

Oral Submucous Fibrosis: A Review of Literature and Different aspects for Diagnosis and Treatment Modalities

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Abstract:

Southeast Asian patients are the main ones affected by oral submucous fibrosis, a chronic illness of the oral cavity¹. Collagen fibrous bands forming in the soft palate, buccal mucosa, labial mucosa, and associated structures are characteristic of it¹. One of the known causes is vitamin and iron deficiency; other known causes include chewing betel nut and its products; excessive consumption of spices and chilies; poor nutrition; and immunological factors. However, the exact cause is unknown. Treatment involves both nonsurgical and surgical procedures¹.

When treating patients without surgery, Pentoxifylline, lycopene, and other multivitamin supplements are taken in addition to other prescription drugs (like intralesional injections of chymotrypsin, collagenase, hyaluronidase, and steroids). In one surgical procedure, fibrous bands are cut¹. Heat treatment, or thermodynamics, can also lessen the severity of submucous fibrosis.

Keywords: Oral submucous fibrosis, Areca nut, Betal nut, medicinal therapy, surgical treatment.

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INTRODUCTION:

Schwartz coined the term "atrophia idiopathica trophica") mucosae oris in 1952 and also gave the first account of OSMF⁷. Other names for this condition that have been proposed by several authors include idiopathic scleroderma of the mouth, sclerosing stomatitis, and idiopathic palatal fibrosis⁴. Pindborg and Sirsat described this illness as "an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx." Even though it can occasionally occur before or be connected to vesicle formation, it is always associated with the juxtraepithelial inflammatory response. Response, which is followed by fibroblastic alterations in the lamina propria. Epithelial atrophy

causes the oral mucosa to stiffen, which results in trismus and the inability to eat.

Sushruta, an ancient medical text, classified a disorder related to OSMF as "Vidari," which falls under the category of diseases of the mouth and throat³. Chewing areca nuts and their products is linked to a well-known and chronic potentially fatal disorder called Open Source Mental Fever (OSMF), which is common among South Asians¹. This review's goal is to highlight different OSMF treatment approaches that have been previously published in the literature¹.

ETIOPATHOGENESIS:

When the illness was initially discovered in 1952, it was categorized as an idiopathic disorder. Oral submucous fibrosis has a 7%–13% chance of progressing to oral malignant lesions, especially squamous cell carcinoma⁵. So far, areca nuts, deficiencies in essential vitamins, capsaicin found in chilies, immunological factors, and micronutrient deficiencies in iron and zinc have been identified as the etiological factors¹¹. In addition to these variables, some people may be predisposed to OSMF due to a genetic predisposition. Literature suggests various predisposing factors:

1. Areca nut alkaloids cause stimulation of fibroblast leading to proliferation and collagen synthesis¹¹.
2. Increased number of fibroblasts with a high amount of collagen production due to the long-term intake of areca nut ingredients¹².
3. Catechin and tannins from the areca nut cause stabilization of collagen structure¹⁵.
4. Reduction in secretion of collagenase.
5. Increased production of more stable structured collagen (collagen type I trimer) by fibroblast⁵.
6. And upregulation of lysyl oxidase leads to an increase in collagen cross-linkage.
7. Reduced collagen phagocytosis.
8. Activated macrophages and T lymphocytes recreates fibrogenic cytokines which act on fibroblasts.

AIM:

In this article, an attempt is made to include various treatment modalities related to oral submucous fibrosis.

Treatment Options

Pain, a burning sensation, and difficulty eating after trismus are the primary symptoms of OSMF. The degree of clinical involvement of a patient is the primary determinant of their treatment plan in OSMF. Surgery and non-surgical methods are used in the management of OSMF¹.

Conservative Management

Conservative Management involves stoppage of habits, nutritional supplements or supportive therapy and oral physiotherapy¹.

1. Breaking of Habits: People in India are consuming more areca nut, chilies, pan, spices, and commercially produced pan masala and gutka. The most crucial treatment step in the early stages of oral and submucous fibrosis is patient motivation to kick the habit, as this could slow the disease's progression¹.
2. Nutritional supplement or supportive therapy - Magnesium, zinc, copper, iron, selenium, B, C, D, and E vitamins, and iron are examples of micronutrients and minerals that can effectively lower oxidant levels. Reduced fruit and vegetable consumption is associated with a higher risk for cancers and their precursors. Owing to their ability to raise antioxidant levels and provide protection against the increased risk of cancer, fruits and vegetables should be consumed in greater quantities as part of a regular diet. Lycopene, a carotenoid present in tomatoes, has been shown to possess several potent antioxidant and anti-carcinogenic qualities. It has also demonstrated enhanced advantages in precancerous lesions such as leukoplakia¹.

Green tea's polyphenols can boost a cell's defense against reactive oxygen species-induced DNA damage and have significant free radical scavenging activity. It can also trigger apoptosis and lessen the growth of tumor cells. As a result, the potent antioxidant activity of tea polyphenols has been linked to numerous possible positive unique effects of tea. Based on available research, oral submucous fibrosis etiopathogenesis may involve iron deficiency as a cause or consequence¹. Therefore, the treatment plan should include routine hemoglobin level testing and iron supplementation. (Immune milk contains a fair amount of vitamins, including A, B1, B2, B6, B12, C, nicotinic acid, pantothenic acid, folic acid, iron, copper, and zinc, and it has a strong anti-inflammatory effect. The main factor that will increase improvement is if immunological milk containing IgG antibodies can control cytokine assemblage and limit inflammatory response in patients with OSMF.

c. Oral physiotherapy - A physical exercise program and splints or numerous other devices are part of oral physiotherapy for OSMF patients. To prevent further restriction of mouth movements, mouth-

specific muscle stretching exercises may be helpful. The goal is to apply pressure to fibrous bands. Using a mouth gag and an acrylic surgical screw, a forceful mouth opening is recommended.

d. Microwave diathermy - Heat treatment induces band fibrinolysis. Only the juxta-epithelial connective tissue is heated selectively by microwave diathermy, which also restricts the treatment area. Therefore, it is simple to apply and causes little discomfort. Medical Care includes injecting placentex, fibrinolytic agents, and steroids intralesional. The goal of medical care is to increase mouth opening and symptoms¹.

e. Steroids - Steroids have been shown to function as immunosuppressive agents, which reduce inflammation in lesions of oral submucous fibrosis and, consequently, the fibro-collagenous condition. Moreover, it inhibits fibroblast proliferation, which reduces the quantity of collagen fibers. For patients with moderate OSMF, topical steroid application or weekly submucosal intralesional injections may prevent additional damage. Local application of steroid ointment may be beneficial for painful oral mucosa and ulcers. It is discovered that a 1.5 cc injection of hydrocortisone locally works well¹.

f. Hyaluronidase - Research indicates that hyaluronidase targets the collagen of OSMF patients more quickly than it does normal collagen. The enzyme hyaluronidase activates specific plasmatic mechanisms, breaks down the hyaluronic acid matrix, and thins the intracellular cemental materials. Resulting in the softening and reduction of fibrous tissue. According to Kakar et al., a local injection of 1500 IU of hyaluronidase and 4 mg of dexamethasone for 7 weeks produced the best results, and this was followed by 3 weeks of hyaluronidase injections¹.

g. Collagenase - As can be seen, one of the mechanisms causing collagen accumulation in OSMF patients is a decreased level of functional collagenase. According to Lin and Lin, intralesional collagenase injections improve mouth opening more than usual and lessen a person's sensitivity to heat, colds, and spices, which relieves symptoms of OSMF¹.

h. Placental extracts- Nucleotides, enzymes, amino acids, steroids, and vitamins are all present in the aqueous extract of the human placenta used in the

injection placentex. Via "biogenic stimulation" and "tissue therapy," it works. In 1933, Filatov reported using it. When implanted or injected into the body following a conflict with pathogenic factors, these tissues or their extracts stimulate the body's metabolic or regenerative processes, which alleviates symptoms¹.

i. Chymotrypsin: Proteolysis can be carried out by the endopeptidase enzyme chymotrypsin. Gamma-interferon (IFN) because IFN-gamma has an immunoregulatory effect, it is important in treating OSMF. According to research by Haque et al., IFN-gamma is thought to be an anti-fibrotic cytokine that affects collagen synthesis by stimulating collagen-stimulated osteoblast-like fibroblasts. This treatment with IFN gamma intra-lesional injections increased mouth opening and relief from symptoms¹⁰.

j. Aloe vera- Aloe vera has antibacterial, anti-inflammatory, and restorative qualities, as does its extract and resin⁶. A preliminary study was conducted by Sudarshan et al. to compare the effectiveness of antioxidants and Aloe vera in treating oral submucous fibrosis. Research indicates that the application of Aloe vera enhances response to all symptoms of OSMF. Aloe vera has also been shown to reduce burning sensation and enhance cheek and mouth opening flexibility. According to reports, the Aloe vera group improves the patient's quality of life¹.

k. Turmeric-Turmeric's natural yellow pigment, curcumin (diferuloylmethane), has enhanced antioxidant, anti-inflammatory, and anti-cancer properties. Together, turmeric oleoresin and oil protect against DNA deterioration. Consequently, it showed greater efficacy in OSMF as a chemo preventive and anti-inflammatory agent. Proved to be an easy, secure, palatable, and economical course of treatment. Curcumin was also used in a study by Rai et al. to treat oral precancerous lesions. The study included 25 patients with OSMF, and it was shown that curcumin could cure them by improving their systemic and local antioxidant status¹⁹.

L. Lycopene- One carotenoid with strong antioxidant qualities is lycopene. Its enhanced ability to quench other free radicals in vitro and its maximum singlet oxygen quenching capacity account for its antioxidant qualities. According to studies, lycopene

inhibits the growth of cancer cells both in vivo and in vitro. It inhibits dysplastic activity in oral premalignant lesions. Because it increases connexin synthesis and creates gap junctional communication, numerous studies have documented its anticancer activity².

m. Interferon (IFN)-gamma-IFN- gamma plays an important role in the reduction of oral submucous fibrosis symptoms as it shows an immunoregulatory effect⁹. Haque et al. studied that IFN-gamma is recognized for its antifibrotic cytokine and proved effective on collagen synthesis by arecoline-stimulated OSMF fibroblasts. The literature suggests that there was inhibition of collagen synthesis in the presence of IFN gamma. Thus, intra-lesional injections of IFN-gamma showed an increase in symptoms like burning sensation & mouth opening²⁰.

n. Oxitard- *Emblica officinalis*, *Vitis vinifera*, *Glycyrrhiza glabra*, *Daucus carota*, *Mangifera indica*, *Withania somnifera*, *Yashada bhasma*, and *Triticum sativum* are the extracts that make up this antioxidant. "*Mangifera indica*" demonstrates antiviral and antibiotic properties. "*Withania somnifera*" reduces inflammation, stress, and anxiety while enhancing general health and well-being. One of the best sources of vitamin A is "*Daucus carota*"². "*Glycyrrhiza glabra*" is an immune-stimulating plant that also lowers inflammation and regularizes husky speech. Because "*Vitis vinifera*" is caustic and lowers inflammation, it lessens the burning feeling. "*Yashada bhasma*" and "*Emblica officinalis*" both contain zinc and vitamin C, which promotes wound healing and cell formation. Vital minerals found in "*Triticum sativum*" help to lessen oxidative stress. Each of these elements contributes to a decrease in OSMf symptoms².

o. Salvianolic acid- Chinese natives are familiar with and use the dried root of "*Salvia miltiorrhiza* badge," or *Radix Salviae miltiorrhizae* (danshen). Danshen contains salvianolic acid B, or Sal-B, an efficient and biologically active ingredient. Sal-B has seven hydroxyls that are phenolic and have high redox potentials, meaning they have antioxidant properties. Jiang et al. evaluated the effectiveness of triamcinolone acetonide and SA-B in easing OSMF symptoms².

p. Colchicine - By blocking the synthesis of microtubules and preventing collagen from being extruded from fibroblasts, it lowers the amount of collagen synthesized. In the submucosa, collagenase activity is increased and the increased fibroblast formation is halted. It neutralizes cytokines like TGF- β , IL-6, and IL-4 that are involved in the synthesis of collagen. When administered to patients with liver disorders, potent side effects are not seen at higher doses. 0.5 ml of intralesional injection of hyaluronidase 1,500 IU and oral 500 mg of colchicine were studied by Krishnamoorthy B et al. for the treatment of OSMF².

q. Pentoxifylline therapy - A derivative of methyl xanthine, pentoxifylline exhibits dose-related side effects. Its mode of operation consists of 1. There is an increase in microcirculation and a decrease in granulocyte adhesion and platelet aggregation. 2. Leukocyte activation and adhesion are reduced while leukocyte deformability is elevated. It possesses fibrinolytic, anti-plasmin, and anti-thrombin properties. 3. It may cause neutrophils to degranulation and increase natural killer cells. Activity and prevent the activation of B- and T cells. 4. Aids in preserving homeostasis and cellular integrity following acute injury. 5. Demonstrated to enhance vascularity and lessen symptoms in individuals with oral submucous fibrosis. Pentoxifylline was described by Rajendran et al. as an adjunct medication for OSMF treatment. Following a 7-month trial and a 6- to 12-month follow-up, the patients' symptoms and signs decreased in comparison to the control group¹.

r. Tulsi (*Ocimum sanctum* Linn) - Tulsi is regarded as the queen of herbs because of its many therapeutic benefits. Its analgesic, anti-inflammatory, anti-stress, and antioxidant qualities improve its application in OSMF. Tulsi's anticarcinogenic properties are a result of its diverse contents. The carcinogens increase NF-KB activity, which ursolic acid (UA) suppresses. IKB α and p65 are not phosphorylated when UA is present. Moreover, apoptosis limits the initial stages of the increased production of cancer cells. Strong antioxidants include rosmarinic acid. Comparing the anti-inflammatory qualities of ibugesic and paracetamol, they are equal. By stimulating the adrenal gland, it lowers cortisol levels, which has an

anti-stressor effect. Srivastav et al. conducted studies on 41 OSMF patients using turmeric in conjunction with the treatment². In a small group of twenty OSMF patients, Madhulatha et al. assessed the effectiveness of 500 mg of herbal Tulsi paste given twice daily for one month. Both studies yielded satisfactory results².

s. Tea pigments- tea pigments are created by the oxidation of polyphenols found in tea leaves. The flavones found in tea pigments have anti-inflammatory, antioxidant, and anti-tumor effects. Aflatoxin and polyphenols both inhibit nuclear factor-kappa B (NF-kappa) activity, which in turn controls the rise in proinflammatory cytokine production. The tea pigments also lessen blood viscosity, enhance microcirculation, and control the activity of superoxide dismutase. These qualities thus support its application in the management of OSMF².

t. Immunomodulators- Levamisole is an immunomodulatory anti-helminthic medication. It strengthens humoral and cellular immunity. Hence employed as a voluntary regimen for the management of OSMF. Jirge et al. conducted a randomized, single-blind clinical trial wherein 50 mg of levamisole was administered three times a day for three consecutive days in a week, compared to three alternate weeks with capsule antitoxin. Serum levels of IgA, IgM, and IgG increased, and mouth opening improved in the levamisole group. There was also a decrease in the burning sensation. To improve immunity, speed up the healing process, and lower the risk of malignant transformation, levamisole should be used as an adjuvant therapy in future research².

u. Molecularly targeted therapies- According to recent research, TGF β regulates the synthesis and breakdown of extracellular matrix (ECM) products, which is a key factor in the pathophysiology of OSMF and has been shown to be a helpful treatment option for the disease.

Imatinib

Imatinib inhibits TGF β signaling pathways to exhibit anti-fibrotic properties. Demonstrates promising outcomes in preclinical models when used as an antifibrotic medication to treat scleroderma.

Demonstrates a role that has been shown to be effective in treating OSMF².

Pirfenidone (PFD)

Pirfenidone (5(1H)-pyridone) has been used recently to treat idiopathic lung fibrosis (ILF), an inflammatory condition also mediated by transforming growth factor beta (TGF- β). Is an anti-fibrotic agent with anti-inflammatory properties. Therefore, it is regarded as an anti-fibrotic agent that is helpful in treating OSMF conditions that are mediated by TGF- β . PFD functions by suppressing proinflammatory cytokines TNF- α , fibroblast growth factor (b-FGF), and tissue inhibitors of metalloproteinases-1 (TIMP1), all of which are elevated in OSMF. Ninetenedanib. Mostly prescribed as a second-line treatment for adenocarcinoma subtype lung cancer. It lowers excessive ECM production and stops the TGF- β 1 receptor from becoming phosphorylated, both of which are advantageous in OSMF. By targeting the PDGF receptors- α and β , it lowers the PDGF level, which is elevated in OSMF. It also goes after the receptor for the fibroblast growth factor². 1, -2, and -3 and consequently lowers the amount of fibroblast growth factor, which may serve as a biomarker for OSMF's malignant transformation².

Simtuzumab

Simtuzumab-Collagen cross-linking is catalyzed by lysyl oxidase-like 2 (LOXL2), which is implicated in the pathophysiology of OSMF. An antibody that targets the human LOXL2 is called simtuzumab, which has been humanized².

u. Hyperbaric oxygen therapy (HBO) - Studies have demonstrated that TNF- α and IL-1 can enhance collagenase synthesis and fibroblast proliferation in vitro. TNF- α can cause increased fibrosis by blocking the phagocytes that break down collagen. HBO inhibits TNF- α and IL-1, 6, 8, promotes wound healing, and lowers fibrosis to control its action. HBO increases angiogenesis improvement by enhancing vascular VEGF expression while concurrently lowering the levels of hypoxia-inducible factor-1 α (HIF-1 α). Hence employed in the management of OSMF².

v. Personalized precision medicine (PPM-) PPM is a modern immunotherapy treatment option where

genomic, proteomic, and metabolic analysis is carried out²¹.

SURGICAL TREATMENT

When a biopsy reveals dysplastic or neoplastic changes, or when a patient has limited mouth opening, surgery is the best option. Several surgical techniques consist of⁸:

1. Fibrotomy
2. Fibrotomy with graft replacements
3. Treatment through lasers
4. Therapy including mononuclear stem cells

Fibrotomy- The surgical procedure involves cutting away fibrous bands and forcing open the mouth, leaving the surface of the wound raw. Relapses are the most typical post-Fibrotomy complication¹.

Fibrotomy with graft replacement- The primary goal of surgery is always to surgically remove the fibrotic bands, which can cause scarring and a reduction in mouth opening issue, a number of surgeons recommended different interposition graft materials. The idea is to make an incision (sometimes called an excision, but technically correct term is "surgical release of fibrous bands"), widen the region or tissue that was incised by forcing the mouth open, and cover the surgical sites and defects with flaps or artificial biological material¹.

Extra-oral flaps - Various options include split-thickness skin graft. Superficial temporal fascia pedicled flap. Nasolabial flap. Platysma myocutaneous muscle flap.

Intraoral flaps - Palatal island flap, Tongue flap, and buccal fat pad Microvascular free flaps - Radial forearm free flap, Anterolateral thigh flap

Alloplasts - Collagen membrane, artificial dermis.

Laser treatment: Recently, it has been shown that using lasers to treat oral submucous fibrosis is a very effective option¹⁶. The Er Cr: YSGG laser, which has a wavelength of 2780 nm, can be applied to soft tissue in the mouth without causing thermal damage because it is well absorbed by water¹. With laser surgery, there is no blood on the operating field, better visibility, less need for local anesthetic, less risk of bacterial infection, less mechanical tissue trauma, fewer sutures, faster and more uneventful healing, and less post-operative edema, scarring, and

tissue shrinkage. In a moderate case of bilateral OSMF, Chaudhary et al. reported success using Er Cr; follow-up results with the YSGG laser were positive.

Mononuclear Stem Cell Therapy: Sankaranarayanan et al. (2013) conducted a number of studies to assess the efficacy of stem cell therapy as a treatment option for OSMF by describing a functional improvement and assessing a five-year follow-up of the outcome¹. Four of the seven patients received treatment using stem cells acquired through the point-of-care delivery system, and three patients received treatment using stem cells extracted using the Ficoll method. Histological advancement was accompanied by improvements in the clinical state. Follow-up revealed lessening of symptoms such as blanching, increased mucosal elasticity, less burning when eating spicy food, and more mouth opening. In the follow-up period, it was discovered that the aforementioned outcomes persisted.

CONCLUSION

Depending on the severity and clinical manifestations of the condition, there are a number of treatment options for oral submucous fibrosis, including corticosteroids, hyaluronidase, placentrix, IFN, microwave diathermy, and others. In severe cases such as Fibrotomy, surgical treatment is also thought to be beneficial, as is covering the defect with grafts. As of yet, no single technique has been found to be the most effective way to treat OSMF. A larger number of cases and more parameters must be included in comprehensive clinical trials before a specific treatment modality for OSMF can be determined. According to recent studies, the combination of drugs produces effective treatment options in the management of this disease.

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