Oral Submucous Fibrosis: A review of etiology, pathogenesis and treatment.

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Abstract

Oral submucous fibrosis is a condition that can cause burning sensation of oral cavity resulting in inability to open mouth. The cause of the disease includes various factors like arecanut, chilies, nutritional deficiencies and genetic factors. The management of OSMF has been the subject of controversy ever since Schwartz first described the condition in 1952. As the disease presents in different forms, the treatment also differs with the various stages of the disease. Through this article, an effort is made to update the knowledge regarding aetiology therapeutic and surgical management which improves the life expectancy of patients suffering from OSMF.

Keywords: Arecanut, Etiopathogenesis, Medicinal, Oral submucous fibrosis.

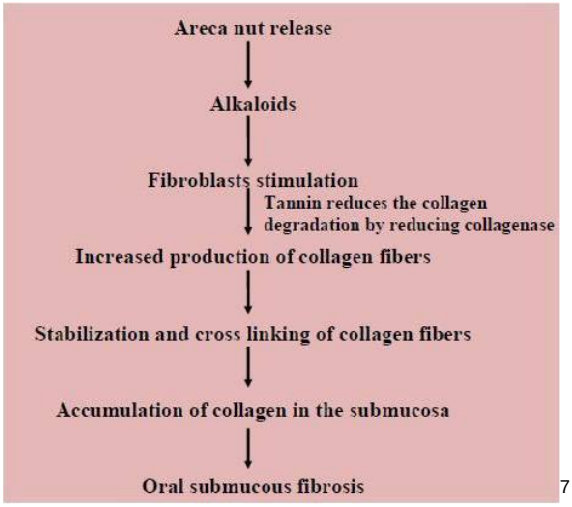
Introduction:

Oral submucous fibrosis (OSMF) is an unrelenting, crippling condition of the oral mucosa, which is related with betel quid chewing habit extensively widespread in Southeast Asia. OSMF is a potentially malignant disease characterized by inflammation and progressive fibrosis of the submucosal tissues resulting in marked rigidity and trismus.[1] It occurs mostly in India and in South East Asia and other parts world like Kenya, China, UK, Saudi Arabia.[2] Various factors such as tobacco chewing, chillies and arecanut have been suggested in pathogenesis of this condition. The strongest risk factor for OSMF in resident of the Indian sub-continent is the chewing of betel quid containing areca nut and has a reported incidence of between 0.2–1.2 percent of the urban population attending dental clinics[3]. Cox and Aziz stated that progressive inability to open the mouth is because of accumulation of inelastic fibrous tissue in the juxta epithelial region of the oral mucosa. 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[4].The purpose of this review article is to consider its aetiology, pathogenesis and its successful prevention and management.

Etiology and pathogenesis:

Previous studies have shown the following a) arecanut alkaloids causing stimulation of fibroblasts and collagen synthesis b) Fibrogenic cytokines secreted by activated macrophages and T lymphocytes in the OSMF tissue. (c) Clonal selection of fibroblasts with a high amount of collagen production during the long-term exposure to areca quid ingredients.(d) Deficiency in collagen phagocytosis by OSMF fibroblasts. (e) By decreased secretion of collagenase. By stabilization of collagen structure by (+) catechin and tannins from the areca nut(f) By production of collagen with a more stable structure (collagen type I trimer) OSMF fibroblasts[5].

Tumor Growth Factor (TGF)-b is known to be a potent stimulator of extracellular matrix (ECM) synthesis and thus has been implicated in fibrosis (Cohen 2003). It has been shown to be expressed in OSMF tissues and a probable role in the progression in OSMF. Arecoline, a principal constituent of betel nut has been shown to influence fibrosis, and several profibrogenic cytokines such as, endothelin-1, platelet derived growth factor, basic fibroblast growth factor, and connective tissue growth factor (CTGF) are known to be associated with fibrosis[6].



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High copper content in areca nut and fibrosis: The average daily copper intake of copper by adults from diet in developing countries is between 0.6 and 1.6 mg/ day. An adult Indian chewing areca nut daily consumes over 5 mg of copper /day. The copper is either bound to protein metallothione or transferred across the basolateral membrane. At cellular level, there is evidence to support the role of membrane bound copper andits uptake by the cells. The absorption of copper was noted higher in epithelium compared to deeper connective tissues and muscle layer and therefore the length of time chewed and consistency of the quid also affects the uptake of copper absorption by the epithelium[8].

Nutritional deficiencies: Many metabolic and potentially malignant disorders including oral cancer are accompanied by

alterations in the concentration of one or more trace elements such as iron, zinc and magnesium in body fluids, blood serum or plasma. Trace elements are required in essential components such as enzyme systems or structural portions of biologically active constituents and among them iron has been recognized as an important element for maturation of epithelium and its abnormalities related to malignant conditions. Thus, deficiencies of iron concentrations in patients with potentially malignant disorders can help in early diagnosis and also as an indicator for prognosis[9].

Chilies: The use of chilies has been thought toan etiological role in oral submucous fibrosis and the ingredient causing isvanillyl amideof 8-methyl-6-nonenic acid, it aids in degrading epithelium structure and stimulates fibroblastic activity[10].

The role of tobacco addition: There is increase in the incidence of OSMF when areca nut and tobacco consumption are combined. The consumers of mixed products are often younger and it develops faster in these patients than alonein betel quid chewers. Both genotoxicity and carcinogenicity of areca nut and betel quid chewers with or without tobacco mixture are well documented[11].

Inflammatory Cytokines and Growth Factors: Changes in cytokines and growth factors cause fibroblast proliferation and collagen synthesis thereby resulting in fibrosis. In addition to this, fibrosis by TGF&IL-6 is more evident across different tissues, such as heart, lung, skin, liver, colon, and kidney, and thus indicates that IL-17 and its downstream pathways are closely related to the initiation and propagation of fibrosis[12].

Malignant transformation of OSMF: OSMF is a well-recognized potentially malignant disorder of the oral mucosa. Recently it has been proposed that oral cancers arising due to OSMF constitute a distinct disease, and the differences is believed to happen from different mechanisms of arecanut carcinogenesis. OSCC originated from OSMF is clinically more invasive and also exhibits higher metastasis and recurrence rate than OSCCnot originated from OSMF[13].

Treatment:

The drugs used to treat this erratic condition till date includes steroids, fibrinolytic vasodilators, anti-oxidants, nutritional supplements, ayurvedic supplements and biogenic stimulants incuding physiotherapy,all of which have delivered better results. Most drugs have shown quick relief of symptoms, namely the burning

sensation and ulceration, reducing the stiffness of the mucosa to a certain extent. Various treatment modalities are available to treat this condition which are as follows.

Medical management: Includes vitamins and minerals, vasodilators, colchicine, curcumin / turmeric, osteopathy treatment, tea pigments, placental extracts, physiotherapy, lasers, ayurvedic treatment, ultrasound / cryotherapy and homeopathy.

Surgical treatment

Vitamins & Minerals: Vitamin A 50,000 IU orally daily for 12 weeks decrease the growth of premalignant cells and invasive malignant potential is slowed, arrested or even reversed,and this helpsin reduction of fibrous bands and improve mouth opening. A study done to evaluate effectiveness of mouth opening in 64 patients of OSMFwith the use micronutrients which showedsignificant improvement at the end of 6 weeks as compared to the initial mouth opening[14].

In one study OSMF patients received supplementation of vitamins and minerals for one to three years. Significant improvement in symptoms, like intolerance to spicy food, burning sensation, and mouth opening, was observed. Vitamins A, B, C, D, E and minerals like iron and magnesium stabilize and deactivate the free radicals.

In a study by Shetty P et al the efficacy of spirulina as an antioxidant adjuvant to corticosteroid injections in the management of 40 OSMF subjects was evaluated. Clinical improvements in mouth opening and reduction in burning sensation was noted in the post treatment period in both Spirulina and placebo groups. Spirulina can bring improvements in OSMF patients and can be used as an adjuvant therapy in the initial management of OSMF patients[15 16].

Vasodilators: Pentoxifylline is methylxanthine derivative that has vasodilating properties and increases mucosal vascularity. It helps in suppressingleukocyte function, changing fibroblast physiology and stimulating fibronylysis. Pentoxifylline 400 mg three times daily for 7 monthswas used as an adjunct therapy for OSMF[17].

Colchicine: Colchicine inhibits collagen synthesis and increases collagenolytic activity and has found to be of use in OSMF. In a study by Krishnamoorthy *et al.* reported that 0.5 mg colchicinesorally, twice daily along with intralesional 0.5 ml &hyaluronidase 1500 IU gives noteworthy improvement in burning sensation and mouth opening[18].

Curcumin and Turmeric: Curcuma longa is commonly known as haldi, turmeric or Indian saffron belonging to the family

Zingiberaceae. It is well known for its anti-inflammatory and antioxidant action[19]. Dasin a study found curcumin and turmeric oil as significantly beneficialin non-invasive herbal therapy for OSMF[20]. Ramsevak et al. described in his study the anti-inflammatory, cytotoxic and antioxidant activity of curcumin I, II, III from Curcuma longa[21].

Curcumin has been found to restrain many disease processes through their anti-inflammatory, antioxidant, and anticancer properties[22]

Srivastava et al**.** have verified the scavenging effect of curcumin on superoxide radicals, hydroxyl radicals, and lipid peroxidation. These studies also put forward that curcumin readily decreases atrophy of mucosa thereby reducing burning sensation[23].

Agarwal conducted a study to check the efficacy of turmeric in 30 OSMF patients. An improvement in mouth opening and burning sensation was noticed. It was hypothesized thatit exerts anti-inflammatory activity by inhibiting a number of dissimilar molecules that contribute in the process of inflammation. They also reveal fibrinolytic property due to its ability to reduce lipid peroxidation and check cellular proliferation, thereby reducing the rate ofcollagen synthesis[24].

Osteopathy treatment

The osteopathic idea states that the structure and function within the human body are interrelated. The osteopathy approach stimulates the body's internal mechanisms to heal itself by the use of human hands[25].

The osteopathic treatment acts on the circulatoy system, the spine, the viscera, and the thoracic and pelvic diaphragms. Few studies have shown its use in the managing temporomandibular dysfunctions. This treatment modality is the cautious first step in integrating this therapy in the support of the treatments of patients with OSMF[26].

Tea Pigments: Li and tang found that tea pigments which are oxidized products of polyphenols improve microcirculation by reducing blood viscosity when administered in OSMF patients and thus improve microcirculation stimulating activity of superoxide dismutase[27].

Placental extracts: Acts essentially as a "biogenic stimulators." It contains nucleotides, enzymes, vitamins, amino acids, and steroids, an aqueous extract of human placenta which stimulates the pituitary and the adrenal cortex, and regulates the metabolism of tissues and helps in dissolving ground substance and

2cc intralesional injection of this extract in the predetermined areas, once a week for one month showed improvement in the mouth opening of about 28.26%[28].

Physiotherapy: Cox S et al. conducted a study in which physiotherapy using mouth opening exercise by tongue spatula was done, their study showed improvement in mouth opening but no change in the symptom of pain and burning sensation. It aids in tissue remodeling through promotion of physical movements and heat.[29]

Muscle stretching exercises: For the mouth may be helpful to prevent further restriction of mouth movements and to prevent relapse. Mouth gag, acrylic surgical stent, ballooning of mouth, hot water gargling, inter positioning spatula between the teeth and adding a new spatula every 5 - 10 days can be used for performing these stretching exercises.[30]

Diode Lasers: Talsanil JR *et al*. used laser with follow-up physiotherapy to reduced trismus in OSMF and concluded that diode laser is an inexpensive and an alternative method which requires less hospital stay and follow-up compared to other surgical methods[31].

ErCr:YSGG lasers: With the advent of lasers a new treatment is being tried where the Erbium Chromium Yttrium Scandium Gallium Garnet (ErCr:YSGG) laser having wavelength of 2780 nm, is seen being well absorbed enabling it to be used on oral soft tissue without causing thermal damage.It's been used to treat mild to moderate cases of OSMF.[32]

Aloe vera: Aloe vera is an emollient resin and a mannoprotein containing many amino acids is called 'wound healing hormones'[33]. The polysaccharides contained in the gel of the leaves has anti-inflammatory, immunomodulatory, antioxidant and wound-healing properties, it also has antiseptic, antiviral, antibacterial and antifungal properties. It is known to boost the immune system[34]. It improves wound healing by increasing blood supply, which in turn increases oxygenation. Aloe vera has soothing and cooling properties. This property of Aloe vera reduces pain and burning sensation in OSMF patients.[35]

Tulasi: Tulasi is rich antioxidant and renowned for its restorative powers from ancient ages, it has several benefits like relieving stress, boosting immunity, increasing stamina and promoting healthy metabolism. Some of the main chemical constituents of tulasi are: oleanolic acid,

ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, β-caryophyllene (about 8%), β-elemene (c.11.0%) and germacrene D (about 2%). The proposed mechanism of action of this medicament in OSMF is anti-inflammatory, antioxidant, anti-stress, analgesics and others.[36]

Ultrasound equipment (electroson) and Cryotherapy: In a study conducted by Vijayakumar M., *et al*. all the patients were treated with ultrasound equipment (electroson) followed by finger and thumb kneading at the buccal region inside the mouth with mild stretching over the fibrous bands with in tolerable pain limits. They were provided with cryotherapy before and after the treatment for 5 - 7 minutes. The study resulted with a mean improvement in mouth opening and significant improvement in tongue protrusion.[37]

Homeopathy: Homoeopathy enhances the entire state of health and treats various dental problems. Calcareaphosphorica, a homeopathy medicament is used when mouth cannot be opened without pain and for trismus of muscles.[38]

Surgical Treatment: Long standing oral sub mucous fibrosis usually requires surgical approach. Release of fibrosis and split skin grafting has a high recurrence rate due to graft shrinkage. Use of island palatal flap has limitations such as its involvement with fibrosis and second molar tooth extraction is required for flap cover without tension.

Surgical management is better than conservative approach. Flap cover is better than split skin graft in term of recurrences. Other treatment method such as nasolabial flap cover can also be used in elderly with lax skin. The superficial temporal artery fascial flap cover also has advantage of lesser morbidity and more suited in cases of severe restriction of mouth opening.[39]

Conclusion: "An *ounce of prevention is worth a pound of cure"* -Benjamin franklin. Oral submucous fibrosis is a crippled irreversible disease, incurable disease, and no treatment modality; either surgical or medical has been satisfactory in completely eliminating the disease. The initial treatment of OSMF is counseling with multivitamin/antioxidants/lycopene. The later stage includes intralesional steroids, pentoxifylline and surgery is last option. The treatment of OSMF has to be based on individual case.

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