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Oral submucous fibrosis - A collective review

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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. The pathogenesis of OSMF is said to be multifactorial. Areca nut chewing is the main risk factor. The sites mostly affected are oral cavity and upper third of esophagus. Because of the high morbidity and high malignant transformation rate, efforts have been made to develop effective management for OSMF. Diagnosis is based on different clinical features, with mucosal blanching, burning sensation, hardening of mucosa, presence of characteristic fibrous bands associated with gradually increasing inability to open the mouth. Treatment of OSMF is difficult; a combination drug treatment is administered. In patients with severe disease, Surgery and physical therapies are added to drug therapy.

In this review we discuss various components of OSMF, including the classification, etiology, clinical

presentation, pathogenesis, and an overview of its management.

Keywords: Oral submucous Fibrosis, Areca nut, Precancerous.

Introduction: In 1952 Schwartz described Oral Submucous Fibrosis (OSMF) as "Atropica idiopathica mucosae oris"[1]. Jens J. Pindborg in 1966 described as "an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx [1]. Sometimes it is present with the formation of vesicles, and always associated with juxtaepithelial inflammatory reaction, followed by fibroelastic changes in lamina propria and epithelial atrophy which causes stiffness of the buccal mucosa, trismus and inability to eat" [1].The definition by the World Health Organization (WHO) of a precancerous oral condition: "it is a generalized pathological state of the oral mucosa associated significantly with increased risk of cancer" [2,3].

OSMF is also called as idiopathic scleroderma of mouth, juxtaepithelial fibrosis, idiopathic palatal fibrosis, diffuse oral submucous fibrosis, and sclerosing stomatitis [4-7].The disease is seen in any age group, including children and adults, but prevalence is higher in the age group 18–35 years. Prevalence of OSMF cases have raised from 0.03% to 6.42% in the previous four decades, making it a significant public health problem in India. The disease contributes significantly to mortality because of its high malignant transformation rate[1,8,9,10].Various factors are suggested to trigger the disease process including areca nut chewing, genetic predisposition and immunologic processes. Deficiency of nutrition and chilli ingestion may lead to the course of the disease [8-10].

Epidemiology

OSMF occurs predominantly in India, South Pacific Islands, South Africa, South east Asia. Worldwide around 600 million people consume betel, that makes betel the 4th most consumed drug after nicotine, caffeine and ethanol [11,12].

Classification

1. Wahi et al. [13] classified OSF into three clinical groups on the basis of clinical features, severity and extent of involvement.

Group I: Usually there are no symptoms referable to mucosal involvement. The lesions affect one or other commonly involved anatomical sites, are focal in character, show pallor or whitish coloration, wrinkling of mucosa and minimal induration.

Group II: Cases might present symptoms of soreness of the mucosa or increased sensitivity to chilli. The lesions are diffuse, white, extensive and indurated, involving one or more anatomical sites.

Group III: Symptoms are mainly due to restricted mobility such as trismus, stretching at the angles of the mouth and altered pronunciation. Firm mucosal bands can be palpated, and the surface might be fissured or ulcerated.

2. Gupta et al. [14] clinically classified four stages of submucous fibrosis according to the increasing intensity of trismus.

I. Very early stage: Complaints of burning sensation in the mouth or ulceration without any difficulty opening the mouth

II. Early stage: Along with symptoms of burning sensation, complaints of slight difficulty opening the mouth.

III. Moderately advanced stage: Marked trismus, to the extent that the patient cannot open their mouth more than two finger-widths. Associated difficulties with mastication are apparent.

IV. Advanced stage: Patient is undernourished, anemic and shows marked trismus and/or other symptoms, as

mentioned above.

Clinical features

Mathur and Jha[15] classified clinical features of OSF into three stages.

Stage 1: Early OSF

a. Mild blanching

b. No restriction in mouth opening.

c. No restriction in tongue protrusion, measuring from mesio-incisal angle of an upper central incisor to the tip of the tongue when maximally extended with mouth at maximal opening.

d. Burning sensation only on ingesting spicy foods, hot liquids, etc.

Stage 2: Moderate OSF

a. Moderate to severe blanching

b. Mouth opening reduced by 33%, tongue protrusion reduced by 33%, and flexibility also demonstrably decreased.

c. Burning sensation even in absence of stimuli.

d. Presence of palpable bands.

e. Lymphadenopathy, either uni-or bilateral.

f. Demonstrable anemia on hematological examination.

Stage 3: Severe OSF

a. Very severe burning sensation, patient unable to perform day-to-day work.

b. More than 66% reduction in mouth opening, cheek flexibility and tongue protrusion. In many cases, the tongue may appear fixed.

c. Ulcerative lesions may appear in cheek.

d. Thick palpable bands.

e. Lymphadenopathy evident bilaterally.

Aetiology

The strongest risk factor for OSMF considered is areca nut, the duration, frequency and the amount of chewing areca nut is directly related to development of the disease. Tannins is found in areca nut, of which D-catechol and gallotannic acid are important. It also contains several alkaloids, of which arecoline is most abundant, and arecaidine, guvacine, arecolidine, and guvacoline are found in small quantities[16].The increasing use of pan masala/gutka (which is mixture of tobacco, areca, and beetle quid) which seems to be occur in an earlier age of onset of the OSMF. The Oral tissues contacts directly with the quid mixture resulting in irritation by various components such as tannis, catechins, copper and biologically active alkaloids [16].

Nutritional deficiencies

Iron deficiency (anemia), minerals, Vitamin B complex,and malnutrition are the factors that disturbs the process of repair of inflamed oral mucosa, leading to deranged healing and resulting scarring and fibrosis. In atrophic oral mucosa the effects of chilies, betel nuts, and other irritants is more susceptible [17].

Genetics and immunology

Involvement of a genetic component in OSMF is believed , because some cases reported in medical literature in some people without having any history of betel nut chewing or chili intake. Patients having OSMF have increased frequency of HLA-A10, HLA-B7, and HLA-DR3.[18]

Pathogenesis

In the pathogenesis of OSMF areca nut plays a key role in the development of the disease. It contains alkaloids, flavonoids, and copper, which all interfere with homeostasis of the extracellular matrix. Four alkaloids: arecoline, arecaidine, guvacine, and guvacoline are known to stimulate fibroblasts to produce collagen [19]. Flavonoids like tannins and catechins inhibit collagenase, stabilise the collagen fibrils, and render them resistant to degradation by collagenase [19,20].The localised mucosal inflammation caused results in the

recruitment of activated T-cells and macrophages that lead to an increase in cytokines and tumour growth factor beta (TGF- β)[21]. Simultaneously, TGF-β inhibits collagen degradation by activating the tissue inhibitor of matrix metalloproteinase (TIMP) genes and plasminogen activator inhibitor (PAI) [21]. The high concentration of copper in areca-nut has been found to stimulate lysyl oxidase activity, an enzyme essential to the final cross-linking of collagen fibres [21]. Increased copper has been seen in mucosa affected by OSMF, which supports its role in fibrogenesis by enhancing lysyl oxidase activity [19]. Continually chewing areca-nut leads to increased activity of the masticatory muscles, depletion of glycogen, and muscle fatigue. The reduced blood supply following fibrosis further promotes muscle fatigue and causes extensive degeneration and fibrosis in the muscles [22].

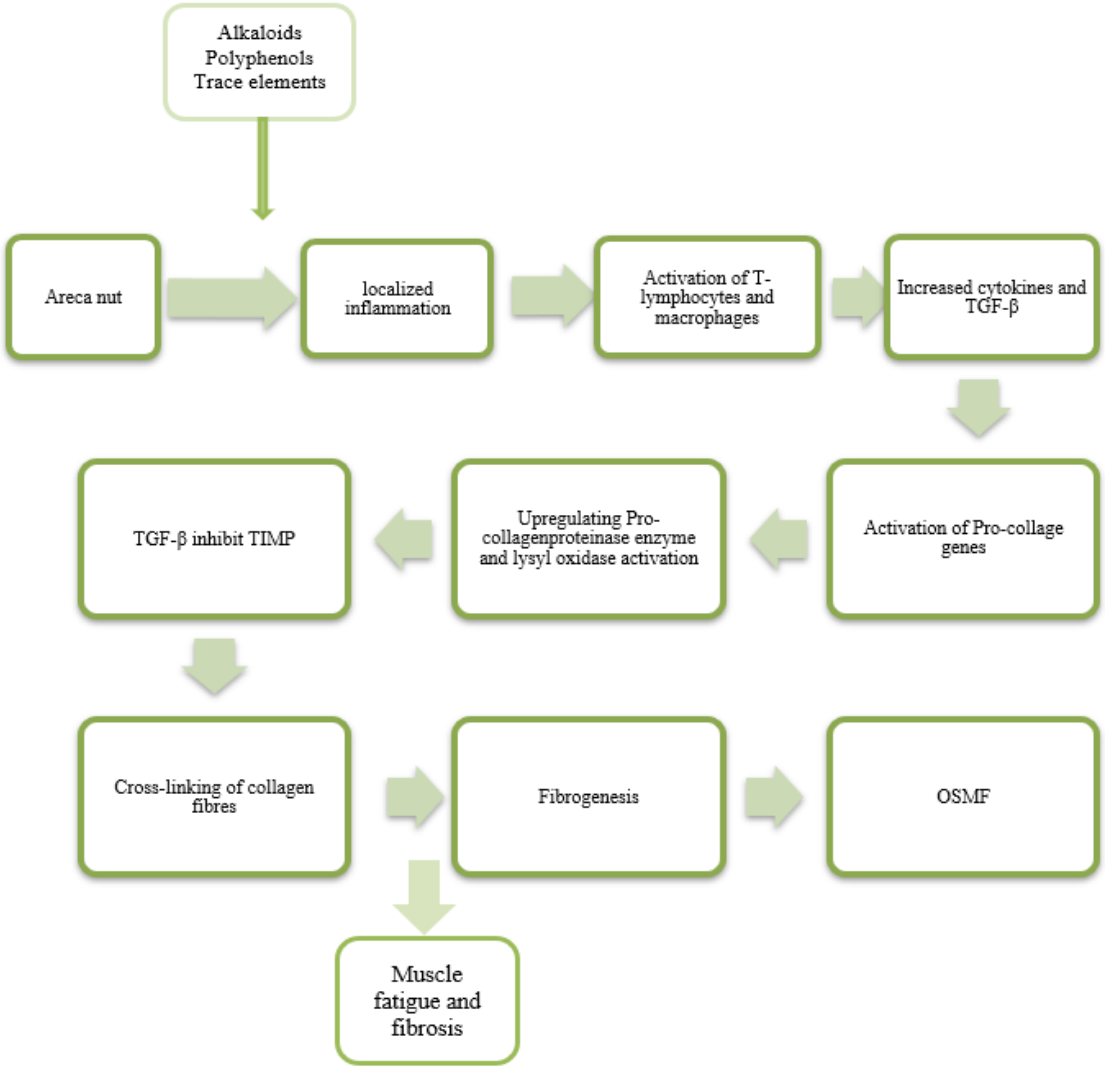

Fig 1: Pathogenesis of OSMF [19,20,21,22]

Histopathological features

1. Connective tissue

The connective tissue changes in four stages of OSMF described by pindborg JJ are as following[1]:

Very early stage

characterized by finely fibrillar collagen dispersed with marked edema. Inflammatory cells, mainly polymorphs with occasional eosinophils, are present in very early stage.

Early stage

The juxtaepithelial area showed early hyalinization. Separated bundles of collagen is still seen, which are present in moderate number and thickened in young fibroblasts. Mostly Inflammatory cells are eosinophils, mononuclear lymphocytes, and occasionally plasma cells.

Moderately advanced stage

The collagen is moderately hyalinized, amorphous changes starts from the juxtaepithelial basement membrane. Thickened collagen bundles occasionally seen separating by slight residual edema. Mostly presented cells are adult fibroblast with elongated spindle shaped nuclei, with scanty cytoplasm blood.

Advanced stage

The collagen is completely hyalinized and is seen as a smooth sheet with no separate bundles. Edema is not present, in hyalinized area fibroblasts are devoid, a thin elongated cell or vestigial nucleus can be seen in a rare integral fibre bundle. Blood vessels are completely obliterated or narrowed. Plasma cells and lymphocytes are the mainly seen inflammatory cells..

2. Epithelium

J. P Caniff [23] studied histological sections of thirty patients with OSMF, in which 87% of the patients had an atrophic epithelium, of which 27% were reported as having a flattened epidermal/demial junction.

None of them had any evidence of epithelial hyperplasia, 33% of patients had non-keratinized or poorly keratinized epithelium, but in the remaining 67% of the cases, epithelium showed keratinized metaplasia, parakeratinization in 13% and hyper orthokeratinization in 23% of patients.

Grading

Kerr et al.[5]proposed a disease grading system in five grades:

Grade 1: Milld: any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported －and interincisal opening ＞ 35 mm

Grade 2: Moderate: the above features of OSMF ＋ interincisal opening limited to 20-35 mm

Grade 3－Severe: the above features of OSMF ＋ interincisal opening＜20 mm

Grade 4: A －OSMF ＋other potentially malignant disorder on the clinical examination Grade 4B －OSMF with the any grade of oral epithelial dysplasia on biopsy

Grade 5: OSMF ＋oral squamous cell carcinoma

Management

The reduction or even elimination of the habit of areca nut chewing is an important preventive measure [24]. To improve the current treatment regimens of OSF, the following strategies have been proposed [24]:

1. Nutritional support- High proteins and calories, vitamin B complex and other vitamins and minerals.
2. Immunomodulatory drugs- Glucocorticoids local and systemic application
3. Physiotherapy-Forcefully mouth opening and heat therapy, satisfactory results has been noticed by heat .
4. Local drug delivery- Local injections of corticosteroids and placental extract have been tried, in addition to hyaluronidase, collagenase and similar substances, which break down intercellular cement substances and also decrease collagen formation.
5. Surgical management- Submucosal resection of fibrotic bands, myotomy, coronoidectomy.

Conclusion

OSF shows a gradual onset and might take years to develop along with the other features. The most important, outstanding and reliable feature of OSF is the presence of palpable fibrous bands in the buccal mucosa,

along with other characteristic features such as diffuse blanching of the mucosa, occurrence of hyperpigmented areas adjacent to zones with loss of pigment, loss of tongue papillae and leathery consistency of the mucosa. Furthermore, the patient might suffer from a burning sensation aggravated by spicy foods, dryness of the mucosa or hypersalivation and trismus. OSF patients should be periodically investigated for different parameters to assess changes in the mucosa as well as changes at the cellular level. Long -term follow up is essential.

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