**Etiopathogenesis and Treatment Strategies of Oral Submucous Fibrosis**

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ABSTRACT

The etiopathogenesis and management of oral submucous fibrosis has been the subject of controversy ever since Schwartz first described the condition in 1952. Population estimates of OSMF indicated that 2.5 million people were affected worldwide. This number has risen to 5 million on the Indian subcontinent itself. It calls for the need to treat such a critical precancerous condition with aggressive steps. Before one goes to treat this disease it is required to have a look at all the modalities tried so far in the literature.

This article aimed at the same signature facts of the etiopathogenesis and various treatment modalities of OSMF.

**Keywords:** OSMF, Etiopathogenesis, Treatment

Oral submucous fibrosis (OSMF) is not only a chronic debilitating disease but a premalignant condition of the oral cavity strongly associated with betel nut and gutkha chewing, and characterized by:

- Generalized submucosal fibrosis of the oral soft tissue, resulting in marked rigidity and progressive inability to open the mouth and restricted movements of tongue.
- Reduction in the vasculature which appears as oral mucosal pallor.
- Atrophy of the surface epithelium.
- Dysphagia, which may occur in severe cases.

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Specific findings include the following:
- Reduction of the mouth opening (trismus)
- Stiff and small tongue
- Blanched and leathery floor of the mouth
- Fibrotic and depigmented gingiva
- Rubbery soft palate with decreased mobility
- Blanched and atrophic tonsils
- Shrunken bud like uvula
- Sinking of the cheeks, not commensurate with age or nutritional status.

Stage 3: Sequelae of OSMF

Leukoplakia, a precancerous lesion, is found in more than 25% of individuals with OSMF. Speech and hearing deficits may occur because of involvement of the tongue and the eustachian tubes.

II. Khanna JN and Andrade NN in 1995 developed a 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
- Not associated with mouth opening limitation (interincisal distance greater than 35 mm).

Group II: Early cases
- Buccal mucosa appears mottled and marble like
- Widespread sheets of fibrosis palpable
- Patients with an interincisal distance of 26 to 35 mm.

Group III: Moderately advanced cases
- Trismus evident, with an interincisal distance of 15 to 25 mm
- Buccal mucosa appears pale and firmly attached to underlying tissues
- Atrophy of vermilion border
- Vertical fibrous bands palpable at the soft palate, pterygomandibular raphe and anterior faucial pillars.

Group IVA: Advanced cases
- Trismus is severe, with an interincisal distance of less than 15 mm and extensive fibrosis of all the oral mucosa.

Group IVB: Advanced cases with premalignant and malignant changes
- Hyperkeratosis, leukoplakia or squamous cell carcinoma can be seen.

III. Haider SM, Merchant AT, Fikree FF, Rahbar MH (1999) have staged the disease clinically and functionally depending on the location of bands as well as the maximum mouth opening:

A. Clinical staging:
   a. Faucial bands only
   b. Faucial and buccal bands
   c. Faucial, buccal and labial bands

B. Functional staging:
   a. Mouth opening < 10 mm
   b. Mouth opening > 20 mm
   c. Mouth opening < 10 mm

The most common initial symptoms are burning sensation, ulceration and recurrent stomatitis. Intraoral petechiae, defective gustatory sensation and dryness of mouth, and/or hypersalivation have also been indicated as early symptoms. Pain in the ear or a decrease in the patient’s hearing ability may also occur if the fibrosis extends into the pharynx and causes a blockage of the eustachian tube.

Another feature of the oral mucosa affected by oral submucous fibrosis is pigmentation. This is caused by an increase in the activity of enzyme tyrosine which is affected by the increased copper levels found in betel nut chewers. An additional feature that may be observed in betel quid chewers is a brownish red discoloration of the mucosa. Such mucosa has an irregular surface which tends to desquamate.

Hematological abnormalities reported in oral submucous fibrosis include:
- Increased erythrocyte sedimentation rate
- Iron-deficiency anemia
- Decrease in serum iron and increase in total iron binding capacity (TIBC)
- Eosinophilia
- Increased gamma globulin

Etiopathogenesis
Various factors have been thought as causative agents for OSMF. Some of the factors implicated in the etiology of this disease include arecanut chewing, ingestion of chillies, genetic processes, immunologic process and nutritional deficiencies.

High copper content of arecanut upregulate lysyl oxidase activity which result in fibrosis. The major arecanut alkaloids are arecoline, arecaidine, arecolidina, guyacoline and guacine. Arecoline, the most abundant alkaloid, might have cytotoxic effects on cells and is also demonstrated to promote collagen synthesis.

Ingestion of chillies is common in Indians, which was considered as a source of allergens for causing oral submucous fibrosis. Also Sirsat and Khanolkar observed oral submucous fibrosis like response in wistar rats on application of capsaicin, an active principle of chillies. But Hamner et al failed to support chillies as one of the cause for OSMF, in a study carried out in hamster cheek pouch.

Genetic processes have also been thought to be major causative factor. Studies carried out on oral submucous fibrosis indicated that genetic factor allele A6 which is a major histocompatibility complex—class I chain related gene A, confers the risk to develop the disease. Liu et al reported that there is increased risk of oral submucous fibrosis associated with cytotoxic T lymphocyte associated antigen 4 + 49 G allele which has shown susceptibility to various autoimmune diseases. Due to involvement of genetic process, raised values of human leukocyte antigen (HLA) A10, B7 and DR3 were found in OSMF patients when compared to normal individuals.

Immunologic process as natural killer cells also plays vital role in OSMF. Reduced natural killer cell activity was observed in patients with oral leukoplakia and OSMF, so it is suggested that its modulation with interferon may help in control of malignant transformation of oral precancer.

Higher frequencies of deficiencies of vitamin A, B, C and multiple vitamin deficiencies have been indicated to be of etiologic importance in oral submucous fibrosis.

Rajalalitha P and Vali S 3 in 2002 reviewed the etiopathogenesis of OSMF wherein it is stated that collagen forms a major component in OSMF and hence, it is a collagen disorder. Synthesis of collagen is influenced by variety of mediators, including growth factors, hormones, cytokines and lymphokines. Transforming growth factor beta (TGF-beta) plays a major role in wound repair and fibrosis. It causes deposition of extracellular matrix by increasing the synthesis of matrix proteins like collagen and decreasing its degradation by stimulating various inhibitory mechanisms.
TGF-beta on the genes implicated in the formation and degradation of the ECM is mostly exerted at the transcription level through ill-defined intracellular pathway. The molecular events in the causation of OSMF takes place through collagen production pathway and collagen degradation pathway. In the initial events of disease arecanut acts as a major initiative agent.

Luquman M, Dinesh V, Prabhu, Vidya M (2004) evaluated serum copper and iron level in normal individuals and OSMF patients. Increased serum copper could cause an upregulation of the enzyme lysyl oxidase leading to cross-linking of collagen and elastin. Whereas serum iron level was found to be decreased, that might be due to lack of consumption of normal diet.

Management

As the exact causative factor for OSMF is a matter of conflict, the failure to achieve proper or specific treatment for it may be the reason for its incomplete regression or abolition.

Paissat DK (1981) reviewed the overall aspect of OSMF and management of the condition. The various modalities discussed are surgical, medical and conservative. Though the surgical treatment resulted in initial improvement, eventually led to more severe fibrosis, the modern grafting techniques have improved prognosis in many cases. As a medical treatment, submucosal steroid injection gave relief in signs and symptoms of OSMF along with increase in mouth opening (which was temporary improvement) with variable dose. Conservative treatment includes stopping the consumption of chilies and other irritants, treating anemia, and encouraging a balanced diet with vitamin B supplements and regular review.

In a study by Yen DJC (1982), the author has discussed about various treatment modalities of OSMF like local injection of fibrinolytic agent, gold or vitamin A, E, injection of sene typhoid and iodides internally, corticosteroids and also surgical cutting of fibrotic bands. Surgical resection of bands was done with or without split thickness skin graft where treatment with grafting gave satisfactory and successful result along with stoppage of habit.

Hayes PA (1985) reported a case of 4-year-old girl with OSMF for which she was given conservative mode of treatment that involved stoppage of habit, vitamins supplements, balanced diet and stretching exercises aimed at increasing the oral opening. The increased maximum mouth opening resulted was 3 mm with decreased blanching of oral mucosa. Other observations include increased buccal mucosal resiliency, no recurrence of vesicles, less tenderness to palpation. The short duration of pan supari intake, the total cessation of habit and the greater healing potential of young age were given as possible explanations for improvements.

Caniff JP, Harvey W, Harris M (1986) stated that OSMF has multifactorial etiology. Patients with genetic predisposition render their oral mucosa susceptible to chronic inflammatory changes if they chew betel nut. They stated added that medical management of the disease has been both empirical and unsatisfactory, and includes injections of hyaluronidase, hydrocortisone, placental extract, triamcinolone, vitamin and iron supplements. Although intraleosional steroid may improve mouth opening in mild cases, surgical therapy is the only effective treatment for severe cases.

Gupta Deepak, Sharma SC (1988) carried out clinical study by using injection dexamethasone in combination with chymotrypsin and hyaluronidase for treatment of OSMF in one group, as well as placental extract and placental graft in another group. Patients treated with submucosal placental graft had early and significant relief of symptoms although recurrence of fibrotic bands was there. Drugs given to group one gave good results while response to placental extract was poorest.

Borle RM, Borle SR (1991) studied comparative effect of submucosal injection of triamcinolone in one OSMF group and chewable tablets of vitamin A with ferrous fumarate and topical betamethasone drops in another group of patients. In both the groups the burning sensation, feeling of stiffness and vesicles disappeared, but no improvement in mouth opening at any stage was observed. However, trismus was more pronounced in group one patients in follow-up period compared to group two patients. It is also quoted that all surgical treatments tried so far are useful in advanced cases of OSMF whereas conservative treatments are better option at earlier stage of OSMF with proper habit restriction.

Katharia SK, Singh SP, Kulshreshtha VK (1992) studied the effect of placental extract in management of OSMF, by injecting it locally in the predetermined areas once a week for 1 month. They observed statistically highly significant improvement in the mouth opening of about 28.26% and color of the oral mucosa improved up to 38.55%. They also stated that vitamin A plays a major role in induction and control of epithelial differentiation in mucous secretory and keratinization tissues, as well as in adequate concentration it delayed, slowed, arrested or even reversed the progress of premalignant cells to cells with invasive malignant potential. The cellular concentration of amino acids, enzymes and vitamins help in regeneration of tissues.

Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC (1995) treated 150 patients of OSMF over 10 years by either medical or surgical therapies which involved vitamin B complex, vasodilator, topical and submucosal injection of steroid and surgical flaps in different subgroups. The medical treatment (vitamins and steroid injections) gave symptomatic relief in mild cases of OSMF whereas surgical treatment showed significant improvement in interincisal opening in severe cases but with varying amount of wound contraction.

Khanna JN, Andrade NN in 1995 studied a series of 100 cases which were divided into two groups as early and advanced cases. Disease in early stage was treated by giving local injection of triamcinolone acetonide which revealed improvement in the clinical picture and mouth opening. While advanced cases were treated with surgical intervention and gave highly encouraging results in the form of increased mouth opening ranging preoperatively from 3 to 25 mm to postoperative readings of
injection of placental extract intralesionally associated with antioxidants and jaw dilator exercises has been found useful in 52 cases. They recommended the treatment protocol to be given as follows:
  
- Local injection of placental extract 2 ml (market preparation manufactured from 0.1 gm of fresh human placenta) given at multiple sites at soft palate and anterior to anterior pillars (as shown in the figure with red marking) every week for 10 weeks
  - Lycopene (10%) 2000 mcg orally
  - Methylcobalmin injection (1500 mcg) given intramuscularly every week
  - Jaw dilators exercises explained to the patients to be taken every day
  - Advanced cases of trismus are treated by jaw dilation under general anesthesia with incision of fibrous bands.

CONCLUSION

As long span of time has been passed since first diagnosis of OSMF and treatment given for it till this era, no complete success has been achieved. Reasons for this may be the unpredictable etiology, immune response or immune status of individual patient, and pros and cons of every treatment modality depending on the stage of the OSMF. After having a glance on vast literature on OSMF, it can be said that there is hope for further detail evaluation of etiopathogenesis as well as management of this disorder for having better life to these patients suffering from this precancerous condition.

REFERENCES