

CLINICAL PRACTICE GUIDELINES FOR MANAGEMENT OF DIFFERENT GRADES OF ORAL SUBMUCOUS FIBROSIS

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Abstract

Introduction: Oral submucous fibrosis (OSF) is a chronic condition characterized by progressive fibrosis of the oral mucosa, leading to reduced elasticity and mobility of affected tissues. OSF can potentially transform malignantly, emphasizing the need for a multidisciplinary approach to its management, including cessation of causative habits and close monitoring for malignant changes. **Objectives:** This study aims to review the etiological factors contributing to OSF, understand its pathophysiology, and propose a comprehensive treatment strategy based on evidence-based trials and clinical relevance. **Materials and methodology:** A thorough analysis of literature was conducted to identify the causative factors and pathophysiological mechanisms underlying OSF with pertinence to Kerr et al grading for oral submucous fibrosis. This study also reviewed various treatment modalities, focusing on topical therapies as the initial approach due to their favorable safety profile. **Results :** The study outlines a graded management strategy for OSF, ranging from topical therapies for early-stage cases to more invasive interventions such as laser therapy, systemic medications, surgical procedures, physiotherapy, and targeted drug therapy for advanced cases. The effectiveness of each treatment modality is discussed in light of existing evidence. **Conclusion:** This study provides a structured framework for clinicians and researchers to understand and manage OSF comprehensively. Early identification, categorization based on severity, and tailored treatment plans can improve outcomes and reduce the risk of malignant transformation. The importance of interdisciplinary collaboration and patient education in managing OSF is emphasized, highlighting the clinical relevance of this study in improving patient care and outcomes.

Keywords: Clinical Practice Guidelines, Areca Nut, Tobacco, Habit Cessation, Fibrosis, Trismus, Mucositis.

INTRODUCTION

The Indian subcontinent and surrounding regions have experienced a long history of oral cancer as a serious health concern. Ancient scripts make significant mention to

this illness. The term oral potentially malignant disorders came into existence after numerous researchers started researching cancer and its associated diseases [1]. It was the 1960s and 1970s when The Basic Dental Research Unit of the Tata Institute of Fundamental Research in Mumbai conducted spear headed studies on OPMD and oral cancer and established a relationship with traditional betel quid chewing habits and OPMD [2].

Oral submucous fibrosis (OSMF) is one of the most common disease among OPMD. It is defined as a chronic, insidious and progressive oral mucosal disease that involves oral and pharyngeal mucosa and upper digestive tract characterised by blanching of mucosa staining of gingiva and teeth and restricted mouth opening[3].

It is multifactorial and has a high incidence among areca nut (AN) chewers. The likelihood that this oral potentially malignant condition will develop into oral squamous cell carcinoma (OSCC) is substantial (7%–30%) [4]. It is common in Asia and has taken hold in North America and Europe. According to reports, the prevalence of OSF was 1.0%–3.03% in Taiwan, 0.086%–17.6% in Vietnam, and 0.15%–14.4% in Hunan Province, mainland China[5]. With a wide age range from 11 to 60 years old, OSMF prevalence in India was observed to be 0.2-2.3% in males and 1.2-4.6% in females [6].

The prevalence of OSMF and other OPMD diseases increased after the extensive marketing of commercial tobacco and areca nut products such as gutkha, pan masala, mawa and flavoured areca nuts [7]. The main risk factors for OPMDs and oral cancer include other lifestyle factors such as alcohol intake, betel nut derivatives, and sexually transmitted infections with the human papilloma virus (HPV, primarily type 16) [8]. Moreover, a growing number of clinical and scientific investigations have focused on chronic mucosal inflammation and oral mucosal injuries caused by tooth and prosthetic devices [9]. Alteration of the microbiome, systemic sclerosis, genetic disorders with dysregulation of DNA metabolism (such as Zinsser-Engman-Cole syndrome, Fanconi anemia, and Xeroderma pigmentosum), hematinic insufficiency, and micronutrient deficit are further suggested associations between oral cancer and premalignant lesions [10].

Through early detection of OPMD and population surveillance, periodic dental checkups and removal of involved environmental and behavioral risk factors are the most efficient approaches to prevent cancer transformation. But different treatments are needed for each stage of OPMD. For the treatment of OPMDs, a variety of therapeutic modalities have been proposed, including electrosurgery, cryosurgery, surgical excision, CO₂ laser therapy, and administration of topical and systemic medicines (vitamin A, lycopene, retinoids, antibiotics, and corticosteroids)[11]. Another possible treatment is photodynamic therapy (PDT), a non-invasive procedure that combines oxygen and a photosensitizer to activate reactive oxygen species (ROS) and trigger the death of microorganisms by apoptosis or necrosis. Despite said, there is currently no proof that treatment prevents the spread of cancer, and occasionally undesirable side effects (such as scarring, recurrence, etc.) have been noted [12].

These treatment modalities differ with each stage of OPMD. With respect to OSMF, there are various classifications according to their clinical features, histopathological features and severity. Only with the knowledge of these classifications, treatment of OSMF and other OPMD can be managed to prevent it from turning into carcinoma

Classification

Kerr et al in 2017 classified OSMF into grading system based on clinical features [13] This classification has a drawback that it only represented the clinical and not the histopathological or functional features.

Passi D et al in 2017 proposed a new classification of OSMF into 4 grades [14]. But this classification was too complicated to plan the treatment and the latest classification came into place in 2023 by Sonia Gupta et al [15]. This system considered all the parameters to classify OSMF. It has 4 grading systems namely: clinical, functional, histopathological and cumulative. This closely resembles TNM classification of cancer.

Clinical grading was divided from mild to severe with evidence of OSCC (Much closer to Kerr et al classification). Functional grading was divided according to mouth opening from 40 mm to less than 10 mm. Histopathologically again it is divided into 5 categories from hyperkeratosis to dysplastic changes progressing into OSCC. Cumulatively it has been given 5 grades with grade 1 being mild and grade 5 being malignant. This classification is the recent one in the existing literature.

Aetiology

Various researches were conducted to find the aetiology of OSMF and areca nut chewing was the most important risk factor with a genetic susceptibility to the condition. Some other researchers suggested lime, nutritional disorders, immunological and collagen disorders and consumption of tobacco and rarely chillies.

Areca nut

The inner kernel or seed of the betel and arecanut trees is what remains after the husk has been removed. Arecoline, an active alkaloid included in betel nuts, induces fibroblasts to produce collagen at a faster rate than usual.

Arecanuts contain a lot of copper as well, and chewing them for 5 to 30 minutes raises the amount of soluble copper in oral secretions, which is a trigger for OSMF. Areca nuts are chewed for a wide range of purposes, including digest after meals, mouth freshening, and reducing stress and anxiety. Mawa, paan masala and gutka with its dried form are commercially available high concentrated areca nut per chew [16]. Also they implicit more oral mucosal irritation than home prepared betel quid. The withdrawal symptoms of this addictive substance include mood fluctuations, anxiety and irritability, lack of focus, disturbed sleep, and craving [17].

Nutritional disorders

Subclinical vitamin B complex deficiency contributes to OSMF patients. Malnutrition, iron deficiency anemia and anemia are aggravating factors that interfere with the repair of inflamed oral mucosa, resulting in scarring and poor healing [18].

Immune system and genetics

The decrease of growth factor beta (TFG - B) and interferon -gamma in OSMF cases are correlated with the use of areca nut [19].

Human leukocyte antigen (HLA), the collagen correlation gene, and genes associated to detoxifying enzymes are some of the genes whose regulation affects the development and occurrence of OSMF. Additionally, distinct stages of OSMF showed

decreased expression of cytochrome P450 (CYP) subtype genes, including CYP2B6, CYP2C18, CYP2F1, and CYP3A5 genes, increasing OSMF prevalence [20].

Pathogenesis

The pathogenesis of OSF involves numerous molecular pathways, cytokines, and cells. Numerous biological processes contribute to its occurrence, and factors that contribute to its development comprise an imbalance in the metabolism of collagen, epithelial-mesenchymal transition (EMT), differentiation of myofibroblasts, a lack of oxygen etc [21].

Collagen metabolism

The extracellular matrix (ECM), which maintains tissue shape and cell polarity, is primarily composed of collagen. The primary factor contributing to OSF is an unbalanced metabolism [22].

Differentiation of myofibroblast

Oral keratinocytes stimulated by arecoline can be transdifferentiated to produce myofibroblast. According to a study, the expression of stage-specific embryonic antigen-4 (SSEA-4), a sialylglycolipid produced by arecoline in buccal mucosal fibroblasts, was significantly higher in the OSF tissues connected to AN chewing. Myofibroblast activity in fibrotic buccal mucosal fibroblasts may be eliminated by inhibiting SSEA4 production[23].

Mesenchymal transition

Areca nut chewing causes changes of keratinocyte morphology, its inflammation and their cycle in S phase [24].

Clinical Presentation

Oral submucous fibrosis can happen at any age, but it is more frequently observed in people between the ages of 20 and 50. Its clinical lesions can appear anywhere in the oral cavity, including the pterygomandibular raphe, cheek, palate, lips, tongue, and even the upper respiratory tract and oropharynx [25]. Burning sensations or intolerance to spicy food, as well as the occurrence of vesicles on the palate, are the most common clinical signs of OSMF. Patients may experience a marble-like stiffening and blanching of the oral mucosa as the disease progresses, followed by palpable fibrous bands in the soft palate and buccal region with shrunken bud like fibrous uvula (Figure 1). Small vesicles could rupture and create erosions, which are then followed by discomfort and ulceration. These are the early signs of OSMF [6].



Figure 1: Shrunken bud like uvula in Oral submucous fibrosis

When this condition is in a moderate stage , it includes a burning sensation, stomatitis, a progressive decrease in mouth opening, taste sensation loss, xerostomia, difficulty blowing cheeks, rigid oral mucosa, soft palate, soft tongue, thick palpable fibrous bands, a compressed uvula and blanching of buccal and labial mucosa [26]. With moderate stage presentation, de-papillation of the tongue, and involvement of the pharyngeal and esophageal mucosa, the oral mucosa takes on a mottled, opaque, or white marble-like look at the advanced stage [27].

In most cases, a biopsy of the OSMF lesion is required, particularly if there are ulcerative, nodular and erythematous. Severe or moderate epithelial dysplasia that has been histologically confirmed must be treated along the same lines as cancer. Non-dysplastic cases must be observed carefully over time, and after quitting a habit, antioxidant therapy must be recommended.

Management

In the management of OSMF, their staging plays a major role. The management can be divided into topical, systemic, physiotherapy, intralesional, targeted drug therapy, laser and surgical (Figure 3). In the present review, Kerr et al classification is considered for treatment plan and management (Figure 2).

Grade	Severity	Features
Grade 1	Mild	Any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported and inter-incisal opening greater than 35 mm.
Grade 2	Moderate	Above features of OSMF and inter-incisal limitation of opening between 20 to 35 mm.
Grade 3	Severe	Above features of OSF and inter-incisal opening less than 20 mm.
Grade 4A	-	Above features of OSMF with other potentially malignant disorders on clinical examination.
Grade 4B	-	Above features of OSMF with any grade of oral epithelial dysplasia on biopsy.
Grade 5	-	Above features of OSMF with oral squamous cell carcinoma.

Figure 2: Kerr et al classification of Oral Submucous Fibrosis

In grade I OSMF -

- Topical (Curcumin gel and oil [28], Aloe vera [29], Tulsi and tumeric [30], spirulina [31] ,0.1% triamcinolone acetone [32] and 0.5% betamethasone [33])
- Systemic - Curcumin tablets [34] and lycopene 16 mg [35]

In grade 2 OSMF

- Topical
- Physiotherapy (Muscle stretching exercise with heat therapy, Ice cream stick exercise, Figure of 8 tongue movements, Ballooning of mouth, hot water gargling [36], intra oral appliance - oral stent [37]and ultra sound therapy [38])
- Intralesional (Dexamethasone - 4 mg/ml [39], Hyaluronidase 1500 IU and Interferon gamma 0.01 - 10.0 U/m [40], Placental extract - 2.0 cc [41], Chymotrypsin 5000 IU [42])
- Systemic (Lycopene 16 mg, Immune milk 45 mg, pentoxyphylline - 400 mg [43],, Colchicine - 0.5 mg, Levamisole - 50 mg, beta carotene, levamisole 50 mg [44], curcumin tablets, Vitamin A, E and Iron supplements [45])

In Grade 3 OSMF

- Surgical - Surgical resection of fibrous bands , Grafts - nasolabial flap, tongue flap, palatal island flap [46], artificial dermis, superficial temporal fascia flap, buccal fat pad [47]
- Laser (Diode laser 805 nm to 980 nm [48], KTP5322 laser 532 nm, CO2 laser <1000nm [49]and ErCr:YSGG laser - 2780 nm [50])
- Physiotherapy
- Targeted drug therapy - Pirfenidone - TGF Beta [51], Tanshinone - p53 and p21 [52]

In grade 4A

- Topical
- Systemic

In grade 4B

- Topical
- Systemic
- Physiotherapy
- Surgical

In Grade 5

- Surgical
- Laser
- Physiotherapy
- Chemoradiation

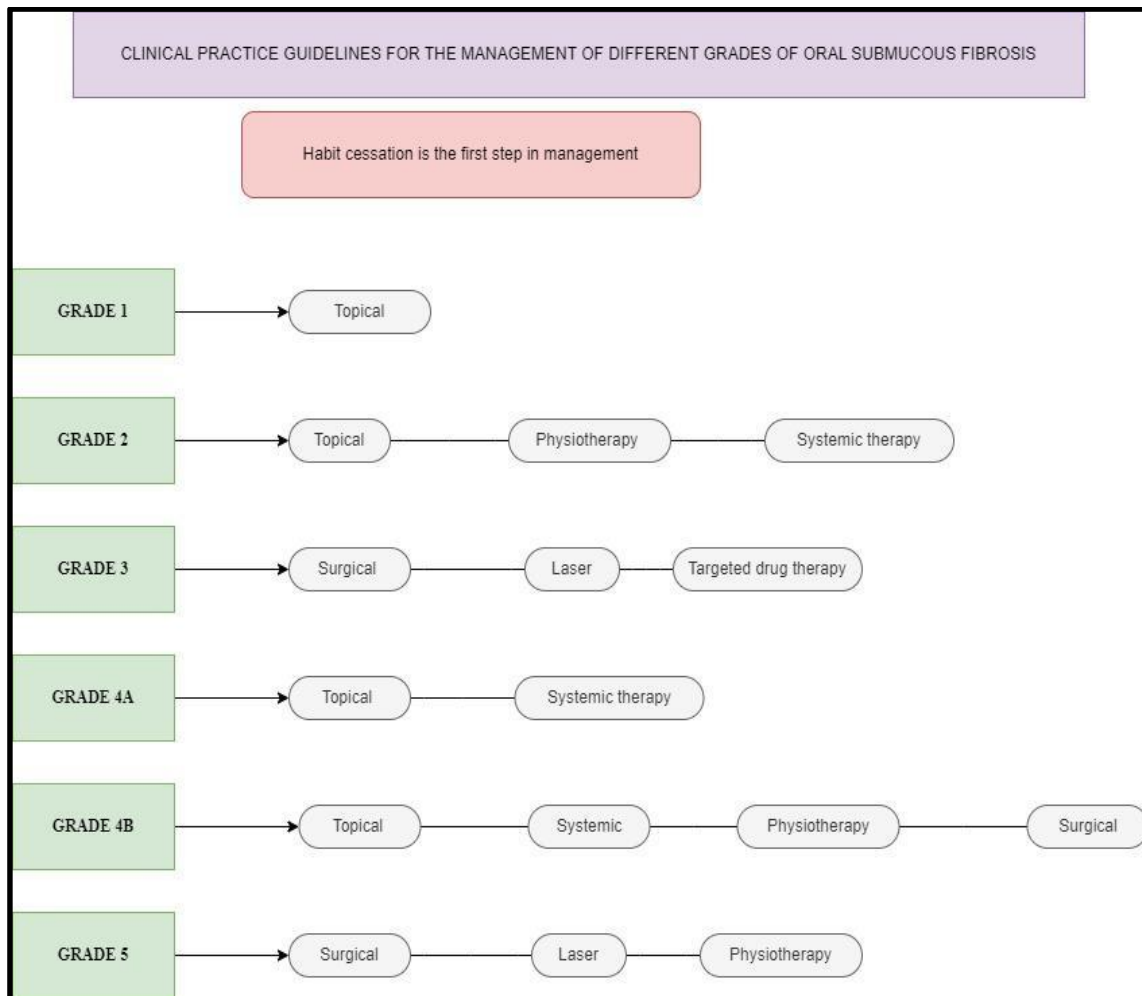


Figure 3: Clinical guidelines in the management of OSMF

CONCLUSION

The clinical practice recommendations offered in this article, which provide a thorough foundation for the therapy of oral submucous fibrosis (OSMF), a crippling illness with important public health implications, are summarized. These recommendations, which aim to enhance patient care and outcomes, are based on the most recent evidence-based research and expert consensus.

The comprehensive strategy described here places a strong emphasis on early diagnosis, risk assessment, and customized intervention strategies. Healthcare professionals can treat a wide range of OSF presentations, from mild to severe cases, by combining behavioral changes, medication, surgical alternatives, and continued monitoring.

These recommendations also stress the value of patient education and collaboration, enabling people to take an active role in their own care. A good care strategy must include regular follow-up sessions and vigilant monitoring of illness development.

It is important to recognize that the management of OSF is an area that is always changing, and current research projects will continue to improve our knowledge and therapeutic strategies. Therefore, it is encouraged for healthcare professionals to keep up with the most recent developments and modify their procedures accordingly.

Following these clinical practice recommendations could ultimately considerably improve the quality of life for those suffering from oral submucous fibrosis and provide them the best opportunity at a healthier and more functional future.

Declarations

- A. Ethics approval and consent to participate: Not applicable
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- C. Conflict of interest : Not applicable

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