

Review Article

Oral Submucous Fibrosis: An overview

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ABSTRACT:

Oral submucous fibrosis is a potentially malignant disorder predominantly seen in Central, Southern, and Southeast Asia. It is a collagen related disorder associated with betel quid chewing and characterized by progressive hyalinization of the submucosa.¹ Majority of patients present with an intolerance to spicy food, rigidity of lip, tongue and palate leading to varying degrees of limitation of opening of the mouth and tongue movement. It can lead to squamous cell carcinoma. Oral submucous fibrosis is diagnosed based on clinical symptoms and confirmed by histopathology. Various treatment modalities include drugs, local injections with chymotrypsin, hyaluronidase, dexamethasone and in advanced cases surgery.

Key Words: Betel quid, Squamous cell carcinoma, Oral submucous fibrosis.

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INTRODUCTION

Submucous fibrosis is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. It is predominantly seen in people of Asian descent. The combination of areca nut and tobacco has led to a sharp increase in the frequency of Oral Submucous Fibrosis.²

It was first reported by Schwartz in 1952 which he called as "atrophica idiopathica mucosae oris" Later in 1953 Joshi reported it as "submucous fibrosis of palate". Oral submucous fibrosis (OSMF) has also been previously described as "idiopathic scleroderma of mouth", "idiopathic palatal fibrosis" and "sclerosing stomatitis".³

Its precancerous potential was first reported by Paymaster in 1956. Its malignant transformation rate is 2.3-7.6%.¹ Majority of patients present with an intolerance to spicy food, rigidity of lip, tongue and palate leading to varying degrees of limitation of opening of the mouth and tongue movement.⁴ In advanced cases loss of puffiness of cheek when a

patient blows, blockage of Eustachian tube which impairs hearing and oesophageal fibrosis which causes difficulty in swallowing.²

Various surgical and nonsurgical modalities have been proposed for the management of OSMF. The former includes excision of fibrous bands, placental grafts,⁵ skin grafts, splitting of the temporalis tendon and coronoid process,⁶ and lingual pedicle flaps.⁷ The latter includes local injections of steroids, hyaluronidase, human placenta extracts, and chymotrypsin, multivitamin therapy, and physiotherapy.

AETIOLOGY

Areca nut is the main aetiological factor for Oral submucous fibrosis.⁸ A case-control study showed that the risk of developing OSF was almost double for subjects below 21 years of age compared with that for the 21-40 year age group.⁹

In a study, a clear dose-dependent relationship was observed for both frequency and duration of chewing

areca nut (without tobacco) in the development of OSF¹⁰.The severity and the time taken for the development of the disease may also vary according to the preparation of areca nut consumed¹¹.

PATHOGENESIS

Role of arecanut and its constituents in pathogenesis of submucous fibrosis has been studied for past few years. The clinical features are a result of fibrosis and subepithelial hyalinization. Research on pathogenesis has been mainly focused on changes in extracellular matrix. The development of disease has been mainly due to increase in collagen production and decrease in collagen degradation. Various factors are involved in upregulation or downregulation of collagen synthesis. A few of them are:

- a) Chemical constituents of arecanut; alkaloids stimulate fibroblast proliferation and collagen synthesis.
- b) Tannin present in areca nut reduced collagen degradation by inhibiting collagenase and also by

- c) Copper content of areca nut is high. The enzyme lysyl oxidase is found to be upregulated in OSF.¹³This is a copper dependent enzyme¹⁴ and plays a key role in collagen synthesis and its cross linkage.
- d) Arecanut may induce the development of the disease by increased levels of cytokines in the lamina propria.

CLASSIFICATION

The severity of disease is measured by mouth-opening, and the sites of bands in the mouth. Mouth opening is measured by distance between the corresponding upper and lower central incisors in millimeters with a ruler after the patient opened his or her mouth as wide as possible without assistance.²The functional(mouth opening) and clinical staging (sites of bands) of Oral Submucous Fibrosis are as follows (Table 1)².

Table 1 Table 1 – Clinical and functional staging

Clinical stage
1. Faucial bands only
2. Faucial and buccal bands
3. Faucial, buccal, and labial bands
Functional stage
A Mouth opening ≥ 20 mm
B Mouth opening 11–19 mm
C Mouth opening ≤ 10 mm

CLINICAL FEATURES

The onset of the condition is insidious and is often of 2 to 5 years’ duration. It is often preceded by burning sensation in mouth while having spicy food. Other early symptoms are blisters (especially on the palate), ulcerations, or recurrent stomatitis, excessive salivation, defective gustatory sensation¹⁶ and dryness of the mouth.

In later stages loss of pigmentation of oral mucosa, depapillation of tongue, leathery texture and blanching of oral mucosa are noted. Blanching may be localized, diffuse or reticular because of increasing fibrosis of the oral mucosa and results in a marble-like appearance (Fig 1)

Figure 1: Blanching seen over right buccal mucosa



In advanced stages fibrosis extends into tongue result in its reduced mobility, buccal mucosa restricts the mouth opening. It may also extends into soft palate and uvula causing uvula to be

shrunk or bud like.(Fig2).Fibrosis has also been reported in pharynx¹⁷ leading to referred pain in ear and also oesophagus result in dysphagia.

Figure 2: Soft palate showing blanching and shrunken uvula seen in the posterior part



DIAGNOSIS

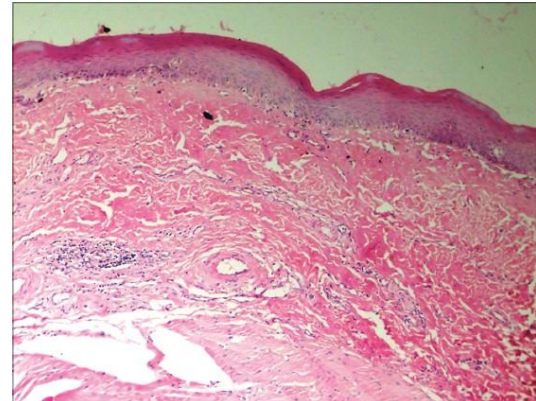
Oral submucosis fibrosis is diagnosed based on clinical and histopathological findings. Clinically, one or more of the following symptoms should be present:

- a) Blanching of oral mucosa defined as a persistent, white, marble-like appearance of the oral mucosa, which may be localized, diffuse or reticular.
- b) Tough, leathery texture of the mucosa .

c) Palpable, whitish, fibrous bands.

The clinical findings are accompanied by histopathological investigations. Initially the pathology appears to be inflammation and edema with large fibroblasts. Later collagen bundles with hyalinization are seen which later extend into submucosal tissue. Inflammatory infiltrate contains lymphocytes and plasma cells¹⁸(Fig 3).

Fig3: Histopathological picture of Oral Submucous Fibrosis



Based on histopathology submucous fibrosis has been staged into four categories.(Table 2)¹⁵

Table 2 Histopathological classifications of oral submucous fibrosis

Very early (stage I)	Early (stage II)	Moderately advanced (stage III)	Advanced (stage IV)
A finely fibrillar collagen, dispersed with marked edema.	The juxta-epithelial area shows early hyalinization.	The collagen is moderately hyalinized.	The collagen is Completely
The fibroblastic response strong.	Plump young fibroblasts are present in moderate numbers.	The fibroblastic response is less marked, the cells present being mostly adult fibrocytes.	The hyalinized is areas are devoid of fibroblasts.
The blood vessels are sometimes normal, but more often they are dilated and congested.	The blood vessels are dilated and congested.	Blood vessels are normal or constricted.	Blood vessels are completely obliterated or narrowed.
Inflammatory cells, mainly polymorphonuclear leukocytes with an occasional eosinophil, are present.	Inflammatory cells are mostly mononuclear lymphocytes, eosinophils, and an occasional plasma cell	Inflammatory exudates consist of lymphocytes and plasma cells, although an occasional eosinophil is seen.	Inflammatory cells are lymphocytes and plasma

It was also found that in patients with submucous fibrosis the blood sedimentation rate is increased and anemia was also noticed.^{19,20}

TREATMENT

The treatment modalities of submucous fibrosis can be categorized into:

- a) General management.
- b) Medical management.

c) Surgical intervention.

General Management mainly involves behavioral modification as submucous fibrosis is a progressive disease and its extension increases with use of arecanut. Complete stoppage or even reduction of the

habit of areca nut chewing is the most important aspect of management. In addition a combination of micronutrients, vitamins, proteins were required for patients with anemia.²¹

Medical Management involves mainly corticosteroids, placental extracts, Interferon gamma, pentoxifylline and immunised milk.²² Steroids with its anti-inflammatory and immunosuppressive action reduces fibro-collagenous formation and hence hinders the progress of submucous fibrosis. In early stages topical application of triamcinolone acetonide 0.1% and Betamethasone 0.5% has been found to be effective in reducing burning sensation. In later stages of fibrous band formation intralesional injections of Triamcinolone 10mg/ml and Betamethasone-4mg/ml biweekly for 3 months has been the treatment of choice.²³

Interferon Gamma with its immunoregulatory and anti fibrotic effect has been used as intralesional injections of 0.01- 10.0U/ml 3 times a day for 6 months. This has a direct impact on mouth opening, burning dysaesthesia.²⁴ Placental extracts regulates metabolism of tissues and act as "biogenic stimulation." Placentrex contains nucleotides, enzymes, vitamins, amino acids, and steroids. Intralesional injection of Placenta extract 2.0cc given locally once a week for one month showed improvement in the mouth opening.²⁵

Immune milk is produced from cows immunized with multiple human intestinal bacteria. It contains 20-30% higher concentration of IgG type I antibody. It acts by upregulation of fibrogenic cytokines and down regulation of anti fibrotic cytokine. 45 g milk powder twice a day for 3 months showed significant reduction in symptoms.²⁶

Pentoxifylline has antithrombin and anti plasmin activity. It increases red cell deformability, decreases red cell and platelet aggregation. It also decreases granulocyte adhesion, fibrinogen levels, and whole blood viscosity. A dose of 400 mg thrice a day for 7months was found to be effective.²⁷

Hyaluronidase is a fibrinolytic enzyme. It helps in the breakdown of hyaluronic acid (intercellular substance) and also decreases collagen formation with dosage of 1500 IU biweekly for 10 weeks. It was found to be more effective when used in combination with 4 mg Dexamethasone.²⁸

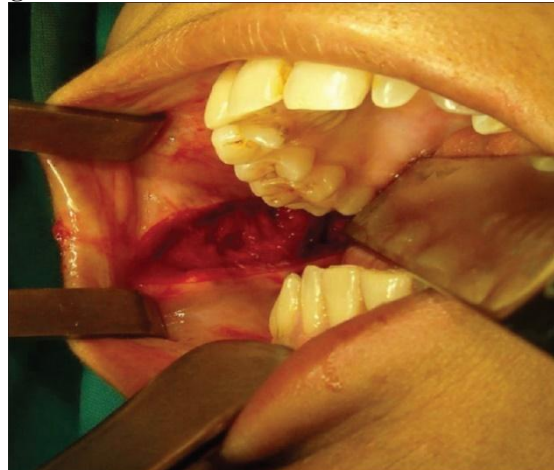
Chymotrypsin is an endopeptidase with proteolytic and anti inflammatory action. Submucosal injections of 5000IU biweekly for 10weeks showed significant results.²⁹ In addition to this lycopene(antioxidant), turmeric, spirulina, aloe vera have also been efficient in treatment of submucous fibrosis.

Apart from medical management, physiotherapy has significant role to play in treatment regimen. Physiotherapy modifies tissue remodeling through physical exercises and heat. Physiotherapy mainly involves muscle stretching exercise, forceful mouth opening with the help of sticks, tongue movement in

the figure of 8, ballooning of mouth and hot water gargling.³⁰

Surgical therapy involves complete release of fibrotic tissue and if required, a coronoidectomy and temporal muscle myotomy to achieve sufficient mouth opening.³¹ The fibrous bands in the buccal mucosa were palpated and incised along the occlusal line, starting from the angle of the mouth extending posteriorly up to the retromolar region(Fig 4)³².

Fig 4:Excision of fibrotic bands



Traditional methods of releasing the fibrotic bands with cold knife are associated with increased peri-operative bleeding which is difficult to control. Lasers(ErCr:YSGG, KTP-532)can provide an alternative and better means for surgical fibrotomy in moderate OSMF as they are minimally invasive and have the advantage of short operating time, less hemorrhage, faster healing, less morbidity, less surgical-site scarring and relapse.³³

Reconstruction of the resultant defect is problematic and various methods have been described including split thickness skin grafts, Buccal Fat Pad(BFP) Grafts, Microvascular Free Radial Forearm Flaps, Tongue Flap and Nasolabial Flaps.

CONCLUSION

Oral Submucous Fibrosis being a chronic and debilitating disease intervened at earliest can make a major impact on the prognosis and quality of life of patient. Cessation of arecanut and its products, medical management, surgical management remains to be the mainstay in treatment of submucous fibrosis till date.

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