Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies

ABSTRACT
Oral submucous fibrosis (OSMF) is an oral precancerous condition characterized by inflammation and progressive fibrosis of the submucosal tissues resulting in marked rigidity and trismus. OSMF still remains a dilemma to the clinicians due to elusive pathogenesis and less well-defined classification systems. Over the years, many classification systems have been documented in medical literature based on clinical, histopathological, or functional aspects. However, none of these classifications have achieved universal acceptance. Each classification has its own merits and demerits. An attempt is made to provide and update the knowledge of classification system of OSMF so that it can assist the clinicians, beneficial in researches and academics in categorizing this potentially malignant disease for early detection, prompt management, and reducing the mortality. Along with this, pathogenesis and management have also been discussed.

Keywords: Areca nut, blanching, collagen, fibrosis, oral submucous fibrosis

INTRODUCTION
Oral submucous fibrosis (OSMF) precancerous condition and is chronic, resistant disease characterized by juxta-epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues. In 1966, Pindborg(1) defined OSMF as “an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. It is associated with juxta-epithelial inflammatory reaction followed by fibroelastic changes in the lamina propria layer, along with epithelial atrophy which leads to rigidity of the oral mucosa proceeding to trismus and difficulty in mouth opening.” 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.[2]

It occurs at any age but most commonly seen in young and adults between 25 and 35 years (2nd–4th decade). Onset of this disease is insidious and is often 2–5 years of duration.

It is commonly prevalent in Southeast Asia and Indian subcontinent.[3] The prevalence rate of OSMF in India is about 0.2%–0.5%. This increased prevalence is due to increased use and popularity of commercially prepared areca nut and tobacco product - gutka, pan masala, flavored supari, etc.[4] The malignant transformation rate of OSMF was found to be 7.6%.

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How to cite this article: Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y. Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies. Natl J Maxillofac Surg 2017;8:89-94.
ETIOPATHOGENESIS

OSMF was first described by Schwartz in 1952, where it was classified as an idiopathic disorder by the term atrophiap idiopathica (tropica) mucosae oris. Since then, many hypotheses are being suggested that OSMF is multifactorial in origin with etiological factors are areca nut, capsaicin in chilies, micronutrient deficiencies of iron, zinc, and essential vitamins. Autoimmune etiological basis of disease with demonstration of various autoantibodies with a strong association with specific human leukocyte antigen (HLA) antigens has also been suggested.

Areca nut (betel nut) chewing is one of the most common causes of OMSF which contains tannins (11%–12%) and alkaloids such as arecoline, arecaidine, guvacine, and guvacoline (0.15%–0.67%). Out of all arecoline is the main agent. Arecaidine is an active metabolite in fibroblast stimulation and proliferation, thereby inducing collagen synthesis. With the addition of slaked lime (Ca(OH)2) to areca nut, it causes hydrolysis of arecoline to arecaidine making this agent available in the oral environment. Tannin present in areca nut reduces collagen degradation by inhibiting collagenases. OSMF is induced as a combined effect of tannin and arecoline by the mechanism of reducing degradation and increased production of collagen, respectively.

Nutritional deficiencies
Deficiency of iron (anemia), Vitamin B complex, minerals, and malnutrition are promoting factors that disturbs the repair process of the inflamed oral mucosa, thus leads to deranged healing and resultant scarring and fibrosis. The resulting atrophic oral mucosa is more susceptible to the effects of chilies, betel nuts, and other irritants.

Genetics and immunology
A genetic component is believed to be involvement in OSMF because there are cases reported in medical literature in people without any history of betel nut chewing or chili ingestion. Patients with OSMF have increased frequency of HLA-A10, HLA-B7, and HLA-DR3.

An immunologic phenomenon is thought to play a role in the etiopathogenesis of OSMF. The increase in CD4 cells and cells with HLA-DR in these diseased tissues shows activation of most lymphocytes and increased number of Langerhans cells. These immunocompetent cells and high of CD4:CD8 ratio in OSMF tissues show the activation of cellular immune response which results in deranged immunoregulation and an altered local tissue morphology. These changes may be due to direct stimulation from exogenous antigens such as areca alkaloids or due to changes in tissue antigenicity leading an autoimmune response. The major histocompatibility complex Class I chain-related gene A (MICA), which is expressed by keratinocytes and epithelial cells, interacts with gamma/delta T cells localized in the submucosa. MICA has got a triplet repeat (guanine, thymine, cytosine) polymorphism in the transmembrane domain, which results in five different allelic patterns. The phenotype frequency of allele A6 of MICA is higher in OSMF. Increased levels of pro-inflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) also contribute to the pathogenesis of OSMF.

Various staging/grading classification systems have been documented in medical literature by various authors in the past. Some of the staging system is routinely used in the clinical practice and help in early diagnosis and treatment.

This classification system is based on clinical presentation and progression of the disease only. It has not pointed any functional component (mouth opening), histological component treatment, and prognosis.

This classification system is based on the functional component. Although commonly used, this classification has not highlighted clinical features, histological features, treatment, and prognosis.

This classification system is based on the histological features of the disease only. No clinical part, functional component, treatment, and prognosis are discussed.

This classification system includes all the parameters/ component of OSMF such as clinical features, histopathological features, functional component, treatment part, and prognosis. None of the previous classifications have included all these features in one classification. The main drawback of this classification is that it is bit complex and lengthy to read.

Treatment of oral submucous fibrosis
The treatment of OSMF depends on the degree of disease progression and clinical involvement. At early stages, stopping habit and nutritional supplements are done. At moderate stages, conservative treatment such as intraleisional injections along with medical treatment is provided. At advanced stages, surgical interventions are needed.

Cessation of habit
The stoppage of habit such as betel quid, areca nut and other local irritants, spicy and hot food, alcohol, and smoking through education and patient motivation. All affected
patients should be educated and warned about the possible malignant transformation.

Supplementary care
Diet rich in iron, vitamins, and minerals should be advised to patients with OSMF. Deficiency of iron plays an important role in both etiology and pathogenesis of OSMF. Hence, routine hemoglobin level should be monitored along with iron supplements should be given in diet.[3] Vitamin B deficiency plays an important role in the etiology of degenerative changes in oral mucosa before malignant transformation. Vitamin B complex supplement may relieve glossitis, inflammation of tongue, and cheilosis in OSMF patients.[3]

Antioxidants
Carotenoids (lycopene) induce stimulation of immune system or direct action in tumor cells. Lycopene inhibits hepatic fibrosis genes in LEC rats and also exerts a similar inhibition on the abnormal fibroblasts in OSMF.[14]

| Clinical classification | Histopathological classification | Clinical and histopathological |
|-------------------------|---------------------------------|-------------------------------|
| Desa J.V (1957) | Pindborg J.J. and Sirsat S.M. (1966) | Khanna J.N. and Andrade N.N. (1995) |
| Wahi P.N. and Kapur V.L. et al. (1966) | Utsunomiya H. et al. (2005) | |
| Ahuja S.S. and Agarwal G.D. (1971) | | |
| Bhatt A.P. and Dholakia H.M. (1977) | | |
| Gupta D.S. and Golhar B.L. (1980) | | |
| Pindborg J.J (1989) | | |
| Katharia S.K. et al. (1992) | | |
| Bailoor D.N. (1993) | | |
| Lai D.R. et al. (1995) | | |
| Maher R. et al. (1996) | | |
| Haider S.M. et al. (2000) | | |
| Ranganathan K. et al. (2001) | | |
| Rajendran R. (2003) | | |
| Bose T. and Balan A. (2007) | | |
| Kumar K. et al. (2007) | | |
| Mahatra D. et al. (2009) | | |
| More C.B. et al. (2011) | | |
| Kerr A.R. et al. (2011) | | |
| Patil S. and Maheshwari S. (2014) | | |
| Prakash R. et al. (2014) | | |

Table 2: Clinical staging/classification

| Stage I/early OSMF | Stage II/moderate OSMF | Stage III/severe OSMF |
|--------------------|-----------------------|-----------------------|
| Stomatitis and vesiculation: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae | Fibrosis: Blanching of the oral mucosa, vertical and circular palpable fibrous bands in the buccal mucosa and lips, mottled, marble-like appearance of the mucosa. Reduction of mouth opening, stiff and small tongue, blanched and leathery floor of the mouth, fibrotic and de-pigmented gingiva, rubbery soft palate with reduced mobility, atrophic and blanched tonsils, shrunken cheeks and bud-like uvula, not commensurate with age or nutritional status | Sequelae of OSMF: Leukoplakia and erythroplakia is present in about 25% of OSMF cases Speech and hearing difficulties may occur because of involvement of tongue and the eustachian tube |

OSMF: Oral submucous fibrosis

Table 3: Functional staging/classification: Based on mouth opening between upper and lower central incisors

| Grading/ Staging | Maximum Interincisal mouth opening |
|------------------|------------------------------------|
| Stage I | Maximum interincisal mouth opening up to or >35 mm |
| Stage II | Maximum interincisal mouth opening between 25 and 35 mm |
| Stage III | Maximum interincisal mouth opening between 15 and 25 mm |
| Stage IV | Maximum interincisal mouth opening 5 and 15mm |
| Stage V | Maximum interincisal mouth opening <5 or nil |

Steroid therapy, placental extracts, and chymotrypsin
Steroids → reduction of proliferation of fibroblasts → a number of collagen fibers decreases. Steroids release cellular proteases enzymes in extracellular compartment in connective tissues → activation of collagen and zymogens → ingestion of insoluble collagen → collagen breakdown stimulation.

Steroids also act by reducing inflammatory response. Steroid ointment and intralesional dexamethasone injection are generally used. Placentrex is an aqueous extract of human placenta having nucleotides, enzymes, steroids, vitamins, and amino acids. It acts by biogenic stimulation. It is injected into
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IFN-gamma experienced improvement of symptoms. It has immino-regulatory effect. It is also known as antifibrotic cytokine, patients treated with an intralesional injection of IFN-gamma experienced improvement of symptoms.

Interferon-gamma
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Immune milk
Immune milk consists anti-inflammatory component which suppresses the inflammatory process and stimulates the cytokine production. Good symptomatic relief in OSMF patients is due to micronutrients in the immune milk powder.

Turmeric
Turmeric powder provides benzopyrene-induced stimulated production of micronuclei in circulating lymphocytes. It also acts as an excellent scavenger of free radical. Turmeric oil and turmeric resin both act synergistically to protect against DNA damage.

Physiotherapy
Muscle stretching exercises for the mouth are helpful in preventing further reduction in mouth opening. Forceful jaw opening exercise is with mouth gag or heisters jaw opener.

Diathermy, ultrasound, lasers: Microwave diathermy
Microwave diathermy acts by physio-fibrinolysis of fibrous bands through selective heating of juxta-epithelial connective tissue. Ultrasound has a role in deep heating modality. Its selectivity raises the temperature in accumulated areas. CO₂ laser techniques involve multiple small incisions which provide surgical relief of restricted oral aperture because the laser beam seals all the blood vessels, thus allowing the surgeon a perfect visibility and accuracy in fibrous band excision.

Cryosurgery
It is the method of locally destroying the abnormal tissue by freezing it in situ and applying liquid nitrogen or argon gas.

Surgical treatment
In patients with severe trismus, surgical intervention is done which includes simple excision of fibrotic bands with reconstruction using buccal fat pad and split thickness graft along with temporalis myotomy and coronoidectomy. The surgery is performed under general anesthesia. The intubation is difficult due to restricted mouth opening. Endotracheal intubation under deep inhalational anesthesia or using muscle relaxants with regional block is preferred. Fiber-optic guided intubation techniques have also been used.

CONCLUSION
OSMF is a premalignant condition and is enigma to maxillofacial surgeon for its chronic, progressive, recurrent, and malignant transformation potential. An attempt is made by us to update the knowledge of the recent histopathological staging/classification of OSMF.

Table 4: Histopathological staging/classification

| Grading/Stage | Histological features |
|---------------|-----------------------|
| Early stage   | Fine collagen fibers dispersed with marked edema. Young fibroblast contains abundant cytoplasm. Congested blood vessels. Inflammatory cells, mostly polymorphonuclear leukocytes and occasional eosinophils are found. Large number of lymphocytes in subepithelial, connective tissue, zone along with myxodematous changes |
| Intermediate stage | Initial hyalinization seen in juxta-epithelial area. Collagen is in separate thick bundles. Moderate amount of young fibroblasts is seen. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils, and occasional plasma cells. Collagen is moderately hyalinized. Thickened collagen bundles are separated by slight residua edema. Fibroblastic activity is less. Inflammatory exudate composed of lymphocytes and plasma cells. Granulation changes occur close to the muscle layer, and hyalinization appears in subepithelial layer where compression of blood vessels by fibrous bundles takes place. Inflammatory cells are reduced in subepithelial layer |
| Advanced stage | Collagen is completely hyalinized. A smooth sheet with no separate bundles of collagen is present. No edema. Hyalinized area is deficient of fibroblasts. Blood vessels are completely obliterated. Inflammatory cells are lymphocytes, and plasma cells inflammatory cell infiltrate hardly seen. A number of blood vessels much reduced in subepithelial zone. Marked fibrous areas are present with hyaline changes which extend from subepithelial to superficial muscle layers are seen. Muscle undergo degenerative and atrophic changes |

the body after resistance to pathogenic factors and stimulates the metabolic or regenerative processes. Chymotrypsin is an endopeptidase enzyme which causes hydrolysis of ester and peptide bonds and hence acts as proteolytic and anti-inflammatory agent.

Hyaluronidase
It acts by breaking down hyaluronic acid, lowers the viscosity of intracellular substances, and decreases collagen formation. It produces burning sensation and trismus. Combination of steroids and hyaluronidase shows better long-term results than either used alone.

Pentoxifylline
Pentoxifylline is a tri substituted methyl methylxanithine derivative. It is a rheological modifier; it improves microcirculation and decreased platelet aggregation as well as granulocyte adhesion and also has good improvement in radiation-induced superficial fibrotic lesions of skin and direct effect on inhibiting burn scar fibroblasts. It has also been used to alleviate the symptoms in patients with OSMF.

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developmentsthat enhances the understanding of the etiology of this premalignant condition and its medicinal and surgical management which improves the life expectancy. Furthermore, a newer classification is derived which provides all the components of OSMF functional, clinical, histopathological, treatment, and prognostic component.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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