

## **Oral Sub mucous Fibrosis- A Controversial Treatment When Accompanied With Systemic Disorders**

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### **Abstract**

‘Vidari’ As Named by Sushruta is a crippling fibrotic disorder affecting mouth commonly seen in India and South East Asia. Being a potentially malignant disorder it has high risks of malignant transformation. As already stated by Pinborg, Osmf Is A Chronic, Insidious, Complex, disorder which affects mostly at the age of 2<sup>ND</sup> to 5<sup>th</sup> decade of their life when they are at the peak of developing systemic conditions.

We have special SPECIAL 26 treatment plans as to treat this disease but which to follow still remains an ENIGMA for dentists even till date. Whether Diabetic or alcoholic, cardiac patient or having kidney disorder, anaemic or having dermatological lesion, treatment varies having a thin line of transparency which most of us skip during

planning. Thus here giving correlation of the disease with systemic manifestations we discuss the most appropriate treatment plan for the lesion.

### **Keywords**

OSMF, Systemic disorders, treatment plan.

### **Introduction**

Since time immemorial when Sushruta discovered VIDARI it has been a topic of heated discussion, this has been a topic of heated discussion due to the multifactorial pathology and multicomplex pathogenesis. Having a potentially malignant disorder in our clinical setup is very common these days but variety of treatment options these days makes it difficult to decide as to which treatment plan suits best for the patient.<sup>[1]</sup>

Oral submucous fibrosis (OSMF) is a potentially malignant disorder that primarily affects any part of the oral cavity and sometimes the pharynx. The disease is chronic, insidious and progressive in nature.<sup>[1,2]</sup> The definition as given by PINDBORG and SIRSAT(1966) runs as “oral submucous fibrosis is a chronic insidious disorder affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by/ and or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by a fibroelastic change of lamina propria leading to stiffness of the oral mucosa and causing trismus and inability to eat.”<sup>[1,2,3]</sup> This generalized condition of the mouth eventually becomes a debilitating disease with mucosal rigidity causing discomfort, burning and limitation of opening of the mouth. People with OSMF carry a high risk for development of oral cancer. OSMF is predominantly found among the people of South Asia and is closely associated with the habit of betel quid chewing.<sup>[2,3]</sup>

Clinically this potentially malignant condition can show vast variety of symptoms and signs in the patients. The patient experiences diffuse blanching of the oral mucosal tissues with loss of flexibility of oral musculature. The patient experiences burning sensation in the oral mucosal tissues more often on eating anything spicy. The patient also experiences difficulty in mouth opening and as a result the interincisal distance also decreases.<sup>[4]</sup> Increased salivation and loss of gustatory sensation also turns out to be the classic feature of oral submucous fibrosis. Sometimes the fibrosis may extend to the Eustachian tube and the patient may have auricular stenosis.<sup>[5,6]</sup> There is vesicular formation and ulcerations seen in the oral cavity leading to stomatitis. Uvula often gets deviated and mucosal melanosis or erythematosis becomes prominent. Restriction of the tongue movement and stiffening of the

buccal musculature leads to difficulty in carrying out various facial and oral expressions. On palpation of the mucosa, vertical bands of fibers are palpated which often leads to definite diagnosis.<sup>[4,6]</sup>

### **Etiology**

The basic etiology for this potentially malignant disorder is ARECA NUT. In India chewing of areca nut and its commercial availability is quite widespread. Areca nut is the seed *Areca catechu*, and it grows in much of the tropical Pacific, Asia and parts of East Africa. It is also called as betel nut and is often chewed wrapped inside betel leaves (paan) or with tobacco (betel quid), the composition of which varies in different populations and countries. It is one of the most widely consumed addictive substances in the world after nicotine, ethanol and caffeine, and is consumed by approximately 10% of the world's population. Arecoline has been isolated from the basic nut and has major effects on various neurotransmitters particularly on cholinergic neurones, but there are a variety of other alkaloids—namely, arecaine, guvacine, guacine, and arecolidine, as well as unidentified peaks on chromatography of the extracts. The recent development of capillary electrophoresis techniques should facilitate the identification of further bioactive molecules including carcinogens as well as providing diagnostic and treatment monitoring aids.<sup>[4,5]</sup>

The role of areca products in causing oral fibrosis and malignancy and possibly contributing to other diseases has raised important public health issues. These products are inadequately labelled. There are no health warning labels and no restrictions on its sale to children or consumption in public places.<sup>[6,10]</sup>

There is substantial evidence for carcinogenicity of areca nut in cancers of the mouth and esophagus. Areca nut affects almost all organs of the human body, including the brain, heart, lungs, gastrointestinal tract and reproductive

organs. It causes or aggravates pre-existing conditions such as neuronal injury, myocardial infarction, cardiac arrhythmias, hepatotoxicity, asthma, central obesity, type II diabetes, hyperlipidemia, metabolic syndrome, etc. Areca nut affects the endocrine system, leading to hypothyroidism, prostate hyperplasia and infertility. It affects the immune system leading to suppression of T-

cell activity and decreased release of cytokines. It has harmful effects on the fetus when used during pregnancy. Thus, areca nut is not a harmless substance as often perceived and proclaimed by the manufacturers of areca nut products such as Pan Masala, Supari Mix, Betel quid, etc.<sup>[5,6]</sup>

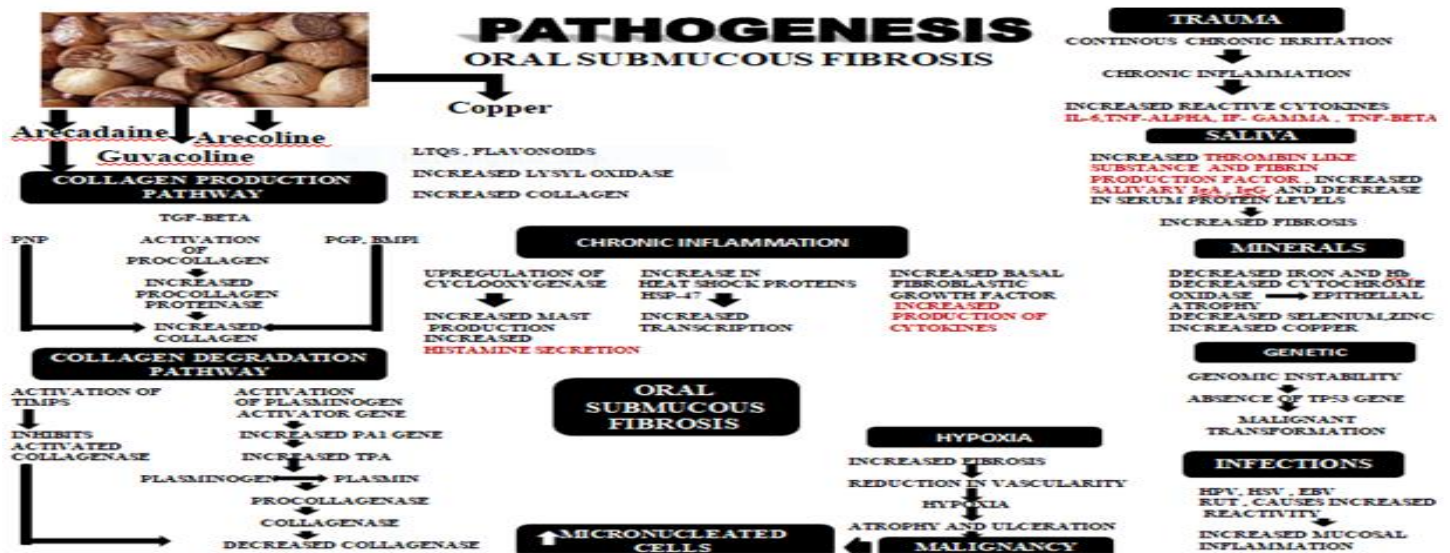


Figure 1

### Pathogenesis

Oral Sub mucous fibrosis is a chronic potentially malignant disorder which occurs due to disturbance in collagen formation and degradation. It has multifactorial etiology which makes it more complex to understand the underlying cause likewise to decide the treatment plan becomes all the more controversial. The diversity in etiology all occurs due to the sweet poison ARECA NUT prevalent to be eaten in south east Asian countries prominently. Areca nut chewing, alcoholism, ingestion of chillies, nutritional deficiencies, immunological and genetic mechanism and smoking all proves to be synergistic somehow or the other causing this potentially there were four– arecoline, guvacoline, guvacine and arecadine among which arecoline was the most potentone. Catechins and tannins were the flavonoid

components present and the trace elements had the increased concentration of copper.<sup>[8]</sup>

Disturbed collagen metabolism is the basic reason for the increased fibrosis in the oral mucosal tissues. Tissue microtrauma and arecoline causes increased production of TGF-Beta, interleukins and TNF-Alpha, FGF's, BMP's and other inflammatory cytokines. These cause the formation of procollagen and procollagen proteinase which causes increased collagen production and fibrosis. Improper collagen degradation further worsens the condition synergistically initiating it to increased fibrosis. Inactivity of collagenase caused due to activation of TIMP's tissue inhibitor of matrix metalloproteinase and plasminogen activator gene results in speedy fibrosis. This results in the increased synthesis of tissue plasminogen activator causing increased collagen fibres formation. Copper causes increased levels of lysyl oxidase, an

enzyme which causes increased super coiling and linkage of the collagen fibers increasing the fibrotic activity and decreasing the collagenase activity.<sup>[9]</sup>

The major pathogenesis of oral submucous fibrosis is the result of chronic inflammation due to sweet poison and hyperactivity of the muscle. This results in the release of inflammatory mediators due to chemo taxis, up regulation the arachidonic acid pathway. As a result cyclooxygenase pathway and lipo-oxygenase pathways are activated. It results in the release of chemical mediators, increased activity of mast cells and histamine secretion. It in turn also increases the oxidative capacity of the tissues resulting in the generation of reactive oxygen species (ROS) causing local oxidative stress. It also releases the heat shock proteins which undergo repeated transcription, and also exaggerates the release of fibroblast growth factor causing increased fibrogenesis.<sup>[8,9]</sup>

Trauma serves to be one of the basic causes of chronic inflammation which repeatedly inflames the tissue and chemotactically releases harmful mediators such as interferons, cytokines and tumour necrosis factors. Genetic instability most commonly also tends to increase

the risk of Oral Submucous Fibrosis by inhibiting the tumour suppressor genes TP53 causing increased malignant transformation of the condition.<sup>[10]</sup> Disturbances in saliva secretion and increased salivary thrombin and fibrin levels in saliva along with secretory IgA Levels due to chronic inflammation also serves to be synergistic to increase the risks of oral submucous fibrosis. Viral infections such as HSV, HPV and other acute and chronic infections results in increased reactivity of the oral mucosa causing fibrogenesis.<sup>[11]</sup>

Increased fibrosis in the oral cavity results in the blanching of the oral mucosa, stiffening of the oral musculature causing reduced vascularity. As a result of reduced vascularity in the oral cavity, hypoxic environment is created in the tissues which increase the mucosal atrophy and ulcerations in the tissues. These ulcerations results in the increased production of micronucleated cells, a classic feature of transformed malignancy.<sup>[12]</sup>

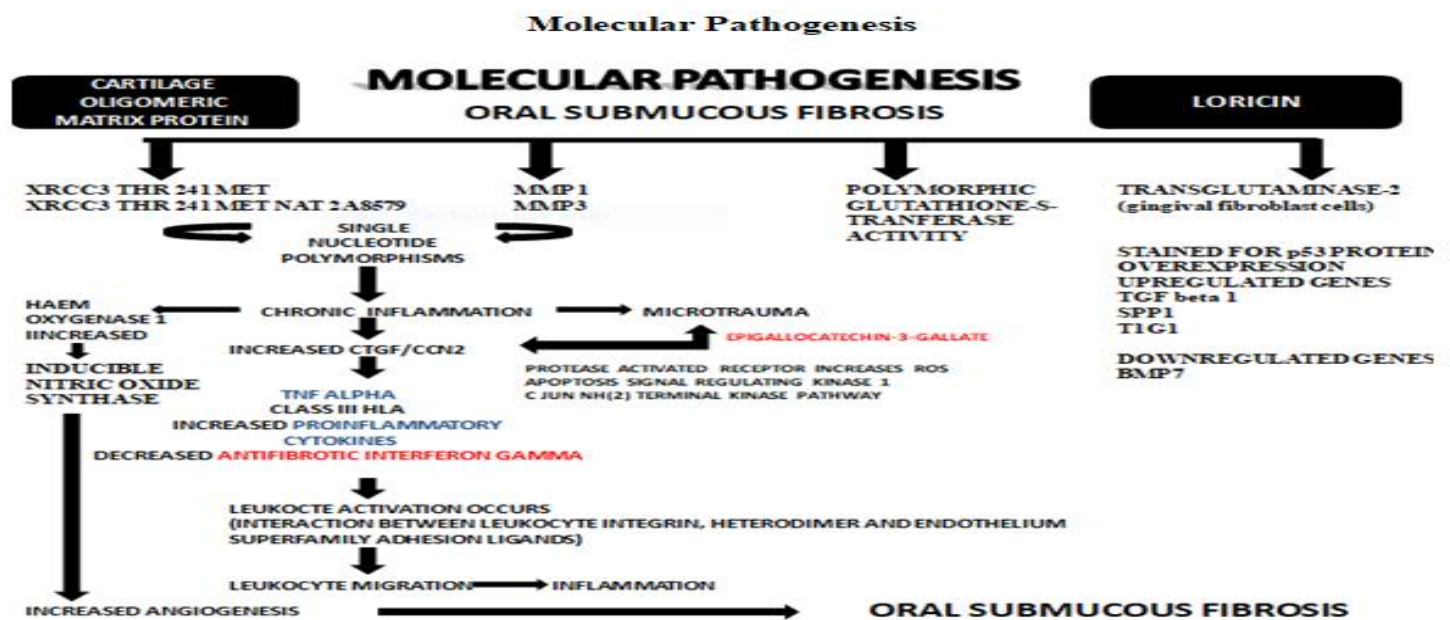


Figure 2

## Treatment Options

When patients with initial stages of OSMF are encountered they should be emphasized and educated with the importance of long term follow up after habit cessation. Habit cessation through proper habit counseling is the first and foremost treatment plan of Oral Submucous Fibrosis, since a lot of emphasis is laid on the arecanut chewing habit in contribution of OSMF. Physiotherapy can be used as an adjuvant treatment for OSMF as it is non invasive, more patient compliant and economical.<sup>[13,15,16]</sup>

Intralesional steroid injection is one of the modalities for the symptomatic relief of burning and may also be combined with hyaluronidase and placental extract intralesional injections to improve mouth opening. The primary mechanism of action of corticosteroids is through immunomodulation. Corticosteroids suppress inflammation; decelerate fibrosis and up regulate immune-mediated fibrinolytic pathways. due to its anti-inflammatory property is useful in controlling burning sensation and improving trismus.<sup>[15,16]</sup>

Turmeric as a spice and household remedy has been known to be safe for centuries. Turmeric oil is proven to be effective in OSMF. The anti-inflammatory, antioxidant and antifibrotic properties of curcumin interfere with the progression of OSMF at multiple stages in the pathogenesis of this complex disease. The antioxidative and scavenger properties of curcumin, make it a very effective chemopreventive agent in the prevention of cancer and malignancy. Vasodilators like pentoxifylline have vasodilating properties and reduced mucosal vascularity in OSMF could be increased by the use of pentoxifylline. Pentoxifylline suppresses leucocyte function and alters fibroblast physiology and stimulates fibres degradation.<sup>[14,15]</sup>

Enzymes such as collagenase, hyaluronidase and chymotrypsin are being used for the treatment of OSMF. Hyaluronidase by breaking down hyaluronic acid (the ground substance in connective tissue) lowers the viscosity of intercellular cement substance.<sup>[17]</sup>

Colchicine an alkaloid found in the crocus like plant, *Colchicum Autumnale*, named for the land of Colchis near Black Sea. Chemically, it is Colchicinum-N-(5, 6, 7, 9-Tetrahydro-1, 2, 3, 10-tetramethoxy-9-oxobenzo [a] heptalen-7-yl) acetamide. Colchicine is an ancient drug-at least 2,000 years old, which is attracting renewed interest because of its actions at a subcellular level. Important anti-inflammatory properties of colchicine are related to the drug's effect on polymorphonuclear leukocytes and monocyte chemotaxis, leukocyte adhesiveness, the drug's action in potentiating factors that increase leukocyte cyclic adenosine monophosphate (CAMP) levels, thereby causes inhibition of lysosomal degranulation that accompanies phagocytosis and its effect on the release of prostaglandin E, which suppresses the leukocyte function.<sup>[15,19]</sup>

Placentex an aqueous extract of human placenta contains nucleotides, enzymes, vitamins, amino acids, and steroids. It acts by biogenic stimulation and increasing the vascularity of tissues based on the principle of tissue therapy introduced by Filatov in 1933.<sup>[15,22]</sup>

Complicated OSMF has surgical modalities chosen according to the stage of clinical progression to gain maximal interincisal distance (ID) includes the excision of fibrotic tissues and covering the defect with split-thickness skin, fresh human amnion, or buccal fat pad (BFP) grafts. Khanna & Andrade treated advanced cases by a new surgical technique of a palatal island flap based on the greater palatine artery in combination with temporalis myotomy and bilateral coronoidectomy.<sup>[18]</sup>

Tea pigments are oxidized products of polyphenols, derived from tea leaves that could improve microcirculation and hemorrheology. After administering tea-pigment tablets in the treatment of OSF, it is found that it has an overall effective rate and believed that tea pigment's acts by decreasing high blood viscosity, improving microcirculation, and increasing the activity of superoxide dismutase.<sup>[21]</sup>

Heat has been adequately used in the form of hot rinses, lukewarm water or selective deep heating therapies like shortwave and microwave diathermy. Heat therapy acts by fibrinolysis of bands. Short-wave produces sharp localized deep heat, avoids the unintentional heating of superficial facial tissues like skin and adipose tissue. Microwave diathermy selectively heats only juxta-epithelial connective tissue and limiting the area to be treated. Thus, it is easy to apply with minimum discomfort.<sup>[19]</sup>

IFN-gamma plays a significant role in the treatment of OSMF for the reason that it has immuno-regulatory effect. IFN-gamma is a known antifibrotic cytokine, effect of which was considered on collagen synthesis by arecoline stimulated OSMF fibroblast. It was shown that there was inhibition of collagen synthesis in existence of IFN-gamma. It gave a major progress in mouth opening.<sup>[23]</sup>

Low levels of hemoglobin and serum iron are suggestive of iron deficiency anemia. Iron deficiency anemia in patients with OSMF could be related to the precancerous nature of this condition. Cytochrome oxidase is an iron-dependent enzyme which is required for the normal maturation of the epithelium. In iron deficiency state, the levels of cytochrome oxidase are low, consequently leading to epithelial atrophy. An atrophic epithelium makes the oral mucosa vulnerable to the soluble irritants. Fibrosis dictates that OSMF is basically a disorder of collagen metabolism. Hydroxyproline is an amino acid found only in collagen, which is incorporated in the

hydroxylated form. This hydroxylation reaction requires ferrous iron and ascorbic acid. Utilization of iron, for the hydroxylation of proline and lysine, leads to decreased serum iron level. In OSMF patients, there is an increase in the production of highly cross-linked insoluble collagen type I loss of more soluble procollagen type III and collagen type VI. The cross-linking of collagen due to the up regulation of lysyl oxidase, plays a crucial role in the development and progression of the condition.<sup>[22]</sup>

The local and systemic up regulation of fibrogenic cytokines and down regulation of antifibrotic cytokine are central to the pathogenesis of oral submucous fibrosis (OSF). The milk from cows immunized with human intestinal bacteria (immune milk) contains an anti-inflammatory component that may suppress the inflammatory reaction and modulate cytokine production. Therefore, it was decided to test whether immune milk may have some beneficial effects on controlling the symptoms and signs in OSF patients. Honey has both nutritional as well as medicinal value. It is composed of compounds like organic acids, proteins, amino acids, minerals, polyphenols, vitamins and aromatic compounds. Honey has antimicrobial, antiviral and antiparasitic activity. Honey possesses strong bactericidal and bacteriostatic property. It is mainly effective against gram-positive bacteria such as *A. pyogenes*, *S. mutans*, *S. aureus* etc. Honey has shown strong antimicrobial activity because of its low water content and low pH. Other than these, honey contains glucose oxidase which produces hydrogen peroxide which has a strong bactericidal action. Jungle honey acts as chemotactic inducer for neutrophils. It also shows strong antioxidant activity by scavenging free radicals and by preventing the formation of free radicals released from the inflamed tissues. Antioxidant property is due to its content of glucose oxidase, catalase, ascorbic acid, flavonoids compounds. Furthermore, honey

helps in increasing absorption and activity of some antioxidants like vitamin C (47%), carotene (3%), uric acid (12%), and glutathione reductase (7%). The antioxidant activity is responsible for preventing several chronic diseases including cancer.<sup>[32,33]</sup>

Tomato is a rich source of lycopene which is a natural pigment synthesized by plants and microorganisms. It is not synthesized *de novo* by the human body and hence is available from diet only. It is mostly found in human buccal mucosa and immediately enter the plasma when consumed. Lycopene is an acyclic isomer of  $\beta$ -carotene. They are found abundantly in tomatoes and in red fruits and vegetables, such as red carrots, watermelons, papayas, and grapes. Non oxidative mechanism for anticarcinogenic effects of lycopene is through regulation of gap junction communication. Lycopene is a significant

Anticancer agent by its various mechanisms. Lycopene's ability for quencher of single oxygen is twice as high as  $\beta$ -carotene and ten times higher than vitamin A.<sup>[23]</sup> It is a scavenger of free radicals preventing oxidative stress, which causes DNA damage. Lycopene also inactivates free radicals which are responsible for lipid peroxidation process thus preventing tissue damage. Another anticancer mechanism is the suppression of carcinogen-induced phosphorylation of p53, Rb antioncogenes and stopping the cell division at the G0-G1 cell cycle phase. It acts as an ant proliferative agent by inhibiting insulin like growth factor and thus reduces proliferative capacity of cells. Modulation of immune functions is carried out by regulation of intrathymic T-cell differentiation. It also acts as an antitumor agent by induction of apoptosis and modulation of carcinogen metabolizing enzyme.<sup>[25,33,36]</sup>

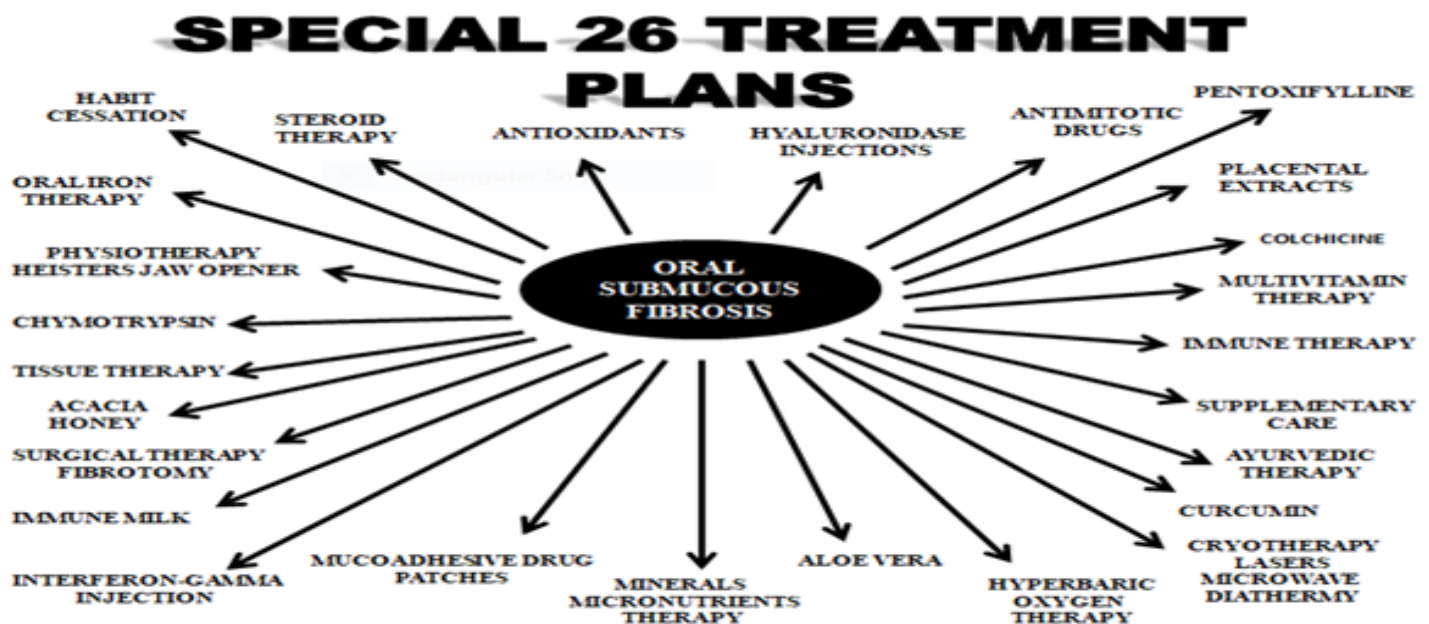


Figure 3

### OSMF and Liver Disorders

Liver disorders are the tenth most common cause of death in India. There has been a paradigm shift in the occurrence of liver cirrhosis as the emerging new lifestyle of present

day has proven that alcoholism is the most commonly acquired habit by present day population. Cirrhosis is the end result of variety of liver diseases characterized by fibrosis and architectural distortion of the liver having

several clinical and systemic complications. It also results in several disturbances in the enzyme patterns of the liver.<sup>[6]</sup>

Areca nut being the etiology of Oral Submucous Fibrosis is the most toxic member of the family of the factors causing potentially malignant disorders. It contains Aflatoxin 1, polyphenols and other alkaloids including Arecoline, Arecadine, Guvacine and Guvacoline. This toxin liberated is metabolized in liver. It forms aflatoxin albumin adducts which causes Mutagenesis in liver. Aflatoxin 1 epoxide is generally accepted as active electrophile that may attack nucleophilic nitrogen, oxygen and sulphur heteroatom's in cellular constituents. It combines with Guanine, causes G-T transversion, and causes alterations in DNA and mutations. This activates the cytochrome p 450 which metabolises AFB1 to mutagenic AFB1-8,9-Epoxide which stops the functioning of tumour suppressor gene P-53 causing mutations leading to liver damage. All the liver enzymes, alkaline phosphates', serum transaminase all are increased suggesting liver damage. Thus we see how great a controversy it is when oral submucous fibrosis is involved to cause any systemic complications.

The best treatment plan involved in this apart from conventional treatment plans involves the use of Curcumin tablets 1250-2500mg a day along with multivitamins therapy as it is hepatoprotective giving fibrinolytic action in the liver and lungs as well and inhibits collagen synthesis. Along with that physiotherapy acts as an adjuvant therapy and use of antioxidants is very necessary as it prevents lipid peroxidation and acts as a superoxide scavenger.

### **OSMF and Cardiovascular Disorders**

Cardiovascular disorders have become one of the major causes of death in India since the last decade. One in four deaths today in India is because of cardiovascular disorders, this serves to be the most common cause of distress for people in India.<sup>[1,21]</sup> Stress being the most common etiology for cardiovascular disorders serves as a domino effect for increasing the incidence of this problem in our country. Considering oral cavity as mirror of the body cardiovascular disorders also aggravate the occurrence of cardiovascular disorder. It also gets aggravated due to cardiovascular disorders.<sup>[33]</sup>

Major etiology of Oral Submucous Fibrosis as seen is chewing of Areca Nut. Areca nut contains several alkaloids like Arecadaine, Arecoline, Guvacoline and Guvacine. These alkaloids increase the release of a potent vasoconstrictors in the body Adrenaline. This adrenaline aggravates the vasoconstriction causing domino effect for myocardial infarction and stroke, the two most common burdens of death in india since the last few Decades.<sup>[35]</sup> Moreover continous inflammation and microtrauma in the oral cavity serves to increase the levels of homocysteine and C-Reactive proteins in the blood due to continous acute and chronic inflammation leading to endothelial and leukocyte adhesion.<sup>[46]</sup> This homocysteine is the classic cardiac risk marker thus depicts us that OSMF can serve to aggravate the cardiovascular disorders.<sup>[47,48]</sup>

Various cardiac risk markers are aggravated directly or indirectly in Oral submucous fibrosis and high density lipoproteins are attenuated somehow aggravating cardiovascular disorders. Still not proven but serve to be controversial as to whether this potentially malignanat disorder aggravates cardiovascular disorder or vice versa but treatment of OSMF in a patient with this combination serves to be very challenging. Use of drugs such as ACE



inhibitors and HMG Coa reductase inhibitors suppresses cardiovascular disorder and also helps to control fibrosis in the oral cavity, use of pentoxifylline injections and hyaluronidase injection, topical application of aloe vera gel.<sup>[49,50]</sup>

### **OSMF and Blood Disorders**

A wide range of hematological disorders encountered in medicine have direct or indirect implication on our oral cavity. The contribution of these disorders may be specific or non specific, contributory or regulatory, thus making it a serious controversy. Considering patients with oral submucous fibrosis, iron deficiency anaemia is the most commonly associated with them. Low serum iron levels serve as a novel biomarker of oral submucous fibrosis but the association of iron deficiency anaemia with osmf is controversial as iron is required as the major component is the hydroxylation of proline and lysine which occurs in the fibrogenesis and fibrosis.<sup>[31,41]</sup> Iron is utilized in fibrosis aggravating oral submucous fibrosis. Moreover due to malnutrition and improper nutrition to individuals the serum iron level falls dramatically resulting in the iron deficiency anaemia later propagating to produce oral manifestations leading to increase incidence of atrophy in the oral mucosa potentiating oral potentially malignant disorders.<sup>[30,31,32]</sup>

Such patients have to be dealt with care as the treatment focus of such patients should be heading on to save the fluid connective tissue and prevent the potentially malignant disorder to aggravate. Oral iron therapy, multivitamins therapy and immune milk ingestion is the best way to treat such combination of disorder. Immune milk is obtained from the cows immunized with human intestinal bacteria, produce high quantities of immunoglobulins, suppresses the inflammation and modulates cytokines production. It also inhibits collagen

synthesis has increased antiviral and antibacterial properties improving cancer surveillance. Iron therapy in oral or intravenous route helps regulate anaemia preventing further complications. Thus it serves to be a newer treatment modality not proning the patient to any other systemic complication apart from the conventional treatment modality.<sup>[31,36]</sup>

### **OSMF and Lung Disorders**

The burden of chest disorders in India continues its toll and is prevalent in a substantial manner in our country.<sup>[22,27]</sup> Present day scenario says that habits such as smoking has worsened the condition of human lungs making it more vulnerable for several malignancies and disorders shortening life span of human beings.

Oral submucous fibrosis worsens Asthma and Emphysema and these systemic disorders worsens this premalignant condition in turn. Arecoline, metabolite of Areca Nut results in the secretion of EOTOXIN 1 chemokine which in turn exaggerates hypersensitivity causes Asthma. Chemokines results in chemotaxis and attraction of leucocytes and eosinophils which causes allergy. Oral submucous fibrosis caused due to Areca Nut which contains several alkaloids like arecoline, arecadaine, guvacoline and guvacine. These alkaloids stimulates the release of Catecholamine's which causes bronchoconstriction worsening asthma and chronic obstructive pulmonary disorder.<sup>[28]</sup>

Moreover it initiates the release of hypoxia inducing factor 1 alpha, (HIF-1alpha). The fibrotic adaptation of cells to hypoxia is facilitated by HIF-1alpha and decreased oxygen tension leads to transcriptional induction of series of genes that participate in neoangiogenesis, iron metabolism, glucose metabolism and cell proliferation or survival. Thus, Oral Submucous Fibrosis caused due to areca nut chewing results in decreased Pulmonary

functions which serves to be the warning signs for the obstructive or restrictive type of pulmonary disease worsening Asthma and COPD.<sup>[29]</sup>

Pentoxifylline, a rheologic modifier serves to be the most commonly used drug in patients with OSMF and pulmonary disease. It is used so because it reduces the T-cells and B-cells production and also prevents degranulation of mast cells and leukocytes. Curcumin, steroid therapy and hyaluronidase injection are the other routinely applied methods of treatment of OSMF in patients with pulmonary disorders.<sup>[30]</sup>

### **OSMF and Diabetes Mellitus**

Diabetes mellitus, a metabolic disorder or a syndrome, commonly is caused due to the reduced secretion of insulin by the beta cells of pancreas. It causes disturbed metabolism of glucose, fats and proteins. The sweet poison Areca nut contains several alkaloids which disturbs the mechanism of metabolism causing diabetes mellitus and other lipolytic disorders in the human body.<sup>[37]</sup>

Arecoline in areca nut causes blockage in the Insulin signaling and glucose uptake in 3T3-L1 Adipocytes by inhibiting the glucose transporters 4 and lipid droplets protein, perilipin and adipophilin.<sup>[31]</sup> It also reduced lipid storage and inhibited fatty acid synthesis expression stimulating lipolysis in adipocytes. Arecoline also disturbs the G1 and G2 phases of the cell cycle by modulating the expression of cell cycle related proteins p21 and CDK Cyclin dependent kinase, altering the production of reactive oxygen species.<sup>[37,38]</sup>

Arecoline also tends to increase the basal level of IRS1 Serine Phosphorylation and decreased the insulin stimulated tyrosine kinase phosphorylation thus inducing diabetogenic potential on the adipocytes resulting in aggravation of Diabetes Mellitus in patients suffering from OSMF.<sup>[39]</sup>

The best treatment option of these cases which are most commonly encountered in clinical practice is habit cessation with antioxidant therapy, use of aloe vera gel is also commonly used, but is contraindicated in gestational diabetes because it is known to increase the risk of uterine contractions. But it is one of the most safest drugs to be given to diabetic person suffering from OSMF because it tends to reduce the blood glucose levels, has anti-inflammatory capacity, quick healing nature and antineoplastic. Physiotherapy and other mouth exercises serves as an adjuvant treatment and quickens for the OSMF relief and also reduces blood glucose levels improving the lipid profile in patients.<sup>[39,40]</sup>

### **Conclusion**

The ability of malignant transformation of OSMF is quite less around 7.6% approximately. Systemic diseases have direct or indirect implications on the individual giving rise to the VIDARI. No definitive treatment plan has yet been emerged for this condition due to its PATHOGENIC COMPLEXITY. Evaluation of merits and demerits of individual management protocols is not possible due to its combined treatment modality, which is inevitable at present due to its empirical nature.

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