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### Oral Submucous Fibrosis: Medical Management.

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#### ABSTRACT

Oral submucous fibrosis (OSF) is a debilitating, potentially cancerous oral condition, caused primarily by chewing areca nut and its mixtures, as demonstrated by numerous epidemiological studies and other corroborative evidence. The condition may sometimes extend beyond the mouth to the oesophagus. OSF is well established as a condition with high malignant potential and is considered irreversible. Urgent public health measures are required to curb this new but avoidable epidemic, that increased occurrence of OSF in the younger age groups would lead to an earlier development of oral cancer from OSF was confirmed by the demonstration of a significant increase in the incidence of oral cancer in the Ahmedabad population-based cancer registry data. This paper's purpose is to discuss current literature on OSF and help the reader to be better acquainted with the possible etiology, clinical manifestations, differential diagnosis, and current medical treatment modalities of OSF

Keywords: Oral Submucous Fibrosis+ Medical Treatment

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#### Introduction

Oral submucous fibrosis (OSMF) is a chronic disease of oral mucosa characterized by inflammation and progressive fibrosis of lamina propria and deeper connective tissues, followed by stiffening of an other wise yielding mucosa resulting in difficulty in opening the mouth. (Pindborg et al;<sup>[1]</sup> WHO).<sup>[2]</sup>

OSF has been reported almost exclusively among Indians living in India and among other Asiatics with a reported prevalence ranging up to 0.4% in Indian rural population (3) This condition affects approximately 0.5% (5 million people) of the population in the Indian subcontinent. The major presenting complaint is a progressive inability to open the mouth due to the accumulation of inelastic fibrous tissue in the juxta-epithelial region of the oral mucosa. This severely impairs eating and oral hygiene care. The epithelium overlying the fibrous condensation becomes atrophic in 90% of cases and is the site of malignant transformation in 4.5% of patients<sup>4</sup>.

In recent years marked increase in the occurrence of OSMF was observed in many parts of India like Bihar, MP, Gujarat and Maharashtra and the younger generation are suffering more due to incoming of areca nut products in different multicolored attractive pouches. The younger generation is very much addicted to these products especially gutkha and panmasala<sup>5</sup>.

**History:** Oral submucous fibrosis (OSMF) has a very interesting history. Sushruta, a renowned Indian physician who lived in the era from 2500 to 3000BC, had already recognized it as a mouth and throat melody and had labeled it as Vidhari<sup>6</sup>. The features of which were described as a progressive narrowing of the mouth, blanching of the oral mucosa, pain and burning sensation on taking food, hypomobility of the soft palate and tongue, loss of gustatory sensation and occasional mild hearing impairment due to the blockage of the Eustachian tube. There has been nearly no change in these symptoms till today.

This condition was described first by Schwartz(1952)<sup>7</sup> while examining five Indian woman from Kenya, to which he ascribed the descriptive term “atrophia idiopathica (tropica) mucosae oris.” Later in 1953, Joshi from Bombay re-designated the condition as oral submucous fibrosis<sup>7</sup>.

**Incidence:** The condition is found in 4/1,000 adults in rural India and as many as 5 million young Indians are suffering from this precancerous condition as a result of the increased popularity of the habit of chewing pan masala. Pan masala is a mixture of spices including, betel nuts, catechu, menthol, cardamom, lime and others. It has a mild stimulating effect and is often eaten at the end of the meal to help digest food and as a breath mint.<sup>8</sup>

**Epidemiology:** OSMF is predominantly seen in people in south Asian countries<sup>9</sup> such as India, Bangladesh, Bhutan, Pakistan and Sri Lanka, or in south Asian immigrants to other parts of the world.<sup>10,11</sup> Cases have occasionally been reported in Europeans; it also occurs in people from Taiwan, China, Nepal, Thailand and Vietnam.<sup>12</sup>

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Outside the subcontinent, cases have been reported among Indians living in Kenya, Malaysia, Uganda, South Africa, the Fiji Islands,<sup>4</sup> and the UK.<sup>9</sup> 3 Ethnic clusters among Burmese and Pakistanis have been reported. 14 Sporadic cases have been reported in other ethnic groups from countries such as Taiwan

**Age:** Oral submucous fibrosis is widely prevalent in all age groups and across all socioeconomic strata in India. A sharp increase in the incidence of oral submucous fibrosis was noted after pan parag came onto the market, and the incidence continues to increase. Sirsat and Khanolkar<sup>13</sup> reported majority of OSMF cases belonged to the age group of 20-40 years of age. Sinor et al<sup>14</sup> re-ported 79 per cent of the OSMF cases were under the age of 35 years and maximum numbers of cases were in 25-44 years of age group. Shah and Sharma<sup>15</sup> in their study numbers of cases were in 25-44 years of age group. Younger generations in India are getting attracted to the advent of attractive, conveniently packed sachets and mass and media advertisements

**Sex:** A case-control study of 185 subjects in Chennai, South India revealed a male-to-female ratio 9.9:1<sup>16</sup>. In Patna, Bihar (also in India), the male-to-female ratio was 2.7:1<sup>5</sup> Hazarey et al from Nagpur also reported that most of their patients were in the younger age group (< 30 years) with a similar male to female ratio of 5:1.<sup>43</sup>

**Etiology:** Since many years there have been suggested various predisposing factors for oral submucous fibrosis like areca nut/betel nut, tobacco, lime, malnutrition, immunological disorders, collagen disorders, capsaicin(a prime component in chillies),etc; association of areca nut catechu in the occurrence of Oral Submucous fibrosis has been proved by many studies<sup>17-21</sup>. It's been shown that areca nut plays a role in OSMF by generating free radicals as well as by causing immunosuppression. Commercially available of economical sachets of gutka, paan contains areca nut cut in to small pieces coated with various chemicals and have strong association with this.

**i) Areca nut:** The betel nut has psychotropic and anti helminthic property due to presence of areca alkaloids. Four alkaloids have been conclusively identified in biochemical studies, arecoline, arecaidine, guvacine & guvacoline, of which arecoline is the main agent. Recently suggested pathogenesis of oral submucous fibrosis is by dual action of areca nut. It is suggested that arecoline not only stimulates fibroblastic proliferation and collagen synthesis but also decreases it's breakdown. This suggests that arecoline is the active metabolite in fibroblast stimulation<sup>22</sup>. Areca nut plays a role in OSMF by generating free radicals as well as by causing immunosuppression. Recent evidence suggests upregulation of the copper-dependent extracellular enzyme lysyl oxidase by fibroblasts in oral submucous fibrosis is important, leading to excessive crosslinking and accumulation of collagen<sup>23</sup>.

OSF is thought to be caused by the chewing of areca nut but research has shown patents presenting with OSF who do not report having an areca nut habit, this further adds to the mystery surrounding OSF and its etiology (Rajendran, Rani, Shaikh, 2006)<sup>24</sup>. A study of 100 000 villagers in India (Maharashtra), 4.2% of females who chewed areca nut and did not use tobacco suffered from OSMF (9). Thus chewing of areca nut may be an important factor in the etiology of OSMF<sup>25</sup>.

**ii) Tobacco & Lime:** The commercially freeze dried products such as Pan masala, Gutka and Mawa (areca, tobacco and lime) have high concentrates of areca nut per chew and appear to cause OSF more rapidly than by self prepared conventional betel quid which contain smaller amounts of areca nut. (Shah & Sharma, 1998; Sinor et al, 1990)<sup>14,15</sup>. These are known irritants and

causative factors in oral malignancy. They may act as local irritants<sup>22</sup>.

**iii) Chillies:** Chillies are thought to irritate the oral mucosa and cause an inflammatory reaction and along with continued use of chillies and other spices, continued irritation of the mucosa causes chronic inflammation which leads to fibrosis formation (Ahmad et al., 2006)<sup>5</sup>.

The use of chillies (*Capsicum annum* and *Capsicum frutescence*) has been thought to play an etiological role in oral submucous fibrosis. Capsaicin, which is vanillylamide of 8-methyl-6-nonenic acid, is the active ingredient of chillies, play an etiological role in oral submucous fibrosis (Rajendran, 1994)<sup>26</sup>.

Chillies and spices were observed as one of the predisposing factors of OSMF. Several workers like Sirsat and Khanolkar<sup>13</sup>, Shiau and Kwan,<sup>27</sup> McGurk and Crag,<sup>28</sup> Rajendran et al,<sup>26</sup> Pillai et al<sup>29</sup> and Van Wyk<sup>30</sup> have reported that use of spices and chillies as one of the predisposing factors of OSMF.

It may be mentioned that chillies can damage the cells of the mucosa and if this is continuous, it probably causes chronic inflammation, which leads to the formation of excessive fibrosis. So chillies have indirect effect on the pathogenesis of OSMF as hypersensitivity to chillies is often explained as a common factor in the development of OSMF<sup>5</sup>.

**iv) Nutritional deficiency:** A subclinical vitamin B complex deficiency has been suspected in cases of OSF with vesiculations and ulcerations of oral cavity. The deficiency could be precipitated by the effect of defective nutrition due to impaired food intake in advanced cases and may be the effect, rather than the cause of the disease<sup>22,26</sup>. (Rajendran, 1994).

The reason for OSMF cases coming from low socioeconomic group might be due to poor quality of food, low vitamins particularly in iron deficiency and use of more spices and chillies to make the food tasty, coupled with lack of health consciousness<sup>5</sup>.

Shiau and Kwan<sup>27</sup> observed OSMF mostly in farmers belonged to low socioeconomic class. Ramanathan<sup>31</sup> also found most of the OSMF cases from India were also of low socioeconomic group. Rajendran et al<sup>26</sup> who reported that vitamin and iron deficiency together with malnourished state of the host leads to derangement in the inflammatory reparative response of the lamina propria with resultant defective healing and scarification which ultimately leads to OSMF.

**v) Immunological disorders:**

Raised globulin levels are indicative of immunological disorders. Serum immunoglobulin levels of IgA, IgG and IgM are raised significantly in oral submucous fibrosis. These raised levels suggest an antigenic stimulus in the absence of any infection. Circulating autoantibodies are also present in some cases of oral submucous fibrosis<sup>32</sup> (Canniff et al, 1985).

**Clinical Manifestations:** Early OSMF includes a burning sensation in the mouth when consuming spicy food, appearance of blisters especially on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa<sup>33</sup>. The most common initial symptoms of submucous fibrosis are burning sensation of the oral mucosa aggravated by spicy food (42%), followed by either hyper salivation or dryness of the mouth (25%)<sup>34</sup>.

1. Blanching, i.e., marble-like appearance of the oral mucosa and stiffness of the oral mucosa<sup>33</sup>
2. Trismus<sup>35</sup>
3. Burning sensation in the mouth when consuming spicy food<sup>33</sup>
4. Appearance of blisters especially on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa<sup>36</sup>
5. Reduced mobility of the soft palate and tongue<sup>34</sup>
6. Excessive salivation<sup>34</sup>
7. Defective gustatory sensation and dryness of the mouth<sup>34</sup>
8. Intolerance to eating hot and spicy foods<sup>42</sup>
9. Mild hearing loss due to blockage of Eustachian tube<sup>42</sup>

In advanced OSMF, oral mucosa becomes blanched and slightly opaque and white fibrous bands appear involving the buccal mucosa, lips, soft palate, faucial pillars and tongue. With progressive fibrosis, the stiffening of certain areas of the mucosa occurs difficulty in opening the mouth, inability to whistle or blow out a candle and difficulty in swallowing<sup>34</sup>. In severe submucous fibrosis, the patient cannot protrude the tongue beyond the incisal edges and there is a progressive closure of the oral opening.

The oral mucosa is involved symmetrically and the fibrous bands in the buccal mucosa run in a vertical direction<sup>34,36</sup>. The density of the fibrous deposit varies from a slight whitish area on the soft palate causing no symptoms to a dense fibrosis causing fixation and shortening or even deviation of the uvula and soft palate<sup>37</sup>.

Depending on if the OSF patient chews the areca nut or swallows it after chewing, the fibrotic change in the mucosa can also occur in the pharynx or esophagus<sup>38, 39</sup>.

Some OSMF subjects showed unilateral fibrosis in the mouth. On examination one side of the buccal mucosa was fibrosed where as other side was completely normal. The patients used to keep the gutkha on the fibrosed side for few minutes and after that partially swallowed and partially spitted out.

**Differential Diagnosis:** Some differential diagnoses for OSMF could be leukoplakia due to smoking, tobacco keratosis (from smokeless tobacco), plaque-type lichen planus, or chronic hyperplastic candidiasis (Newland et al., 2005)<sup>40</sup>. The difference between smoking-related leukoplakia, hyperplastic candidiasis, and tobacco keratosis compared to OSF is that the leukoplakia, keratosis, and candidiasis will be painless (OSMF can be painful); they will also have a different histological appearance when biopsied<sup>40</sup>

Oral submucous fibrosis has a characteristic clinical appearance and there are very few conditions that need to be differentiated from it. One is oral manifestation of scleroderma. Compared to submucous fibrosi, however, the occurrence of scleroderma is rare. Usually pale mucosa seen in anemic conditions may be mistaken for oralsubmucous fibrosis. More often, pale mucosa, coupled with pigmentation seen in anemic conditions, may be mistaken for blanching in submucous fibrosis

**Diagnostic criteria:** The presence of palpable fibrous bands is a diagnostic criterion for submucous fibrosis. The fibrous bands occur especially in the buccal mucosa retromolar areas, and around the rima oris. When the tongue is affected, it is devoid of papillae and becomes smooth. Its mobility, especially the protrusion, is impaired. The opening of the mouth is restricted. Some investigators adhered to the earlier signs and symptoms such as pain, history of vesicles and ulcers, and blanching of the mucosa for diagnosis of OSMF<sup>41</sup>.

**Laboratory investigations:** Some oral submucous fibrosis studies have reported the laboratory findings in including decreased hemoglobin, iron, protein and vitamin B complex levels and increased erythrocyte sedimentation rate<sup>44, 45</sup>.

#### **Management:**

**Restriction of the habit:** Reduction or even elimination of the habit of areca nut chewing is an important preventive measure. The preventive measure should be in the form of stoppage of the habit. Patients should be explained about the disease

- Abstention from chewing areca nut (also known as betel nut) and tobacco.
- Minimizing consumption of spicy foods, including chilies, Maintaining proper oral hygiene.

-Supplementing the diet with foods rich in vitamins A, B complex, and C and iron.

#### **Medicinal Therapy:**

Many authors are of the opinion that conservative treatment is preferable than the conventional ones<sup>42</sup>. There is a dizzying array of reported medical interventions including dietary supplementation (vitamins, anti-oxidants), anti-inflammatory agents (principally corticosteroids) and proteolytic agents (such as hyaluronidase and placental extracts), and anti-cytokines. Such agents may be administered orally, topically or via submucosal injection.

**Nutritional support:** Vitamin Rich Diet along with iron preparation is helpful to some extent. The rationale of giving nutrients in OSMF patients is to correct deficiency states and promote normal cellular processes present in health that help to protect against adverse events including carcinogenesis. Such as Vitamin A (chewable tablets also give some topical application)<sup>49, 50</sup>, vitamin A & Vitamin B complex ( Khanna and Andrade)<sup>51</sup>, Vitamin B complex with iodine injections ( Gupta et al)<sup>52</sup>.

Nidhi Thakur<sup>53</sup> evaluated effectiveness of Micronutrients and Physiotherapy in the management of Oral Submucous Fibrosis in 64 patients with oral submucous fibrosis. Mouth opening in patients showed significant improvement at the end of 6 weeks as compared to the initial mouth opening. Another study by (Maher et al)<sup>54</sup> evaluated the efficacy of combination of micronutrients (vitamins A, B complex, C, D, and E) and minerals (iron, calcium, copper, zinc, magnesium, and others) in controlling the symptoms and signs of OSMF. Significant improvement in symptoms, notably intolerance to spicy food, burning sensation, and mouth opening, was observed at exit. Borle *et al* (18) reported that Vitamin A, 50,000 IU chewable tablets, if given once daily could cause symptomatic improvement. Trismus (Tonic spasm of masticatory muscles) did not improve with this treatment<sup>59</sup>.

**Lycopene therapy:** Lycopene is a safe antioxidant of utmost importance. Lycopene is a bright red carotene and carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons and papayas. It has been shown to have several potent anti-carcinogenic and antioxidant properties and has demonstrated profound benefits in precancerous lesions such as leukoplakia.<sup>55</sup> & OSMF. Lycopene exhibits the highest physical quenching rate constant with singlet oxygen<sup>56</sup>. The role of lycopene in oral submucous fibrosis is Inhibition of abnormal fibroblast, increase resistance to stress, decrease in inflammatory response. It has found to improve mouth opening and reduces burning

sensation<sup>58</sup> – singly or in combination of intralesional steroids. (Kumar *et al*, 2007)<sup>46</sup>. Lycopene (taken at a dose of 16 g daily) has shown promise for oral submucous fibrosis<sup>46</sup>.

**Pentoxifylline therapy:** Pentoxifylline is a tri-substituted methylxanthine derivative, the biologic activities of which are numerous. This includes increasing red cell deformability, leukocyte chemotaxis, antithrombin and anti-plasmin activities, and more importantly to the present context, its fibrinolytic activity<sup>60</sup>. Pentoxifylline decreases red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and whole blood viscosity<sup>61</sup>.

Rajendran *et al* 62, 2006 divided the 29 participants into two groups that took either oral pentoxifylline or multi-vitamins. All those enrolled completed the 7-month study period. The authors reported statistically significant improvements in the oral pentoxifylline group ( $n = 14$ ) compared with controls with respect to objective criteria (mouth opening, tongue protrusion and relief from circum-oral fibrotic bands) and subjective criteria (intolerance to spices, burning sensations, tinnitus, difficulty in swallowing, and difficulty in speech). In a study published in 2006 in the Indian Journal of Dental Research on the effects of the drug pentoxifylline, it was suggested that due to results from the study pentoxifylline may, with further studies and tests; prove to be a cure or partial cure for OSF (Rajendran *et al.*, 2006)<sup>62</sup>.

#### **Intralesional injections:**

**Steroids:** in patients with moderate OSMF, weekly submucosal intralesional injections or topical application of steroids are helpful. Hydrocortisone injection along with the local anaesthetic injection locally given in the area of fibrosis. Injections are given fortnightly. The early cases show good improvement with this therapy. (Roa and Raju)<sup>63</sup> recommended combination of oral and injection therapy: 7 weeks of treatment with dexamethasone in gradually decreasing dose; this was supplemented with local injection of hydrocortisone.”

A Therapy with hydrocortisone 25 mg tablet, in doses of 100mg/day is useful in relieving burning sensation. This is supplemented with local injection of hydrocortisone 25mg at biweekly intervals at the affected site. Increased vascularity of the site is observed, which is due to fibrinolytic, anti-allergic and anti-inflammatory action of corticosteroid<sup>64</sup>.

**Placental extracts:** The rationale for using placental extract in patients with oral submucous fibrosis derives from its proposed anti-inflammatory effect,—hence, preventing or inhibiting mucosal damage. Cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human placental extract (Placentrex) has shown marked improvement of the

condition. Placental extract accelerates cellular metabolism, aids in absorption of exudates, and stimulates regenerative process, increases physiological function of organs, produces significant enhancement of wound healing and it has anti-inflammatory effect<sup>64</sup>. Doses: injected around fibrous bands, intra-muscularly, at the interval of 3 days for 15 days. Each time 2 ml solution is deposited<sup>64</sup>.

Katharia S K. Singh S P. K Kulshretra V K<sup>65</sup> studied the effect of placenta extract in management of Oral submucous fibrosis and stated that there was significant improvement in mouth opening, colour of oral mucosa and reduction of fibrous bands. Sudhakar Vaidya, V K Sharma<sup>42</sup> got good results with injection of placental extract intra lesion ally associated with antioxidants and jaw dilator exercises has been found useful in 52 cases.

**Hyaluronidase:** Breaks down hyaluronic acid (ground substance of connective tissue), lowers the viscosity of intracellular cement substance i.e hyaluronidase decreases cell formation by virtue of its action on hyaluronic acid, which plays an important role in collagen formation<sup>64</sup>. The use of topical hyaluronidase has been shown to improve symptoms more quickly than steroids alone. Hyaluronidase can also be added to intralesional steroid preparations. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone. Improvement in health of mucous membrane, burning sensation and trismus was observed by using hyaluronidase injections<sup>66</sup>.

P. K. Kakar<sup>48</sup> *et al* investigated A total of 96 patients with Oral Submucous Fibrosis, who had received four regimens of treatment—local dexamethasone, local hyaluronidase, local combination of dexamethasone and hyaluronidase, and local placental extract. The patients were followed up for a period varying from 3 months to 2 years. The group of patients receiving hyaluronidase alone showed quicker improvement in symptoms although its combination with dexamethasone gave somewhat better longer-term results. A new regimen for the treatment of submucous fibrosis is recommended.

In a study by singh M *et al*<sup>66</sup> on Patients of OSMF (100) which were randomly divided into two groups A and B. Group A patients received combination of hydrocortisone acetate (1.5 ml)/hyaluronidase (1500 IU) at weekly interval submucosally in pterygomandibular raphe, half dose on each side for 22 wk. Group B patients received combination of triamcinolone acetonide (10 mg/ml)/ hyaluronidase (1500 IU) at 15 days interval for 22 wk. No statistically

significant difference in symptom score, sign score and histopathological improvement was seen between the two groups. Treatment regimen of group B was more convenient to the patients because less number of visits required and cheap. No side effects were seen.

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