oral cavity and sometimes the pharynx. Although, occasionally preceded by or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction. It is important that preventive efforts be carried out by the concerned authorities and public health professionals in establishing tobacco cessation clinics and tobacco awareness education in such masses (especially the young generation) along with a long standing and a close knit motivation program that enables our future generations to come to avoid the menace of tobacco and its subsequent health effects.

Keywords: Oral submucous fibrosis, OSF, oral cavity, Bihar.

Introduction

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Oral submucous fibrosis results in marked rigidity and an eventual inability to open the mouth. The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx. [1]

The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing, the main component of betel quid. Betel quid chewing is a habit practiced predominately in Southeast Asia and India that dates back for thousands of years. It is similar to tobacco chewing in westernized societies. The mixture of this quid, or chew, is a combination of the areca nut (fruit of the Areca catechu palm tree, erroneously termed betel nut) and betel leaf (from the Piper betel, a pepper shrub), tobacco, slaked lime (calcium hydroxide), and catechu (extract of the Acacia catechu tree). Lime acts to keep the active ingredient in its freebase or alkaline form, enabling it to enter the bloodstream via sublingual absorption. Arecoline, an alkaloid found in the areca nut, promotes salivation, stains saliva red, and is a stimulant.

The ingredients and nomenclature of betel quid vary by region as detailed below [2]:

Pan: This is freshly prepared betel quid (with or without tobacco).

Gutka (gutkha, guttkha, or guthka): This is a manufactured version of betel quid with tobacco sold as a single-use sachet. It is primarily used on the Indian subcontinent (ie, India, Pakistan, Bangladesh). Betel quid without tobacco is mostly used in Southeast Asian

countries (ie, Taiwan, Myanmar, Thailand, China, Papua New Guinea, Guam).

Pan masala: This is a commercially manufactured powdered version of betel quid without tobacco used in the Indian subcontinent.

Pan Parag: It is a brand name of pan masala and gutka used in India.

Mawa (kharra): This is a crude combination of areca, tobacco, and lime.

Mainpuri tobacco: Popular in parts of northern India, Mainpuri tobacco is a mixture of areca nut, tobacco, lime, and various condiments. Depending on local preferences, sweeteners or spices (ie, cardamom, saffron, clove, anise seed, turmeric, mustard) are also added as flavorings. In most patients with oral submucous fibrosis, areca nut was chewed alone more frequently than it was chewed in combination with pan (ie, betel leaf plus lime plus betel catechu, with or without tobacco) or had a higher areca nut content. [3]

The pathogenesis of the disease is not well established, but the cause of oral submucous fibrosis is believed to be multifactorial. A number of factors trigger the disease process by causing a juxtaepithelial inflammatory reaction in the oral mucosa. Factors include areca nut chewing, ingestion of chilies, genetic and immunologic processes, nutritional deficiencies, and other factors.

The areca nut component of betel quid plays a major role in the pathogenesis of oral submucous fibrosis. In a 2004 study, a clear dose-dependent relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of oral submucous fibrosis. [14] Smoking and alcohol consumption alone, habits common to areca nut chewers, have been found to have no effect in the development of oral submucous fibrosis, but their addition to areca nut chewing can be a risk for oral submucous fibrosis. Commercially freeze-dried products such as pan masala, guthka, and mawa have higher concentrations of areca nut per chew and appear to cause oral submucous fibrosis more rapidly than self-prepared conventional betel quid, which contains smaller amounts of areca nut. [3]

Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150%. In one study, arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated in a variety of fibrotic diseases, in a dose-dependent manner in persons with oral submucous fibrosis. [4]

In 3 separate but similar studies, keratinocyte growth factor-1, insulin-like growth factor-1, and interleukin 6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up-regulated in persons with oral submucous fibrosis due to areca quid chewing, and arecoline may be responsible for their enhanced expression. Further studies have shown that arecoline is an inhibitor of metalloproteinases (particularly metalloproteinase-2) and a stimulator of tissue inhibitor of metalloproteinases, thus decreasing the overall breakdown of tissue collagen. [5]

Insertion/deletion5A polymorphism in the promoter region of the matrix metalloproteinase-3 gene, which results in alteration of transcriptional activities, has also been found in persons with oral submucous fibrosis but not in those with oral squamous cell carcinoma. Conversely, insertion/deletion 2G polymorphism in the promoter of the matrix metalloproteinase-1 gene has been implicated in oral squamous cell carcinoma but not oral submucous fibrosis.

Flavanoid, catechin, and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation. This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown. Oral submucous fibrosis remains active even after cessation of the chewing habit, suggesting that components of the areca nut initiate oral submucous fibrosis and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen. Chewing areca quid may also activate NF-kappaB expression, thereby stimulating collagen fibroblasts and leading to further fibrosis in persons with OSF. [6]

Areca nuts have also been shown to have a high copper content, and chewing areca nuts for 5-30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in persons with oral submucous fibrosis by stimulating fibrogenesis through up-regulation of copper-dependent lysyl oxidase activity. Further, a significant gradual increase in serum copper levels from precancer to cancer patients has been documented, [7] which may have a role in oral fibrosis to cancer pathogenesis.

The role of chili ingestion in the pathogenesis of oral submucous fibrosis is controversial. The incidence of OSF is lower in Mexico and South America than in India, despite the higher dietary intake of chilies. A hypersensitivity reaction to chilies is believed to contribute to OSF. One study demonstrated that the capsaicin in chilies stimulates widespread palatal fibrosis

in rats, while another study failed to duplicate these results. [8]

A genetic component is assumed to be involved in oral submucous fibrosis because of the existence of reported cases in people without a history of betel nut chewing or chili ingestion. Patients with oral submucous fibrosis have been found to have an increased frequency of HLA-A10, HLA-B7, and HLA-DR3.

An immunologic process is believed to play a role in the pathogenesis of oral submucous fibrosis. The increase in CD4 and cells with HLA-DR in OSF tissues suggests that most lymphocytes are activated and that the number of Langerhans cells is increased. The presence of these immunocompetent cells and the high ratio of CD4 to CD8 in OSF tissues suggest an ongoing cellular immune response that results in an imbalance of immunoregulation and an alteration in local tissue architecture. These reactions may be the result either of direct stimulation from exogenous antigens, such as areca alkaloids, or of changes in tissue antigenicity that lead to an autoimmune response. [9]

Further, the major histocompatibility complex class I chain–related gene A (MICA) is expressed by keratinocytes and other epithelial cells and interacts with gamma/delta T cells localized in the submucosa. MICA has a triplet repeat (GCT) polymorphism in the transmembrane domain, resulting in 5 distinct allelic patterns. In particular, the phenotype frequency of allele A6 of MICA in subjects with oral submucous fibrosis is significantly higher and suggests a risk for oral submucous fibrosis. [10]

Some authors have demonstrated increased levels of pro-inflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) in patients with OSF, which may be central to the pathogenesis of OSF. [11]

Iron deficiency anemia, vitamin B complex deficiency, and malnutrition are promoting factors that derange the repair of the inflamed oral mucosa, leading to defective healing and resultant scarring. The resulting atrophic oral mucosa is more susceptible to the effects of chilies and betel nuts.

Some authors have found a high frequency of mutations in the APC gene and low expression of the wild-type TP53 tumor suppressor gene product in patients with oral submucous fibrosis, providing some explanation for the increased risk of oral squamous cell carcinoma development in patients with OSF. Other studies have suggested that altered expression of retinoic acid receptor-beta may be related to the disease pathogenesis. [12]

The term oral submucosal fibrosis derives from oral (meaning mouth), submucosal (meaning below the mucosa of the mouth), and fibrosis (meaning hardening and scarring). Chewable agents, primarily betel nuts (Areca catechu), contain substances that irritate the oral mucosa, making it lose its elasticity. Nutritional deficiencies, ingestion of chilies, and immunologic processes may also have a role in the development of OSF. Oral submucous fibrosis is rare in the United States and is found only in the immigrant members of the South Asian population who chew betel nuts.

Worldwide, estimates of OSF indicate that 2.5 million people are affected, with most cases concentrated on the Indian subcontinent, especially southern India. The rate varies from 0.2-2.3% in males and 1.2-4.57% in females in Indian communities. Oral submucous fibrosis is widely prevalent in all age groups and across all socioeconomic strata in India. A sharp increase in the incidence of OSF was noted after pan-parag came into the market, and the incidence continues to increase. Oral submucous fibrosis also occurs in other parts of Asia and the Pacific Islands. Migration of endemic betel quid chewers has also made OSF a public health issue in many parts of the world, including the United Kingdom, South Africa, and many Southeast Asian countries. [13]

OSF occurs on the Indian subcontinent, in Indian immigrants to other countries, and among Asians and Pacific Islanders as a result of the traditional use of betel quid endemic to these areas. The male-to-female ratio of oral submucous fibrosis varies by region, but females tend to predominate. In a study from Durban, South Africa, a distinct female predominance was demonstrated, with a male-to-female ratio of 1:13. This was later confirmed by others, with a male-to-female ratio of 1:7. In addition, a female predominance in areca nut chewing was also noted in this region. Studies in Pakistan reported a male-to-female ratio of 1:2.3.

Conversely, a case-control study of 185 subjects in Chennai, South India revealed a male-to-female ratio 9.9:1. In Patna, Bihar (also in India), the male-to-female ratio was 2.7:1. [14] With the onset of new commercial betel quid preparations, trends in sex predominance and age of occurrence may shift.

The age range of patients with oral submucous fibrosis is wide and regional; it is even prevalent among teenagers in India. In a study performed in Saipan, 8.8% of teenagers with a mean age of 16.3 years (± 1.5 y) were found to have oral submucous fibrosis. Generally, patient age ranges from 11-60 years [14] ; most patients are aged 45-54 years and chew betel nuts 5 times per day.

OSF has a high rate of morbidity because it causes a progressive inability to open the mouth, resulting in difficulty in eating and consequent nutritional deficiencies. Oral submucous fibrosis also has a significant mortality rate because of it can transform into oral cancer, particularly squamous cell carcinoma, at a rate of 7.6%. No treatment is effective in patients with OSF, and the condition is irreversible. Reports claim improvement of the condition if the habit is discontinued following diagnosis at an early stage.

Patients with oral submucous fibrosis have an increased risk of developing oral cancer. The malignant potential and the origin of cancer are attributed to the generalized epithelial atrophy associated with it. Tobacco is the component of the quid believed to be most associated with cancer development. However, the carcinogenic property of the areca nut was discovered after noticing that cancer occurred in patients who chewed the nut without tobacco. In vitro, betel nut extracts increase the rate of cell division, reduce cell cycle time, induce DNA strand breaks, and induce unscheduled DNA synthesis. Whether the use of tobacco in addition to areca nuts is responsible for the increased risk of oral cancer is controversial because evidence is conflicting. [15]

Instruct patients regarding the importance of discontinuing the habit of chewing betel quid. Inform patients that eliminating tobacco from the quid product may reduce the risk of oral cancer. Instruct patients to avoid spicy foodstuffs. Instruct patients to eat a complete and healthy diet to avoid malnutrition. Instruct patients regarding maintaining proper oral hygiene and scheduling regular oral examinations.

Intervention studies and public health campaigns against oral habits linked to oral submucous fibrosis may be the best way of controlling the disease at the community level. Educate the community regarding the local adverse effects of chewable agents, which although not inhaled, are still not harmless.

Oral submucous fibrosis (OSF) is a chronic progressive and irreversible disease affecting the oral, oropharyngeal, and sometimes the esophageal mucous. OSF is a disease that causes changes similar to those of systemic sclerosis (scleroderma) but limited to oral tissues. The disease is seen in those from the Indian subcontinent and from many parts of South East Asia. It causes significant morbidity (in terms of loss of mouth function as tissues become rigid and mouth opening becomes difficult) and mortality (when transformation into squamous cell carcinoma occurs). The introduction of chewing tobacco containing areca nut into the market has been associated with a sharp increase in the frequency of OSF. Hence based on above findings the present study was planned for Evaluation of Factors Responsible for the Occurrence of Oral Submucous Fibrosis in Patients Referred to Darbhanga Medical College and Hospital.

Methodology:

The present study was carried out in the Department of Dentistry, Darbhanga Medical College and Hospital Laheriasarai, Darbhanga Bihar. In the present study 30 cases of the oral submucous fibrosis were enrolled.

Informed consent was taken from all the patients before including them in the study. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results and Observation:

The patients age ranged from 31 to 60 years, majority of patients were noted in the 3rd and 4th decade. Male predominate was seen compared to females with a ratio of 3.3:1 (Table 1). The patients had different habits like area nut chewing, Gutaka chewing and eating spicy food (Table 2). These were the three different habits which were predominantly found among the patients and can be attributed as major etiological factors for development of cancer.

Majority of the patients had difficulty in opening the mouth. The Lai DR (1995) criteria was used for measuring the mouth opening.[16] The mouth opening was measured using a vernier caliper. The patients predominantly had less than 20mm mouth opening. (Table 3)

The patients presented with varied clinical presentation from burning sensation to hot and spicy food, dryness of mouth, presence of white fibrous bands, limitations of mouth opening and restricted tongue movement.

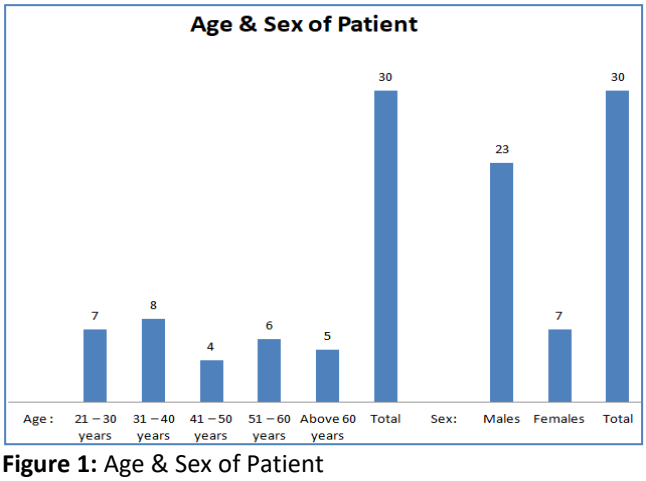

Figure 1: Age & Sex of Patient

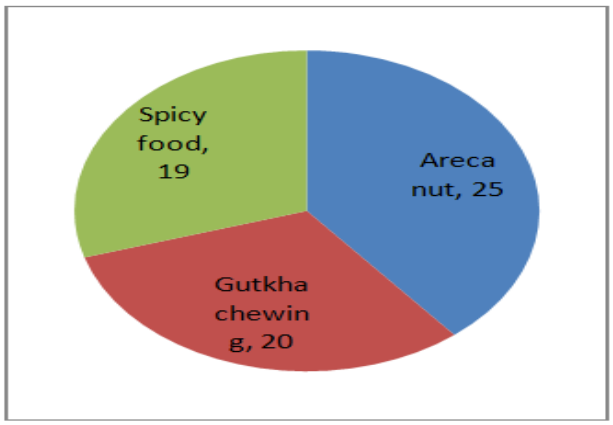

Figure 2: Oral Habits

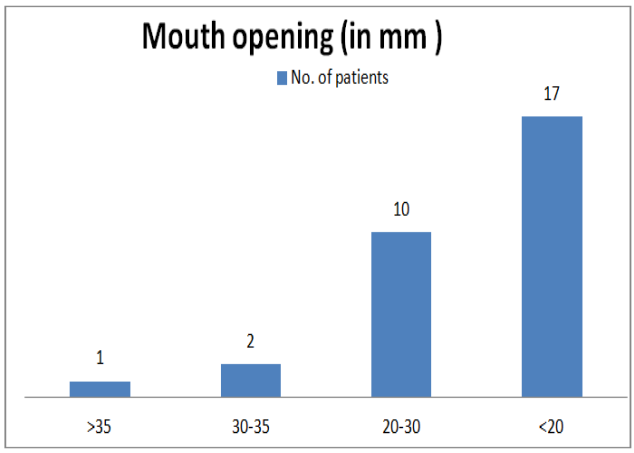

Table 3: Distribution as per Clinical Grades

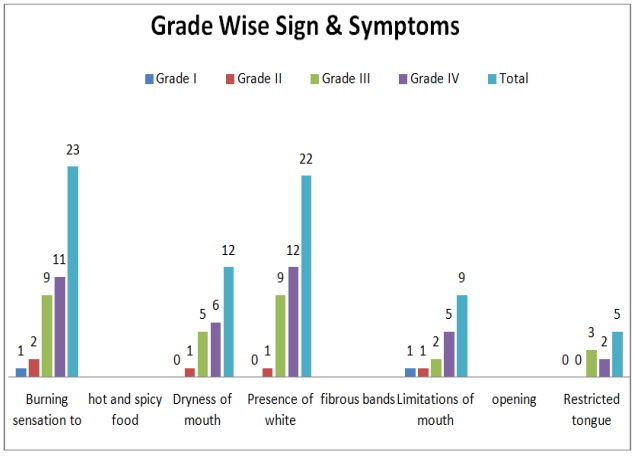

Table 4: Sign & Symptoms

Discussion:

Oral submucous fibrosis (OSMF) is a chronic insidious disease affecting any part of the oral cavity and sometimes the pharynx. Although, occasionally preceded by or associated with vesical formation, it is always associated with a juxta-epithelial inflammatory reaction followed by fibroelastic changes of lamina propria with epithelial atrophy, leading to stiffness of oral mucosa and causingtrismus and inability to eat. [17]

OSF was first reported in India in 1953 by Joshi and he coined the term submucous fibrosis of palate and faucialpillars. Various other names suggested were diffuse oral submucous fibrosis (Lal, 1953), idiopathic scleroderma of the mouth (Su,1954), idiopathic palatal fibrosis (Rao, 1962) and sclerosing stomatitis (Behl, 1962). [18]

OSF is a disease commonly occurring in the South East Asians and Indian population.[19] Indian population has the highest rate of incidence from the past to the present. Reports from the North Western India give an incidence of 2.6 and 8.5 per 100,000 per year for males and females, respectively; figures in south of India were higher 9 and 20 per 100,000 per year for males and females, respectively. [20-21]

The symptoms and signs of OSF are due to inflammation and, primarily, fibrosis. The most common initial symptoms and signs are a burning sensation, dry mouth, blanching oral mucosa, and ulceration. The burning sensation usually occurs while chewing spicy food. [22] Blanching of the oral mucosa is caused by impairment of local vascularity because of increasing fibrosis and results in a marble-like appearance. [23] Blanching may be localized, diffuse, or reticular. In some cases, blanching may be associated with small vesicles that rupture to form erosions. Patients complain that these vesicles form after they eat spicy food. These features can be observed at all stages of OSF. In the more advanced stage of the disease, the essential feature is a fibrous band restricting mouth opening and causing difficulty in mastication, speech, swallowing, and maintaining oral hygiene. [24] Development of fibrous bands in the lip makes the lip thick, rubbery, and difficult to retract or evert; a band around the lips gives the mouth opening an elliptical shape. Fibrosis makes cheeks thick and rigid. When a patient blows a whistle or tries to inflate a balloon, the usual puffed-out appearance of the cheeks is missing. In the tongue, depapillation of the mucosa around the tip and lateral margins may occur with blanching or fibrosis of the ventral mucosa. Fibrosis of the tongue and the floor of the mouth interfere with tongue movement. Hard palate involvement includes extensively blanched mucosa.

Main contributing factor, as thought by Jayanthi et al.[25] is the use of areca nut, tobacco, and crude lime wrapped in betel leaf. Experimentally, an alkaloid component of the areca nut, “Arecoline,” can induce fibroblast proliferation and collagen synthesis and may

penetrate the oral mucosa to cause progressive crosslinking of collagen fibers. The direct contact of the quid mixture with oral tissues results in their continuous irritation by various components, including biologically active alkaloids (arecoline, arecaidine, arecolidine, guvacoline, guvacine, flavonoids, tannins, and catechins) and copper. Other factors, such as genetic and immunologic predisposition, probably also play a role as OSF has been reported in families (both children and adults) whose members are not in the habit of chewing betel quid or areca nut. [26]

Various classifications have been purposed depending on the clinical features such as by Wahi et al.[27] (1966) who classified OSF on the basis of clinical features, severity, and extent of involvement into three clinical groups; another classification was by Sirsat and Pindborg (1967)[28] who classified the histological picture of OSF into four stages. Lai et al.[15,29] classified patients on the basis of mouth opening. We have staged our patients as per the classification of Lai et al.

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."[30]

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. Genomic instability and altered keratinocyte phenotype has been reported to play an important role in malignant transformation. [31]

The factors that have been discussed as possible etiological factors to date 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. [32]

Four alkaloids are responsible for the pathologic effects of the areca nut, of which arecoline is the main agent. The other alkaloids present in areca nut are arecoline, arecaidine, guvacine and guvacoline. Arecoline undergoes nitrosation and leads to the formation of areca nut specific nitrosamine namely nitrosoguvacoline, nitrosoguvacine and 3-methyl nitrosominopropionitrile. These nitrosamines alkylate deoxyribonucleic acid (DNA) and metabolism of these areca nut specific nitrosamine lead to formation of cyanoethyl, which binds with o'methyl guanine in DNA. Prolonged exposure to this chemical irritant leads to malignant transformation. [33]

Conclusion:

Oral submucous fibrosis (OSMF) is a chronic insidious disease affecting any part of the oral cavity and sometimes the pharynx. Although, occasionally preceded by or associated with vesical formation, it is always associated with a juxta-epithelial inflammatory reaction. It is important that preventive efforts be carried out by the concerned authorities and public health professionals in establishing tobacco cessation clinics and tobacco education in such masses (especially the young generation) along with a long standing and a close knit motivation program that enables our future generations to come to avoid the menace of tobacco and its subsequent health effects.

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