International Research Journal of Natural and Applied Sciences
Volume-2, Issue-5 (May 2015) IF- 2.818 ISSN: (2349-4077)

ORAL SUBMUCOUS FIBROSIS- A Review of literature

Dr. Shalini Nawabadkar

MDS, Oral Medicine and Radiology

Dr. Deepa V

BDS, MDS, Oral Medicine and Radiology

Department Of Dentistry

Kodagu Institute of Medical Sciences, Madikeri 571201

Dr. Rupesh

BDS

Dr. Ashford Lidiya

BDS, MDS Oral Surgery

Assistant Professor

Department of Oral Surgery, Kannur dental college.Kerala.

ABSTRACT

Arecanut chewing has resulted in various Oral mucosal lesions and are potentially malignant . large population are affected world wide. Easy availability of Pan masala ,Guthka ,Mawa containing high concentration of arecanut per chew and also the traditional betel quid chewing has resulted in a high intensity of Oral sbmucous fibrosis among the general population.The ingredients interfere with the molecular process of deposition and degradation of extra cellular matrix molecules such as collagen ,resulting in imbalance .There is reduced Phagocytosis of collagen , impairement in copper dependent enzyme lysyl oxidase , matrix metalloproteinases,

increased levels of cytokines in lamina propria.Various treatment modalities are currently available.

Key words:

Oral Submucous fibrosis

INTRODUCTION

Oral sub mucous fibrosis (OSMF) is a chronic insidious disease of the oral sub epithelial connective tissue resulting in stiffness of the oral mucosa and inability to open the mouth.[1] Shushrutha in 600 BC had coined it has "Vidari" .

Pindborg and Sirsat (1964) defined Oral submucous fibrosis as "An insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat"

The condition has also been described as idiopathic scleroderma of mouth (Su 1954), idiopathic palatal fibrosis (Rao 1962) and sclerosing stomatitis (Behl 1962). [2]

In 1952, Schwartz described five Indian women from Kenya with a condition of the oral mucosa which he called "atrophia idiopathica (tropica) mucosae oris". In 1953, Joshi redesignated it as "Oral submucous fibrosis" implying to its histological nature.[2]

OSMF mostly occurs in Asian countries including India, China, Pakistan Sri Lanka, and Bangladesh, where Betel quid(BQ) chewing habit is popular.

In India a marked increase in the use was noted in Kerala, Bihar, Madhya Pradesh, Gujarat and Maharashtra. The morbidity of OSF among Beetle Quid users is 3.2%. The younger generation are suffering more.[3,4]

Prevalence

An epidemiological assessment of the prevalence of OSF among Indian villagers based on baseline data recorded was 0.2% (n¯10071) in Gujarat , 0.4% (n=1027) in Kerala, 0.04% (n=10169) in Andhra Pradesh, and 0.07% (n ¯ 20388) in Bihar. In Ernakulam , the incidence was 8 per 100,000 men and 19 per 100, 000 women per year. In Bhavnagar in north western India, the incidence was 2.6 per 100, 000 men and 8.5 per 100, 000 women per year. In the state of Wardha, the prevalence of gutka usage by men and women was 46.4% and 20% respectively.[4,5,6]

The general female preponderance may be related to factors like oral habits, deficiency states of iron and vitamin B complex in Indian women.[3]

Worldwide estimates in 1996 indicate that 2.5 million people were affected by the disease.In 2002, the statistics for OSF from the Indian continent alone was about 5 million people (0.5% of the population of India).[4,5,6]

In an epidemiological study on oral cancer and precancerous lesions in a rural Indian population, the malignant transformation rate of OSMF was 7.6% over a 17-year period observation.[5,6]

ETIOLOGY

It is multifactorial. The most common factor that has been implicated in the development of OSMF is chewing areca nut.[1,2,3]

ARECANUT: It contains alkaloids arecoline, arecaidine, guvacine , guvacoline which if consumed for longer duration and frequencies is responsible for causing addiction, leading to OSMF. Commercial freeze dried products(pan masala, Guthka, mawa) have high concentrate of areca nut per chew .[3]

Nicotine in tobacco acts synergistically on cytotoxicity induced by arecoline , thereby increasing vulnerability of buccal mucosal fibroblasts to damage and increase collagen production upto 70%.[3]

Gutka contains fine grains of areca nut , which besides causing mechanical injury to oral tissues, also allow ground tobacco to adhere to the traumatized mucosa, leading to morphological changes and membrane damage , and also causes cross links.[3]

Chillies : It 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. A hypersensitivity reaction to chillies is believed to contribute to OSMF. The frequent intolerance to spicy food, vesiculation following the intake of food laced with chillies had led to the hypothesis.[3,5]

Nutritional deficiency: Vit A, C, B complex has been suspected in cases of OSMF. The resultant atrophic oral mucosa is more susceptible to the effects of chilies & betel nuts.

Rajendran et al (1994) 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 Precipitation by defective nutrition due to impaired food intake in advanced cases , may be effect rather than cause of the disease. [3]

Ramanathan (1981) observed prolonged iron and vitamin B complexed deficiency in OSF patients and hypothesized that OSF could be the Asian version of sideropenic dysphagia.[3]

Genetic susceptibility : Patients with OSMF have increased frequencies of HLA-DR3, -A10 and –B7.[3,6]

Immunological : Raised levels of serum IgA, IgG and IgM suggests antigenic stimulus in absence of any infection. Eosinophilia, gammoglobulinaemia, high mast cell response are noted in early stages.[3]

Auto immune disorder: Circulating autoantibodies are also present in some cases(Canniff et al, 1985). Female predilection, age of onset, alteration in serum immunoglobulins autoantibodies such as Antigastric parietal cell antibody(38%), Anti thyroid microsomal (23%), Anti nuclear (8%), Anti reticulin (4%), Anti smooth muscle (4%) forms the basis for being an auto immune disorder.[3]

PATHOGENESIS

Increased collagen production, reduced collagen degradation ,Nitrosation of arecoline (areca nut alkaloids) leads to formation of areca nut specific nitrosamine such as Nitrosoguvacoline , Nitrosoguvacine, 3-methyl nitrosominopropionitrile resulting in Glycogen depletion .[3](illustration 1)

Fibrogenic cytokines (illustration 2)

TGF β : It's the main trigger factor for increased collagen production and decreased collagen degradation. Studies have shown that connective tissue growth factor (CTGF) is required for increased ECM production. TGF β induces fibrotic tissue formation, CTGF maintains fibrosis.[3]

Collagen related genes: Ingredients in the quid alter collagen related genes**.** The genes CoL1A2, COL3A1,CoL6A1, COL6A3 and COL7A1 have been identified as definite TGF-β targets.[3]

Transcriptional activation of procollagen genes by TGF-β (illustration 3).

Due to slaked lime, pH of saliva changes from neutral to alkaline(9.9). Areca nut ingredients release ROS under alkaline conditions.[3]

Role of ROS : Auto oxidation of arecanut poly phenols (Tannins, catechins) also lead to production of ROS. Tumor initiation occurs by inducing gene mutation. ROS attacks salivary proteins and oral mucosa, structural change in mucosa occurs due to easy penetration of arecanut ingredients. Inflammatory cells are increased hence release of ROS which leads to mutation of adjacent cells and tumor promotion occurs.[3,7]

ROLE OF FLAVANOIDS (TANNINS, CATECHINS) IN ARECA NUT : Flavanoids enhances the crosslinking of collagen fibres. Catechin can raise LOX activity. Catechin might be oxidatively converted to quinones and hence might resemble lysine tyrosyl Quinone(LTQ) , which is a cofactor for LOX activity .Tannins, catechins inhibit collagenases. Combined effect of arecoline and tannins results in increased collagen production and reduced degradation. Type III collagen gets replaced by Type I collagen . Excess alpha 1(I)chains relative to alpha 2(I)

chains. Copper in nut results in fibrosis. Enzyme lysyl oxidase is upregulated leading to collagen synthesis and its crosslinkage.[3,7,8]

Fibroblasts from OSF patients & controls were incubated with collagen beads – proportion of phagocytic cells to be 35% and 75% respectively. Disruption of equilibrium between matrix metalloproteinases (MMP) and tissue inhibitor of matrix metalloproteinases (TIMP) occur.In OSF fibroblasts, cell doubling time was 3.2 days while 3.6 days for normal fibroblasts. OSF fibroblasts grew in 5 days compared to 6 days for normal.[3]

Inhibition of collagen phagocytosis were noted in OSMF Patients. OSF fibroblasts produce more TIMP. Arecoline MMP- 2 secretion , TIMP – 1 levels ,COX-2 Expression. The formation of COX 2 parallels the increase in prostaglandin production after stimulaton with tumor promoters. It plays an important role in inflammatory diseases, important in carcinogenesis. In a study it was observed that stimulated buccal mucosal fibroblasts by arecoline expressed high levels of COX2.[3,8]

EFFECT OF BETEL QUID ON

A) CELL MEDIATED IMMUNITY(CMI) PGE2

Powerful immuno suppressor which can induce CD4+ helper Th2 lymphocytes to synthesize immunosuppressive cytokines (IL-4, IL-5,IL-6, IL-10, IL-13). Also inhibits IL-2 production and IL-2 receptor expression by cytotoxic T Lymphocytes. PGE2, IL-6 , GM-CSF can also reduce Major histocompatibity (MHC) molecule expression.[3,9]

b) GENETICS

Sister Chromatid exchange(SCE) involve breakage of both DNA strands, followed by an exchange of whole DNA duplexes. This occurs during S phase and is efficiently induced by mutagens that form DNA adducts or that interfere with DNA replication. The formation of SCEs has been correlated with recombinational repair.[3]

CLINICAL FEATURES

OSMF is diagnosed on clinical criteria including mucosal blanching, burning sensation, and the presence of characteristic fibrous bands and is associated with gradual inability to open the mouth.Onset is insidious, over two to five years.[1-3]

Location: Most frequently affected locations are buccal mucosa , retromolar areas,soft palate, palatal fauces, uvula, tongue, labial mucosa. OSF originates from the posterior part of the oral cavity and subsequently involves the anterior locations.

Early OSMF/ Prodromal symptoms

Burning sensation to spicy foods . Appearance of blisters especially on the palate. Excessive salivation, defective gustatory sensation. Dryness of mouth. The presence of vesicles or a history of vesicle formation is reported in 32% of the cases. These vesicles are small and subepithelial; they rupture easily because of the masticatory trauma.

Often, there is a history of vesiculation following the intake of spicy food, suggesting an allergic reaction to spicy food and/or areca nut.

22% of OSF cases have reported of Petechiae (Rajendran, 1994) ,Mostly on tongue followed by labial and buccal mucosa, Part of a vascular response due to hypersensitivity of the oral mucosa towards arecanut products. They do not represent a hematologic disorder; they occur due to the loss of connective tissue support to the juxtaepithelial vasculature, leading to their dilatation and the extravasation of blood into the tissue. The petechiae are transient in nature, and no specific treatment is necessary. Patients with submucous fibrosis often (43%) complain of ulceration which is more marked in advanced cases.[4]

ADVANCED OSMF

Mucosa becomes blanched , opaque (marble-like appearance of the oral mucosa) .It can be Localised, diffuse, reticular. Palpable fibrous bands in buccal mucosa run in a vertical direction.

Pain in the areas where submucosal fibrotic bands are developing when palpated is a useful clinical test.

Fibrosis extending to pharynx, esophagus lead to dysphagia. (due to subepithelial fibrosis and atrophy of underlying muscle bundles in upper third of esophagus)

Referred pain in ears(due to fibrosis induced obstruction of Eustachian tubes and muscle fatigue leads to lack of coordination of opening and closing muscles, derangement of TMJ and referred pain finally to ears, TMJ region), nasal voice in some patients are noted.[4]

Various stagings have been given . 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

CLASSIFIACTION By Khanna JN, Dave R(1995)

Group I (Very early)

Group 2 (Early)

Group 3 (moderately advanced)

Group 4 A (advanced)

Group 4 B (advanced with premalignant , malignant changes)

Histopathologically: In early stage :Fine fibrillar collagen**,** marked edema, large fibroblasts, dilated and congested blood vessels, Inflammatory infiltrates (PMNs and eosinophils) are found ,epithelium normal with mild hyperplasia.

In moderately advanced stage: Juxta epithelial hyalinization. Thickened collagen bundles. Blood vessels dilated and congested. Moderate numbers of fibroblasts. Inflammatory cells (lymphocytes, eosinophils, and plasma cells). Flattening and shortening of rete ridges are noted.

In advanced stage**:** Juxtaepithelial hyalinization. Thickened collagen bundles separated by residual edema. Blood vessels are constricted. Mature fibroblasts with scanty cytoplasm. Inflammatory cells (lymphocytes, plasma cells). Epithelium atrophic. Loss of rete rigdes are noted.

In malignant transformed cases : Hyalinized collagen eliminating evidence of individual bundles. Extensive fibrosis. Obilteration of vessels and elimination of melanocytes are noted . Absence of fibroblasts. Total loss of rete pegs. Atypia can be seen.

DIFFERENTIAL DIAGNOSIS FOR OSMF includes Oral manifestations of Scleroderma**,** Iron Deficiency Anemia**,** Reticular lichen planus **,**Homogeneous leukoplakia .

PRECANCEROUS POTENTIAL

The precancerous nature of OSMF was first described by Paymaster in 1956 .Pindborg in 1972 had put forward five criteria to prove OSMF precancerous.Epithelial dysplasia in OSF tissues appeared to vary from 7 to 26% .Malignant transformation rate range from 7 to 13% . Incidence of 8 % approximately over 10 year period is noted.[10]

INVESTIGATIONS

Definitive diagnosis : biopsy(in suspicious areas for malignancy)

Hematological investigations :Deficiency of Vitamin B 12, folate and iron, Increased ESR, anemia, eosinophilia, increase in gammaglobulin ,decrease in serum iron, raise in serum mucoproteins mucopolysacrides ,alteration in serum copper and serum zinc.[2]

Silver binding nucleolar organizer region proteins (AgNOR) a cytological test indicative of proliferative status of cells can be used. It was found that pooled mean Ag NOR in clinically advanced OSF was higher than in moderately advanced cases.[2]

Cytogenetics : Chromosomal instability has long been associated with the neoplastic process and the quantitative assay of sister chromatid exchange provides an easy, rapid and sensitive method for studying DNA instability.[2,11]

Micronucleus test (MN test): An early diagnostic test would be highly beneficial to check the progress of OSMF to squamous cell carcinoma.

The variations in the micronucleated cells may be attributed to the factors like ingredients in the quid, the number of quids per day and different lifestyles, gender,age and food habits.[2]

MANAGEMENT

All patients should be biopsed (include areas clinically suspicious for malignancy). Reduction or even elimination of the habit of areca nut chewing is an important preventive measure. Patients should be adviced to maintain good oral hygiene and to reduce the consumption of spicy foods and red chillies. Removal of third molars in some patients, Rounding off sharp tooth, if any can prevent from constant trauma.

Medical management can range from use of Corticosteroids, Antioxidants , Ant fibrotic interferon γ , Placental extract, Curcumin, Oral zinc Therapy, Immune milk, Enzymes, Vasodilators, Vitamins and Minerals, Copper Chelators to Physiotherapy.[12-15]

Conclusion

Presently intralesional corticosteroids hyluronidase is the mainstay of the therapy.Gamma interferon can also been used.Combination therapy are more useful. Prevention is better than cure hence stoping the usage of tobacco is must.

REFERENCES

1. Greenberg MS, Glick M. Burket's Oral medicine: diagnosis and treatment.11th ed. Hamilton ,Ontario: B.C.DeckerInc; p.88-89

2. Shafer WG, Hine MK, Levy BMA. Text book of oral pathology, 6th edition. Philadelphia :W.B Saunders company

3. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnkulasuriya S. Oral submucous fibrosis : review on aetiology and pathogenesis. Oral Oncol.2006 ;42(6):561-8.

4. Ahmad MS, Ali SA, Ali AS, Chaubey KK. Epidemiological and etiological study of oral submucous fibrosis among Gutkha chewers of Patna, Bihar, India. J Indian Soc Pedod Prev Dent 2006;24: 84-89 .

5. Javed F, Chotai M, Mehmood A, Almas K. Oral mucosal disorders associated with habitual gutka usage : a review. Oral surg Oral Med Oral Pathol Oral Radiol Endod. 2010 ;109:857-864.

6. Deng YT, Chen HM, Cheng SJ, Chiang CP. Aerocline stimulated connective tissue growth factor production in human buccal mucosal fibroblasts: Modulation by curcumin Oral oncology 2009; 45:e99-e105.

7. Jeng J.H, Chang M.C. Role of Areca nut in betel quid associated chemical carcinogenesis .Oral Oncology. 2001;37: 477-492 .

8. Tsai CH, Chou MY. The upregulation of cyclooxygenase -2 expression in human buccal mucosal fibroblasts by arecoline: a possible role in the pathogenesis of oral submucous fibrois. J of Oral Pathol Med .2003; 32: 146-53.

9. Chang MC, Chiang CP, Lin CL, Lee JJ, Hahn LJ,Jeng JH.Cell mediated immunity in head and Neck cancer: With special emphasis on betel quid chewing habit .Oral Oncol. 2005; 41(8): 757-775 .

10. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. Community Dent Oral Epidemiol. 1985; 13: 340–41.

11. Anila k, Kaveri H, Naikmasur VG.Comparative study of oral micro-nucleated cell frequency in oral submucous fibrosis patients and healthy individuals.J Clin Exp Dent. 2011;3(3):e201-6.

12. Jiang X, Hu J . Drug treatment of OSF: A review of literature. J Oral Maxillofac Surg .2009;67:1510-5.

13. SK Katharia, SP Singh, VK Kulshreshtha .The effects of placental extract in management of oral submucous fibrosis. Indian Journal of Pharmacology 1992; 24(3): 181-183.

14. A Kumar, SC Sharma, P Sharma, OM Chandra, KC Singhal, Nagar Amit. Beneficial effect of oral zinc in the treatment of Oral submucous fibrosis. Indian J of pharmacology 1991;23:236-241.

15. M F. Haque S. Meghji R. Nazir M. Interferon gamma may reverse OSMF. J of Oral Pathol Med 2001;30;12-21.

Illustration 1

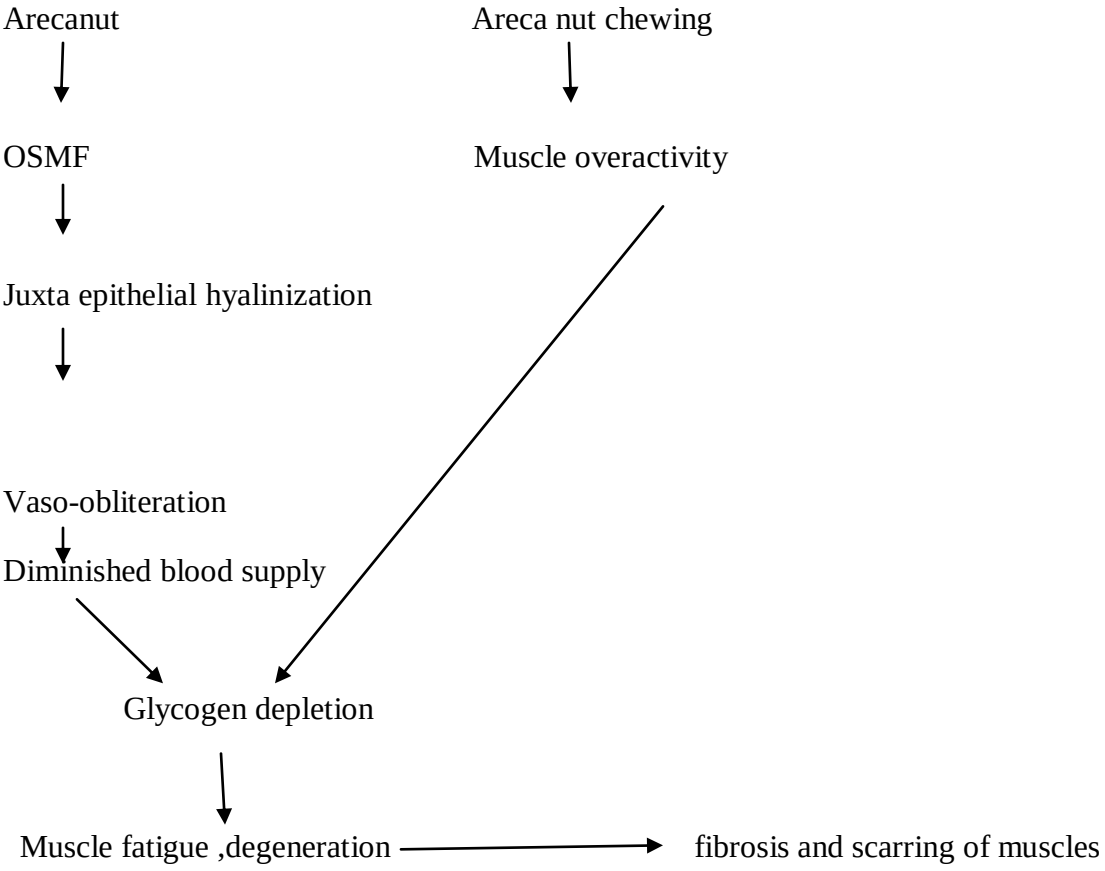

Illustration 2

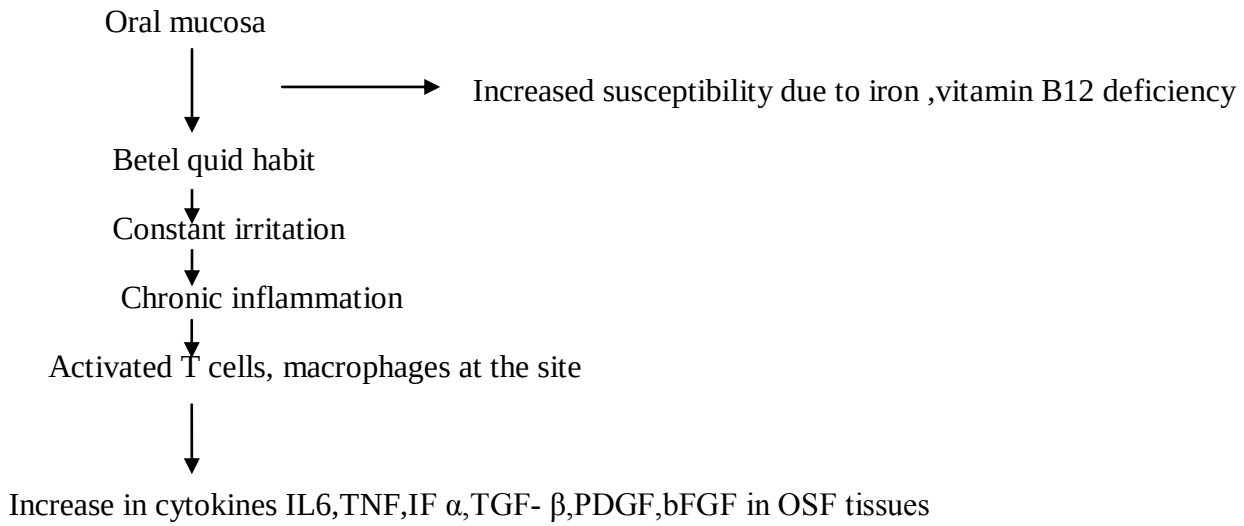

Illustration 3