

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 - gutkha, pan masala, flavored supari, etc.^[4] The malignant transformation rate of OSMF was found to be 7.6%.

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ETIOPATHOGENESIS

OSMF was first described by Schwartz in 1952, where it was classified as an idiopathic disorder by the term atrophica idiopathica (tropica) mucosae oris.^[5] Since then, many hypotheses are being suggested that OSMF is multifactorial in origin with etiological factors are areca nut, capsaicin in chillies, 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.^[6]

Areca nut (betel nut) chewing is one of the most common causes of OSMF 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.^[5]

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 chillies, betel nuts, and other irritants.^[7]

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.^[8]

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.^[9] 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.^[10] Increased levels of pro-inflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) also contribute to the pathogenesis of OSMF.^[11]

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 [Table 1].

This classification system is based on clinical presentation and progression of the disease only.^[12] It has not pointed any functional component (mouth opening), histological component treatment, and prognosis [Table 2].

This classification system is based on the functional component.^[12] Although commonly used, this classification has not highlighted clinical features, histological features, treatment, and prognosis [Table 3].

This classification system is based on the histological features of the disease only.^[12] No clinical part, functional component, treatment, and prognosis are discussed [Table 4].

This classification system includes all the parameters/component of OSMF such as clinical features, histopathological features, functional component, treatment part, and prognosis [Table 5]. 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 intralesional 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

Table 1: Different classification, staging, and grading systems

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. <i>et al.</i> (1966)	Utsonumiya H. <i>et al.</i> (2005)	
Ahuja S.S. and Agarwal G.D. (1971)	Kumar K. (2007)	
Bhatt A.P. and Dholakia H.M. (1977)		
Gupta D.S. and Golhar B.L. (1980)		
Pindborg J.J (1989)		
Katharia S.K. <i>et al.</i> (1992)		
Bailoor D.N. (1993)		
Racher S.K. (1993)		
Lai D.R. <i>et al.</i> (1995)		
Maher R. <i>et al.</i> (1996)		
Haider S.M. <i>et al.</i> (2000)		
Ranganathan K. <i>et al.</i> (2001)		
Rajendran R. (2003)		
Bose T. and Balan A. (2007)		
Kumar K. <i>et al.</i> (2007)		
Mehrotra D. <i>et al.</i> (2009)		
More C.B. <i>et al.</i> (2011)		
Kerr A.R. <i>et al.</i> (2011)		
Patil S. and Maheshwari S. (2014)		
Prakash R. <i>et al.</i> (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

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 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.^[5] 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.^[13]

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]

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

Table 4: Histopathological staging/classification

Grading/ Staging	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 myxedematous 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 residual 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.^[15]

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.^[16]

Pentoxifylline

Pentoxifylline is a tri substituted methyl methylxanthine 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.^[17]

Interferon-gamma

It has immuno-regulatory effect. It is also known as antifibrotic cytokine, patients treated with an intralesional injection of IFN-gamma experienced improvement of symptoms.^[18]

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.^[19]

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.^[20]

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. It's 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.^[21]

Cryosurgery

It is the method of locally destroying the abnormal tissue by freezing it *in situ* and applying liquid nitrogen or argon gas.^[22]

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

Table 5: Classification of oral submucous fibrosis: Passi D et al. (2017)

Grading/staging	Clinical	Functional	Histopathological	Treatment	Prognosis
Grade 1	Involvement of less than one-third of the oral cavity Mild blanching, burning sensation, recurrent ulceration, and stomatitis. dryness of mouth	Mouth opening up to 35 mm	Stage of inflammation: Fine edematous collagen, congested blood vessels, abundant neutrophils along with lymphocytes with myxomatous changes in subepithelial, connective tissue layer of epithelium	Cessation of habit, nutritional supplement, antioxidants, topical steroid ointment	Excellent
Grade 2	Involvement of one-third to two-third of the oral cavity Blanching of oral mucosa with mottled and marble like appearance, fibrotic bands palpable and involvement of soft palate and premolar area	Mouth opening 25-35 mm Cheek flexibility reduced by 33%	Stage of hyalinization: Juxta-epithelial collagen hyalinization with lymphocytes, eosinophils. Dilated and congested blood vessels. Less fibroblastic activity. Granulation changes in muscle layer with reduced inflammatory cells in subepithelial layer	Habit cessation, nutritional supplement, intralesional injection of placental extracts, hyaluronidase, steroid therapy Physiotherapy	Good Recurrence rate is low
Grade 3	Involvement of greater than two-third of the oral cavity. Severe blanching, Broad thick fibrous palpable bands at cheeks and lips and rigid mucosa, depapillated tongue and restricted tongue movement and shrunken bud like uvula. Floor of the mouth involvement and lymphadenopathy	Mouth opening 15-25 mm Cheek flexibility reduced by 66%	Stage of fibrosis: Complete collagen hyalinization without fibroblast and edema. Obliterated blood vessels Plasma cells and lymphocytes are present Extensive fibrosis with hyalinization from subepithelial to superficial muscle layers with atrophic, degenerative changes	Surgical treatment including band excision and reconstruction with BFP or split thickness graft bilateral temporalis myotomy and coronoidectomy	Fair Recurrence rate is high
Grade 4	Leukoplakia changes, erythroplakia Ulcerating and suspicious malignant lesion	Mouth opening <15 mm or nil	Stages of malignant transformation: Erythroplakia changes into squamous cell carcinoma	Surgical treatment and biopsy of suspicious lesion	Poor, malignant transformation

developments that 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.

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Conflicts of interest

There are no conflicts of interest.

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