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REVIEW ARTICLE **OPEN ACCESS**

A contemporary narrative review on Oral Sub-Mucous fibrosis with etiopathogenesis and clinical features

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ABSTRACT

Oral submucous fibrosis (OSMF), a known precursor to oral precancer, is characterized by abnormal deposition of collagen. It is a potentially malignant disorder that was described by Schwartz in the year 1952, and a decade later by Pindborg, in the year 1966 as a prolonged sneaky destruction of the oral cavity, often involved with the pharynx and the upper esophagous region. However, several studies have reported the apparent divergences in these characteristics between the groups of patients pave a way to raise the question whether OSMF to be considered as one, or more than one disease.

KEY WORDS: *Submucous fibrosis; tobacco; areca nuts; tannins; collagenase*

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INTRODUCTION

Oral sub-mucous fibrosis (OSMF), a known precursor to oral pre-cancer, is characterized by abnormal deposition of collagen. It was termed as potentially malignant disorder based on the observational output from at least five Indian women came from Kenya made on that was described by Schwartz in the year 1952, where he termed it as "Atropia idiopathica mucosae oris. Subsequently a decade later by Pindborg, in the year 1966 as a prolonged sneaky destruction of the oral cavity, often involved with the pharynx and the upper esophagous region [1]. OSMF will also reflected as decrease in the movement and depapillation of the tongue, along with various other ailments related to oral cavity [2-4]. In addition, it is also termed as diffuse oral submocus fibrosis, idiopathic palatal fibrosis, sclerosing stomatitis and juxta-epithelial fibrosis [5-7]. However, several studies have reported the apparent divergences in these characteristics between the groups of patients pave a way to raise the question whether OSMF to be considered as one, or more than one disease. As per the definition of World Health Organization (WHO), an oral precancerous condition that is in line with the characteristics of OSMF [8].

EPIDEMIOLOGY

In spite of the rapid growth in the both diagnosis and treatment, it's reported that the rate of malignant transformation of OSMF to oral squamous cell carcinoma (OSCC) ranges between 7.0 and 13% [9]. Furthermore the mortality rate of this disease is also reported as highly significant [10]. Worldwide epidemiological studies shown that the number of OSMF was estimated to be >5 million patients globally [11-12]. Several studies have also reported that the incidence of OSMF differes with ethinicity and region and is also closely associated with the diet, habits, and culture [13-15]. Although many case finding studies have been conducted word wide, it is recorded that India has the greatest number of OSMF patients along with Taiwan and other Asian countries as well [16-17]. Quite interestingly, in India, women (1.2 – 4.6%) are more often affected with OSMF than men (0.2 – 2.3%) with a broad range of 11 to 60 y of age [18-20], whereas it is opposite for the other regions.

ETIOLOGY

Even though no clear data is available till date regarding the etiology of OSMF, several of the ideas have been resulted from the already available clinical and epidemiological data. Mostly irritant substances that

can act on the mucosa and chronic iron and/or vitamin B complex deficiencies as considered to be the two common pre-conditioning etiologies. Similar diseases related to fibrosis involving the basal lamina and its underlying muscles are termed as endomyocardial fibrosis. The major systematic factors are conditions including chronic deficiency of iron and vitamin B-complex, anaemia, and genetic predisposition[8] Moreover, extensive usage of the commercially available single-use packets of tobacco and areca nut products called as Gutkha is reported to increase the incidence of OSMF[17]. Earlier studies have reported that an estimate of about 10 – 20% of global population is consuming areca nut in a wide variety of formulations [21-22]. Additionally, having the habits of smokeless tobacco use, high consumption of chilies and copper containing food and beverages, low levels of serum proteins due to malnutrition, anemia and genetic predisposition.

PATHOGENESIS

The role of the constituents of areca nut in the pathogenesis of OSMF has been studied in detail over the last two decades. It is apparent that fibrosis and hyalinization of sub epithelial tissues account for most of the clinical features related to OSMF. Moreover, substantial amount of research on elucidating the aetiology and pathogenesis appear to have been focused on changes in the extracellular matrix (ECM).

Table 2: The most common biological pathways that are involved in the development of OSMF are:

1	Areca alkaloids causing fibroblast proliferation and increased collagen synthesis
2	Stabilization of collagen structure by tannins (and catachins polyphenols)
3	Copper in areca nut and fibrosis
4	Upregulation of cyclo-oxygenase-2 (Cox-2)
5	Fibrogenic cytokines
6	Genetic polymorphisms predisposing to OSF
7	Inhibition of collagen phagocytosis
8	Stabilization of extracellular matrix
9	Collagen-related genes

Areca alkaloids causing fibroblast proliferation and increased collagen synthesis

The fibroblastic proliferation theory and increase in collagen content, that could be we demonstrable in human fibroblasts, has been well studied in vitro and reported [23]. In addition, it was evident that the correlation between the hydrolysis rates of different esters and the extent to which they stimulate collagen synthesis, suggest that hydrolysis of arecoline in to arecaidine is necessary before fibroblast stimulation can occur. This suggests that arecaidine is the active metabolite in fibroblast stimulation. It was also evidenced an elevation in the rate of collagen synthesis by the arecoline in OSMF fibroblast cultures compared to normal fibroblasts [24].

Stabilization of collagen structure by tannins (and catachins polyphenols)

One of the mechanisms that can lead to increased fibrosis is by reduced degradation of collagen by forming a more stable collagen structure. Treatment of reconstituted collagen fibrils and pieces of rat dermis with crude extracts of the nut or purified tannins from areca nut increased their resistance to both human and bacterial collagenases in a concentration- dependent manner. This evidence was also supported by another study which showed that the ability of large quantities of tannin present in areca nut reduced collagen degradation by inhibiting collagenases and proposed the basis for fibrosis by increasing the production of collagen and decreasing the degradation is reported to achieved by the combinatorial effects of tannin and arecoline [25].

Copper in areca nut and fibrosis

Areca nut is reported to have maximum amount of copper content that too the levels of soluble copper in saliva may rise in volunteers who chew areca quid. The same group showed that the oral mucosa of areca nut chewers had significantly raised levels of copper when compared with the control subjects [26]. The enzyme lysyl oxidase is found to be upregulated in OSMF. This is a copper dependent enzyme and plays a key role in collagen synthesis and its cross linkage. Copper as a possible mediator of fibrosis is reported

earlier by demonstrating the upregulation of one or several enzymes in OSMF biopsies and fibroblasts compared to normal fibroblasts grown in culture.

Upregulation of cyclo-oxygenase (Cox-2)

It is quite well known that somewhere or other inflammatory changes are commonly associated with OSMF. Prostaglandin is one of the main inflammatory mediators and its production is controlled by various enzymes such as cyclo-oxygenase (COX). Biopsies from buccal mucosa of OSMF cases and from controls were stained for COX-2 by immunohistochemistry and showed an increased expression of COX-2 even in moderate fibrosis that would disappear in advanced fibrosis. This finding is compatible with the histology of the disease as there is lack of inflammation in the advanced disease.

Fibrogenic cytokines

It is also reported that changes, caused by external stimuli including areca nut, in cytokine secretion such as endothelin and TGF b-1 could also contribute for the development of the disease along with high levels of cytokines in lamina propria. Furthermore, it was also demonstrated that s increased levels of proinflammatory cytokines and reduced anti-fibrotic IFN-c in patients with the disease. These may be important events in the pathogenesis of OSMF [27]. Subsequently, the same group using immunohistochemistry showed little or no expression of IFN-c expression in biopsies from OSMF tissues compared with normal controls. This finding is interesting as the same phenomenon is evident in systemic sclerosis. Up-regulation of pro-inflammatory cytokines such as interleukin 1 and 6 were clearly evident. The most important finding in the above study was the demonstration of increased expression of fibrogenic cytokines namely TGF-b, platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) in OSF tissues compared to normal. These observations may suggest that the disease process in OSF may be an altered version of wound healing as our recent findings show the maturation of granulation tissue are quite very similar to the various ECM molecules as well.

Genetic polymorphisms predisposing to OSMF

It is reported that polymorphisms on the TNF- α coding as potential risk factor for OSMF. A study of 809 patients with OSMF has revealed that the high production allele TNF2, to be significantly lower compared to an areca chewing control group [27]. TNF-α is known to stimulate fibroblastic proliferation in vitro providing evidence for an active role for TNF-α in the pathogenesis of OSMF. In another study has also reported that phenotype frequency of allele A6 of MICA in test subjects was significantly higher than the controls. Some genotypes of cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T-lymphocyte activation seems to have a susceptibility for various autoimmune diseases. Interestingly, the G allele at position +49 of exon 1 was found to be significantly associated with OSMF compared with controls. Whether the above findings drive the pathogenesis of OSMF towards an autoimmune basis needs to be further investigated [28].

Inhibition of collagen phagocytosis

Degradation of collagen by fibroblast phagocytosis is an important pathway of physiological remodeling of the extracellular matrix (ECM) in connective tissue. As OSMF shows a gross imbalance in ECM remodeling, this putative mechanism, *in vitro* studies by using the fibroblasts from OSMF patients and controls incubated with collagen beads showed that the proportion of phagocytic cells to be 35% and 75% respectively. After incubation with fibronectin coated beads, normal fibroblasts exhibited 70% internalization whilst OSMF fibroblast revealed 22% internalization. They also showed that the reduction of phagocytic cells was strongly related to the arecoline levels in fibroblast culture [29]. Interestingly, there was a dose-dependent enhancement of phagocytic cells when the cultures were treated with corticosteroids. In another study, reduced collagen phagocytosis by fibroblasts was inversely dose-dependent to the levels of arecoline and nicotine [30].

Stabilization of extracellular matrix

Disruption on the balance status between the matrix metalloproteinases (MMPs) and other tissue inhibtors of matrix metalloproteinases (TIMPs) could result as continuous dispotion of extracellular matrix. When normal (control) fibroblasts and fibroblasts from OSMF patients were subjected to arecoline and arecadine in culture, expression of TIMP-1 mRNA in OSMF fibroblasts was found to be higher that signifies the increased expression of TIMP-1 at transcriptional level [31]. Similarly, it was also reported that the main gelatinolytic proteins secreted by buccal fibroblasts (MMP-2 and MMP-9) are found in minimal amounts in diseased tissues. The study further showed that arecoline reduced the MMP-2 secretion and increased the TIMP-1 levels resulting in increased deposition of collagen in the extracellular matrix [32].

Collagen-related genes

Collegen-related genes play an important role in the homeostasis of collagen in the body. Different (types of) enzymes such as collagenases and lysyl oxidase together with cytokines, namely TGF-β have been implicated in this context. Earlier studies shown that the ingredients present quid could have significant

role in causing alteration of collagen-related genes [33]. Evidences have also shown that the most significant target of TGF-β are the collagenase 1A2, collagenase 3A2, collagenase 6A1, collagenase 6A3 and collagenase 7A1 genes that can cause the fibroblastic changes during the early stage of the disease. Furthermore, transcriptional activation of the genes during the transcription of procollagen genes by TGF-β could significantly contribution in increasing the levels of collagen in OSMF. It is also evidenced that genotypes associated with highest OSF risk for collagen 1A1, collagen 1A2, collagenase-1, TGF-β1, lysyl oxidase and cystanin C were CC, AA, TT, CC, AA, and AA, respectively in the low-exposure group whilst TT, BB, AA, CC, GG, and AA, respectively for the high-exposure group. Collagen-related genes are considered to be the highly susceptible pathogenic factors of OSMF.

CLINICAL FEATURES

Significant correlation between the sailent clinical features of OSMF have been reported and shown the 2 to 5 years period as insidious for the.

Prodromal Symptoms

Normally, the exacerbation intervals may differ somewhere between three to 12 months period. Clinical manifestation during the early stages of disease includes focal vascular dilatations results as petechiae [34-35]. It might be due to the mucosal hypersensitivity towards the external irritants such as chillies and/or areca nuts. Approximately 22% of the OSMF cases reported with mostly on the tongue along with labila and buccal mucosa would not show any signs of blood dyscrasias of systemic disorders.

Advanced Stage

Despite the palate ad faucial pillars are the primarily involed sites during the progression of OSMF, it could also be identified that blanched and slightly opaque oral mucosa along with whit fibrous bands and thereby affects the buccal mucosa and lips even in the early stages. Normally asymptomatic slight whitish area on the soft palate and the dense fibrosis due to fixation and shortening of the uvula and soft palate could be differentiated by means of the fibrous deposit observed. Furthermore, deposition of the fibrous tissue on to the faucial pillars might differs from slight submucosal accumulation to a dense fibrosis that would deeply extents into the pillars tonsils' strangulation. Such formed dense fibrosis could normally involve the surrounding pterygomandibular raphe and thereby causes differing degrees of trismus. However, several factors are involved in causing the site and extent of trismus such as integrity of the anatomical and physiological musculature those are important for the degree of mouth opening. Electronmicroscopical observations could clearly demonstrate the significance of muscle degeneration during OSMF. The pterygomandibular raphe is also considered to be of equally important where it is one of the common sites of accentuate the extent of trismus. Period of the disease of an affected individuals based on the subjective determination of signs and symptoms is also termed to be an important factor [36-37]. Perceptiveness of oral symptoms including persistent and/or recurrent stomatitis and glossitis are considered as other important factors while recording the extent of mouth opening. Eventually there are chances for the spread of fibrosis to the pharynx and even down to the pyriform fossae as well. Identification of a circular band around the entire rimaoris upon palpation are the changes quite normally noticed in the lower lip. Stiffening of specific areas of the mucosa causing difficulty in mouth opening, incapability of whistle and/or blowing out a candle and difficulty in swallowing are some of the few complaints of the patients with fibrosis progression reported by other researchers. Patients might also experience denoted pain in the ear, and nasal voice as later signs in some patients with involvement of pharynx during fibrosis.

Precancerous nature of OSMF

Paymaster was the one who proposed the precancerous nature of OSMF, based on his observations in one third of the OSMF patients showing slow growth and eventual development of squamous cell carcinoma [38]. Further it was also emphasized by various other researchers and scientist based on the epidemiological data where the prevalence frequency of malignancy in patients with OMFS was observed to be 3% to 6%.

CONCLUSION

Global surveys reveal that the frequency of oral cancer among all cancers in is about 7/0 to 13%. Even though many case finding studies have been conducted word wide, it is recorded that India has the greatest number of OSMF patients along with Taiwan and other Asian countries as well. However, in India, women (1.2 – 4.6%) are more often affected with OSMF than men (0.2 – 2.3%) with a broad range of 11 to 60 y of age. Overall many of the studies worldwide have reported that to prevent OMSF and potential malignancy quitting betel nut chewing could be the best strategy. Despite the strategy to prevent OMSF clinical diagnosis would ensures that patients have normal oral functions and thereby not

only to improve the quality of life but also for clinicians to develop and apply molecular predictive biomarkers to formulate a standard guidelines for the treatment of OSMF.

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