Etiopathogenesis And Management Of Oral Submucous Fibrosis

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Abstract

Areca quid chewing related oral mucosal lesions are potential hazard to a large population worldwide. Commercially freeze dried products such as pan masala, Guthka and mawa have high concentration of areca nut per chew and appear to cause OSMF more rapidly than by self prepared conventional betel quid that contain smaller amounts of areca nut. These chemical appear to interfere with the molecular processes of deposition and or degradation of extracellular matrix molecules such as collagen, causing imbalance in the normal process. There may be reduced phagocytosis of collagen by fibroblasts, up or down regulation of copper dependent enzyme lysyl oxidase, matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases, increased levels of cytokines in the lamina propria. Current evidence implicates collagen related genes in suspectibility and pathogenesis of OSMF.

INTRODUCTION

Oral submucous fibrosis is a chronic insidious disease of the oral mucosa characterized by loss of mucosal elasticity and excessive fibrosis. It is always associated with juxta epithelial inflammation and progressive hyalinization of lamina propria. (1, 2, 3)

It was described by Schwartz in 1952 as a fibrosing condition of the mouth in 5 Indian women from Kenya for which he coined the term“Atrophica idiopathica tropica mucosae oris”. (4)

Oral Submucous fibrosis (OSMF) is a pre-cancerous condition predominantly seen among betel quid chewers. It has characteristic clinical presentation depending on the stage of the disease, but majority of patients with OSMF have intolerance to spicy food, roughness of oral mucosa, and different degrees of difficulty in opening the mouth.

OSMF is a well recognized potentially malignant condition in the oral cavity, & the transformation rate is as high as 7.6% over a period of ten year have been reported from India.(5)

The etiology of oral submucous fibrosis is multifactorial. The etiological factors include local irritants such as Chilli consumption, areca nut chewing, tobacco smoking and chewing. Systemic factors include anemia (iron deficiency), vitamin deficiencies (B-complex and folate) together with the malnourished state (protein deficiency), genetic predisposition to the disease and autoimmunity.

Areca nut use is considered to be most important etiological factor in pathogenesis OSMF. The basic constituent of areca nut is either raw or dried or boiled or baked. Diverse agents including lime, tobacco, catechu, cloves, saffaron, and leaf of piper betel leaves may form a part of formulation. (6)

The aim of the present review is to understand the etiology and pathogenesis of OSMF.

ETIOPATHOGENESIS

The etiology of Oral Submucous fibrosis is obscure, but several factors were put forward to suggest a multifactorial origin for this condition.

Consumption of Chillies

The suspicion that chilli is an etiologic agent arose on the basis of the ecologic observations. The inability of OSMF patients to tolerate chillies and spicy food also supported this hypothesis. Oral submucous fibrosis is found mostly among Indians and other population groups who use chillies to season their food, either in raw or dried or powered form at every meal.(7)

2. Nutritional deficiency:

Several investigators reported anemia, vitamin, protein and

iron deficiencies in OSMF patients. Vitamin A deficiency leads to hyperplasia and excessive keratinization of epithelium. Deficiency of vitamin B- 12, folate and iron can affect the integrity of the oral mucosa. (7)

Above observations did not establish an etiologic or contributory role for nutritional deficiency in OSMF. It is probable that the deficiency of these factors observed among OSMF patients may be secondary as most OSMF patients cannot tolerate spicy food, which is a normal family and community diet and the opening of the mouth in OSMF patients becomes progressively smaller. This functional impairment may affect normal food intake and lead to nutritional deficiencies. (8)

3. Tobacco:

One of the best defined etiologic agents in the pathogenesis of most oral lesions, including OSMF, is tobacco, although it usually is associated with the arecanut, used in making up the betel quid. No difference in the relative risk was observed when pan masala was chewed without and with tobacco. It implies that adding tobacco to the constituents did not have any significant role in the etiology of OSMF. (9, 10)

4. Genetic Susceptibility

Genetic basis alone cannot be etiologic factor in OSMF. In a study conducted by Canniff et al on immunological changes in oral submucous fibrosis, significantly elevated serum IgG levels among 30 submucous fibrosis patients of Asian origin in England was found.(11)[1] Since all the carcinogenic agents cause genetic alterations they proposed a multifactorial model in the pathogenesis of OSMF. (12)

5. Immunologic basis

a. Autoimmunity

The presence of HLA DR antigen indicates an auto immune basis of a disease. OSMF patients demonstrate antigens A24, DRB3 0202/3.These could be considered as markers in OSMF. (12)

b. Cell mediated and Humoral response

Increase in the number of T-lymphocytes and macrophages and a predominance of CD4 lymphocytes over CD8 lymphocytes was observed by Chiang CP et al. They concluded that cellular immune response may play an important role in pathogenesis of OSF. (13)

6. Areca Nut Chewing

Currently areca nut use is considered to be the most important etiological factor in OSMF. This observation has been made in case reports, case control studies, cross sectional studies and interventional studies. (14)

It is apparent that fibrosis and hyalinization of subepithelial tissues account for most of the clinical features encountered in this condition. Moreover, substantial amount of research on elucidating the etiology and pathogenesis appear to have been focused on changes in the extracellular matrix (ECM). It is logical to hypothesize that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in the development of the disease. (15) There are numerous biological pathways involved in the above processes and, it is likely that the normal regulatory mechanisms are either down regulated or up regulated at different stages of the disease. (16) Not a single case of OSMF was found without any chewing habits in a study conducted by Shah et al. (9) Pan Masala chewing was found to have the highest risk for developing OSMF.

ARECA NUT

It is the endosperm of the fruit of Areca catechu. It is orange – yellow in color. Areca nut for chewing is obtained by separating the seed from its pericarp.It is consumed in various ways. It is used fresh or dried and maybe cured before use by boiling, baking or roasting. In India alone 38 different combination of areca nut with tobacco have been documented. The number of patients with a paanmasala chewing habit (68.0%) was higher than the number of patients with betel nut (17.4%) or betel quid chewing habits (14.6%). The chewing of pan masala was associated with earlier presentation of OSF as compared to betel nut chewing. (17)

Quid has been defined as a substance or mixture of substances placed in the mouth or chewed and remaining in contact with the mucosa usually containing one or both of the two basic ingredients tobacco and/or areca nut in raw or any manufactured or processed form. The important flavonoid components in areca nut are tannins and catechins. These alkaloids undergo nitrosation and give rise to N-nitrosamine which might have cytotoxic effect on cells. (18)

MOLECULAR PATHOGENESIS

Over a period of time, due to persistent habit, chronic inflammation sets in at the site. Initial irritation leads to further atrophy and ulceration of the mucosa. It can thus be

considered that induction of oral mucosal inflammation by betel quid ingredients is a critical event in the pathogenesis of OSMF. Cytokines like interlukin-6 (IL-6), tumor necrosis factor (TNF), interferon- (INF-) etc. and growth factors like TGF- are synthesized at the site of inflammation.

TGF-1 is a key regulator of extra cellular matrix (ECM) assembly and remodeling. TGF- increases the collagen production and decreases the collagen degradation. (19)

COLLAGEN PRODUCTION PATHWAY

The three main events that are modulated by TGF-, which favors collagen production, are:

activation of procollagen genes

elevation of procollagen protienases levels

procollagen C-protienase (PCP)/ bone morphogenic protein 1 (BMP1) and

procollagen N-protienase (PNP)

Up-regulation of lysyl oxidase (LOX) activity.

COLLAGEN DEGRADATION PATHWAY

There are two main events modulated by TGF-, which decreases the collagen degradation:

Activation of tissue inhibitor of matrix metalloproteinase gene (TIMPs).

Activation of plasminogen activator inhibitor gene (PAI).

OSMF can be regarded as a disease of collagen metabolic disorder. Overall increased collagen production and decreased collagen degradation results in increased collagen deposition in oral tissue leading to fibrosis. This is further aggravated by the auto regulatory process of TGF-.

ROLE OF HEAT SHOCK PROTEINS (HSP) IN PATHOGENESIS OF OSF

HSP47, is a 47 kDa collagen-binding heat shock protein (HSP), which belongs to the serine protease inhibitor (serpin) super family containing a serpin signature sequence and specifically involved in the processing and quality control of collagen molecules.(18) Shung et al, first found that arecoline is capable of stimulating HSP47 mRNA expression in human buccal mucosa fibroblast (BMFs). (20) Consistently, study by Shung Fa, found that HSP47 mRNA was upregulated by arecoline in human BMFs. Thus, authors propose that the accumulation of collagen in oral mucosal connective tissue may be caused by a simultaneous effect on HSP47 by areca quid chewing.(16)

ROLE OF BASIC FIBROBALSTIC GROWTH FACTOR (BFGF) IN PATHOGENESIS OF OSF

The bFGF may either directly stimulate endothelial cell proliferation or facilitate VEGF-endothelial cell interaction through the modulation of endothelial cell integrin. The increased bFGF expressivity in endothelial cells along with fibroblasts in OSF cases was an important observation, as bFGF potentiates leukocyte recruitment to inflammation by enhancing endothelial adhesion molecule expression.(6)

MANAGEMENT

Various treatment strategies have been tried, such as topical & systemic steroids supplements of vitamins, minerals & micronutrients (Vitamin A, B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium), use of enzymes, repeated dilatations with physical devices & surgery. The mainstay of the management is reduction or even quitting the habit of aracenut chewing. Local & systemic application of glucocorticoids, placental extracts & immunomodulators are most commonly used as they suppress the inflammatory reaction, decrease collagen formation.

Other treatment regimes such as Lycopene 6 to 8 mg twice a day for 2 months, Pentoxyfilline 400 mg 3 times a day for 7 months, Interferon gamma Intralesional injection of interferon gamma (0.01– 10.0 U/mL) 3 times a day for 6 months, Steroids Submucosal injections twice a week in multiple sites for 3 months. Steroids Topical for 3 months, Placental extracts Turmeric30 Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months, Chymotripsin, hyaluronidase and dexamethasone31 Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks have also been suggested. (21) When mouth opening is severely limited surgical interventions are required.

Surgical approach includes submucosal resection of fibrotic bands and myotomy. (7) After fibrotic bands resection, reconstruction can be done by using pedicled buccal pad of fat, tongue flap, superficial temporal flap, nasolabial flap and forearm flap. Alternative procedures, such as physiotherapy, local heat therapy, mouth opening exercises using acrylic block and ice cream sticks, have also been tried with variable rates of success.

CONCLUSION

Evidences suggests that OSMF is multi-factorial, with certain effects on specific subpopulations of fibroblasts, genetic predisposition and molecular mechanisms (Cytokines and Growth factors), which could render the oral mucosa more susceptible to chronic inflammatory changes on exposure to carcinogens. However, the relationship between areca nut and OSMF is well established from epidemiological studies. The chemical constituents of areca nut can stimulate fibroblast proliferation leading to collagen synthesis. Apart from this, these extracts also have the capability to stabilize the collagen fibrils and make it resistant to enzymatic degradation.

Molecular pathogenesis suggests the role of growth factors such as transforming growth factor (TGF-b), connective tissue growth factor (CTGF) and basic fibroblastic growth factor (b-FGF). TGF-b may play an important role in inducing fibrotic tissue formation, while connective tissue growth factor (CTGF) is important in maintaining fibrosis. Arecoline stimulates CTGF production in buccal mucosal fibroblasts (BMF). b-FGF may directly stimulate endothelial cell proliferation & modulate fibroblast properties independently.

Depending on the extent of oral involvement, management consists of a combination of the medicinal and surgical treatment.

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