REVIEW ARTICLE

ORAL SUBMUCOUS FIBROSIS – A SHORT REVIEW

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DOI: 10.5455/ijmsph.2014.071020141 Received Date: 20.09.2014 Accepted Date: 05.10.2014

ABSTRACT
Oral Submucous fibrosis (OSMF) is a well-known debilitating precancerous condition of oral cavity which results due to chewing tobacco, areca nuts and its related products. It is an irreversible condition with very high malignant potential. There is a dire need to curb this common but avoidable condition that is increasingly observed in the younger age groups which leads to early development of oral cancer. The purpose of this article is to comprehend OSMF in totality and help the health professionals to get acquainted with the possible etiology, clinical features, differential diagnosis and current treatment modalities of OSMF along with the planning of promotive and preventive research to elucidate the solutions to the problem.
Key Words: Submucous Fibrosis; Precancerous; Tobacco; Areca Nut; Oral Cancer

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 otherwise yielding mucosa resulting in difficulty in opening the mouth.[1,2] OSMF is a common problem in India. The most common symptom is progressive trismus i.e. inability to open the mouth which is due to accumulation of inelastic fibrous tissue in the juxta-epithelial region of the oral mucosa. Progressive trismus in turn impairs mastication and results in poor oral hygiene. The epithelium overlying the fibrous condensation becomes atrophic in 90% of cases and is the site of malignant transformation in 4.5% of patients.[3]

Historically OSMF is a known entity since centuries. Sushrutha, a renowned Indian physician who lived in the era from 2500 to 3000BC, had recognized OSMF as a mouth and throat malady & termed it Vidhari.[4] The features described by him were progressive narrowing of the mouth, blanching of the oral mucosa, pain and burning sensation on taking food, decreased mobility of the soft palate and tongue, loss of gustatory sensation and occasional mild hearing impairment due to the blockage of the Eustachian tube and apparently there has been no change in these symptoms till today. OSMF was first described by Schwartz (1952) which he originally termed as "atrophia idiopathica (tropica) mucosae oris".[5] Later in 1953, Joshi from Mumbai re-designated the condition as oral submucous fibrosis.[5]

OSMF is predominantly seen in South Asian inhabitants from India, Bangladesh, Bhutan, Pakistan and Sri Lanka or in people immigrated from South Asia to other parts of the world.[6-8] Occasionally it is seen in Europeans and sporadic cases have been reported from Taiwan, China, Nepal, Thailand and Vietnam.[9] India has seen a marked increase in the occurrence of OSMF in recent years especially in states of Bihar, Madhya Pradesh, Gujarat and Maharashtra. The Younger generation has been found to be suffering more due to the their attraction towards different tobacco products and areca nut products available in different multicolored attractive pouches.[10] Considering it to be a major deterrent to the health of Indians, some state governments have banned its sale. As of May 2013, gutka (tobacco product) is banned in 24 states and 3 union territories. Gutka is banned under the provision to ban any food product containing harmful adulterants in the centrally enacted Food Safety and Regulation (Prohibition) Act 2011. The ban is enforced by the state public health ministry, the state Food and Drug Administration and the local police.

Associated Predisposing Factors

There are many predisposing factors associated with occurrence of OSMF e.g. tobacco, lime, areca nut/betel nut, capsaicin (a major component in chilies), malnutrition, immunological disorders, collagen disorders etc.

Tobacco & Lime: Pan Masala, Gutka and Mawa (areca, tobacco and lime) are commercially freeze dried products with high concentrates of areca nut per chew. They act as local irritants and cause OSMF more rapidly than by self-prepared conventional betel quid which contain smaller amounts of areca nut.[11]

Areca Nut: Areca nut is strongly associated with OSMF. It contains many alkaloids such as arecoline, arecaidine, guvacine & guvacoline, of which arecoline is the main agent. Arecoline is the active metabolite in fibroblast stimulation as it not only stimulates fibroblastic proliferation and collagen synthesis but also decreases its breakdown.[11] It exerts this action by upregulating copper-dependent extracellular enzyme lysyl oxidase by fibroblasts leading to excessive cross linking and accumulation of collagen. It also acts by generating free radicals and causing immunosuppression. Commercially available sachets of gutka, paan contains areca nut cut in to small pieces coated with various chemicals.

Chillies: Chillies act as irritant to oral mucosa. Their continued use and use of other spices cause continued irritation of the mucosa and chronic inflammation which leads to fibrosis.[10] Capsaicin, which is vanillylamide of 8-methyl-6-nonenic acid, is the active ingredient of chillies, play a key role in OSMF. Hence 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.[10]

Nutritional Deficiency: Subclinical vitamin B complex deficiency is seen in many cases of OSMF with vesiculations and ulcerations of oral cavity which is probably 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. High prevalence of OSMF in low socioeconomic groups may be due to poor quality of food, low vitamins and iron, use of more spices and chillies to make the food tasty, coupled with lack of health consciousness.[10] combined effect of vitamin and iron deficiency along with malnourished state of the host leads to deranged inflammatory reparative response of the lamina propria with resultant defective healing and scar formation which ultimately leads to OSMF.

Immunological Disorders: Raised serum immunoglobulin levels of IgA, IgG and IgM in OSMF are indirect indicators of immunological problems associated with OSMF.

Clinical Presentation

Pindborg in 1989 divided OSMF into 3 stages on based of clinical features[12]:

- *Stage 1 (Stomatitis):* It includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation, and mucosal petechia.
- *Stage 2 (Fibrosis):* fibrosis occurs in ruptured vesicles and ulcers when they heal, which is the hallmark of this stage. Early lesions demonstrate 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, resulting in a mottled, marble like appearance of the mucosa because of the vertical, thick, fibrous bands running in a blanching mucosa. Specific findings include the following: (i) Reduction of the mouth opening (trismus); (ii) Stiff and small tongue; (iii) Blanched and leathery floor of the mouth; (iv) Fibrotic and depigmented gingiva; (v) Rubbery soft palate with decreased mobility; (vi) Blanched and atrophic tonsils; (vii) Shrunken budlike uvula; (viii) Sinking of the cheeks, not commensurate with age or nutritional status
- *Stage 3 (Sequelae of OSMF):* (i) Leukoplakia is precancerous and is found in more than 25% of individuals with OSMF. (ii) Speech and hearing deficits may occur because of involvement of the tongue and the Eustachian tubes.

In addition to the above staging, in 1995 Khanna[13] developed a group classification system for the surgical management of trismus.

- *Group I:* This is the earliest stage and is not associated with mouth opening limitations. It refers to patients with an interincisor distance of greater than 35 mm.
- *Group II:* This refers to patients with an interincisor distance of 26-35 mm.
- *Group III:* These are moderately advanced cases. This stage refers to patients with an interincisor distance of 15-26 mm. Fibrotic bands are visible at the soft palate, and pterygomandibular raphe and anterior tonsillar pillars.
- *Group IVA:* Trismus is severe, with an interincisor distance of less than 15 mm and extensive fibrosis of all the oral mucosa.
- *Group IVB:* Disease is most advanced, with premalignant and malignant changes throughout the mucosa.

Early OSMF presents with a burning sensation in oral cavity aggravated by spicy food (42%), followed by either hyper salivation or dryness of the mouth (25%).[14] it presents with blisters especially on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa.[15] Common initial symptoms are:

- Intolerance/Burning sensation in the mouth on consuming hot and spicy food
- Trismus
- Blanching, i.e., marble-like appearance of the oral mucosa and stiffness of oral mucosa
- Reduced mobility of the soft palate and tongue
- Hypersalivation
- Defective gustatory sensation and dryness of the mouth
- Blisters on the palate, ulcerations or recurrent generalized inflammation of the oral mucosa
- Mild hearing loss due to blockade of Eustachian tube

In advanced OSMF, oral mucosa becomes blanched and slightly opaque with appearance of white fibrous bands on buccal mucosa, lips, soft palate, faucial pillars and tongue. With progressive fibrosis, stiffening of certain areas of mucosa occur which results in difficulty in opening of the mouth, difficulty in swallowing and inability to whistle or blow air.[14] In severe cases, the patient cannot protrude the tongue beyond the incisor teeth 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.[14,16] 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.[17] Depending on the habit of chewing or swallowing tobacco, areca nuts and its related products, the fibrotic changes can be seen in the mucosa of the oral cavity or esophagus.[18,19] Laterality of OSMF depends on the fact that which side of the oral mucosa is more exposed to tobacco products. This is usually noted during examination that one side of the buccal mucosa is fibrosed whereas other side is completely normal.

Diagnostic Criteria

The diagnosis in most of the cases is made from the history of repetitive exposure to causative agents, clinical appearance and the texture of tissue.[20] The presence of palpable fibrous bands is a diagnostic criterion for submucous fibrosis. The fibrous bands occur especially in the buccal mucosa, retromolar trigone and around the rima oris which result in restricted mouth opening. Tongue is devoid of papillae and its mobility is impaired especially during protrusion. No specific test will confirm a suspected diagnosis of OSMF. An incisional biopsy will reveal a thinned surface and the excessive deposition of collagen in submucosa. A biopsy of most severe area or of ulceration is recommended to rule out squamous cell carcinoma because tobacco product contains many carcinogens & OSMF is considered to be a pre-malignant lesion for squamous cell carcinoma of oral cavity.

Management

Primordial Prevention

Educating the masses about the risk of developing OSMF due to consumption of tobacco, areca nuts and its related products.

Primary Prevention

- Restriction of the habit: Patients should be counselled about the disease, its complications and the need of abstinence from chewing areca nut and tobacco. Elimination or even reduction of the habit of tobacco and areca nut chewing is an important preventive measure.
- Minimizing consumption of spicy foods and maintaining proper oral hygiene.
- Supplementing the diet with foods rich in iron, vitamins A, B complex, and C.

Secondary Prevention

Early diagnosis can be made by self-assessment of one's own oral cavity in mirror and reporting immediately to the nearest medical or dental practitioner if any abnormality is detected. The doctor will diagnose the patient clinically with above mentioned criteria.

Medical Treatment

There is a dizzying array of reported medical interventions to improve current treatment regimens for OSMF. The patients should be given nutritional support in the form of dietary supplements rich in protein, calories, vitamins and minerals. These are commonly employed in combination with other more specific therapeutic agents like immunomodulatory drugs. Local

and systemic application of glucocorticoids, placental extract and hyaluronidase are commonly used. They act by inhibiting the action of sensitized lymphocytes following activation by specific antigens and by preventing or suppressing inflammatory reactions.[21] The effects of steroids and hyaluronidase are thought to be responsible for the satisfactory results obtained in OSMF patients who have severe limitation in mouth opening.

Placental extracts (aqueous solution of human placenta) in the form of local injections as well as in parenteral form have been tried with varied results.[21] They can be separated into four different fractions: aqueous extract, lipoid extract, immune gamma globulins, and tissue coagulants. Only the aqueous extract of placenta acts as a biogenous stimulator-by accelerating cellular metabolism (through the pituitary-adrenal cortical axis), assisting in the absorption of exudates, stimulating the regenerative process, and increasing the physiological actions of organs. The other actions of placental extract are an anti-inflammatory and significant analgesic effect, increase in blood circulation and tissue vascularity, arrest of tissue growth stagnation, metabolic degenerative conditions, and lowered immunity response factors. Placental extract has been found to contain between 50 and 100 King-Armstrong units of alkaline-phosphatase; it has been used as a local nutrient.[22,23]

Combination therapy has shown better therapeutic efficacy for medical management of OSMF. Local injections of chymotrypsin, hyaluronidase and dexamethasone together yielded significantly better results than with one drug alone or a combination of dexamethasone with either chymotrypsin or hyaluronidase.[21] Combined therapy with nylidrin hydrochloride (a peripheral vasodilator), vitamins D, E and B complex, iodine, placental extract, local and systemic corticosteroids, and physiotherapy claims a success rate of 62% in OSMF.[22]

Surgical Management

Surgery remains a therapeutic option in advanced cases of OSMF which are refractory to conventional conservative therapies. Historically attempts to excise the fibrotic bands has resulted in progressively more scarring in follow up periods resulting in worse quality of life for the patients. In recent years attempts have been made to replace the defects created by excision by split thickness skin grafting, bilateral nasolabial flaps, palatal island flaps, tongue flaps, buccal fat pad graft and temporalis muscle flap graft.[24] A new treatment regimen composed of surgical excision of the fibrotic bands with submucosal placement of fresh human placental grafts, followed by local injections of Dexamethasone was recommended recently for advanced cases.[21] The rationale for using placental grafts in OSMF is that they have both a hormonal and a mechanical effect; the biogenic stimulant effect is because the placenta is a homograft that is immunologically competent and rich in steroids, proteins, chorionic gonadotrophins, estrogens and progesterone. The grafts are easily moldable and undergo total absorption only after prolonged periods, thus mechanically preventing fibrosis.[21]

Physiotherapy and Rehabilitation

Physiotherapy exercises remain undoubtedly the basic, most commonly performed and the modality with longest therapeutic effect on relieving the trismus. This has been used in combination with other medical therapies and surgical procedures.

Way Forward

While dental lasers are still in their infancy, there is no doubt that the medical professionals have started accepting them as an alternative to traditional therapies. ErCr: YSGG laser has utility in both hard and soft tissue procedures as the hydro-photonic process allows it to out-perform other conventional modalities in many ways.[25] Uses of molecular targeted agents like antagonist of TGF-β (transforming growth factor- β) may emerge as a potential therapeutic option. Many more options should be sought by budding researchers in future to make this premalignant condition a less dreaded one. A multidisciplinary palliative care approach is need of the hour for OSMF patients developing severe trismus refractory to conventional medical and surgical treatment.

ACKNOWLEDGMENT

My sincere thanks to Patients of OSMF who encouraged me to review the topic.

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Cite this article as: Samdariya S, Kumar D, Kumar A, Porwal P, Pareek P. Oral submucous fibrosis – A short review. Int J Med Sci Public Health 2014;3:1308-1312.
Source of Support: Nil
Conflict of interest: None declared