REVIEW

ORAL SUBMUCOUS FIBROSIS: A REVIEW

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ABSTRACT

Oral sub mucous fibrosis (OSF) is a high risk precancerous condition, predominantly affecting Indian. Data from recent epidemiological studies provide overwhelming evidence that areca nut is the main etiological factor for OSF. A clear dose-dependent relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of OSF. Limitation of mouth opening result in difficulty in mastication is the main presenting feature. Although nutritional deficiencies and immunological processes may play an important role in the pathogenesis. The available epidemiological evidence indicates that chewing betel quid (containing areca nut, tobacco, slaked lime or other species) is an important risk factor for OSF. It has been postulated that areca nut may also induce the development of the disease by increased levels of cytokines in the lamina propria. Hence the present article OSF reviewed the etiology, pathophysiology, clinical features & management.

Key words:- OSF, Juxtra epithelial, Areca nut, Fibrous, Blanching

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INTRODUCTION

Oral sub mucous fibrosis is a peculiar disease which is considered to be a precancerous condition. Oral sub mucous fibrosis is a chronic, progressive, and irreversible disease of unknown aetiology. It affects oral, oropharyngeal, and at times esophageal mucosa. The earliest description of the disease was by Schwartz in 1952 [1], who coined the term atrophica idiopathic mucosa oris to describe an oral fibrosing disease. Joshi subsequently termed the condition as oral sub mucous fibrosis (OSF) in 1953 and the first Indian cases were reported from Bombay[2] and Hyderabad.[3]

OSF is characterized by inflammation and progressive fibrosis of lamina propria. According to Cox & Aziz (1997) mentioned that if progressive inability to open the mouth is the major complaint, because of accumulation of inelastic fibrous tissue in the juxtaepithelial region of the oral mucosa, along with concomitant muscle degeneration.[4] According to Paissat (1981), the buccal mucosa is the most commonly involved site, but may also involve the other parts of the oral cavity including pharynx[5]. Patients complain of burning sensation while eating spicy food. The fibrosis also leads to difficulty in mastication, speech, and swallowing and pain in throat and ears. It also may lead to relative loss of auditory acuity because of stenosis of the Eustachian tube.

In advance cases, there may be severe trismus, and totally inelastic mucosa is forced against the teeth, leading to chronic ulceration and subsequent infection. In many cases, the fibrous tissue is seen which extends from the anterior pillars into the soft palate as a delicate reticulum of interlacing white strands that later become confluent.

The cheek have mottled marble like appearance, with normal reddish mucosa and the floor of mouth becomes pale and thickened .If the fibrosis extends down to the esophagus, the patient has progressive dysphasia . The current evidences suggest that a combination of various factors could explain the pathogenesis of this unique condition. The purpose of this review article is to consider its epidemiology, aetiology, clinical features and its successful prevention and management.

GEOGRAPHIC DISTRIBUTION AND PREVALENCE

The disease occurs in 0.2%-1.2%Indian population. An epidemiological survey done a decade ago indicated not less than 250,000 cases reported in the country and suggest an overall prevalence of up to 0-4% in places at Kerala.[6]

The total number of cases in India is around two million and other countries Kenya, Malaysia, Uganda, South Africa, and the UK.[7-12] Shear et al (1967) reported a prevalence of OSF is 0.5% in women. The alkaloid and tannin content of areca nuts (betel nuts) are responsible for fibrosis. The composition of nuts differs with the method of cultivation and preparation. Soaking and Boiling, for instance, reduce the concentrations of tannins and alkaloids. It is likely that differences in concentrations of these chemical constituents may be responsible for regional variations in disease frequency. Also, sliced and chewed betel nut is more harmful than betel nut wrapped in the leaf. In the former, the alkaloids are in direct contact with the buccal mucosa for a longer time resulting in greater mucosal penetration.

AETIOLOGY AND PATHOPHYSIOLOGY

The pathogenesis of the disease is not well established, but the cause of OSF is believed to be multifactorial. Caniff et al in 1986[13] and Pindborg in 1968[14] described disease as a form of hypersensitivity to capsaicin, an irritant in chilies, but this was not totally substantiated in experimental work. A number of factors may trigger the disease process by causing a juxtaepithelial inflammatory reaction in the oral mucosa. Factors included are areca nut chewing, ingestion of chilies, genetic & immunologic processes, nutritional deficiencies and other factors.

ARECA NUT (BETEL NUT) CHEWING

In India, Uttar Pradesh, Bihar, Jharkhand, M.P. and Maharashtra states are affected because of oral habits of chewingo nuts, tobacco and pan-masala.

According to Liao (2001), the areca nut component of betel quid plays a major role in the pathogenesis of OSF [15]. Betel nut is frequently used as a psychotropic and antihelminthic agent and used as an after meal digestant which is taken to ease abdominal discomfort. Shear et al in 1967 and Caniff et al (1987) evaluated correlation between betel nut chewing and the onset of oral sub mucous fibrosis.[13,16]

According to Ranganathan (2004) and Ariyawardana (2006) Smoking and alcohol consumption alone, habits common to areca nut chewers, have been found to have no effect in the development of OSF.[17,18] The strongest evidence regarding the etiology of OSF is with the habit of areca nut chewing. In a study of over 1 lakh Indian subjects by Mehta F et al (1968), areca nut was practiced by 52% of the patients with OSF, compared with 2.1 % amongst the total population[19]. Gupta pc et al in 1968 done 10 year prospective study undertaken on 10,000 individuals in India, demonstrated a incidence of 0% OSF amongst those who did not chew areca nut, compared with an incidence of 35 % in 1 lakh per year among areca nut chewers[20]..

Areca nut form may be available in the following form:-

- Supari + Tobacco
- Supari + Pan+ Tobacco
- Supari + Pan + Pan masala
- Pan Parag / Pan masala
- Supari + Pan + Lime
- Supari Roasted / Raw Areca nut

Role of areca nut in pathogenesis of OSF.

Arecoline, an active alkaloid found in betel nuts. Stimulates fibroblasts to increase production of collagen by 150% suggested by Canniff (1981).[13] Chung-Hung (2006), studied that arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated the variety of fibrotic diseases, in a dose-dependent manner in persons with OSF.[21]

Areca nuts have also been shown to have a high copper content, and chewing areca nuts for 5-30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis as an initiating factor in individuals with OSF.[22]

Nutritional Deficiencies

Iron deficiency anemia, vitamin B complex deficiency and malnutrition are promoting factors that dearrange the repair of the inflamed oral mucosa, leading to defective healing and resultant scarring (Aziz, 1997).[4]

The resultant atrophic oral mucosa is more susceptible to the effects of chilies and betel nuts. Mucosal changes similar to those in vitamin B and iron deficiency are seen in oral sub mucosal fibrosis.

Chillies The role of chillies ingestion in the pathogenesis of OSF is controversial. Sirsat in 1960 done a study demonstrated that the capsaicin in chilies stimulates widespread palatal

fibrosis in rats[24], while another study failed to duplicate the results that are done (by Hamner, in 1974).[25] According to Pillai (1992) the incidence of OSF is lower in Mexico and South America than in India, despite the higher dietary intake of chilies[26]. A hypersensitivity reaction to chilies is believed to contribute to OSF (Aziz, 1997)[4].

Genetic & Immunologic Processes

A genetic component is assumed to be involved in OSF Patients with increased frequency of HLA-A10, HLA-B7, and HLA-DR3 (Aziz, 1997)[4] reported in people without a history of betel nut chewing or chili ingestion reported by Seedat, Mar 1988[27].

According to Canniff in 1985 an immunologic process is believed to play a role in the pathogenesis of OSF[13]. The increase in CD4 and cells with HLA-DR in OSF tissues suggests that lymphocytes are activated and that the number of Langerhans cells is increased. The presence of these immunocompetent cells and the with increased of CD4 to CD8 in OSF tissues suggest a ongoing cellular immune response results in imbalance of immunoregulation and an alteration in local tissue architecture. These reactions may be the result either of direct stimulation from exogenous antigens, such as areca alkaloids, or of changes in tissue antigenicity that leads to an autoimmune response reported by Haque in 1997[28].

Haque in 2000 demonstrated increased levels of proinflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) in patients with OSF, which may be central to the pathogenesis of OSF[29].

Other Significant Factors Liao in 2001 reported that a high frequency of mutations in the APC gene and low expression of the wild-type TP53 tumor-suppressor gene in patients with OSF increased the risk of development of oral squamous cell carcinoma.[15]

Rao and others[3] considered the condition to be a localized form of collagen disease of idiopathic origin as in Peyronie's disease, Dupuytren's contracture, Retroperitoneal fibrosis, or Idiopathic mediastinal fibrosis. In view of the numerous factors suggested as possible causes, oral submucosal fibrosis is best regarded as a clinical syndrome rather than a distinct disease entity.

CLINICAL FEATURES

The male-to-female ratio of OSF varies by region, but females tend to predominate. Seedat, in 1988 studied that female predominance was reported in Durban, South Africa, a distinct demonstrated, with a male-to-female ratio of 1:13[27]. With the onset of new commercial betel nut preparations, trends in sex predominance and age of occurrence might shift.

Age:

The mean age was 43 Years. The percentage of chewers increases with age and the frequency of chewing and type of betel nut may influence the individual's susceptibility. Ahmad in 2006 reported that patient age between 11-60 years.

Burning sensation and discomfort in the oral cavity during mastication. Gradually various parts of the mouth lose their natural suppleness and related disabilities develop. With involvement of the tongue, speech and associated functions are affected.

Extension of fibrosis to other areas in the oral cavity results in difficulty in mastication, reduced salivation, dysphasia, pain in the ears, and loss of auditory acuity due to stenosis of the pharyngeal end of the eustachian tubes. In advanced cases, inability to open the mouth, whistling, blowing, and sucking movements are affected. The jaws may become inseparable and totally inelastic and patients can only maintain their nutrition by pushing food into the mouth. The buccal mucosa is frequently ulcerated and secondarily infected consequent to ischemia and constant pressure of the mucosa against the buccal aspect of the teeth.

According to Pindborg in 1989 OSF is clinically divided into 3 stages[19], and the physical findings vary accordingly, reported by Murti, in 1992; Cox, in 1996; Aziz, in 1997& Pindborg, in 1989[4, 19]:

- Stage 1: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechia.
- Stage 2: Fibrosis occurs in ruptured vesicles and ulcers when they heal, which is the hallmark of this stage.

o Early lesions demonstrate blanching of the oral mucosa.

o 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:

- 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 budlike uvula

Sinking of the cheeks, not commensurate with age or nutritional status

- Stage 3: Squeal of OSF are as follows:
- Leukoplakia is precancerous and is found in more than 25% of individuals with OSF.
- 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[23] 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 interincisal distance of greater than 35 mm.

● Group II: This refers to patients with an interincisal distance of 26-35 mm. Group III: These are moderately advanced cases. This stage refers to patients with an interincisal distance of 15-26 mm. Fibrotic bands are visible at the soft palate, and pterygomandibular raphe and anterior pillars of faucets are present.

● Group IVA: Trismus is severe, with an interincisal 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.

DIFFERENTIAL DIAGNOSIS

✍Oral manifestations of scleroderma

✍Oral manifestations of Plumner Vinson syndrome (Iron deficiency Anemia).

INVESTIGATION

- ✍ Complete Hemogram
- ✍ Toludine blue test
- ✍ Biopsy :- Incisional biopsy
- ✍ Immunofluorescent test: -

a) Direct b) Indirect

MANAGEMENT AND PREVENTION

The treatment of patients with OSF depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with OSMF present with moderate-to-severe staging. Moderate-to-severe staging of OSF is irreversible. Medical treatment is symptomatic and aimed at improving mouth movements.

Not to consume areca nut & other chronic irritant such as hot and spicy food.

●Advice green leafy vegetables.

●Administration of Vit. A, B complex & high protein diet.

Administration of Antoxid OD for 6 – 8 weeks.

●Administration of Lycored OD for 6-8 weeks

●Physiotherapy: - It increase mouth opening.

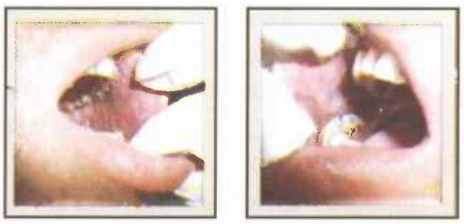

Fig:- Blanching of both side of the buccal mucosa

MEDICAL TREATMENT:-

According to Aziz, in 1997 treatment includes the following[4]

●Steroids: In patients with moderate OSF, sub mucosal intralesional injections given. Topical application of steroids may help, prevent further damage. The recommended dose is 75 to 100 mg twice a week for 4 to 6 weeks.

●Placental extracts: Sur TK[31] in 2003 reported that the rationale for using placental extract (PE) in patients with OSF derives from its proposed anti-inflammatory effect[31]prevents the mucosal damage[31].

Anil in 1993 reported that Sub mucosal administration of aqueous extract of healthy human PE (Placentrex) has shown marked improvement of the condition[32].recommended dose of placental extract is 2ml twice weekly for 4 to 6 weeks.

Hyaluronidase: The use of topical hyaluronidase shows significant improvement than steroids alone. The recommended dose is 1500 i.u twice weekly for 4 to 6 weeks. According to Karkar in 1985 the combination of steroids and topical hyaluronidase showed better long-term results than either used alone[33].

IFN-gamma: It plays a role in the treatment of patients with OSF because of its immunoregulatory effect. IFN-gamma is a known antifibrotic cytokine.

Haque MF[29] in 2001 reported that administration of intralesional injection of IFN-gamma showed marked improvement of symptoms. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with OSF, and intralesional injections of the cytokine may have a significant therapeutic effect on OSF[29].

SURGICALMANAGEMENT:

Surgical treatment is indicated in patients with severe . They are:-

●Simple excision of the fibrous bands: Excision can result in contracture of the tissue and exacerbation of the condition.

● Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy: Trismus associated with OSF may be due to changes in the temporalis tendon secondary to OSF; therefore, skin grafts may relieve symptoms (Canniff, 1986)[13].

● Nasolabial flaps and lingual pedicle flaps: Surgery performed only in patients with OSF in whom the tongue is not involved (Kavarana, 1987; Hosein, 1994)[34].

CONCLUSION

OSF is a disease with a high degree of incidence. It also carries a significant morbidity rate from oral cancer. As no effective medical and surgical treatment is available for this condition. It is desirable OSF is diagnosed at early stages. Cessation of the areca nut chewing & other factors should be advised. Intervention studies and public health awareness programme linked with OSMF condition & habits may prove the best way to control disease process at the community level..

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Source of Support: Nil, Conflict of interest:None declared