Review Article: Oral Submucous Fibrosis

Shivani Bhandari[1] , Upma Tomar[1] , Sanjeev Tomar[2]
[1]Department of Oral and Maxillofacial Pathology and Oral Microbiology, Indraprastha Dental College & Hospital, Ghaziabad
[2]Department of Oral and Maxillofacial Surgery, Santosh Dental College & Hospital, Ghaziabad.

Corresponding Author:
Shivani Bhandari
Email ID : docshivanibhandari@gmail.com

Submission: 08.04.2024 Acceptance: 02.05.2024 Publication: 26.08.2024

Abstract

Many theories linking oral submucous fibrosis (OSMF) to various risk factors have been proposed. The common Asian habit of repeatedly chronically exposing the oral mucosa with spicy, pungent foods and irritants like supari (areca nut), pa an (betel leaves), tobacco (through chewing or smoking) has all been incriminated as causative agents. Systemic factors like nutritional deficiency, genetic predisposition and autoimmunity have also been proposed in the pathogenesis of OSMF. However the precise aetiology of OSMF is still unknown and no conclusive evidence has been found despite many extensive investigations on implicated factors. Most of the ideas proposed have been derived from existing clinical and epidemiological data. We present a comprehensive review of the various theories regarding the pathogenesis of the condition, but have not concentrated on malignant transformation in this article

Keywords

oral submucous fibrosis, review, pathogenesis

Introduction

Oral submucous fibrosis was first described in the Indian medical literature by Schwartz J. in 1952, as "Atropica idopathica Mucosae Oris. Other terminologies which are used -diffused oral submucous fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis and sclerosing stomatitis of the mouth". Oral submucous fibrosis is a common premalignant condition of the mouth with areca nut chewing habit in Asian subcontinent. It is characterized by restricted mouth opening, tongue protrusion and cheek flexibility.[(1)]

It is a well-recognized potentially malignant condition of the oral cavity and is defined 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 a juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat”.

Classification[(2)]:

A. Classifications based on clinical features of OSMF are as follows:

- JV Desa (1957)
- Pindborg JJ (1989)
- SK Katharia et al (1992)
- Lai DR et al (1995)
- R Maher et al (1996)
- Ranganathan K et al (2001)
- Rajendran R (2003)
- Nagesh and Bailoor (2005)
- Tinky Bose and Anita Balan (2007)
- Kiran Kumar et al (2007)
- Chandramani More et al (2011)

B. Classifications based on histopathological features:

- Pindborg JJ and Sirsat SM (1966)
- Utsunomiya H et al (2005)
- Kiran Kumar et al (2007)

C. Classification based on clinical and histopathological features:

- Khanna JN et al (1995)

1. Classification based on clinical features of OSMF:

- **Pindborg JJ in 1989 divided OSMF into three stages as follows:**

- ***Stage I***: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae.
- ***Stage II***: Fibrosis occurs in healing vesicles and ulcers, which is the hallmark of this stage.
  - Early lesions show blanching of the oral mucosa.

- Older lesions include vertical and circular palpable fibrous bands in the buccal mucosa and around the mouth opening or lips.
- This results in a mottled marble like appearance of the mucosa because of the vertical thick, fibrous bands in association with a blanched mucosa.
- Specific findings include reduction of mouth opening, stiff and small tongue, blanched and leathery floor of the mouth, fibrotic and de- pigmented gingiva, rubbery soft palate with decreased mobility, blanched and atrophic tonsils, shrunken bud like uvula and sunken cheeks, not commensurate with age or nutritional status.

- ***Stage III****:* Sequelae of OSMF are as follows:

- Leukoplakia is found in more than 25% of individuals with OSMF.
- Speech and hearing deficit may occur because of involvement of tongue and the eustachian tube.

• **Nagesh and Bailoor (1993):**

– ***Stage I early OSMF****:* Mild blanching, no restriction in mouth opening (normal distance between central incisor tips: Males 35 to 45 mm, females 30 to 42 mm), no restriction in tongue protrusion (normal mesioincisal angle of upper central incisor to the tip of the tongue when maximally extended with the mouth wide open: Males 5 to 6 cm, females 4.5 to 5.5 cm. Cheek flexibility CF = V1-V2, two points measured between; V2 = is marked at 1/3rd the distance from the angle of the mouth on a line joining the tragus of the ear and the angle of the mouth and V1 = the subject is then asked to blow his cheeks fully, and the distance measured between the two points marked on the cheek. Mean value for males = 1.2 cm, females = 1.08 cm. Burning sensation on taking spicy food or hot beverages.

– ***Stage II moderate OSMF****:* Moderate to severe blanching, mouth opening reduced by 33%, cheek flexibility also demonstrably reduced, burning sensation also in absence of stimuli, palpable bands felt. Lymphadenopathy either unilateral or bilateral and demonstrable anemia on hematological examination.

– ***Stage III severe OSMF****:* Burning sensation is very severe patient unable to do day-to-day work, more than 66% reduction in the mouth opening, cheek flexibility and tongue protrusion. Tongue may appear fixed. Ulcerative lesions may appear on the cheek, thick palpable bands and lymphadenopathy bilaterally evident.

2. Classifications based on histopathological features of OSMF:

• **Pindborg JJ and Sirsat SM (1966)** were the first to divide OSMF depending only on histopathological features alone are as follows:

- ***Very early stage****:* Finely fibrillar collagen dispersed with marked edema. Plump young fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorphonuclear leukocytes with occasional eosinophils are found.
- ***Early stage****:* Juxta-epithelial area shows early hyalinization. Collagen still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils and occasional plasma cells.
- ***Moderately advanced stage****:* Collagen is moderately hyalinized. Thickened collagen bundles are separated by slight residual edema. Fibroblastic response is less marked. Blood vessels are either normal or compressed. Inflammatory exudate consists of lymphocytes and plasma cells.
- ***Advanced stage****:* Collagen is completely hyalinized. Smooth sheets with no separate bundles of collagen is seen. Edema is absent. Hyalinized area is devoid of fibroblasts. Blood vessels are completely obliterated or narrowed. Inflammatory cells are lymphocytes and plasma cells.

3. Classification based on clinical and histopathological features:

• **Khanna JN and Andrade NN** (1995) developed a group classification system for the surgical management of OSMF.

– ***Group I:***

- ***Very early cases:*** Common symptom is burning sensation in the mouth, acute ulceration and recurrent stomatitis and not associated with mouth opening limitation.
- ***Histology:*** Fine fibrillar collagen network interspersed with marked edema, blood vessels dilated and congested, large aggregate of plump young fibroblasts present with abundant cytoplasm, inflammatory cells mainly consist of polymorphonuclear leukocytes with few eosinophils. The epithelium is normal.

– ***Group II:***

- **Early cases:** Buccal mucosa appears mottled and marble like, widespread sheets of fibrosis palpable, interincisal distance of 26 to 35 mm.
- ***Histology:*** Juxta-epithelial hyalinization present, collagen present as thickened but separate bundles, blood vessels dilated and congested, young fibroblasts seen in moderate number, inflammatory cells mainly consist of polymorphonuclear leukocytes with few eosinophils and occasional plasma cells, flattening or shortening of epithelial rete-pegs evident with varying degree of keratinization.

– ***Group III:***

- **Moderately advanced cases:** Trismus, interincisal distance of 15 to 25 mm, buccal mucosa appears pale firmly attached to underlying tissues, atrophy of vermilion border, vertical fibrous bands palpable at the soft palate, pterygomandibular raphe and anterior faucial pillars.
- ***Histology:*** Juxta-epithelial hyalinization present, thickened collagen bundles, residual edema, constricted blood vessels, mature fibroblasts with scanty cytoplasm and spindle-shaped nuclei, inflammatory exudate which consists of lymphocytes and plasma cells, epithelium markedly atrophic with loss of rete pegs, muscle fibers seen with thickened and dense collagen fibers.

– ***Group IVA:***

- **Advanced cases:** Severe trismus, interincisal distance of less than 15 mm, thickened faucial pillars, shrunken uvula restricted tongue movement, presence of circular band around entire lip and mouth.

– ***Group IVB:***

- **Advanced cases:** Presence of hyperkeratotic leukoplakia and/or squamous cell carcinoma.
- ***Histology:*** Collagen hyalinized smooth sheet, extensive fibrosis, obliterated the mucosal blood vessels, eliminated melanocytes, absent fibroblasts within the hyalinized zones, total loss of epithelial rete pegs, presence of mild to moderate atypia and extensive degeneration of muscle fibers.

Etiology

This condition is associated with arecanut chewing habit. In India, there has been a consistent rise in the number of patients with oral submucous fibrosis since 1990's. The high prevalence of commercial areca product (gutkha / pan masala etc.) use among youngsters has been documented. The experimental evidences point towards the role of chemical constituents of arecanut such as arecoline and arecaidine in the formation of fibrosis of mucosal tissues.[3]

Pathogenesis

The role of the constituents of areca nut in the pathogenesis of OSF has been studied in detail over the last two decades. It is apparent that the fibrosis and hyalinization of subepithelial tissues account for most of the clinical features encountered in this condition. Various studies have hypothesized that the increased collagen synthesis and or reduced collagen degradation as possible mechanisms in the development of the disease.[4]

Studies on the pathogenesis of oral submucous fibrosis have suggested that the occurrence may be due to:

1. Areca alkaloids causing fibroblast proliferation and increased collagen synthesis-

Four alkaloids which have been conclusively identified are arecholine, arecaidine, guvacine, guvacholine, of which arecholine is the main agent. Hydrolysis of arecholine produces arecaidine that has pronounced effects on fibroblasts. Arecholine in high doses is cytotoxic and cells show detachment from the culture surface. There was a concentration dependent stimulation of collagen synthesis when fibroblasts were exposed to both arecholine and arecaidine and the stimulation was greater with arecaidine. In addition, it was evident that the correlation between the hydrolysis rates of different esters and the extent to which they stimulate collagen synthesis, this suggests that hydrolysis of arecholine into arecaidine is necessary before fibroblast stimulation can occur.

2. Stabilization of collagen structure by tannins and catachins polyphenols –

Effects of betel nut polyphenols on collagen synthesis indicated that one of the mechanisms that can lead to increased fibrosis is by reduced degradation of collagen, forming a more stable collagen structure.

3. Copper in areca nut and fibrosis-

The copper content in areca nut is high and the level of copper in saliva is raised in areca chewers. The association between copper and OSF has been linked on the basis that excess copper is found in tissues of other fibrotic disorders – Wilson's disease, Indian childhood cirrhosis and primary biliary cirrhosis. The enzyme lysyl oxidase is found to be unregulated in OSF. Lysyl oxidase is a copper dependent enzyme and plays a key role in collagen synthesis and its cross linkage.[5]

4. Fibrogenic cytokines –

Endothelial and TGFβ1 estimated by radioimmunoassay and ELISA respectively were increased in OSF fibroblasts compared to fibroblasts of normal individuals. Therefore, it has been postulated that external stimuli such as areca nut may induce the development of the disease by increased levels of cytokines in the lamina propria. subjects. They were able to demonstrate increased levels of proinflammatory cytokines and reduced antifibrotic IFN -γ in patients with the disease.

5. Stabilization of extracellular matrix–

Increased and continuous deposition of extracellular matrix may take place as a result of disruption of the equilibrium between MMPs and tissue inhibitors of MMPs. When normal control fibroblasts and fibroblasts of OSF patients were subjected to arecholine and arecaidine in culture, OSF fibroblasts produced more tissue inhibitors MMPs protein

than normal fibroblasts. mRNA expression of tissue inhibitors MMPs in OSF fibroblasts was also higher.[6]

6. OSF as an autoimmune disorder –

Autoimmunity as an etiological factor for OSF has been examined. The reasons for investigating an autoimmune basis included, slight female predilection and occurrence in the middle age as reported in some of the studies. The presence of varying autoantibodies at varying antibody titers has been reported in several studies suggesting the possibility of an autoimmune basis to the disease. The frequencies of HLA A10, DR 3 and DR 7 proved to be significantly different compared with an ethnically, regionally and age-matched control group.

7. Collagen related genes – molecular aspects of OSF-

Collagen related genes play an important role in the homeostasis of collagen in the body. As OSF is a disease with dysregulation of collagen metabolism, it is important to identify the enzymes and various other molecules that may contribute to genetic modulation during the progression of the disease which includes different type of enzymes such as collagenases and lysyl oxidase together with cytokines namely the TGFβ. There is evidence to suggest that the collagen related genes are altered due to ingredients in the quid. The genes COL1A2, COL3A1, COL6A1, COL6A3, and COL7A1 have been identified as definite TGFβ targets and induced in fibroblasts at early stages of the disease.

Pathology

Structural and Microstructural Changes:

The epithelial changes in the different stages of OSF are predominantly hyperplasia (early) and atrophy (advanced), associated with an increased tendency for keratinizing metaplasia. The epithelial atrophy reported by Pindborg et al, (1966) is the marked epithelial change in advanced OSF, which contrasts with the predominantly hyperplastic epithelium of early OSF. Lesions involving the palate showed predominantly orthokeratosis and those of the buccal mucosa, parakeratosis. The high mitotic count in parakeratotic epithelium, which is more common with OSF, and the association with parakeratotic leukoplakia and atrophic epithelial changes predisposes OSF to malignancy.[7]

Subepithelial changes. Based on the histopathological appearance of stained (H&E) sections, OSF can be grouped into four clearly definable stages: very early, early, moderately advanced and advanced. These stages are based not only on the amount and nature of the subepithelial collagen, but also on the following criteria taken together:

1. Presence or absence of edema

2. Physical state of the mucosal collagen

3. Overall fibroblastic response (number of cells and age of individual cells)

4. State of the blood vessels

5. Predominant cell type in the inflammatory exudate.

A vascular response due to inflammation, apart from the connective tissue repair process, has been very commonly found in OSF. Normal, dilated and constricted blood vessels have been seen often in combination, in the same section. The apparent narrowing of the smaller vessels appears first in the upper mucosa and spreads gradually to the larger, deeper vessels. Persistent dilatation has also been seen in many moderately advanced and advanced biopsies. A rise in mast cells occurs in the earlier stages of the tissue reaction but in advanced stages, the counts are fewer in number.

The inflammatory cells seen are mainly lymphocytes and plasma cells. The connective tissue in advanced stages is characterized by the submucosal deposition of extremely dense and avascular collagenous tissues with variable numbers of chronic inflammatory cells. Epithelial dysplasia without carcinoma is found in 10–15% of cases submitted for biopsy and carcinoma is found in at least 5% of sampled cases. The excessive fibrosis in the mucosa seems to be the primary pathology in OSF. The atrophic changes in the epithelium are secondary.

Management

OSMF is well known for its resistant and chronic nature. Being a premalignant condition with debilitating consequences, no conservative treatment that has given complete resolution of symptoms is identified till date. Various treatment modalities are available to treat this condition which includes medicinal approach, surgical management and physiotherapy.[8] Proper treatment begins with education of the patient regarding the ill effects of arecanut and related chewing products. The patient should be informed about the irreversible nature of the disease despite quitting the habit and possibilities of developing oral cancer.[9]

Medical Management includes:

Antioxidants

Micronutrients

Intralesionalinjections

Corticosteroids

Hyaluronidase

Placental extracts

IFN-γ.

Medical Management

- 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 palmitate 2500 IU, vitamin E acetate, beta carotene 50mg, vitamin C, zinc, copper and manganese. There was improvement in the symptoms of all the patients.

- Lycopene is a major carotenoid which is found in tomato have antioxidant and chemopreventive properties against potentially malignant disorders. A combination of lycopene with intralesional steroids and hyaluronidase to be highly efficacious in reducing the symptoms and mouth opening of OSMF patients.[10]
- Several glucocorticoids are used for the treatment of OSMF, short acting (hydrocortisone), intermediate acting (triamcinolone) and long acting (betamethasone and dexamethasone). 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. Current concept is based on the use of intralesionals injected into fibrotic band biweekly for 6 to 8 weeks along with mouth-opening exercises.
- 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, color of mucosa and reduction in fibrotic bands.
- IFN-γ is proposed to reduce fibroblast proliferation and collagen synthesis and upregulate collagenase synthesis and antifibrotic cytokines. Previously injection when given intralesionally have showed clinical improvement in the cases of hypertrophic scars and keloids. When intralesional IFN-γ was tried in OSMF patients it showed increased mouth opening, suppleness of the mucosa and reduction in burning sensation.
- Pentoxifylline is methylxanthine derivative that has vasodilating properties and increases mucosal vascularity. It acts by suppressing leukocyte function, altering fibroblast physiology and stimulating fibronylysis. Pentoxifylline 400mg three times daily for 7months was used as an adjunct therapy for OSMF. Levamisole 50 mg TDS for three alternate weeks alone have sure significant improvement in mouth opening and burning sensation.
- 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 colchicine orally, twice daily along with intralesional 0.5 ml hyaluronidase 1500 IU gives significant improvement in burning sensation and mouth opening.[11]
- 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.
- Tea pigments are oxidized products of polyphenols that are derived from tea leaves found to improve haemorheology and microcirculation. Li and Tang found that tea pigments when administered in OSMF act by decreasing high blood viscosity, improving microcirculation and activity of superoxide dismutase.
- Aloe vera acts as a wound-healing hormone and serols in aloe vera have strong anti-inflammatory properties. Sudarshan et al. reported use of aloe vera topically in mild stage OSMF and has found improvement in burning sensation and mouth opening as compared to antioxidant therapy.
- Spirulina, a microalgae which contains beta carotene, tocopherols and phenolic acid has antioxidant properties. Shetty et al. in a study used 500 mg spirulina twice daily as an adjuvant therapy in early management of OSMF.

Physiotherapy:

This includes measures such as forceful mouth opening and heat therapy. Heat has been commonly used and the results have been described as satisfactory.

Surgical Management:

- Surgical modalities for the treatment of OSMF are chosen according to the clinical stage of OSMF measures such as forcing the mouth open and cutting the fibrotic bands have resulted in more fibrosis and disability. Submucosal resection of fibrotic bands and replacement with a partial thickness skin or mucosal graft have also been attempted along with procedures such as bilateral temporalis myotomy.
- Surgical excision of fibrotic tissue and covering the defect with fresh human amnion, buccal pad fat grafts.Flap for reconstruction of intraoral defect after release of OSMF and revelled that both the procedure is equally effective in management, but extraoral scar was not aesthetically

acceptable in the nasolabial group.

Financial Support and Sponsorship

Nil.

Conflict of interests

The authors declare that they have no conflict of interests

Source of Support: Nil

References

1. Arakeri G, Brennan PA. Oral submucous fibrosis: an overview of the aetiology, pathogenesis, classification, and principles of management Br J Oral Maxillofac Surg 2013;51:587 -93. 2.
2. Ekanayaka RP, Tilakaratne WM. Oral submucous fibrosis: review on mechanisms of pathogenesis and malignant transformation. J Carcinogene Mutagene 2013:S5. doi:10.4172/2157 -2518.S5 -002
3. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. Oral Oncol 2006;42:561 –8.
4. Paymaster JC. Cancer of the buccal mucosa; a clinical study of 650 casesin Indian patients. Cancer 1956;9: 431 –5.
5. Reichart PA, Van Wyk CW, Becker J, Schuppan D. Distribution of procollagen type III, collagen type IV and tenascin in oral submucous fibrosis. J Oral Pathol Med 1994;23:394 – 98.
6. Angadi PV, Rao SS. Areca nut in pathogenesis of oral submucous fibrosis: revisited. Oral Maxillofac Surg 2011; 15:1 –9.
7. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: a review of the current management and possible directions for novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol 2016; 122:232 -41.
8. Pindborg JJ. Oral submucous fibrosis: a review. Ann Acad Med Singapore 1989;18:603 –7.
9. Angadi PV, Rao SS. Areca nut in pathogenesis of oral submucous fibrosis: revisited. Oral Maxillofac Surg 2011; 15:1 –9.
10. Gupta SC, Yadav YC. “MISI” an etiologic factor in oral submucous fibrosis. Indian J Otolaryngol 1978; 30: 5 -6.
11. Arakeri G, Patil SG, Ramesh DN, Hunasgi S, Brennan PA. Evaluation of the possible role of copper ions in drinking water in the pathogenesis of oral submucous fibrosis: a pilot study. Br J Oral Maxillofac Surg 2014;52:24 -8.