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Review Article

A contemporary narrative review on Oral Submucous Fibrosis

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ABSTRACT:
Oral Submucous fibrosis (osmf) has traditionally been described as "a chronic, insidious, scarring, disease of the oral cavity, often with involvement of the pharynx and the upper esophagus."Millions of individuals are affected, especially in South and South East Asian countries. The main risk factor is areca nut chewing. Due to its high morbidity and high malignant transformation rate, constant efforts have been made to develop effective management. Despite this, there have been no significant improvements in prognosis for decades. This expert opinion paper updates the literature and provides a critique of diagnostic and therapeutic pitfalls common in developing countries and of deficiencies in management.
Keywords: Areca nut, betel, oral submucous fibrosis, malignant potential, Aetiology and Management, fibrosis

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INTRODUCTION

Oral submucous fibrosis is potentially malignant disorder which was described by Schwaertz in 1952 as "Atropica idiopathica mucosae oris" and later by Jens J. Pindborg in 1966 as "a insidious, chronic disease that affects any part of the oral cavity, and sometimes the pharynx [1]. Although, occasionally preceded by or associated with vesical formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroblastic changes of lamina propria with epithelial atrophy, leading to stiffness of oral mucosa and causes trismus and an inability to eat"[1].OSMF is also characterized by reduced movement and depapillation of the tongue ,blanching and leathery texture of the oral mucosa, progressive reduction of mouth opening and shrunken uvula[2,3,4]. Other terms used to describe OSMF include idiopathic scleroderma of the mouth, juxtaepithelial fibrosis, idiopathic palatal fibrosis, diffuse oral submucous fibrosis, and sclerosing stomatitis[5,6,7,8].

EPIDEMIOLOGY

Worldwide, the number of cases of OSMF was estimated to be 25 million in 1966[9].It occurs predominantly in the India, Southeast Asia, the South Pacific Islands, and South Africa [10]. Around 600 million persons consume betel worldwide, which makes the betel fourth most consumed drug after nicotine, etanol and caffeine[11,12].The habit is prevalent in South Asia and South Africa and is also becoming common i western world. Betel is composed of Arecanut (Areca catechu), the fresh leaf of betel pepper (Piper betel), spices and calcium hydroxide(lime)[13].Various areca nut mixtures ,i.e.,pan, mawa and gutkha, are very popular in South Asia[14]. The precancerous nature of OSMF was first postulated by Paymaster, who observed the onset of sloe growing squamous cell carcinoma in one tgird of OSMF cases seen in Tata Memorial Hospital, Bombay[15].Epidemiological studies have shown that OSMF is a precancerous condition with the risk of malignant transformation as high as 7.6%[16].

HISTOPATHOLOGY

Microscopically, the principal feature is trophy of the epithelium and subjacent fibrosis. Epithelial dyplasia occasionally may be evident. The lamina propria is poorly vascularized, hyalinized with few fibroblast. A

diffuse mild to moderate inflammatory infiltrate is present.Type1collagen predominates in the submucosa, whereas type3 collagen tends to localize at the epithelium- connective tissue interface and around blood vessels, salivary glands, and muscle[8].

CLASSIFICATION
More et al. 2012 classification of OSMF[17,18]

CLINICAL STAGING
Stage1(S1) -Stomatitis and or blanching of oral mucosa
Stage2(S2)-Presence of palable fibrous bands in buccal mucosa and/or oropharynx, with/without stomatitis
Stage3(S3)-Presence of palable fibrous bands in buccal mucosa and in any other parts of oral cavity with/without stomatitis
Stage(S4)-Any one of the above stages along with other potentially malignant dosorders (eg oral leukoplakia, oral erythroplakia)

FUNCTIONAL STAGING
M1 staging-Interincisal mouth opening upto or greater than 35mm
M2 staging -Interincisal mouth opening between 25 and 35mm
M3 staging-Interincisal mouth opening between 15 and 25mm
M4 staging-Interincisal mouth opening less than 15mm

PATHOGENESIS
1.COLLAGEN ACCUMULATION
1) Increased collagen production: Under the infuence of areca nut, fibroblasts differentiated into phenotypes that produces more collagen. Arecoline gets converted in to arecadine which is the active metabolite. There is dose dependent increase in production of collagen by fibroblasts
b) Stabilization of collagen structure and decreased collagen breakdown: One of the mechanisms that can lead to increased fibrosis is by reduced degradation of collagen by forming a more stable collagen structure. Betel nut contains tannin. Tannin has ability to stabilize collagen by cross linking it

2. INCREASED IMPRESSION OF FIBROGENIC CYTOKINES
The most important finding in the various studies was the demonstration of increased expression of fibrogenic cytokines namelyTGF B-1,PDGF and bFGF in OSF tissues compared to normal

3.GENETIC POLYMORPHISMS PREDISPOSING TO OSF
Polymorphisms of the genes coding for TNF-a has been reported as a significant risk factor for OSF.TNF-a is known to stimulate fibroblastic proliferation in vitro[19].

ETIOLOGY
The etiology of OSMF is obscure ,although various hypothesis are proposed ,suggesting multifactorial origins, such as chewing of areca nut and its flavoured formulations (most common),chronic nutritional deficiencies (especially iron ,Vitamin B complex and protein)tobacco and lime, genetic predisposition, autoimmunity.

ARECA NUT
Excessive use of arecanut and its flavoured formulations disrupts the hemostatic equilibrium between synthesis and degeneration. The copper ionin areca nut increases the activity of lysyl oxidase leading to unregulated collagen production ,thereby causing oral fibrosis. This leads to the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation- peroxidation of polyunsaturated fatty acids[20].

IMMUNE SYSTEM
In OSMF cases, the transforming growth factor-beta(TGF-B)and interferon-gamma(IFN-y) levels are low and the results are correlated with use of betel quid[21].

NUTRITIONAL DEFICIENCIES
OSMF cases have been suspected with subclinical vitamin B complex deficiency[22]. Iron defeciency anaemia, vitamin B complex deficiency and malnutrition are promoting factor that damage the repair of inflamed oral mucosa leding to scarring and defective healing[23]. Chilles also play an aetiological role in OSMF, [24,25] as its active ingredient Capsicum(vanilly lamide of 8-methyl-6-nonenic acid) acts as a predisposing factor for fibrosis
Tobacco and lime
Freezed dried forms of mawa, gutkha and pan masala are commercially available with high concentration of arecanut per chew. They cause more irritation to the oral mucosa than self-prepared betel quid[26].
Genetic and immunologic processes
A genetic component is assumed to be involved in OSF. Patients with increased frequency of HLA-A10,HLA-B7,and HLA-DR3 reported in people without a history of betel nut chewing or chilli ingestion[27].

CLINICAL FEATURES
OSMF is a disease of middle age group with peak incidence observed in the second to fourh decade of life. The sex distribution of OSMF varies geographically .The most common oral site for OSMF is buccal mucosa and retromolar region, followed by soft palate, faucial pillars, floor of mouth, tongue, labial mucosa and gingiva.
Intra- and extra-oral manisfestations of OSMF at different stages

INTRAORAL
EARLY STAGE
Stomatitis, excessive salivation, burning sensation, blanching of mucosa, blister formation, presence of thin palable fibrous bands, sparse brown/black pigmentation

MODERATE STAGE
Stomatitis, burning sensation, xerostomia, loss of taste sensation, gradual decrease in mouth opening, difficulty in whistling, vesicle formation, petechiae, rigid oral mucosa, difficulty in blowing the cheeks, defective gustatory sensation, blanching of oral mucosa, labial mucosa, tongue, floor of mouth and faucial pillars. Presence of thick palpable fibrous bands, shrunken uvula with altered shape(inverted hockey stick, bud like, deviated)

ADVANCED STAGE
Stomatitis, burning sensation ,xerostomia, reduction in mouth opening, restricted tonuge movement loss of taste sensation ,unable to blow the cheeks, defective gustatory sensation, inability to whistle, blanching of oral mucosa:esp soft palate, buccal mucosa, tongue, labial mucosa, floor of mouth, and faucial pillars. Loss of suppleness of mucosa, mottles or opaque or white marble like appearance of oral mucosa, thick palpable fibrous bands on buccal and labial mucosa, depapillation of tongue ,shrunken uvula with altered shape(inverted, hockey stick, bud like, deviated),involvement of the pharyngeal and esophageal mucosa[4,28,29].

EXTAORAL
EARLY STAGE
No significant extraoral features are observed

MODERATE
Prominent masster muscle, nasal twang, sunken cheeks, thinning of lips, difficulty in deglutition, loss of nasaolabial fold, prominent antegonial notch, hoarseness of voice, mild hearing impairment, weight loss

ADVANCED STAGE
Hypertrophic and stiff masster muscle, nasal intonation of voice, sunken cheeks, multiple folds on cheeks when attempting wide opening mouth, thinning of lips, difficulty in deglutition, loss of nasolabial fold, prominent antegonial notch, hoarseness of voice, mild hearing impairment, weight loss, atrophy of facial musculature. in severe cases, radio graphically, there is alteration in condylar form and fibrous ankylosis of the temporomandibular joints [4,28,29].

DIAGNOSTIC APPROACH
Diagnosis of OSMF is based on clinical signs and symptoms that include burning sensation, pain and ulceration[4,28,29] Progressive restriction in mouth, blanching of the mucosa, depapillation of the tongue, and loss of taste are classic features[28]. Dysphonia and hearing impairment is also observed in advanced cases[30,31]

MANAGEMENT
Early diagnosis of OSMF is important in both prevention and therapeutic procedures of oral cancers. The treatment of OSMF in the last few decades is varied and ineffective, but till date there is no consensus on the most important management of OSMF. Various treatment modalities are available to treat this condition which includes medicinal approch, surgical management and physiotherapy. Proper treatment begins with education of the patient regarding the ill effects of arecanut and related products chewing products. The patient should be informed about the irreverssible nature of disease despite quitting the habit and possibilities of developing oral cancer[32]

MEDICAL MANAGEMENT
1. Nutritional support[32,33]-Micronutrients and minerals, e.g. Vitamin A,B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium, lycopene
2. Local drug delivery[34,35]-Local injections of dexamethasone, hyaluronidase, chymotryosin and placental extract
3. Physiotherapy[35,36,37]-Forceful mouth opening and heat therapy in the form of hot rinses, lukewarm water, or selective deep heating therapies like short wave and microwave diathermy
4. Surgical management[35,38]- Submucosal resection of fibrotic bands, myotomy, coronoidectomy

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