Etiopathogenesis and management of oral submucous fibrosis

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ABSTRACT

Oral submucous fibrosis (OSF) is an insidious, chronic, progressive, debilitating disease. It is mostly prevalent in the South-east Asian countries. Areca nut chewing usually causes the condition. The hallmark of the disease being sub mucosal fibrosis that affects most parts of the oral cavity, pharynx and upper third of the oesophagus and its clinical presentation depends on the stage of the disease at detection. As the disease has a spectrum of presentation, the management differs with the various stages of the disease. This article reviews the etiopathogenesis and the various medical management techniques of oral submucous fibrosis.

Keywords: Areca nut; Etiopathogenesis; Management; Oral submucous fibrosis; Treatment

Introduction

Oral submucous fibrosis was first described by Schwartz in 1952 among five Indian females living in Kenya and he coined the term Atrophia Idiopathica Mucosae Oris.1 OSF is defined by Pindborg J.J. and Sirsat S.M. (1966) as an “Insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx, although occasionally preceded by and /or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria with epithelial atrophy leading to stiffness of mucosa and causing trismus and inability to eat”.3,4

The various terminologies used are Atrophia Idiopathica Mucosae Oris 3 Submucous fibrosis of the palate and pillars 4 Diffuse Oral submucous fibrosis5 Idiopathic scleroderma of the mouth Sclerosing stomatitis 6 Idiopathic palatal fibrosis Juxta epithelial fibrosis, Asian Sideropenic Dysphagia.1 The global incidence in 1996 of submucous fibrosis was estimated as 2.5 million individuals.9 In Indian populations the prevalence is 5% for women and 2% for men. Age groups below 20 years are more often contracted with submucous fibrosis.6-11

Clinical presentation of OSF

Early stages

1. The first sign of OSF is erythematous lesions sometimes in conjunction with petechiae, pigmentation, vesicles, and the presence of excessive salivation( as a physiological effect of body and chewing of betel nut causes excessive salivation).6,11
2. These initial lesions are followed by a paler mucosa, which may comprise “marble stone appearance” (Figure 1).1,11

Later stages:

3. In the later stage of the disease it presents as fibrotic bands located beneath an atrophic epithelium.1,11
4. Palpable fibrous bands occur with the frequency of:
   • Circular band around the entire rima oris(mouth orifice).
   5. “Hockey stick” (Figure 2) or bud shape Uvula.
   6. Increased fibrosis eventually leads to loss of resilience, which interferes with speech, decreased tongue mobility, [normal in males= 35 to 45 mm; females= 30 to 42 mm]13 and a decreased ability to open the mouth. Tongue protrusion is measured from mesioincisal angle of upper central incisor to the tip of the tongue when maximally extended; normal in males=5 to 6 cm; females= 4.5 to 5.5 cm.13
   7. Hyposalivation due to fibrosis of the salivary gland duct opening and the fibrosis reaching upto the submucosa and minor salivary glands.13
   8. Hearing loss due to stenosis of the Eustachian tubes.12
   9. Dysphagia to solids (if esophagus is involved).12,13
   10. Inability to blow cheeks.11
11. The atrophic epithelium causes a smarting sensation and inability to eat hot and spicy food.1,11

The early histopathologic characteristics for submucous fibrosis are fine fibrils of collagen, edema, hypertrophic

Figure 1. Blanching and marble stone appearance of buccal mucosa.
fibroblasts, dilated and congested blood vessels, and an infiltration of neutrophilic and eosinophilic granulocytes. This picture is followed by a down-regulation of fibroblasts, epithelial atrophy, and loss of rete pegs, and early signs of hyalinization occur in concert with an infiltration of inflammatory cells. Epithelial dysplasia in submucous fibrosis tissues appeared to vary from 7 to 26% depending on the study population.

Malignant transformation of oral submucous fibrosis has been estimated in the range of 7 to 13% and the incidence over a 10-year period at approximately 8%. In rural Indian population, the malignant transformation rate of OSF was found to be 7.6% over a 17-year period.

OSF has been classified by various authors according to the clinical presentation, histopathological picture and combination of both. Two classifications of OSF based on the interincisal opening given by Haider et al and Lai D R have a broader usage for clinical diagnosis and management.

Etiopathogenesis

OSF has multifactorial origin with the main etiological factor for OSF being arecanut (supari in hindi).

Areacnut

Areca nut constitutes of alkaloids, flavonoids and other trace elements like copper (Figure 3). The major alkaloids found in areca nut are arecoline, arecaidine, gauvaccine, gauvacoline which cause fibroblastic proliferation and increased collagen formation, of which arecoline and arecaidine are the major causative factor. Hydrolysis of arecoline produces arecaidine that has pronounced effects on fibroblasts.

The stimulation of fibroblasts is greater with arecaidine, and there was a concentration-dependent stimulation of collagen synthesis when fibroblasts were exposed to both arecoline and arecaidine, addition of slaked lime calcium hydroxide (Ca(OH)₂) to areca nut in pan facilitates hydrolysis of arecoline to arecaidine making this agent available in the oral environment and hence causing greater stimulation of fibroblast.

Flavonoid component of areca nut have some direct influence on collagen metabolism, enhancing the cross linking of collagen fibers and hence raise the lysyl-oxidase (LOX) activity. During the biosynthesis of LOX, copper is incorporated into LOX. LOX also contains a co-factor lysine tyrosylquinone (LTQ), a covalently bound carbonyl prosthetic group. The LTQ is essential in the formation of cross-links in the collagen fibers for the reaction mechanism of LOX. Copper has been suggested to play a structural role in stabilizing the LTQ. During the process of cross-linking, copper plays an important role in reoxidizing the reduced enzyme facilitating the completion of the catalytic cycle. Areca nuts have been shown to have a high copper content, and chewing areca nuts for 5–30 min significantly increases soluble copper levels in oral fluids. This increased level of soluble copper could act as an important factor in OSF by stimulating fibrogenesis through up-regulation of LOX activity.

Copper causes up-regulation of lysyl-oxidase (LOX) enzyme. The LOX is dependent on copper for its functional activity. During the biosynthesis of LOX, copper is incorporated into LOX. LOX also contains a co-factor lysine tyrosylquinone (LTQ), a covalently bound carbonyl prosthetic group. The LTQ is essential in the formation of cross-links in the collagen fibers for the reaction mechanism of LOX. Copper has been suggested to play a structural role in stabilizing the LTQ. During the process of cross-linking, copper plays an important role in reoxidizing the reduced enzyme facilitating the completion of the catalytic cycle. Areca nuts have been shown to have a high copper content, and chewing areca nuts for 5–30 min significantly increases soluble copper levels in oral fluids. This increased level of soluble copper could act as an important factor in OSF by stimulating fibrogenesis through up-regulation of LOX activity.

To summarize the action of the major etiological factor arecanut in the pathogenesis of OSF, the alkaloids cause the stimulation of fibroblast and gene expression hence leading to increased collagen production. The flavonoids increase the cross-linking of collagen and copper causes the up-regulation of lysyl oxidase and hence stimulating fibrogenesis.

Genetic susceptibility

Collegen-related genes COL1A2, COL3A1, COL6A1,
COL6A3 and COL7A1 have been identified as targets of transforming growth factor-β (TGF-β) and induced fibroblasts at an early stage of the disease. These genes play an important role in the homeostasis of collagen in the body. The genetic modulation of different enzymes such as collagenases and lysyl oxidase together with cytokines, namely TGF-β, has been implicated in this context. The transcriptional activation of procollagen genes by TGF-β may contribute to increased collagen levels and hence increased expression of procollagen genes and thereby contributing to increased collagen level in OSF. Chiu et al. analyzed two groups of betel chewers, one with OSF and the other without in order to compare the association of OSF and polymorphisms of six collagen related genes. They used PCR-based restriction fragment length polymorphism assays to determine the genotypes of the six collagen-related genes situated on different chromosomes and found that the genotypes associated with the highest OSF risk for collagen 1A1, collagen 1A2, collagenase-1, transforming growth factor beta1, lysyl oxidase, and cystatin C, an increased risk of OSF was noted with an increasing number of high-risk alleles for those with both high and low exposures for betel quid. The cell selection mechanism of oral fibroblasts is proposed to explain the effect of the modification of cumulative betel quid exposure on the risk profiles of collagen-related genes, susceptibility to OSF could involve multigenic mechanisms modified by the betel quid-exposure dose.

Autoimmunity

The role of autoimmunity in OSF can be determined due to the presence of circulating immune complexes, their immunoglobulin contents and the detection of various autoantibodies in patients’ sera. Anti-nuclear antibodies (ANA) (23.9%), anti smooth muscle (SMA) antibodies (23.9%) and anti gastric-parietal cell (GPCA) (14.7%) were positive in OSF patients compared with healthy control subjects. Increased levels of IgG, IgA and IgM immune complexes and raised serum levels compared with control groups have also been reported. The frequencies of HLA A10, DR3 and DR7 were significantly different compared with an ethnically, regionally and age-matched control group. Study using polymerase chain reaction (PCR) showed an increase in frequencies of HLA A24, DRB 1–11 and DRB3-0202/3. Two new HLA DRB1 alleles were identified by sequencing-based typing and named as HLA DRB1-0903 and DRB1-1145.

Role of Heat shock proteins (HSP)

HSP4, is a 47 kDa collagen-binding heat shock protein (HSP), known as a molecular chaperone belongs to the serine protease inhibitor (serpin) superfamily and is involved in the synthesis, processing, and assembly of various collagenases. Shung et al., first found that arecoline has the tendency to upregulate HSP47 mRNA expression in human buccal mucosal fibroblasts (BMFs). HSP47 and hence cause the accumulation of collagen in oral mucosal connective tissue and cause OSF.

Management

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. To improve the condition the current treatment regimens of OSF have been proposed. Modulators of inflammation

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 fibro-collagenous condition. It can be applied topically or intralobial injections depending upon the clinical stage of the disease. In the early stages when patient presents with the burning sensation, topical corticosteroids Triamcinolone acetonide 0.1% and Betamethasone – 0.5% are applied locally for 3 months. In the clinical stages with palpable fibrous bands intralobial injection of Dexametasone – 4mg/ml, Triamcinolone -10 mg/ml given biweekly for 3 months, at multiple sites; parallel to the mucosal surface as possible to avoid unnecessary trauma of the submucosal vessels and subsequent release of hemosiderin, which will stimulate fibroblastic activity. A study done using biweekly submucosal injections of 40 mg triamcinolone for 12 weeks showed significant improvement in mouth opening and improvement in symptoms of burning sensation.

Interferon gamma have immuno-regulatory effect and has anti-fibrotic cytokine effect and hence its major role in altering collagen synthesis. In vivo studies of Intra-lesional injection of 0.01-10.0U/ml 3 times a day for 6 months showed improvement of symptoms. Increase in collagen synthesis in vitro in response to arecoline was inhibited in the presence of IFN-γ (0.01–10.0 U/ml) in a dose-related way. In an open uncontrolled study intra-lesional IFN-γ treatment showed improvement in the patients mouth opening from an inter-incisal distance before treatment of 21±7 mm, to 30±7 mm immediately after treatment and 30±8 mm 6-months later, giving a net gain of 8±4 mm (42%) (range 4–15 mm) and reduced burning dysaesthesia and increased suppleness of the buccal mucosa. The post-treatment immunohistochemistry showed a decreased amount of inflammatory cell infiltrate and an altered level of cytokines compared with the pre-treatment lesional tissue.

Placental extracts acts 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. Its use is based on the tissue therapy method. According to this theory when animal and vegetable tissues are severed from the parent body and exposed to unfavorable conditions, but not mortal to their existence, undergo biogenic readjustment leading to development of substance in the state of their survival to ensure their vitality biogenic stimulators. Such tissues or their extract when implanted or injected into the body after resistance of pathogenic factors stimulates metabolic or regenerative process. Intralobial injection of Placenta extract 2.0cc given locally in the predetermined areas, once a week for one month showed improvement in the mouth opening of about 28.26%.

Immune milk has anti-inflammatory effect and contains vitamins such as Vit. A, C, B1, B2, B6, B12, nicotinic acid pantothenic acid, folic acid, iron, copper and zinc. It is produced from cows immunized with multiple human intestinal,
bacteria and contains 20-30% higher concentration of IgG type I antibody. Its role in OSF is due to its local and systemic upregulation of fibrogenic cytokines and down regulation of anti fibrotic cytokine and hence has an anti-inflammatory action and modulate cytokine production. Symptomatic relief in patients also may be attributed to the micronutrients in the immune milk powder. 45 g milk powder twice a day for 3 months showed significant improvement in the symptoms.45

**Modulators of vascularity or relief of ischaemia:**

**Pentoxifylline** is a tri-substituted methylxanthine derivative. It increases red cell deformability, leukocyte chemotaxis, antithrombin and anti- plasmin activities and has fibrinolytic activity. Pentoxifylline also decreases red cell and platelet aggregation; it also decreases granulocyte adhesion, fibrinogen levels, and whole blood viscosity. Dosage of 400 mg 3 times a day for 7 months showed significant improvement in the symptoms.46 They have their role in OSF as pathologically occluded blood vessels due to collagen deposition and hypercoagulated status of blood restrict the nutrients and other therapeutic substances from reaching the affected tissue. A study showed significant improvement in signs and symptoms with Pentoxifylline 400mg given over a period of 7 months.45

**Fibrinolysis**

**Hyluronidase** is a fibrinolytic enzyme. It helps in the breakdown of hyaluronic acid, which lowers viscosity of the intercellular cement substance; it also decreases collagen formation with dosage of 1500 IU/biweekly for 10 weeks. A study used different regimens of intralesional injections in patients, 4mg dexamethsone biweekly; 1500 IU of hyluronidase with 1cc of lignocaine biweekly; 4mg of dexamethsone and 1500 IU of hyluronidase; 2cc placentrex biweekly and found out that combination of dexamethsone and hyluronidase for seven weeks gave maximum improvement.45

**Chymotrypsin**, an endopeptidase, hydrolyses 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.49

**Nutritional support and to combat reactive oxygen species**

**Lycopene** is an antioxidant obtained from tomatoes. Lycopene have two major kinds of biological effects: antioxidative effects and non-oxidative mechanisms. Acting as potent antioxidants, it inactivates free radicals and attenuates free radicals-initiated oxidative reactions, particularly lipid peroxidation and DNA oxidative damage, thereby preventing tissue damage as well as potential cancerization. The non-oxidative effects are regulation of gap-junction communication (GJC), gene function regulation, hormone and immune modulation, and antiproliferation and prodifferentiation activities. These mechanisms may be interrelated or operate simultaneously to reduce risk for various types of cancers, as well as oral precancerous lesions and cancer.50 A study used 16 mg of lycopene per day in patients with OSF and found significant improvement in mouth opening.51

**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 secretary and keratinization tissues and maintains the integrity of epithelium. Vitamin A 50,000 IU orally daily for 12 weeks decrease the progress of premalignant cells, invasive malignant potential is slowed, delayed, arrested or even reversed, it improves the reduction of fibrous bands and mouth opening. A study done to evaluate effectiveness of Micronutrients in 64 patients with oral submucous fibrosis, mouth opening in patients showed significant improvement at the end of 6 weeks as compared to the initial mouth opening.52

**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) expression.53,54 Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months decreased the number of micronucleated cells observed in both the exfoliated oral mucosal cells and circulating lymphocytes. It was observed in a study that all these compounds offered protection against benzo[a]pyrene induced increase in micronuclei in circulating lymphocytes. Patients suffering from sub mucous fibrosis were given a total oral dose of turmeric oil (600 mg turmeric oil mixed with 3 g turmeric /day), turmeric oleoresin (600 mg + 3 g turmeric day) and 3 g turmeric /day as a control for 3 months. It was observed that all three-treatment modalities decreased the number of micro nucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes. Turmeric oleoresin was found to be more effective in reducing the number of micronuclei in oral mucosal cells, but in circulating lymphocytes the decrease in micronuclei was comparable in all three groups.55

**Physiotherapy** modifies tissue remodeling through promotion of physical movements and heat. Physical exercise regimen like muscle stretching exercise, forceful mouth opening with the help of sticks, tongue movement in the figure of 8, ballooning of mouth, hot water gargling, using mouth gag and acrylic surgical screws for forceful opening of mouth. 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 improvement in the symptom of pain and burning sensation.56

The Rationale for surgical management of OSF is surgical release of fibrous bands followed by forceful opening of the mouth (widening of the incised tissue or region), and covering of surgical defects using various flaps or synthetic biological material.54 Various effects of the surgical management seen for example in cases of Buccal fat pad, there is inadequate anterior reach and areas anterior to canine have to be left covered. In nasolabial flap there is limited width of flap material for coverage. In palatal pedicle flap there is fibrotic involvement of the site. In split skin grafts there is increased incidence of contracture.57

**Conclusion**

“An ounce of prevention is worth a pound of cure- Benjamin
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*Franklin.* Oral submucous fibrosis is a crippled irreversible disease; hence educating the population about the habit and its effect is of utmost importance. OSF is an incurable disease, no treatment modality; either surgical or medical has been successful in completely eliminating the disease, proper habit restriction is required in OSF to ensure the progression of the disease.

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