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ORAL SUBMUCOUS FIBROSIS, CLINICAL PRESENTATION & TREATMENT MODALITY: A REVIEW OF LITERATURE

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ABSTRACT

Oral submucous fibrosis (OSMF) is an oral precancerous condition characterized by inflammation and progressive fibrosis of the submucosal tissues resulting in marked rigidity and trismus.Clinicians continue to have difficulties with OSMF because of its unclear etiology and imprecise classification schemes. Several classification schemes based on clinical, histological, or functional features have been reported in medical literature over time. None of these classifications, meanwhile, have been accepted by everyone. Every classification has benefits and drawbacks of its own. In an effort to aid physicians, researchers, and academics in classifying this potentially malignant condition for early detection, prompt therapy, and mortality reduction, an effort is made to disseminate and update the knowledge of the OSMF classification system. Furthermore, pathogenesis andmanagement have also been discussed.

INTRODUCTION

Oral submucous fibrosis is a chronic, insidious illness with the potential to be cancerous. It affects the entire oral cavity and occasionally the pharynx. Its great potential for malignancy and its persistently debilitating and resistant nature have garnered significant attention in recent times. People of Asian heritage are more likely to have it, particularly Indians.[1] In 600 B.C., Sushrutha named a disorder akin to OSMF as "Vidari".[2] The word "atrophicaidiopathica mucosae oris" was first used in modern literature by Schwartz in 1952 to characterize an oral fibrosing disease that he found in five Indian women living in Kenya.[3] Later, in 1953, Joshi came up with the acronym "OSMF" to describe the illness.[4]

Previously believed to be idiopathic, the aetiology is now known to be complex in origin. Potential etiological variables include deficits in iron, zinc, and vital vitamins, as well as capsaicin found in chillies.[5-8]

ETIOLOGY

ARECA ALKALOIDS CAUSING FIBROBLAST PROLIFERATION

Chewing on areca nut (betel nut), which includes tannins (11%–12%) and alkaloids such arecoline, arecadine, guvacoline, and guvacine, is one of the most common causes of OMSF. Of all of these, arecoline is the primary chemical that causes the proliferation of fibroblasts. Arecoline hydrolyzes to arecadine when exposed to slaked lime (Ca(OH)2), which has a noticeable effect on fibroblasts.[9] Harvey et al.'s study shown that arecoline at concentrations of 0.1–10 μg/ml stimulates fibroblasts, but arecoline at concentrations greater than 25 μg/ml inhibits the proliferation of fibroblasts and the synthesis of collagen.[10]

CLONAL SELECTION OF OSMF FIBROBLASTS BY ARECOLINE

Research has demonstrated that, in comparison to normal fibroblasts, arecoline leads OSMF fibroblasts to synthesize more collagen. This may represent clonal selection of a cell population in modified tissues influenced by indigenous elements like IL-1 produced by inflammatory cells.[11]

HIGH COPPER CONTENT IN ARECA NUT AND FIBROSIS

Between 0.6 to 1.6 mg of copper is consumed daily by adults in underdeveloped nations through their diet. An adult Indian who chews areca nut on a regular basis takes in more than 5 milligrams of copper.[12] Increased tissue copper levels were found in buccal mucosal biopsies of OSMF patients, according to studies evaluating serum and tissue copper levels in OSMF patients. Mass absorption spectrometry measurements of tissue copper levels revealed that non-areca nut chewers had tissue copper levels of 4μg/gm, while OSMF sufferers had tissue copper levels of 5.5μg/gm. Additionally, the lining mucosa's concentration gradient of copper was observed, with epithelium having a higher concentration of copper than deeper connective tissues and muscle layers.[13]

Nutritional deficiencies

Deficiency of iron (anemia), Vitamin B complex, minerals, and malnutrition are promoting factors that disturbs the repair process of the inflamed oral mucosa, thus leads to deranged healing and resultant scarring and fibrosis. The resulting atrophic oral mucosa is more susceptible to the effects of chilies, betel nuts, and other irritants.

GENETICS AND IMMUNOLOGY

A genetic component is believed to be involvement in OSMF because there are cases reported in medical literature in people without any history of betel nut chewing or chilli ingestion. Patients with OSMF have increased frequency of HLA-A10, HLA-B7, and HLA-DR3.[14] The increase in CD_4 cells and cells with HLA-DR in these diseased tissues shows activation of most lymphocytes and increased number of Langerhans cells. These immunocompetent cells and high value of CD_4:CD_8 ratio in OSMF tissues show the activation of cellular immune response which results in deranged immunoregulation and an altered local tissue morphology. These changes may be due to direct stimulation from exogenous antigens such as areca alkaloids or due to changes in tissue antigenicity leading to an autoimmune response.[15]

Increased levels of pro-inflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) also contribute to the pathogenesis of OSMF. Various staging/grading classification systems have been documented in medical literature by various authors in the past. Some of the staging system is routinely used in the clinical practice and help in early diagnosis and treatment.[16]

CLASSIFICATION BASED ON CLINICAL FEATURES

1) **Pindborg JJ**[17](1989) divided OSMF into three stages:

Stage 1: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae.

Stage 2: Fibrosis occurs in healing vesicles and ulcers, which is the hallmark of this stage.

Stage 3: Sequelae of OSMF are as follows:

- Involvement of one-third or less of the oral cavity (if three or less of the above sites are involved).
- Involvement of one to two-thirds of the oral cavity (if four to six intraoral sited are involved).
- Involvement of more than two-thirds of the oral cavity (if more than six intraoral sites are involved).

2) **Haider et al**[18] (2011) study based on severity of the disease with functional staging and objective measures inter-incisal opening:

Clinical Staging:
Stage 1: Facial bands only
Stage 2: Facial and buccal bands
Stage 3: Facial and labial bands

Functional Stage:
Stage A: Mouth opening 13 to 20 mm
Stage B: Mouth opening 10 to 11mm
Stage C: Mouth opening <10mm

CLASSIFICATION BASED ON HISTO - PATHOLOGIC FEATURES

3) **Utsonumiya H et al**[18] (2005) divided OSMF based on the concept of Pindborg J.J. and Sirsat S.M. and modified it as follows:
Early stage: Large number of lymphocytes in the sub epithelial and connective tissue zones along with myxedematous changes.
Intermediate stage: Granulation changes close to the muscle layer and hyalinization appears in sub epithelial zone where blood vessels are compressed by fibrous bundles. Reduced inflammatory cells in sub epithelial layer are seen.
Advanced stage: Inflammatory cell infiltrate hardly seen. Number of blood vessels dramatically less in the sub epithelial zone. Marked fibrous areas with hyaline changes extending from sub epithelial to superficial muscle layers are seen. Atrophic, degenerative changes start in muscle fibres.

CLASSIFICATION BASED ON RADIOLOGIC FEATURES

4) **Prakash R et al**[19] (2014) assessed the morphologic variants of soft palate by conducting a clinico-radiological study. The authors based on these variants assessed the severity of OSMF to establish it as a basis for staging of OSMF.
Six morphologic variants were delineated as follows:
Type 1: Leaf shaped
Type 2: Rat tail shaped
Type 3: Butt shaped
Type 4: Straight line
Type 5: Deformed S
Type 6: Crook shaped

Although these classifications are helpful in clinical diagnosis of patient into different categories but these classification have not highlighted, treatment, and prognosis of the disease.[20]

5) Passi D et al classification (2017)[20]

Passi D et al. (2017) have proposed a new classification which incorporates treatment and prognosis of OSMF. The newer classification system includes all the parameters/ component of OSMF such as clinical features, histopathological features, functional component, treatment part, and prognosis. None of the previous classifications have included all these features in one classification. The main drawback of this classification is that it is bit complex and lengthy.[20] As per new classification system following treatment options are available which can be given alone or in combination to the patient.

Grading / Staging	**Clinical**	**Functional**	**Histopathological**	**Treatment**	**Prognosis**
Grade 1	Involvement of less than one-third of the oral cavity Mild blanching, burning sensation, recurrent ulceration, and stomatitis. Dryness of mouth	Mouth opening up to 35 mm	Stage of inflammation: Fine edematous collagen, congested blood vessels, abundant neutrophils along with lymphocytes with myxomatous changes in subepithelial, connective tissue layer of epithelium	Cessation of habit, nutritional supplement, antioxidants, topical steroid ointment	Excellent
Grade 2	Involvement of one-third to two-third of the oral	Mouth opening 25-35 mm Cheek	Stage of hyalinization: Juxta-epithelial collagen	Habit cessation, nutritional supplemen	Good Recurrence rate is low

	cavity Blanching of oral mucosa with mottled and marble like appearance, fibrotic bands palpable and involvement of soft palate and premolar area	flexibility reduced by 33%	hyalinization with lymphocytes, eosinophils. Dilated and congested blood vessels. Less fibroblastic activity. Granulation changes in muscle layer with reduced inflammatory cells in subepithelial layer	t, intralesional injection of placental extracts, hyaluronidase, steroid therapy Physiotherapy	
Grade 3	Involvement of greater than two-third of the oral cavity. Severe blanching, Broad thick fibrous palpable bands at cheeks and lips and rigid mucosa, depapillated tongue and restricted tongue movement and shrunken bud like uvula. Floor of	Mouth opening 15-25 mm Cheek flexibility reduced by 66%	Stage of fibrosis: Complete collagen hyalinization without fibroblast and edema. Obliterated blood vessels Plasma cells and lymphocytes are present Extensive fibrosis with hyalinization from subepithelial to superficial muscle layers	Surgical treatment including band excision and reconstruction with BFP or split thickness graft bilateral temporalis myotomy and coronoid-ectomy	Fair Recurrence rate is high

	the mouth involvement and lymphadenopathy		with atrophic, degenerative changes		
Grade 4	Leukoplakia changes, erythroplakia Ulcerating and suspicious malignant lesion	Mouth opening <15 mm or nil	Stages of malignant transformation: Erythroplakia changes into squamous cell carcinoma	Surgical treatment and biopsy of suspicious lesion	Poor, malignant transformation

MANAGEMENT OF OSMF

Cessation of habit

The stoppage of habit such as betel quid, areca nut and other local irritants, spicy and hot food, alcohol, and smoking through education and patient motivation. All affected patients should be educated and warned about the possible malignant transformation.[20]

Supplementary care

Diet rich in iron, vitamins, and minerals should be advised to patients with OSMF. Deficiency of iron plays important role in both etiology and pathogenesis of OSMF. Vitamin B complex supplements may relieve glossitis, inflammation of tongue, and cheilosis in OSMF patients.[21]

Antioxidants

Carotenoids (lycopene) induce stimulation of immune system or direct action in tumor cells. Lycopene inhibits hepatic fibrosis genes in LEC rats and also exerts a similar inhibition on the abnormal fibroblasts in OSMF[22].

Steroid therapy

Steroids → reduction of proliferation of fibroblasts → number of collagen fibers decreases. Steroids release cellular proteases enzymes in extracellular compartment in connective tissues → activation of collagen and zymogens → ingestion of insoluble collagen → collagen breakdown stimulation.[23]

Hyaluronidase

It acts by breaking down hyaluronic acid, lowers the viscosity of intracellular substances, and decreases collagen formation. It produces burning sensation and trismus. Combination of steroids and Hyaluronidase shows better long-term results than either used alone.[24]

Pentoxifylline

Pentoxifylline is a tri substituted methyl methylxanithine derivative. It is a rheological modifier; it improves microcirculation and decreased platelet aggregation as well as granulocyte adhesion and also has good improvement in radiation-induced superficial fibrotic lesions of skin and direct effect on inhibiting burn scar fibroblasts. It has also been used to alleviate the symptoms in patients with OSMF.[25]

Interferon-gamma

It has immuno-regulatory effect. It is also known as antifibrotic cytokine, patients treated with an intralesional injection of IFN-gamma experienced improvement of symptoms.[26]

Immune milk

Immune milk consists of anti-inflammatory component which suppresses the inflammatory process and stimulates the cytokine production. Good symptomatic relief in OSMF patients is dueto micronutrients in the immune milk powder.[27]

Diathermy, Ultrasound, Lasers: Microwave diathermy

Microwave diathermy acts by physio-fibrinolysis of fibrous bands through selective heating of juxtaepithelial connective tissue. Ultrasound has a role in deep heating modality. Its selectivity raises the temperature in accumulated areas. CO_2 laser techniques involve multiple small incisions which provide surgical relief of restricted oral aperture because the laser beam seals all the blood vessels, thus allowing the surgeon a perfect visibility and accuracy in fibrous band excision.[28]

Cryosurgery

It is the method of locally destroying the abnormal tissue by freezing it in situ and applying liquid nitrogen or argon gas.[29]

Surgical treatment

In patients with severe trismus, surgical intervention is done which includes simple excision of fibrotic bands with reconstruction using buccal fat pad and split thickness graft along with temporalis myotomy and coronoidectomy. The surgery is performed under general anesthesia. The intubation is difficult due to restricted mouth opening. Endotracheal intubation under deep inhalational anesthesia or using muscle relaxants with regional block is preferred. Fiber-optic guided intubation techniques have also been used.[20]

Turmeric

Turmeric powder provides benzopyrene-induced stimulated production of micronuclei in circulating lymphocytes. It also acts as an excellent scavenger of free radical. Turmeric oil and turmeric resin both act synergistically to protect against DNA damage.

Physiotherapy

Muscle stretching exercises for the mouth are helpful in preventing further reduction in mouth opening. Forceful jaw opening exercise is with mouth gag or heisters jaw opener.

CONCLUSION

In OSMF, the initial diagnosis is of utmost importance, as the treatment and its prognosis greatly depend on its staging. An attempt is made to update the knowledge on classification schemes for OSMF so as to assist in categorisation of this premalignant condition and to aid in early diagnosis thereby leading to timely management. An increased emphasis is placed on clinical staging as clinical appearance holds the most important value in staging OSMF. Treatment if done according to the staging and grading helps in management & better prognosis for the patient. Hence treatment should be done as per the staging and grading. We hope this review helps academicians, clinicians as well as researchers in getting a broad view on various classification systems and contribute to optimal patient management.[20]

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