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RESEARCH ARTICLE

ETIOPATHOGENESIS AND CLINICAL MANIFESTATIONS OF ORAL SUBMUCOUS FIBROSIS, A POTENTIALLY MALIGNANT DISORDER: AN UPDATE

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ABSTRACT

Oral Submucous Fibrosis (OSMF) is a chronic, insidious, irreversible, progressive, scarring and debilitating potentially malignant disorder (PMD) involving the oropharynx and the upper part of the esophagus. It is characterized by juxta-epithelial inflammatory reaction and progressive fibrosis of lamina propria, leading to blanching, stiffness and rigidity of oral mucosa, and further trismus. OSMF is frequently seen in countries of south and south-east asia. The etiology of this disease is multifactorial, but studies have confirmed its strong association with chewing of arecanut and its commercially available products. The molecular pathogenesis of OSMF is unclear and complex. Hence, the authors through this article are proposing additional information to the existing pathogenesis of OSMF and have made an attempt to simplify the same. This article also highlights the new clinical manifestations of OSMF, observed by the authors.

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INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a chronic, insidious, irreversible, slowly progressive, scarring and debilitating potentially malignant disorder (PMD) involving the oropharynx and the upper part of the esophagus. The similar type of condition was described as *Vidari* by Sushruta, the renowned Indian physician in early 600 B.C. OSMF is also reffered to as *atropica idiopathica mucosae oris, diffuse oral submucous fibrosis, idiopathic scleroderma of the mouth, sclerosing stomatitis, idiopathic palatal fibrosis, juxtaepithelial fibrosis,* etc (More, 2012; Warnakulasuriya, 2007; Glick, ?; More, 2012; More, 2010 Rajendran, 1994 and Pindborg, 1966). This disorder was first reported by Schwartz in 1952, in five Indian women of African continent – Kenya (More, 2012).

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Subsequently, Oral Submucous Fibrosis was reported, studied or classified by various clinicians and researchers like Joshi SG (1953), Desa JV (1957), Pindborg JJ and Sirsat SM (1966), Agarwal GD (1971), Pindborg JJ (1989), Katharia (1992), Nagesh and Bailor (1993), Maher R (1996), Ranganathan K (2001), Rajendran R (2003), Kiran Kumar (2007), Tinky bose and Anita Balan (2007) and Chandramani More (2012) (More, 2012 and Glick, ?). OSMF is a collagen metabolic disorder of the oral cavity and oropharynx, characterized by fibroelastic changes and inflammation of the oral mucosa, leading to progressive inability to open the mouth, swallow or speak. These reactions may be because of either direct stimulation from arecanut or due to changes in tissue antigenicity that leads to an autoimmune response (Rajendran, 1994 and Gupta, 2015). The disease is predominantly seen in people of south asia and south-east asia – India, Bangladesh, Sri Lanka, Pakistan, Taiwan, Southern China, etc. where chewing of arecanut or its flavoured formulations is frequently practiced (More, 2012; More, 2012; Glick, ? and Pindborg, 1966). The rapid increase in the prevalence of this disease is due to an upsurge in the popularity of commercially available arecanut and tobacco preparations (gutkha, pan masala, mawa, etc.) in

Asian countries. Oral cancer is a key public health problem in Asian countries, where over 90% of the lesion arises from potentially malignant lesions like OSMF, Oral Leukoplakia, Oral Erythroplakia, Nicotina Stomatitis, etc (More, 2012; Glick, ?; More, 2010; Gupta, 2015; Jontell, 2008; Nigam, 2014). Discrepancies in the prevalence rate of OSMF are often noticed in different studies because of no uniformity in clinical criteria for diagnosis and differs geographically. The prevalence rate in India is about 0.2 to 6.42% and is higher in males (Jontell, 2008). Recent epidemiological data indicates that, the number of cases of OSMF has raised rapidly in India from an estimated 2, 50,000 cases in 1980 to an estimated 2.5 million cases in 2015 (Nigam, 2014; Nanavati, 2015; Tak, 2014). A significant variation in the prevalence of OSMF in other continents has been reported in Asian migrants of Europe, UK, USA, etc. Isolated cases among the non-asians have also been reported in the literature (Shah, 2012; Prabhu, 1993).

Etio-pathogenesis: The pathogenesis of the disease is not well established. The etiology is multifactorial, but chewing of Arecanut and its flavoured formulations are the main causative agents. The associated or supplementary factors which trigger the fibrosis are tobacco use, anemia, vitamin and protein deficiency, genetic and immunologic predisposition. It is now known that the arecanut alkaloids, especially arecoline, play a major role in the pathogenesis of OSMF by inducing collagen production and accumulation. Evidence suggests that the effect on specific subpopulations of fibroblasts, genetic predisposition and molecular mechanisms (Cytokines and Growth factors), renders the oral mucosa more susceptible to chronic inflammatory changes on exposure to carcinogens (Tak, 2014; Shah, 2012; Tilakaratne, 2006; Gupta, 2009; Khan, 2012; More, 2015 and Basoya, 2015).

Prime factor

- **Arecanut and its formulations:**

Arecanut, commonly called as betelnut, is an endosperm (nut/fruit) from tropical tree *Areca catechu Linnaeus*. It is considered as group 1 human carcinogen and is known to produce mutagenic and genotoxic effects on body tissues. It is the fourth commonly used psychoactive substance, chewed for digestion and as a stimulant (Shah, 2012 and Prabhu, 1993). The nut is used alone or added with different tobacco or non-tobacco substances to make different combinations [Table no. 1].The commercially available products of arecanut (ghutka, pan masala, mawa, flavoured supari, etc.) are strongly associated in the formation of OSMF, with the risk being the highest with ghutka. The nut also causes loss of appetite, insomnia, loss of concentration, dementia, staining of teeth etc. The nut majorly contains Alkaloids (*arecoline, arecaidine, guvacine, guvacoline*), Flavonoids (*tannins and catechins*) and Copper (Shahc, 2012; Tilakaratne, 2006; Khan, 2012; Rajendran, ?; Reddy, 2011; Ratheesh, 2015). Arecoline is the most abundant alkaloid. The arecoline and arecaidine stimulates fibro-genesis, by causing proliferation of fibroblast and gene expression, leading to increased collagen formation. These alkaloids undergo nitrosation to form N- nitrosamines which may have cytotoxic effects on cells. Arecaidine, which is produced by hydrolysis of arecoline, has marked effect on fibroblast stimulation. The slaked lime calcium hydroxide and /or catechu when added to arecanut in betel quid, mawa, pan masala, ghutka etc., facilitates hydrolysis of arecoline to arecaidine, making it freely available in the oral cavity thereby increasing stimulation of fibroblast. The target cells of arecanut are oral fibroblast/ myofibroblasts and keratinocytes. Among Flavonoids, tannins and catechins are the most important components in arecanut. Flavonoids have direct effect on collagen metabolism, increasing the cross linking of collagen fibers thereby leading to lysyl-oxidase (LOX) activity. This enzyme activity plays an important role in formation of insoluble collagen due to cross-linking. The process of cross-linking makes the collagen fibers resistant to proteolysis and increases the tensile strength and mechanical properties of the fibers. The LOX is an important enzyme to convert collagen fibers into a stabilized covalently cross-linked mature fibrillar form (Tak, 2014; Tilakaratne, 2006; Khan, 2012; Ratheesh, 2015; Pillai, 1992; Trivedy, 1999 and Trivedy, 2000), [Figure 1]. Arecanut has high Copper content, ranging from 205–535 nmol/g(mean 302 $\pm$ 92 nmol/g). (Trivedy, 1999 and Trivedy, 2000). Copper initiates functional activity and causes up-regulation of LOX enzyme leading to increase in insoluble collagen formation. The copper is incorporated in LOX, during its biosynthesis. The co-factor lysine tyrosyl quinone (LTQ) present in LOX is essential in the formation of cross-links in the collagen fibers. Copper plays a structural role in stabilizing the LTQ and in re-oxidizing the reduced enzyme for completion of the catalytic cycle. The chewing of arecanut for more than 10 minutes significantly increases soluble copper levels in oral fluids; thereby stimulating the fibro-genesis through up-regulation of LOX activity (Tak, 2014; Shah, 2012; Trivedy, 2000; Rooban, 2006 and Khan, 2012).

Supplementary factors

Tobacco: Tobacco is an addictive substance, used in various form- smokeless and smoking. It contains thousands of chemical compounds, out of which few are carcinogens, toxins and irritants to skin or mucosa. Tobacco is one of the important ingredient of commercially available products of Arecanut. It has proved that tobacco has no role in the formation of fibrosis, but because of presence of active carcinogens, tobacco helps in inducing carcinogenesis (More, 2012; Warnakulasuriya, 2007; Glick, ?; Prabhu, 1993).

Role of Minerals: The minerals like Iron, Copper, Zinc and other trace elements like K, Si, Ca, V, Cr, Ni, Mn, Br, Rb, Sr, Co and Pb, have no direct role in the formation of fibrosis but may help in creating the favourable environment at the tissue level (Reddy, 2011; Ratheesh, 2015; Pillai, 1992; Sinor, 2014) Iron, Copper and Zinc are biologically essential for normal development, growth and function of tissues. The presence of these elements can be demonstrated on serum analysis. These elements are essential for cellular metabolism and it gets altered during the pathogenesis of all premalignant and malignant lesions (Glick, 2012; Reddy, 2011; Pillai, 1992; Trivedy, 2000 and Rooban, 2006). Iron is utilized in high amount in fibrosis formation, there by leading to low levels of serum iron and heamoglobin. The low level affects the vascular channel formation causing decrease in mucosal vascularity. The serum Iron levels will be significantly decreased as the stage of disease increases, attributing the fact that iron is required for the synthesis of collagen, by the hydroxylation of proline and lysine. Deficiency of iron also causes defective healing and scarification, may be because of altered inflammatory response in the lamina propria.

Further, it causes decrease in the levels of cytochrome oxidase, leading to epithelial atrophy. The decreased level of serum zinc associated with the carcinogenesis may be due to increased utilization of zinc by tumor tissues, but the reason for the decreased level of serum zinc in OSF patients is not known (Rooban, 1993 Basoya, 2015; Ratheesh, 2015; Pillai, 1992; Shettar, 2010; Hosthor, 2014). Trace elements have been critically examined in etiology of various diseases, especially cancer. As micronutrient deficiencies are common in India and have been related to oral and upper aero-digestive tract cancers, it is considered necessary to study the impact of nutrients on oral premalignant lesions. Magnesium deficiency may trigger carcinogenesis by altering fidelity of DNA replication and increasing membrane permeability (Shettar, 2010; Hosthor, 2014).

Genetic and Immunologic role: Although oral submucous fibrosis is strongly influenced by arecanut chewing but, genetic factor plays a major role in deposition of collagen. There is significant increase in the frequency of human leukocyte antigen 10 (HLA10), DR3and DR7 in OSMF. This may be because of genetic susceptibility to the action of alkaloids and tannins. [23]The collagen related genes COL1A2, COL3A1, COL6A1, and COL6A3 are found to be associated with the progression of the disease. The polymorphism of gene coding for Tumor Necrosis Factor - β (TNF- β) is associated with OSMF, which in turn prevents collagen degradation. The Plasma fibrin degradation products are increased in connective tissue, causing excessive deposition of fibrin leading to restriction of mouth opening (Basoya, 2015 and Pillai, 1992). The connective tumor growth factor (TGF) is highly expressed in OSMF. Also Glutathione S- transferases (GSTs) is recorded at higher level in OSMF. The single nucleotide polymorphisms in Thr 241 Met - NAT2 A857G increases the risk of OSMF. The Matrix Metaloprotease 1 (MMP1) is increased due to chewing of Arecanut and its related commercial products. The polymorphism in MMP3 promoter, increases the susceptibility to develop OSMF (Pillai, 1992). The expression of heme oxygenase 1 gets elevated due to arecoline in fibroblast, Inflammatory cells and endothelial cells. (Basoya, 2015 and Pillai, 1992). There is high risk of OSMF in the development of oral malignancy. The circulating immune complexes (CIC) and the immunoglobulin contents are highly elevated in OSMF and oral malignancy. The Immunohistochemistry reveals presence of T-lymphocytes and macrophages in epithelium and sub-epithelial connective tissue with CD4+ to CD8+ lymphocyte ratio of 2.1:1. (Pillai, 1992). The immunologic or autoimmune role in OSMF is determined because of presence of various autoantibodies, circulating immune complexes and immunoglobulin contents. The altered auto-antigens released from arecanut ingredients and damaged cells may induce autoantibody production. The autoimmune disorder like scleroderma has complete similarity with OSMF, including the ultra-structural changes. The presence of Cytotoxic T-lymphocyte antigen 4 pleomorphism in OSMF suggests the role of autoimmune origin (Basoya, 2015; Ratheesh, 2015; Pillai, 1992; Trivedy, 2000; Rooban, 2006; Khan, 2006; Wollina, 2015). Thus, OSMF is a cause and effect disorder associated with arecanut habit, rather than a disease of genetic susceptibility (Basoya, 2015 and Ratheesh, 2015).

Molecular pathogenesis

The continuation of arecanut chewing habit for a long duration leads to chronic inflammation of oral mucosa, thereby leading to atrophy and ulceration. This feature becomes an important stage in the pathogenesis of OSMF. The cytokines are proteins that regulate immune and inflammatory responses. They regulate fibroblast functions, like proliferation, migration and matrix synthesis. These mediators regulate the initiation and progression of scarring in any fibrotic disease. The pro inflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is sufficient evidence that interlukin -1β (IL-1β), interlukin-6 (IL-6), interferon-α (INF-α), tumor necrosis factor- α (TNF-α) and tumor growth factor - β (TGF-β) are synthesized at the site of inflammation and are involved in the process of pathological pain (Tak, 2014; Prabhu, 1933; Trivedy, 2000; Khan, 2012; Wollina, 2015). The TGF-β plays an important role in extra cellular matrix formation thereby leading to increase in the collagen production and it decreases the collagen degradation.IL-6 is involved in proliferation of human fibroblast and up-regulates the fibroblast-ά 1 pro-collagen. TNF- α is a mediator with multiple functions, including the regulation of inflammatory reaction and transcriptions of collagen and collagenase (Tak, 2014; Wollina, 2015; Kiran, 2007; Shettar, 2010). The collagen production is modulated by tumor growth factor - β (TGF- β) through activation of procollagen genes, elevation of procollagen protienases levels and up-regulation of lysyl oxidase (LOX) activity; whereas the collagen degradation pathway is modulated by tumor growth factor - β (TGF- β) through activation of tissue inhibitor of matrix metalloproteinase gene (TIMPs) and plasminogen activator inhibitor gene (PAI). The insoluble form of collagen production is increased leading to decrease vascularity, thereby causing atrophy of epithelium, defective healing and scarification (More, 2012; Glick, ?; Tak, 2014; Shettar, 2010; Sinor, 1990). Various findings indicate the disease to be a consequence of disturbances in the homeostatic equilibrium between synthesis and degradation of extracellular matrix (ECM), wherein collagen forms a major component, and thus OSMF is considered as collagen metabolic disorder. Transforming growth factor – beta (TGF-beta) is a potent stimulator of production and deposition of the ECM. The development of OSMF is based on increased collagen synthesis or decreased collagen degradation. Various biological pathways are involved in both these processes and probably the normal regulatory mechanism is either, down regulated or up regulated at different stages of OSMF. The alkaloids and tannins have major role at this stage (Tak, 2014; Tilakaratne, 2006; Hosthor, 2014; Joshi, 1952). These chemicals interfere with the process of collagen deposition and/or degradation of extracellular matrix. It has been postulated that arecanut induces the development of OSMF by increasing levels of cytokines in the lamina propria. Recent evidence suggests collagen-related genes in the susceptibility and pathogenesis of OSMF (Tak, 2014). The condition is aggravated by the auto regulatory process of TGF-β, which is responsible for trigger for both the increased collagen production and decreased collagen degradation pathways. It is proved that OSMF undergoes inflammatory changes in atleast some stage of the disease. The cyclo-oxygenase-2 (COX-2) enzyme was expressed at higher level in moderate type of fibrosis but did not exist in severe type of fibrosis (Tak, 2014; Tilakaratne, 2006; More, 2010; Cox, 1996). The basic fibroblastic growth factor (bFGF) may stimulate endothelial cell proliferation or facilitate vascular endothelial growth factor (VEGF) – endothelial cell interaction through modulation of endothelial cell integrin or VEGF - receptor

expression (Tak, 2014; Basoya, 2015 and Ratheesh, 2015). The increased bFGF expression in endothelial cells along with fibroblasts in OSMF is an important observation, as bFGF potentiates leukocyte recruitment to inflammation by enhancing endothelial adhesion molecule expression. The endothelial cell and fibroblast dysfunction may be linked through the paracrine activity of soluble endothelial cell products (Tak, 2014; Basoya, 2015; Ratheesh, 2015; Taneja, 2011; Hazarey, 2007). The role of heat shock proteins (HSP) in pathogenesis of OSMF is obscure. It is found that arecoline stimulates HSP47 mRNA expression in human buccal mucosa fibroblast. HSP47 plays an important role in the synthesis, processing, and assembly of various collagens. The accumulation of collagen in the connective tissue may be because of simultaneous effect on HSP47 by betel quid chewing (Tak, 2014; Prabhu, 1993; Hazarey, 2007; Martin, ?). The above mechanism may explain the induction, maintenance and progression of fibrosis in OSMF, but the mechanism leading to carcinogenesis in this fibrotic oral mucosa is yet to be studied. The transformation of OSMF to Oral malignancy can be identified mainly through histopathology, at any stage of OSMF (Tak, 2014; Prabhu, 1993; Ratheesh, 2015; Hazarey, 2007; Van der Waal, 2009).

Clinical Manifestation: Oral submucous fibrosis affects mainly the young adults and middle aged individual, with peak incidence noted in 2nd to 4th decade of life. There is always a variation in gender distribution of OSMF geographically, although, the disease is more common in males with the ratio of 6:1.It involves buccal mucosa, labial mucosa, pterygo-mandibular raphe, anterior faucial pillars, hard and soft palate, pharynx, uvula, dorsal and ventral surface of tongue, floor of mouth, lips, gingiva and vestibule. [Figure 2]The brief symptoms and signs of this disease are mentioned in table no. 2 (More, 2012; Warnakulasuriya, 2007; Glick, ?; More, 2010 and Pindborg, 1966). The arecanut and its flavoured formulations [Figure 3]when chewed or sucked or placed in the mouth, the secretion or juices get mixed with saliva. This mixture will act as an irritant to the oral mucosa. The continuous irritation leads to the early mucosal changes like local or generalized erythema, vesicle formation, ulcerations, melanotic pigmentation and petechiae (More, 2012; Warnakulasuriya, 2007; Glick, ?; More, 2010; Gupta, 2015). On continuation of the habit, the oral mucosa undergoes transformation leading to blanching and initial formation of fibrosis, the hallmark of the diseases. The oral mucosa may also have brownish black pigmented patches. The connective tissue changes are progressive and continuous, because of functioning disorder of fibroblast. The oral mucosa will further undergo change at epithelial and connective tissue level. The affected oral mucosa becomes white or mottled/ marble like and leathery because of excessive and uncontrolled synthesis of collagen fibres in the connective tissue (More, 2012; Warnakulasuriya, 2007; Glick, ?; Prabhu, 1993; Basoya, 2015 and Rajendran, ?). On palpation, the affected mucosa will have thick, rigid, vertical fibrous bands and will differ according to the severity of the condition.

The mouth opening is significantly reduced due to stiff buccal mucosa and pterygomandibular raphe. Sometimes, the mouth opening is reduced to Zero. The tongue becomes de-papillated, fibrosed, thin, smaller in size and has restricted movements. The soft palate appears blanched and has no movements on saying 'ah'. The morphology of uvula is altered. It becomes shrunken and will appear like *inverted, hockey stick, bud like and deviated.* In severe form of OSMF, thinning of lips, sunken cheeks, masseter muscle hypertrophy, slurred speech and hearing impairment is observed. The OSMF occasionally, may be associated with other Oral potentially malignant lesions like Oral leukoplakia, Oral lichen planus, Nicotina stomatitis etc. and Oral cancer. The malignant transformation rate of OSMF is 10-12%, which is highest amongst all the OPMDs (More, 2012; Warnakulasuriya, 2007; Glick, ?; Rajendran, 1994; Basoya, 2015; Ratheesh, 2015; Van der Waa, 2009).

Conclusion

Oral Submucous Fibrosis is the most poorly understood and unsatisfactorily treated oral potentially malignant disorder. Not a single drug has provided a complete relief or remission of the disease and this is mainly because of lack in the knowledge of etiopathogenesis, although there is strong association with chewing of arecanut and its commercially available products. The molecular pathogenesis of OSMF is unclear and complex. The authors through this article have provided additional information to the existing pathogenesis of OSMF and have made an attempt to simplify the same. The present article also highlights the new clinical manifestations of OSMF, observed by the authors. This all will help in proper assessment of the condition, and thereby in delivering the appropriate treatment.

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