Oral submucous fibrosis: Etiology and management – A review

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ABSTRACT
Oral submucous fibrosis (OSF) 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. OSF can lead to squamous cell carcinoma, a risk that is further increased by concomitant tobacco consumption. OSF is a diagnosis based on clinical symptoms and confirmation by histopathology. Areca nut has been deeply rooted in Indian culture and been used as a mouth freshening agent that has had various symbolic roles throughout Indian history. Hypovascularity leading to blanching of the oral mucosa, staining of teeth and gingiva, and trismus are major symptoms. Prevention is most important, as no healing can be achieved with available treatments.

KEY WORDS: Areca nut, Blanching, Collagen, Fibrosis, Oral submucous fibrosis, Tobacco

INTRODUCTION
Oral submucous fibrosis (OSMF) is an insidious, chronic fibrotic change affecting any part of oral mucosa and has been considered as a potentially malignant disorder. OSMF is a chronic disease of oral mucosa characterized by inflammation and progressive fibrosis of the lamina propria and deeper connective tissues, followed by stiffening of mucosa resulting in difficulty in opening the mouth. Other terms used to describe this condition are juxta-epithelial fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, submucous fibrosis of the palate and pillars, sclerosing stomatitis, and diffuse OSMF.[¹,²]

Clinical Presentation of Oral Submucous Fibrosis

Signs of early stage
The first and foremost sign of OSF is erythematous lesions sometimes in conjunction with petechiae, pigmentation, vesicles, and the presence of excessive salivation as a physiological effect, i.e., chewing of betel nut causes excessive salivation.[³,⁴] These initial lesions are followed by a paler mucosa, which may comprise “marble stone appearance.”

Signs of later stage
In the later stage of the disease, it presents as fibrotic bands located beneath an atrophic epithelium. Palpable fibrous bands occur with the frequency of: [⁵] Faustral bands > Buccal bands > Labial bands and the circular band around the entire rima oris (mouth orifice). Later to this forms the “Hockey stick” or bud shape uvula. Increased fibrosis eventually leads to loss of resilience, which interferes with speech, decreased tongue mobility and a decreased ability to open the mouth. Tongue protrusion is measured from the mesioincisal angle of upper central incisor to the tip of the tongue when maximally extended. Hyposalivation due to fibrosis of the salivary gland duct opening and the fibrosis reaching up to the submucosa and minor salivary glands may occur. Followed by severe symptoms include, hearing loss due to stenosis of the eustachian tubes, dysphagia to solids if the esophagus is involved, inability to blow cheeks, and the atrophic epithelium causes a smarting sensation and inability to eat hot and spicy food.[⁶]

Classification of OSMF

Clinical classification
Stage I – Early OSMF without trismus and mean interincisal opening (MIO) >35 mm.
Stage II – Mild to moderate OSMF, MIO (26–35 mm)
Stage III – Moderate to severe, MIO 15–25 mm

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Stage IVa – Severe, MIO – <15 mm
Stage IVb – Malignant/premalignant lesion seen intraorally.

**Histological Classification**
Depending on the microscopic features of the lesion, it can be divided into four categories.

Grade I – A finely fibrillar collagen, dispersed with marked edema.
In inflammatory cells, polymorphonuclear leukocytes with an occasional eosinophil are present.

Grade II – The juxta-epithelial area shows early hyalinization.
The inflammatory cells are mostly mononuclear lymphocytes, eosinophils, and an occasional plasma cell.

Grade III – The collagen is moderately hyalinized.
The inflammatory exudates consist of lymphocytes and plasma cells, although an occasional eosinophil is seen.

Grade IV – The collagen is completely hyalinized.
The inflammatory cells are lymphocytes and plasma cells.

**Pathology**
Structural and microstructural changes show that the epithelial changes in different stages of OSF are predominantly hyperplasia (early) and atrophy (advanced) associated with an increased tendency for keratinizing metaplasia. Subepithelial changes are acquired on the basis of histopathological appearance; four different stages have been defined—very early, early, moderate advanced, and advanced. This grouping was based on the amount and nature of subepithelial collagen, presence or absence of edema, the physical state of mucosal collagen, overall fibroblastic response, state of blood vessels, and predominant cell type in inflammatory exudate. Significant hematological abnormalities have been reported in OSF, including an increased erythrocyte sedimentation rate, anemia, eosinophilia, increased gamma globulin, decrease in serum iron, and increase in total iron binding capacity (TIBC). The percentage saturation of transferrin also decreased and a significant reduction in total serum iron and albumin was found.[7]

**Etiology**
Oral submucous fibrosis is a multifactorial origin. Some factors include tobacco, lime, arecanut, capsicain in chilies, deficiency of iron, zinc and essential vitamins, immunological disorders, and collagen disorders. Oral submucous fibrosis, now globally accepted as an Indian disease, has one of the highest rates of malignant transformation among potentially malignant oral lesion and conditions.[8]

**Tobacco and Lime**
Pan Masala, Gutka, and Mawa (areca, tobacco, and lime) are commercially freeze-dried products with high concentrates of areca nut per chew.[9]

**Betel Quid**
The term “betel quid” is often used with insufficient attention given to its varied contents and practices in different parts of the world. A “betel quid” generally contains betel leaf, areca nut, and slaked lime and may contain.[10]

**Areca Nut**
Areca nut is the seed of the fruit of the oriental palm *Areca catechu*. It is the basic ingredient of a variety of widely used chewed products.

**Genetic Susceptibility**
To date, no conclusive etiologic agent has been identified, although plenty of data has been generated on various aspects of the disease. These include genetic, carcinogenic, immunologic, viral, nutritional, and autoimmune possibilities, all of which also have been implicated in the development of oral cancer.[11] However, only a small fraction of those using betel quid develop the disease; this shows a clear genetic susceptibility.

**Nutritional Deficiency**
Several investigators have reported iron, vitamin, and protein deficiencies in OSMF. A subclinical Vitamin B complex deficiency has been suspected in cases of OSMF with vesiculations and ulcerations of the oral cavity.[12] The deficiency could be precipitated by the effect of defective nutrition due to impaired food intake in advanced cases and may be the effect, rather than the cause of the disease.

**Immunological Basis**
An immunologic phenomenon is thought to play a role in the etiopathogenesis of OSMF. Many investigators suggest an autoimmune basis for this disease.[13] It may be due to the presence of HLA A10 and DR3, DR7 antigens found in OSMF patients.

**Diagnostic Criteria and Investigations**
The hallmark of diagnosing OSF is clinical and histological. Clinically, one or more of the following symptoms should be present: Blanching of oral mucosa defined as a persistent, white, marble-like appearance of the oral mucosa, which may be localized, diffuse or reticular; tough, leathery texture of the mucosa.
and palpable, whitish, fibrous bands present in the mucosa.\textsuperscript{[14]} The presence of palpable fibrous bands is a diagnostic criterion for submucous fibrosis. The fibrous bands occur especially in the buccal mucosa, retromolar trigone and around the rima oris which result in restricted mouth opening. Tongue is devoid of papillae and its mobility is impaired especially during protrusion. No specific test will confirm a suspected diagnosis of OSMF. An incisional biopsy will reveal a thinned surface and the excessive deposition of collagen in the submucosa.\textsuperscript{[15]} A biopsy of the most severe area or ulceration is recommended to rule out squamous cell carcinoma because tobacco product contains many carcinogens and OSMF is considered to be a pre-malignant lesion for squamous cell carcinoma of the oral cavity. Some investigation may also include: Blood chemistry, raised ESR, anemia, eosinophilia, increased gamma-globulin, decreased serum iron, increased TIBC, decreased albumin, alteration in serum copper and zinc ratio, and depression of lactate dehydrogenase isoenzyme ratio at the tissue level.\textsuperscript{[16]}

**Treatment Options for Oral Submucous Fibrosis**

The main symptoms of oral submucous fibrosis include trismus, burning sensation, and difficulty to eat. Hence, the treatment modalities have been tried to relieve these symptoms. It has been tried by both surgical and nonsurgical approach.\textsuperscript{[17]}

**Cessation of Habit**

Patient education, reduction or even elimination of the habit of areca nut chewing is an important preventive measure, at least in the early stages of OSF; it could probably slow the progress of the disease.

**Supplementary Care**

Supplementary care includes micronutrients and minerals such as iron, vitamins, and minerals rich diet should be advised to patients with oral submucous fibrosis.\textsuperscript{[18]}

Lycopene is an antioxidant obtained from tomatoes. Lycopene has two major kinds of biological effects: antioxidative effects and non-oxidative mechanisms.

Vitamins; Vitamin E acts as an antioxidant and prevents the formation of toxic substances and enhances the concentration of Vitamin A. Vitamin A plays a major role in induction and control of epithelial differentiation in mucous secretory and keratinization tissues and maintains the integrity of epithelium.\textsuperscript{[19]}

**Steroidal Therapy**

Steroids have their therapeutic effects due to anti-inflammatory and immune-suppressive action for prevention or suppression of the fibro productive inflammation seen in OSF, thus ameliorating the fibrocollagenous condition. Interferon-gamma has immuno-regulatory effect and has anti-fibrotic cytokine effect and hence its major role in altering collagen synthesis.

**Placental Extract**

Placental extracts act essentially as a “biogenic stimulation.” Placentrex contains nucleotides, enzymes, vitamins, amino acids; and steroids; it is an aqueous extract of human placenta which stimulates the pituitary and the adrenal cortex and regulates the metabolism of tissues.\textsuperscript{[20]}

**Immune Milk**

Immune milk has an anti-inflammatory effect and contains vitamins such as Vitamins A, C, B1, B2, B6, and B12, nicotinic acid pantothenic acid, folic acid, iron, copper, and zinc.

**Chymotrypsin**

Chymotrypsin, an endopeptidase, hydrolyzes ester, and peptide bonds, therefore, have a role in OSF cases as a proteolytic and anti-inflammatory agent. A study using Chymotrypsin 5000 IU, biweekly submucosal injections for 10 weeks showed significant results.\textsuperscript{[21]}

**Ayurvedic Treatment**

Curcumin the major yellow pigment in turmeric, curry, and mustard suppresses the expression of extracellular matrix genes in activated hepatic cells by inhibiting CTGF gene (connective tissue growth factor).

**Physiotherapy**

Physiotherapy exercises remain undoubtedly the basic, most commonly performed and the modality with longest therapeutic effect on relieving the trismus, which includes hot rinses, lukewarm water, muscle stretching exercises, and selective deep heating therapies such as short wave and microwave diathermy. This has been used in combination with other medical therapies and surgical procedures.

**Surgical Management**

Surgery remains a therapeutic option in advanced cases of OSMF which are refractory to conventional conservative therapies. Historically attempts to excise the fibrotic bands has resulted in progressively more scarring in follow-up periods resulting in worse quality of life for the patients. Surgical approach includes submucosal resection of fibrotic bands and myotomy.\textsuperscript{[22]} After fibrotic bands resection, reconstruction can be done using pedicled buccal pad of fat, tongue flap, superficial temporal flap, nasolabial flap, and forearm flap.

**CONCLUSION**

OSMF is one of the poorly understood and unsatisfactorily treated oral diseases due to its
multifactorial etiology. Evidence suggests that OSMF is multifactorial, with certain effects on specific subpopulations of fibroblasts, genetic predisposition, and molecular mechanisms, which could render the oral mucosa more susceptible to chronic inflammatory changes on exposure to carcinogens. However, the relationship between areca nut and OSMF is well established from epidemiological studies. An attempt is made by us to update the knowledge of the recent developments that enhance the understanding of the etiology of this premalignant condition and its medicinal and surgical management which improves the life expectancy.

REFERENCES


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