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ORAL SUBMUCOUS FIBROSIS: A CONTEMPORARY MORPHO-PERCEPTIVE

Dental Science

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ABSTRACT

Oral Sub mucous fibrosis (OSMF) has traditionally been described as "a chronic, insidious, scarring and crippling disorder of the oral cavity, characterized by abnormal collagen deposition often with involvement of the pharynx and the upper esophagus". Millions of individuals are affected, especially in South and South East Asian countries. The main risk factor is areca nut chewing other factors include chillies, nutritional deficiencies and genetic processes. Symptoms include sub mucous fibrosis, ulceration, xerostomia, a burning sensation, and restricted mouth opening. Due to its high morbidity and high malignant transformation rate, constant efforts have been made to develop effective treatment modalities using medicines, surgery and physiotherapy, with varying degrees of benefit, but none have been able to cure this disease completely, and hence, it has become a challenging condition. The present review updates the literature review of OSMF from a molecular perspective and summarizes its etiology, pathogenesis, various classification systems and clinical features in various stages of OSMF and therapeutic interventions.

KEYWORDS

Areca nut, oral squamous cell carcinoma, oral sub mucous fibrosis, blanching, collagen

INTRODUCTION:

OSMF is indeed one of the classic "Disease of civilization" with large differences seen between races, geographic areas and individuals and the degree of its transformation into malignancy with continuation of habit and increase in frequency, duration.

OSMF is one of the chronic progressive, scarring disease affecting oral, oropharyngeal, and sometimes the esophageal mucosa and characterized by progressive fibrosis of the submucosal tissues leading to stiffness of oral mucous membrane and restricted mouth opening1. It is associated with juxta-epithelial inflammatory reaction followed by fibro elastic 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 opening2."

Terminology & Definition:

In ancient medicine Sushruta described the condition "Vidari" under mouth and throat diseases. Schwartz (1952) describing the condition in five Indian women in Kenya called it "Atrophica Idiopathica (tropica) Mucosae Oris". Joshi (1953) from Bombay described the disease for the first time in India and coined the term Oral sub mucous fibrosis. Su.I.Pin (1954) reported three cases of a similar condition among Chinese from Taipei in Taiwan and designated the condition as "Idiopathic Scleroderma of Mouth".

Pindborg and Sirsat (1966) termed as "Juxta epithelial Fibrosis". WHO [1978] defined OSMF as a slowly progressive disease in which fibrous bands forms a blanched oral mucosa resulting in severe restriction of movement of the mouth[3].

According to Paissat in 1981, the buccal mucosa is the most commonly involved site, but may also involve the other parts of the oral cavity including pharynx. According to Cox & Aziz in 1997 stated OSMF as a progressive inability to open the mouth is the major complaint, because of accumulation of inelastic fibrous tissue in the juxta epithelial region of the oral mucosa, along with concomitant muscle degeneration[4].

Other terms used to describe this condition are juxta-epithelial fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, sub mucous fibrosis of the palate and pillars, sclerosing stomatitis, and diffuse OSMF2.

Epidemiology:

OSMF is predominantly seen in people of South and Southeast Asia – India, Bangladesh, Sri Lanka, Pakistan, Taiwan, Southern China, etc., where chewing of betel quid, areca nut or its flavored formulations is frequently practiced[5].

According to World Health Organization (WHO) statistics, there are >5 million OSMF patients globally. It occurs at any age but most commonly seen in young and adults between 25 and 35 years (2nd–4th decade). The prevalence rate of OSMF in India is about 0.2%–0.5%. The malignant transformation rate of OSMF was found to be 7.6%2. In 2002, the prevalence rate was estimated to be 5 million in India and more recent data suggest prevalence of OSMF in India has increased from 0.03 to 6.42%. OSMF occurs more often in women than men in India but the opposite is true for other regions. The patient age range is 20–40 yrs6. Male predominance was reported by various authors Sinor et al. and Kumar et al. Wide variation in ages were reported by various authors, Pindborg et al. gave an average range for male 53.6 years and females 37.7 years, Babu et al. and Trivedi et al. reported 23% of patients age ranged between 14 and 19 years7.

ETIOPATHOGENESIS:

Although the etiopathogenesis of this disease is multifactorial, areca nut-chewing in any formulation is considered the main causative agent. Contributory risk factors suggested includes chewing of smokeless tobacco, high intake of chilies, toxic levels of copper in foodstuffs and masticatories, vitamin deficiencies, and malnutrition resulting in low levels of serum proteins, anemia and genetic predisposition.

Major etiology8: (Table 1)

Major etiology	Description
Chewing of Areca nut (Baked or Raw) and/or derivatives such as Gutkha, Pan masala, Mawa, Betel quid, Sweet Supari and other formulations.	Arecoline and Arecaidine nitrosation causes DNA alkylation with proliferation of fibroblasts and elevated collagen synthesis.

Literature review on Areca Nut (Betel Nut) Chewing:

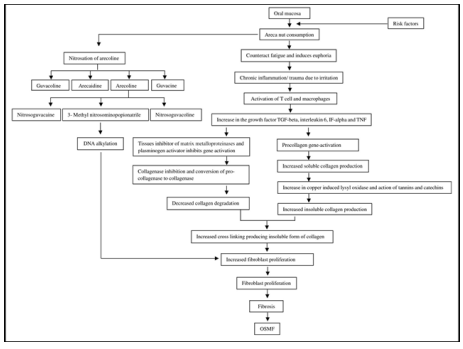
According to Liao in 2001, the areca nut component of betel quid plays a major role in the pathogenesis of OSMF. Shear et al in 1967 and Caniff et al in 1987 evaluated correlation between betel nut chewing and the onset of oral sub mucous fibrosis. The strongest evidence regarding the etiology of OSMF is with the habit of areca nut chewing. In a study of over 1 lakh Indian subjects by Mehta F et al in 1968, areca nut was practiced by 52% of the patients with OSF compared with 2.1 % amongst the total population. Gupta PC et al in 1968 done 10 year prospective study undertaken on 10,000 individuals in India, demonstrated a incidence of 0% OSF amongst those who did not chew areca nut, compared with an incidence of 35 % in 1 lakh per year among areca nut chewers. Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150% suggested by Canniff in 1981. Chung-Hung in 2006, studied that arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated the variety of fibrotic diseases, in a dose-dependent manner in persons with OSMF. 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 as an initiating factor in individuals with OSMF8.

Table 2: Contributing factors [8]:

Contributing factors	Description
Chewing smokeless tobacco	Dip, Snuff, Snus and chewing tobacco have been reported as major contributing factors.
Nutritional	Deficiencies of iron, folate & vitamin B12 result in mucosal atrophy, notably in the mouth. Increased levels of iron enhance hydroxylation of proline and lysine in the process of collagen synthesis.
Chillies	Hypersensitivity reactions to capsaicin might contribute to fibrosis.
Toxic levels of copper	Copper upregulates the enzyme lysyl oxidase, enhancing cross linking of collagen and elastin.
Genetic predisposition	HLA-A10, HLA-B7, HLA-DR3, haplotypes A10/DR3, B3/DR3 and A10/B8 are found in increased frequency in OSMF patients.
Immunological predisposition	Subjects with high endogenous expression of CD4 and HLA-DR on lymphocytes and Langerhans cells may have dysregulation of their immune-inflammatory response with bystander tissue injury.

Fig 1: Etiopathogenesis[8]



Classification of oral sub mucous fibrosis:

This classification system includes all the parameters/ component of OSMF such as clinical features, histopathological features, functional component, treatment part, and prognosis [Table 3]. 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[2].

Table 3: Classification of oral sub mucous fibrosis[2]

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

Table 4: Intra- and extra- oral manifestations of OSMF at different stages[8]

Features	Early stage	Moderate stage	Advanced stage

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Intra oral	Stomatitis, excessive salivation, burning sensation, blanching of oral mucosa, blister formation, presence of thin palpable fibrous bands, sparse brown/black pigmentation.	Stomatitis, burning sensation, xerostomia, loss of taste sensation, gradual decrease in mouth opening, difficulty in whistling, vesicle formation, petechiae, rigid oral mucosa, difficulty in blowing the cheeks, defective gustatory sensation, blanching of oral mucosa – especially of soft palate, buccal mucosa, labial mucosa, tongue, floor of mouth, and faucial pillars. Presence of thick palpable fibrous bands, shrunken uvula with altered shape (inverted, hockey stick, bud like, and deviated).	Stomatitis, burning sensation, xerostomia, reduction in mouth opening, restricted tongue movement, loss of taste sensation, Unable to blow the cheeks, defective gustatory sensation, inability to whistle, blanching of oral mucosa: esp. soft palate, buccal mucosa, labial mucosa, tongue, floor of mouth, and faucial pillars. Loss of suppleness of mucosa, mottled or opaque or white marble like appearance of oral mucosa, thick palpable fibrous bands on buccal and labial mucosa, de-papillation of tongue, shrunken uvula with altered shape (inverted, hockey stick, bud like, deviated), involvement of the pharyngeal and esophageal mucosa.
Extra oral	No Significant extra oral features are observed.	Prominent masseter muscle, nasal twang, sunken cheeks, thinning of lips, difficulty in deglutition, loss of naso-labial fold, prominent antegonial notch, hoarseness of voice, mild hearing impairment, weight loss.	Hypertrophic and stiff masseter muscle, nasal intonation of voice, sunken cheeks, multiple folds on cheeks when attempting wide opening of mouth, thinning of lips, difficulty in deglutition, loss of naso-labial fold, prominent antegonial notch, hoarseness of voice, severe hearing impairment, severe weight loss, hoarseness of voice, difficulty in deglutition, atrophy of facial musculature. In severe cases, radiographically, there is alteration in condylar form and fibrous ankylosis of the temporomandibular joints.

Malignant transformation of OSMF:

Pindborg JJ et al (1968) supported the hypothesis that OSMF is a precancerous condition.

Pindborg JJ (1972) put forward five criteria to prove that the disease is precancerous. They included

a. High occurrence of OSMF in oral cancer patientsb. Higher incidence of OSCC in patients with OSMF

c. Histological diagnosis of cancer without any clinical suspicion in OSMF

d. High frequency of epithelial dysplasia and

e. Higher prevalence of leukoplakia among OSMF cases9.

Patients with OSMF have been reported with higher risk of developing oral squamous cell carcinoma (OSCC). Although 7.6% of OSMF cases transformed to oral squamous cell carcinoma (OSCC) in a 17-year follow up study reported in 1970, other studies with smaller follow up periods report malignant transformation rates ranging from 1.9–9%, depending on diagnostic criteria and duration of follow up. Studies suggest that malignant transformation in patients with OSMF differs from those without OSMF. Better prognostic features associated with OC occurring in a background of OSMF included early tumor stage, thinner lesions, fewer neck metastases with less extra-capsular spread, and more highly differentiated neoplasms. It was suggested that fibrosis in the oral mucosa and tumor stroma, with reduced vascularity, inhibits lymphatic and vascular spread8.

Treatment of oral sub mucous fibrosis2 :

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 patients should be educated and warned about the possible malignant transformation.

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.

Table 5: Evidence-Based Treatment Protocols

Treatment type	Agent	Authors	Study Type	Sample size (n)	Main findings
Antioxidant treatments	Lycopene	Karemore T. V. and Motwani M	Single blinded prospective study	92	Ingestion of 8 g/QD of lycopene (n = 46) for three months was shown to be effective in the reduction of burning mouth and mouth opening ($p < 0.05$) in patients with OSMF when compared to the placebo group (n = 46).
	Curcumin	Hazarey V. et al.	Randomized control clinical trial	30	Sucking 2 g/QD of Curcumin lozenges (n = 15) with physiotherapy for three months showed a significant improvement in both mouth opening and in alleviating the burning sensation ($p < 0.05$) in comparison to the control group (clobetasol propionate 0.05%; (n = 15).

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	Micronutrient therapy	Maher R. et al.	Single arm preliminary prospective study	117	Swallowing micronutrient supplements: vitamins A, B complex, C, D, E; and minerals iron, calcium, copper, zinc, and magnesium was observed to be significantly effective ($p < 0.05$) in reduction of sign and symptoms of OSMF over 3 years.
	Spirulina and Aloe Vera	Patil S. et al.	Double blinded prospective study	42	Ingestion of 500 mg/QD of Spirulina (n = 21) for 3 months was associated with a significant improvement in mouth opening and reduction in ulcers/erosions/ vesicles ($p < 0.05$) in comparison to 5 mg of aloe vera (n = 21) for the same time. Improvement in burning sensation and pain associated with lesions was not found significant between two groups
		Alam S. et al.	Double-blinded, placebo controlled, parallel-group randomized controlled trial	60	Application of aloe vera gel over buccal mucosa, palate, retromolar region, and floor of the mouth twice daily during submucosal injection of hyaluronidase and dexamethasone (n = 15) and surgical treatment (buccal fat pad, nasolabial flap, or collagen membrane, (n = 15) treatment with 6 months of follow up was observed to be a significant adjuvant therapy in reduction of most of the symptoms of OSMF ($p < 0.01$), in comparison to a similar group of medicines alone, (n = 15) and surgical procedures (n = 15)] with no application of aloe vera.

Treatment type	Agent	Authors	Study Type	Sample size (n)	Main findings
Medicinal treatments	Steroids	Goel S. et al.	Longitudinal prospective study	270	4 mg/ml/biweekly injections of Betamethasone diluted in 1.0 ml of 2% xylocaine for 6 months given on buccal mucosa, bilaterally, using an insulin syringe, with a half dose on each side, was showed significant improvement of mouth opening and reduction in burning sensation in a stage II and stage III OSMF group ($p < 0.0001$), in comparison to a control group which received no treatment over two years.
	Hyaluronidase	James L. et al.	Retrospective study	28	Intralesional injection of Hyaluronidase 1500 IU mixed in 1.5 ml of dexamethasone and 0.5 ml of lignocaine hydrochloride biweekly for 4 weeks showed a significant improvement in mouth opening with net gain of 6 ± 2 mm (92%), reducing the burning sensation (89%), number of painful ulceration (78%) and blanching of oral mucosa (71%) for Grade III OSMF patients.
	Colchicine + Hyaluronidase	Krishnamoorthy B. & Khan M	Comparative prospective study	50	1 mg/ day colchicine tablet and 0.5 ml intralesional Injection hyaluronidase 1500 IU/ once a week (group I, n = 25) for twelve weeks showed a significant improvement in mouth opening ($p < 0.05$) and reduced burning sensation (33% by second week) in comparison to subjects treated with 0.5 ml intralesional injection of hyaluronidase 1500 IU and 0.5 ml intralesional injection hydrocortisone acetate 25 mg/ml once a week alternatively (group II, n = 25).
	Placental extracts	Singh P. et al.	Comparative prospective study	10	2 ml intralesional placental extract mixed with 2 ml of 2% lignocaine HCL weekly for an interval of 8 weeks showed an average improvement in mouth opening by 8.02 mm (average pretreatment mouth opening = 18.49 mm, average posttreatment mouth opening = 26.51 mm) with average marked reduction in burning sensation by 4.9 (average pretreatment burning sensation = 8.0, average

Treatment type	Agent	Authors	Study Type	Sample size (n)	Main findings
	Isoxupurine	Bhadage C. J. et al.	Prospective study	40	10 mg Isoxupurine tablets/ QID with oral physiotherapy (Group A, n = 15) plus 2 ml dexamethasone by intralesional injection with 1500 IU hyaluronidase mixed with 1 ml of 2% lignocaine solution with adrenaline 1:80, .

					000 (Group B, n = 15) for six weeks with a follow up of 4 months, showed a significant improvement in mouth opening ($p < 0.05$) and burning sensation ($p < 0.00001$) in comparison to the placebo group (only oral physiotherapy) (Group C, n = 10)
	Pentoxifylline	Rajendran R. et al.	Randomized controlled clinical trial	29	400 mg/ TID of Pentoxifylline tablets (n = 14) for seven months showed a significant improvement in mouth opening ($p < 0.0001$), tongue protrusion ($p < 0.05$), relief from perioral fibrotic bands ($p < 0.0001$), subjective symptoms of intolerance to spices ($p < 0.0001$), burning sensation of mouth ($p < 0.0001$), tinnitus ($p < 0.0001$), difficulty in swallowing ($p < 0.0001$) and difficulty in speech ($p < 0.0001$) in comparison to the control group (multivitamin with local heat therapy, n = 15).
Oral physiotherapy	Ultrasound + Physiotherapy	Kumar V. et al.	Single arm prospective study	15	Ultrasound therapy with 0.7–1.5 W/Cm2 with thumb kneading physiotherapy for six days/ week for two consecutive weeks showed significant improvement in mouth opening ($p < 0.001$) and reduction of burning sensation.
Surgical approaches	Surgery	Kamath V. V	Systematic Review	–	Lasers, tongue flap, palatal flap, buccal fat pad, nasolabial flap, thigh flaps, split skin grafts, collagen membrane, artificial dermis, human placenta grafts, coronoidectomies, muscle myotomies and oral stents. All surgeries have shown significant improvement in the symptoms of OSMF. However there exist no definite protocols and thus author comments that treatment remains subjective to the operating surgeon.

CONCLUSION:

OSMF is accepted globally as an Indian disease, having highest malignant potential than any other oral premalignant lesions. Various available data suggests that the main causative agents for OSMF are the constituents of areca nut, mainly arecoline, which will interfere with the molecular processes of collagen deposition and/or degradation. The understanding of the exact role of alkaloids and other etiological agents with respect to pathogenesis will help in management and minimizing the disease condition. The present article has explored all the existing literature and has suggested the evidence-based treatment protocols for the intervention of OSMF.

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