



## Oral Submucous Fibrosis- A Review on Clinical Presentation, Histology, Epidemiology, Aetiology, Pathogenesis, Malignant Potential and Management (Review Article)

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### ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic, devastating disease characterised by juxtaepithelial fibrosis of the oral cavity. <sup>(1)</sup> Oral submucous fibrosis (OSMF) is a premalignant condition caused by betel chewing. It is very common in Southeast Asia but has started to spread to Europe and North America. OSMF can lead to squamous cell carcinoma, a risk that is further increased by concomitant tobacco consumption. OSMF is a diagnosis based on clinical symptoms and is confirmed by histopathology. Hypovascularity leading to blanching of the oral mucosa, staining of teeth and gingiva, and trismus are major symptoms. Major constituents of betel quid are arecoline from betel nuts and copper, which are responsible for fibroblast dysfunction and fibrosis. A variety of extracellular and intracellular signaling pathways might be involved <sup>(2)</sup>. We review and discuss all OSMF, including the terminology, presentation, aetiology, and pathogenesis, and provide a brief overview of its conservative and surgical management.

**KEYWORDS-** Oral Submucous Fibrosis, Epidemiology, Aetiology, Pathogenesis, Clinical Presentation, Management.

## INTRODUCTION

The most widely accepted definition of the disease by Pindborg and Sirsat is one of an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by, or associated with, formation of vesicles, it is always associated with a juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria and epithelial atrophy that leads to stiffness of the oral mucosa and causes trismus and an inability to eat.

<sup>(3)</sup> A variety of etiologic factors including capsaicin, betel nut alkaloids, hypersensitivity, autoimmunity, genetic predisposition and chronic iron and vitamin B-complex deficiency have been suggested by various authors, the most common of which is chewing areca nut. Excessive use of areca nut may cause fibrosis due to increased synthesis of collagen and induce the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation / peroxidation of polyunsaturated fatty acids which affect essential constituents of cell membrane and might be involved in tumorigenesis. Arecanut chewing is deep rooted in Indian culture and has been used as a mouth freshening agent that has various symbolic roles throughout Indian history. The most alarming fact is that this habit is becoming increasingly popular among adolescents. <sup>(4)</sup>

## CLINICAL PRESENTATION

Clinical presentation depends on the stage of the disease. Initially, most patients present with a burning sensation or intolerance to spicy food, and they may have vesicles, particularly on the palate. Ulceration and dryness of the mouth is later followed by fibrosis of the oral mucosa, which leads to rigidity of the lips, tongue, and palate, and trismus. <sup>(5)</sup> Pindborg in 1989 divided OSMF into 3 stages, on basis of clinical features <sup>(6)</sup>:

**Stage 1 (Stomatitis):** It includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation, and mucosal petechia.

**Stage 2 (Fibrosis):** fibrosis occurs in ruptured vesicles and ulcers when they heal, which is the hallmark of this stage. Early lesions demonstrate blanching of the oral mucosa. Older lesions include vertical and circular palpable fibrous bands in the buccal mucosa and around the mouth opening or lips, resulting in a mottled, marble like appearance of the mucosa because of the vertical, thick, fibrous bands running in a blanching mucosa. Specific findings include the following: (i) Reduction of the mouth opening (trismus) (ii) Stiff and small tongue; (iii) Blanched and leathery floor of the mouth; (iv) Fibrotic and depigmented gingiva; (v) Rubbery soft palate with decreased mobility; (vi) Blanched and atrophic tonsils; (vii) Shrunken budlike uvula; (viii) Sinking of the cheeks, not commensurate with age or nutritional status.

**Stage 3 (Sequelae of OSMF):** (i) Leukoplakia is precancerous and is found in more than 25% of individuals with OSMF. (ii) Speech and hearing deficits may occur because of involvement of the tongue and the Eustachian tubes. In addition to the above staging, in 1995 Khanna et al <sup>(7)</sup> developed a group classification system for the surgical management of trismus. Group I: This is the earliest stage and is not associated with mouth opening limitations. It refers to patients with an interincisor distance of greater than 35 mm. Group II: This refers to patients with an interincisor distance of 26-35 mm. Group III: These are moderately advanced cases. This stage refers to patients with an interincisor distance of 15-26 mm. Fibrotic bands are visible at the soft palate, and pterygomandibular raphe and anterior tonsillar pillars. Group IVA: Trismus is severe, with an interincisor distance of less than 15 mm and extensive fibrosis of all the oral mucosa. Group IVB: Disease is most advanced, with premalignant and malignant changes throughout the mucosa. Early OSMF presents with a burning sensation in oral cavity aggravated by spicy food (42%), followed by either hyper salivation or dryness of the mouth (25%). <sup>(8)</sup> It presents with blisters especially on the palate, ulcerations or

recurrent generalized inflammation of the oral mucosa. Common initial symptoms are: Intolerance/Burning sensation in the mouth on consuming hot and spicy food: <sup>(9)</sup>

- Blanching, i.e., marble like appearance of the oral mucosa and stiffness of oral mucosa
- Reduced mobility of the soft palate and tongue
- Hypersalivation
- Defective gustatory sensation
- Dryness of the mouth
- Blisters on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa
- Mild hearing loss due to blockade of Eustachian tube
- Trismus

In advanced OSMF, oral mucosa becomes blanched and slightly opaque with appearance of white fibrous bands on buccal mucosa, lips, soft palate, faucial pillars and tongue. With progressive fibrosis, stiffening of certain areas of mucosa occur which results in difficulty in opening of the mouth, difficulty in swallowing and inability to whistle or blow air. In severe cases, the patient cannot protrude the tongue beyond the incisor teeth and there is a progressive closure of the oral opening.

The oral mucosa is involved symmetrically and the fibrous bands in the buccal mucosa run in a vertical direction. The density of the fibrous deposit varies from a slight whitish area on the soft palate causing no symptoms to a dense fibrosis causing fixation and shortening or even deviation of the uvula and soft palate. Depending on the habit of chewing or swallowing tobacco, areca nuts and its related products, the fibrotic changes can be seen in the mucosa of the oral cavity or oesophagus. Laterality of OSMF depends on the fact that which side of the oral mucosa is more exposed to tobacco products. This is usually noted during examination that one side of the buccal mucosa is fibrosed whereas other side is completely normal

## HISTOPATHOLOGICAL CLASSIFICATION OF OSMF <sup>(12)</sup>

### Very early stage (Grade I):

- A finely fibrillar collagen, dispersed with marked edema.
- The fibroblastic response is strong.
- The blood vessels are sometimes normal, but more often they are dilated and congested.
- Inflammatory cells, mainly polymorphonuclear leukocytes with an occasional eosinophils are present.

### Early stage (Grade II):

- The juxtaepithelial area shows early hyalinization.
- Plump young fibroblasts are present in moderate numbers.
- The blood vessels are dilated and congested.
- The inflammatory cells are mostly mononuclear lymphocytes, eosinophils and an occasional plasma cell.

### Moderately advanced stage (Grade III):

- The collagen is moderately hyalinized.
- The fibroblastic response is less marked, the cells present being mostly adult fibrocytes.
- Blood vessels are normal or constricted.
- The inflammatory exudates consist of lymphocytes and plasma cells, although an occasional eosinophil is seen.

### Advanced stage (Grade IV):

- The collagen is completely hyalinized.
- The hyalinized areas are devoid of fibroblasts.
- Blood vessels are completely obliterated or narrowed.
- The inflammatory cells are lymphocytes and plasma cells.

## EPIDEMIOLOGY <sup>(10, 11)</sup>

Geographically, OSMF has a specific distribution and affects predominantly Asians (and particularly Indians) from the southern states, and Taiwanese.

Other series of OSMF in Europe, the Far East, and the Pacific Rim have been reported. An estimate from 1996 indicated that globally, about 2.5 million people have OSMF, but studies have found that over 5 million people are affected in India alone (0.5% of the Indian population). It is also estimated that up to 20% of the world's population use betel nut in some form, so the incidence of OSMF is likely to be much higher than current estimates suggest, and it is regarded as a public health issue in the Indian subcontinent, the UK and South Africa. It is predominantly seen in the second or third decade, and recent data suggest a male predominance, however, both sexes are equally at risk. Oral cancer that arises in those who chew betel quid is one of the most common malignancies in south and southeast Asian countries.

#### AETIOLOGY

At first, OSMF was thought to be idiopathic, but it was later concluded to be multifactorial in origin, and possible aetiological factors include capsaicin in chillies, iron, zinc, and deficiencies in essential vitamins.<sup>(13)</sup> Various auto antibodies and specific human leucocyte antigens in some patients have indicated an autoimmune role as well as a genetic predisposition for the disease. However, various epidemiological studies, large cross-sectional surveys, case control studies, and cohort and intervention studies have provided overwhelming evidence that areca-nut is the main aetiological factor in OSMF. The nut is the endosperm of the fruit of the *Areca catechu* palm tree.<sup>(7)</sup> A range of case-control studies have given convincing evidence that there is a definite dose-dependent relation between areca-nut and causation of the disease, and it is well known that the onset of the disease is directly proportional to the concentration, incidence, and duration of chewing the nut (without tobacco). Generally, younger patients develop clinical features of OSMF within 3.5 years from onset of the habit while in older patients it takes 6.5 years.<sup>(14)</sup> Currently, in India, Pakistan, and Bangladesh, betel quid and gutkha

are the most commonly used commercially freeze-dried areca-nut products. Gutkha (also spelled gutka or guthka), thought to be derived from Hindi meaning "a shred or small piece" is a light brown, grainy powder available in compact storable sachets. It consists mainly of areca-nut, tobacco, and flavours, and is typically taken to relieve stress. When chewed it dissolves quickly in saliva and provides central stimulation, which is said to be more intense than tobacco.

#### PATHOGENESIS

The relationship of OSMF to chewing of areca nut/quid or panmasala has been directly related to OSMF, whereas chewing or smoking tobacco did not increase the risk for OSMF. In a case-control study from Kerala, India, betel quid alone increased the odds ratio for OSMF to 56.2.<sup>(15)</sup>

##### (1) Extracellular matrix and fibroblast changes:

The most obvious changes occur in the extracellular matrix of the submucous tissue layer. Fibrosis is associated with quantitative and qualitative alterations of collagen deposition within the subepithelial layer of the oral mucosa. This is partly due to marked deficiencies in collagen and fibronectin phagocytosis by fibroblasts caused by betel nut alkaloids (arecoline, arecaidine). On the other hand, tannins from areca nuts increase collagen fiber resistance to collagenase.<sup>(14)</sup>

In vitro, areca nut extract suppresses the synthesis of 3-Hydroxy-proline and the growth and attachment to collagen of oral fibroblasts in a dose-dependent manner. Pretreatment of oral mucosa fibroblasts with other areca nut compounds such as buthionine sulfoximine or diethyl maleate potentiates the cytotoxic effects.<sup>(16)</sup> Over expression of stress protein colligin was found in 70% of OSMF patients. It has been suggested that colligin may contribute to the increased deposition of collagen I and thereby to fibrosis development in oral submucosa.<sup>(17)</sup> CD34 a marker of mucosal vascular endothelium and basic fibroblast growth factor are both increased

in OSMF and demonstrate an association to the stage of fibrosis. <sup>(18)</sup>

### (2) Arecoline

The major compound of areca nut can induce various growth factors like insulin-like growth factor-1 and keratinocyte growth factor-1, and basic protein cystatin C, but inhibits proinflammatory cytokines like interleukin-6. Arecoline stimulates another key molecule in the regulation of fibrosis – the hypoxia-inducible factor-1 $\alpha$  – in a dose-dependent manner. <sup>(19)</sup>

### (3) Copper

Copper is implicated in the pathogenesis of fibrotic disorders because it stimulates collagen synthesis in oral fibroblasts. Elevated serum copper levels are associated with duration of betel nut chewing and severity of OSMF.

### (4) Areca nuts

It contains high copper concentrations compared to other nuts, and copper becomes liberated during chewing. Mass absorption spectrometry of buccal mucosa detected a mean tissue copper level of 5.5 $\pm$ 2.9  $\mu$ g/g in patients with OSMF compared with 4 $\pm$ 1.9  $\mu$ g/g in controls. Copper has been detected in the epithelium and the connective tissue of the OSMF specimens. Copper levels are significantly higher in commercial areca nut products compared with raw areca nut. <sup>(2)</sup>

### (5) Immune system

Betel quid affects the immune system. The levels of transforming growth factor (TGF)- $\beta$  and interferon (IFN)- $\gamma$  are lower in mononuclear cells from OSMF patients than from controls. <sup>(2)</sup>

### (6) Antioxidant status and cytokines

Glutathione S-transferases (GST) are part of the antioxidant system. GSTT1 and GSTM1 null phenotypes increase the risk of OSMF. Reduced glutathione levels in betel quid users are related to raised levels of the proinflammatory interleukin-6. Diminished levels of superoxide dismutase but increased levels of malondialdehyde – a lipid peroxidation product – have been detected in OSMF. <sup>(20)</sup>

### (7) The role of tobacco addition

Several surveys show an increase in the incidence of OSMF when areca nut and tobacco consumption are combined. A relative risk of 489 has been reported for OSMF in consumers of areca nut/tobacco compared with nonusers. The consumers of mixed products are often younger. OSMF develops faster in these patients (after 2.7 years) than in betel quid chewers (after 8.6 years). Cancerous transformation appeared at an early age.

Both genotoxicity and carcinogenicity of areca nut and betel quid with or without tobacco admixture are well documented. Nitrosamines, reactive oxygen species, and depletion of endogenous antioxidant capacity are the dominant contributors. Oesophageal subepithelial fibrosis is seen more frequently in patients who had consumed areca nut and tobacco for longer than 5 years. <sup>(2)</sup>

### (8) Changes in gene expression and activity

More recently, the expression profiles of genes in OSMF and normal oral mucosa have been studied more intensively. In one study, 14,500 genes were analyzed using gene chip arrays. The study demonstrated 716 genes were upregulated and 149 genes were downregulated in OSMF. The gene expression profiles of normal controls and OSMF patients were clearly distinct, in particular the genes involved in immune response, inflammatory response, and TGF- $\beta$ -induced epithelial-mesenchymal transition. <sup>(21)</sup>

In a comprehensive analysis of water-soluble and ethanol-soluble areca nut constituents, it was demonstrated that both alkaloid and polyphenol fractions induced TGF- $\beta$  signaling in human keratinocytes. Involved genes included TGF- $\beta$ 2, SMAD-3, matrix metalloproteinase (MMP)1, MMP2, and MMP9, and others. In contrast, no TGF signaling was induced in fibroblasts. <sup>(22)</sup>

## RELATED CONDITIONS IN ORAL SUBMUCOUS FIBROSIS

Oral leukoplakia and OSMF are clinically distinct premalignant states that precede the development of oral Squamous Cell Carcinoma (SCC). Oral

leukoplakia is an early sign of mucosal damage. It can appear as macular, plaque-like, erosive, or verrucous lesion with a homogeneous or speckled white appearance. Erythroplakia would be the reddish counterpart that poses a greater risk for malignant transformation into invasive SCC. In more-advanced OSMF, fibrosis is a hallmark leading to impairment in mouth opening, speaking and swallowing.

Oral cancer accounts for up to 40% of all malignancies in Asia. Tobacco smoking and chewing betel quid containing tobacco are the major risk factors for oral cancer, whereas betel quid without tobacco significantly increased oral cancer risk in only one study.

Attempts have been made to identify specific molecular events as prognostic markers to identify oral precancerous lesions with higher malignant

potential. The expression of TGF- $\alpha$  and epidermal growth factor-receptor was upregulated in oral leukoplakia, OSMF, and oral SCC relative to normal oral mucosa.

Arecoline is considered the most important etiological factor, but addition of peroxy nitrite (a reaction product of cigarette smoking) and nicotine acted as a synergistic effect on the arecoline-induced cytotoxicity and glutathione depletion. Other factors associated with malignant transformation of OSMF have been identified. Oesophageal involvement is the most common extraoral manifestation in betel nut chewers. Oesophageal abnormalities were seen more frequently in patients who had consumed a combination of areca nut and tobacco; the oesophagus may also be involved in about two-thirds of patients. <sup>(2)</sup>

**Table 1:** Factors associated with malignant transformation of oral submucous fibrosis.

Molecules	Description	Findings	References
0(6)-methylguanine-DNA	Methyltransferase DNA repair enzyme	Low levels associated with advanced oral SCC and lymph node involvement	23
Mutations of p53	Tumor suppressor gene	Degree of p53 staining increased with morphologic transformation of epithelial cells, associated with progression of oral SCC	24
p16INK4alpha/p19 ARF mutations	p16 regulated G1 proliferation	p53 independent pathway of tumorigenesis	25
MDM2-P2 promoter	Transcriptional target of p53	Elevated levels of MDM2 protein in dysplastic lesions and oral SCCs	26
C-jun	Protooncogene	Chronic stimulation by areca nut and arecoline leading to oral SSC	27
mtDNA mutations	Mitochondrial DNA	Contributor to the early phase of oral carcinogenesis	28
HSP70	Heat shock protein	Significant correlation of HSP70 expression with consumption of betel and tobacco; in patients with premalignant lesions median transition time (pre-malignancy to malignancy) was significantly shorter in HSP70 overexpressing cases; oral cancer patients with elevated levels of HSP70 showed decreased median disease-free survival time	29
HSP27	Heat shock protein	Increased in betel nut-induced oral SCC due to direct action of arecoline	30

## PREVENTION AND TREATMENT

Patients with OSMF characteristically complain of two problems: an inability to open the mouth, which impedes function, and a burning sensation and intolerance to spicy foods (intolerance to normal diet in severe cases). Management aims to reverse or alleviate these signs and symptoms, stop the disease progressing, and minimise the risk of malignant transformation. The current protocol for the management of OSMF can be divided into 3 broad groups: surgical, physical, and medical treatments.

**(1) Surgical treatment:** used mainly to manage trismus, involves incising and releasing the fibrotic areas, and leads to further scarring and fibrosis. The introduction of remote tissue (pedicled, such as a buccal fat pad, nasolabial or platysmal flaps, or free tissue transfer) in an attempt to release fibrosis is one approach but results are variable.

**(2) Physical treatment:** attempts to influence the remodelling of tissue by using movement – for example, exercises and physiotherapy, various splints or other devices to improve mouth opening, or localised heat (such as with microwave diathermy).

**(3) Medical treatment:** includes dietary supplements (vitamins, antioxidants), the use of anti-inflammatory drugs (principally corticosteroids), proteolytic agents (such as hyaluronidase), anticytokines, and other agents that are not available in the UK. They can be given orally, topically, or by submucosal injection. Operation is generally reserved for established cases of OSMF while physical treatment is usually combined with all other interventions.

## CONCLUSION

As management of OSMF aims to slow the progression of the disease and adding different endeavours to control OSMF and better legislation to govern the availability and sale of areca-nut is recommended so that such type of problem can be handled easily. As such type of disease is

controlled by composite work of doctor and patient to cure such type of disease.

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