

Oral Submucous Fibrosis: A Review

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How to citation this article: Dr. N Surya Vamshi, Dr. MB Vinay Kumar, Dr. Revathi Rajeshwarkar, Dr. Ch. Aparanjitha, Dr. Tanya Jain, Dr. Vijaya Awasthi, “Oral Submucous Fibrosis: A Review”, IJMACR- January – February - 2022, Vol – 5, Issue - 1, P. No. 22 – 29.

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Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Oral submucous fibrosis is a chronic insidious disease affecting any part of the oral cavity and sometimes the pharynx. It is well recognised as potentially malignant disorder which is associated mainly with the use of areca nut in various forms. It is characterised by inflammation and progressive fibrosis of the submucosal tissue. The pathogenesis of the disease includes various factors like areca nut chewing, chillies, nutritional deficiencies and genetic processes. Present review of literature aims to

discuss pathogenesis, clinical features and management of oral submucous fibrosis in detail.

Keywords: Oral Submucous Fibrosis, OSMF, Oral mucous membrane

Introduction

Oral mucous membrane is a unique tissue which is continuously exposed to various kinds of stresses such as heat, cold, microorganisms, chemicals and mechanical irritation in the process of food intake. In response to these stresses, both epithelial and connective tissue

layers of the oral mucosa exhibit acute and chronic reactive changes.¹

Oral submucous fibrosis is a disease due to a chronic, insidious change in fibro-elasticity, characterized by burning sensation in the oral cavity, blanching, and stiffening of the oral mucosa and oro-pharynx leading to trismus and inability to open the mouth. The symptoms and signs depend on the progression of the lesions and number of affected sites.² It is characterized by loss of mucosal elasticity and excessive fibrosis and is always associated with juxta epithelial inflammation and progressive hyalinization of lamina propria.^{3,4,5}

Oral submucous fibrosis is a premalignant disorder which is most commonly associated with the chewing of areca nut (betel nut). The habit is mostly prevalent in South Asian populations. OSMF causes significant morbidity. If left untreated this condition can later transform into squamous cell carcinoma (SCC), which is also responsible for mortality. The combine use of areca nut and tobacco has led to a sharp increase in the frequency of OSMF.⁶ Present review of literature aims to discuss pathogenesis, clinical features and management of oral submucous fibrosis in detail.

Etiopathogenesis of OSMF: OSMF represents a failed wound-healing process of the oral mucosa after chronic, sustained injury.⁷ Etiology of Oral Submucous fibrosis is obscure, but several factors were put forward to suggest a multifactorial origin for this condition. It has been suggested that consumption of chillies, nutritional deficiency, chewing of areca nut, genetic susceptibility, altered salivary constituents, and autoimmunity and collagen disorders may be involved in the pathogenesis of this condition.⁵

The alkaloid content found in this whole fruit of areca nut and betel nut is arecoline which stimulates fibroblast

to increase production of collagen in a larger amount. Due to the presence of high amount of copper content found in the areca nut, it leads to the increase of soluble copper levels in oral fluids which can also be considered as initiating factor in OSMF.⁸ More than the self-prepared betel quid, frozen dried forms of mawa, gutka and pan masala cause more irritation to the oral mucosa.⁹

OSMF can also occur due to the deficiency of vitamin B complex. Due to iron deficiency anaemia, vitamin B complex deficiency and malnutrition there is derangement in the repairing of inflamed oral mucosa leading to scarring and impaired healing.¹⁰

OSMF results from increased production of collagen by fibroblasts. In addition to this, there is decreased breakdown leading to accumulation of excessive amount of collagen. Areca nut consumption influences the fibroblasts to differentiate into phenotypes that produce more collagen, due to the presence of the alkaloids, arecadine and arecoline. Arecoline gets converted in to arecadine which is the active metabolite. There is dose dependent increase in production of collagen by fibroblasts under influence of these factors.¹¹

Excessive fibrosis can take place due to reduced degeneration of collagen, by formation of a more stable collagen structure. Tannin, a vital content of betel nut, has the ability to cross-link and thereby stabilizing the collagen. As the disease progresses, type III collagen is almost completely replaced by type I, wherein type I is more resistant to degradation than type III. Another component of betel nut that aids this cross-linking is copper. It is a constituent of enzyme lysyl oxidase. This enzyme also causes cross-linking and makes collagen resistant to degradation by collagenase.¹²

Oral submucous fibrosis is also thought to be an autoimmune disease. The presence of various auto antibodies in varying titers is reported in several studies confirming autoimmune basis to the disease. Few studies have reported on HLA typing of OSMF patients and controls. Higher frequencies of OSMF are found in HLA A10, DR3 and DR7 types when compared to an ethnically, regionally and age-matched control group. Although the data on various HLA types, raised auto antibodies and the detection of immune complexes tend to indicate an autoimmune basis for the disease, substantial number of cases and matched controls may be required to verify these finding.^{13,14}

Clinical feature of OSMF: OSMF majorly affects masticatory, specialized and the lining mucosa of the oral cavity but most commonly it appears in the buccal mucosa, retromolar area and the soft palates. In severe cases it may involves the pharynx and oesophagus.^{15,16}

Dry mouth feel, soreness, taste disorders, limited tongue mobility, trismus and dysphagia are initial symptoms. The oral mucosa becomes soft and pink in colour and with time it becomes nonelastic. The oral mucosa also exhibits blanching and on palpation is tough with vertical bands, just opposite to the premolar part. During subsequent stages of the lesion, it affects the lips and the palate. There is also burning sensation in the mouth on intake of spicy food. If not treated, the lesion progresses and leads to minimal mouth opening thereby hampering the well-being of the patient.¹⁷

Classification of OSMF: Several classifications based on clinical and histological features by various researchers, depending on different aspect of OSMF.

Clinical classification

JV Desa (1957) classified OSMF into three stages as follows:¹⁸

- **Stage 1:** Stomatitis and vesications
- **Stage 2:** Fibrosis.
- **Stage 3:** As its sequelae

Bhatt and Dholakia (1977) clinically grouped patients into three grades:¹⁹

- **Grade 1:** Comprising mild and early cases with very slight fibrous bands and little closure of the mouth
- **Grade 2:** Cases with moderately pronounced symptoms of disease and fibrous banding extending from the cheek to the palate area.
- **Grade 3:** Cases show excessive amounts of fibrous banding involving the cheek, palate uvula tongue and lips and narrowed mouth opening.

Pindborg JJ (1989) separated OSMF into three stages based on clinical features:²⁰

- **Stage 1:** Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal patechiaie.
- **Stage 2:** Fibrosis occurs in healing vesicles and ulcer, which is the hallmark of this stage. Early lesions demonstrate blanching of oral mucosa. Older lesion include vertical and circular palpable fibrous bands in the buccal mucosa and around the mouth opening or lips, resulting in a mottled marble like appearance of the mucosa because of the vertical thick, fibrous bands associated with balanced mucosa.
- **Stage 3:** Sequelae of OSMF: Leukoplakia is found in more than 25% of individuals with OSMF. Speech and hearing deficits may occur because of involvement of the Eustachian tubes.

Histologic classification

Kiran Kumar et al. (2007) suggested OSMF histological grading as follows:²¹

- Grade I: Loose, thick and thin fibres

- Grade II: Loose or thick fibres with partial hyalinization
- Grade III: Complete hyalinization

Oshiro K et al. (2005) graded OSMF histologically grading as follows:²²

- **Early stage:** Evidence of large number of lymphocytes in the subepithelial, connective tissue zone along with some myxomatous changes.
- **Intermediate stage:** Presence of hyalinization in sub epithelial zone where blood vessels are compressed by fibrous bundles. Evidence of granulation changes close to the muscle area and reduced inflammatory cells in subepithelial layer.
- **Advanced stage:** Marked fibrous areas with hyaline changes extending from subepithelial to superficial muscle layers. Number of blood vessels dramatically small in subepithelial zone. Inflammatory cell infiltrates hardly seen. Atrophic, degenerative changes initiated in muscle fibres.

Malignant transformation of OSMF: OSF constitutes a failure in the wound healing process following chronic persistent injury to the oral mucosa. Paymaster first identified the malignant potential of OSF in 1956 but its mechanisms have not yet been elucidated. The high mortality rate associated with oral squamous cell carcinoma (OSCC) is the result of late diagnosis of the malignant potentiality of its associated precancers. Malignant transformation in the OSF background is complex. It involves numerous pathways and molecules associated with hypoxia, the cell cycle, angiogenesis, and epithelial mesenchymal transition.^{23, 24}

Management of OSMF: A number of treatment modalities for OSMF have been proposed with little reliable evidence for the effectiveness of each/any of these in the management of this condition. These

treatment protocols can dilute the signs and symptoms of OSMF, but no single treatment modality can be identified which can provide a complete cure of this disease.

Treatment strategies

Habit alleviation: Areca nut usage has to be completely stopped in an OSMF patient before following any treatment protocol. Areca nut is very addictive and its cessation is arduous by the fact that no other agent is available to replace it in the course of quitting this habit.²⁵

Nutritional supplements: OSMF is associated with impaired nutritional status, therefore, various investigators have supplemented the patients with multiple micronutrients which includes zinc, vitamin A, B, C, iron, folic acid, copper, calcium and manganese.

In a study by Gupta et al. who treated six cases of OSMF with appropriation containing vitamin A 2500 IU, vitamin E acetate, beta carotene 50 mg, vitamin C, zinc, copper and manganese. There was improvement in the symptoms of all the patients.⁸

Antioxidants: Antioxidants have also been tried in treatment of OSMF as reactive oxygen species, free radicals, and peroxidises have been attributed in its pathogenesis. Some of the antioxidants which have been used are lycopene, tea pigments, β carotene, aloe vera, cucurmurin, and spirulina.

Lycopene is a major carotenoid which is found in tomato have antioxidant and chemopreventive properties against potentially malignant disorders. Karemore and Motwani and Sunderraj S *et al.* found that lycopene was highly efficacious in relieving sign and symptoms of OSMF.^{26, 27}

Corticosteroids: Corticosteroids are believed to decrease inflammation and reduce collagen production thereby alleviating symptoms of OSMF.

Various corticosteroids such as short acting (hydrocortisone), intermediate acting (triamcinolone) and long acting (betamethasone and dexamethasone) are used in treatment of OSMF. They act by inhibiting inflammatory factor and increasing apoptosis of inflammatory cell, thereby partially relieving symptoms of early stage OSMF. A combination of chymotrypsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg) twice weekly submucosal injection for 10 weeks.²⁸

Hyaluronidase breaks hyaluronic acid and lowers the viscosity of intercellular cement substance. Dexamethasone acts as immune suppressive and anti-inflammatory agent by its antagonistic activity on soluble factors released by the sensitized lymphocytes succeeding the activation by non-specific antigens.^{29,30}

Placental extract: Placentrex is basically aqueous extract of human placenta which contains enzymes, vitamins, amino acids, nucleotides and steroids. Placentrex causes biogenic stimulation and increases vascularity of tissues based on principal of tissue therapy which was introduced by Filatov in 1933. It has been found by various authors that placenta extract significantly improves mouth opening, burning sensation, colour of mucosa and reduction in fibrotic bands.³¹

Physiotherapy: Physiotherapy along with pharmacology has shown good results in the treatment of oral sub-mucous fibrosis. Physiotherapy management includes exercises which has proven to have a great impact on treatment of oral submucous fibrosis

Various exercises for oral submucous fibrosis patients

- Tongue blade exercise
- Tongue-in-Cheek Push
- Side Tongue Stretch
- Cheek Puff
- Pucker
- "O" Exercise
- Lip Hold
- Up and Down Tongue Stretch
- Teeth Sweep

Although the primary care of oral submucous fibrosis is dental, the role of physiotherapy is important too. Since the action of opening of the mouth is restricted, the usage of physiotherapy has a significant impact. These simple exercises may be performed anywhere.³²

Ultrasound: Therapeutic ultrasound has been used extensively in physical medicine with considerable success. The objectives of ultrasound treatment are to accelerate healing, increase the extensibility of collagen fibers, and provide pain relief.³³

Therapeutic ultrasound should be given as an adjuvant therapy in OSMF patients. Therapeutic effects obtained by ultrasonic energy are due to increased vascular and fluid circulation, increase in cell permeability, and increase in pain threshold and a break in pain cycle. The physiological effects of ultrasound may induce thermal and non-thermal physical effects in tissues. Thermal effects (continuous mode) are those that are due to heating and may include increased blood flow, reduction in muscle spasm, increased collagen fibers extensibility, and pro-inflammatory response. In the cases of OSMF, we want more of thermal effects, so continuous mode is advisable for treatment.³⁴

Surgical management of OSMF: Most treatment modalities in OSMF have centered on relief of the burning sensation and release of the fibrotic bands to assist oral opening. Predictably the release of the fibrotic bands has been the basis of all surgical techniques employed, while medical interventions have dwelt on the suppression of the inflammatory response and prevention of progressive fibrosis.

Surgical management of OSMF has involved excision of the fibrotic bands either by the scalpel or using a laser, with or without the use of interpositional grafts to maintain the oral opening.³⁵

Surgery is generally indicated in advanced OSMF patients or patients with malignant changes. Although surgery can aggravate the condition but surgical intervention is the only treatment available in extremely advanced cases of oral submucous fibrosis.³⁶

Conclusion

Oral submucous fibrosis (OSMF), now labeled as a “potentially malignant disorder”, is rather unique in its clinical presentation. It is mostly linked to betel consumption as a causative factor. The primary problem with oral submucous fibrosis is the stiffness of the mouth or difficulty in mouth opening. The initial presentation of OSMF is inflammation. Inflammation is followed by hypovascularity and fibrosis visible as blanching of the oral mucosa with a marble like appearance. Blanching may be localized, diffuse, or reticular. In some cases, small vesicles may develop that rupture and form erosions. In the later advanced stage of OSMF, a fibrous band that restricts mouth opening (trismus) is characteristic. It causes further problems in oral hygiene, speech, mastication, and possibly swallowing. Development of fibrous bands in the lip leads to thickening and rubbery appearance.

Management of this premalignant condition is mainly based on the level of disease. Most commonly favored line of treatment is medical treatment (Non-Surgical).

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