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REVIEW ARTICLE

Oral Submucous Fibrosis: An Overview

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ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic and potentially malignant condition of the oral cavity. It occurs predominantly in India and Southeast Asia. The pathogenesis of OSMF is not well established, but it is believed to be multifactorial. Chewing of betel quid (containing areca nut, tobacco, and slaked lime) has been recognized as one of the most important risk factors. It is characterized by a juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria and associated epithelial atrophy. The disease affects most parts of the oral cavity as well as the upper third of the esophagus. The abnormal fibrosis causes blanching and stiffness of the mouth, with eventual immobility of the lips, cheeks, tongue, soft palate, and uvula. Treatment of OSMF is difficult; a combination drug treatment is administered. In patients with severe disease, physical therapy and/or surgery is added to drug therapy.

Keywords: Areca nut, Malignant potential, Oral submucous fibrosis, Precancerous.

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INTRODUCTION

Oral submucous fibrosis (OSMF) is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Occasionally, it is preceded by and/or associated with vesicle formation and is always associated with a juxtaepithelial inflammatory reaction followed by progressive hyalinization of the lamina propria. The later subepithelial and submucosal myofibrosis leads to stiffness of the oral mucosa and deeper tissues with progressive limitation in opening of the mouth and protrusion of the tongue, thus causing difficulty in eating, swallowing, and phonation.[1] Epithelial atrophy is marked in advanced stages of the disease. Oral submucous fibrosis is a premalignant condition associated with chewing of areca nut (betel nut).[2]

In 1952, Schwartz described five Indian women from Kenya with a condition of the oral mucosa, including the palate and pillars of the fauces, which he called "atrophia idiopathica (tropica) mucosae oris."[3] Later, it was termed as OSMF.

Epidemiology

It occurs predominantly in India, Southeast Asia, the South Pacific Islands, and South Africa.[4] Around 600 million persons consume betel worldwide, which makes betel the fourth most consumed drug after nicotine, ethanol, and caffeine.[5,6]

The habit is prevalent in South Asia and South Africa and is also becoming common in the Western world. Betel is composed of the areca nut (*Areca catechu*), the fresh leaf of betel pepper (*Piper betel*), spices, and calcium hydroxide (lime).[2] Various areca nut mixtures, i.e., pan, mawa, and gutka, are very popular in South Asia.[7] Mawa is a mixture of tobacco, lime, and areca nut.[8] The prevalence rate in India varies from 0.2 to 10.9% (Table 1).[1,8-12] With an increase in consumption of chewing tobacco-containing areca nut, there will likely be an increase in the prevalence of OSMF.

The precancerous nature of OSMF was first postulated by Paymaster, who observed the onset of a slow-growing squamous cell carcinoma in one-third of OSMF cases seen in the Tata Memorial Hospital, Bombay.[13] Epidemiological studies have shown that OSMF is a precancerous condition with a risk of malignant transformation as high as 7.6%.[14]

Oral submucous fibrosis is more prevalent in males, with peak seen in the 3rd decade of life. The most common affected site is buccal mucosa followed by palate.[15]

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Table 1: Distribution of OSMF according to geographic location

Investigator and year of study	*Place/ethnic origin of patient*	*Prevalence*
Pindborg and Sirsat (1968)[8]	India/Indians	0–0.4
Lay et al (1982)[9]	Bilugyum/Burmese	0.1
Seedat and van Wyk (1988)[10]	Durban/Indians	3.4
Rajendran (1992)[1]	India/Indians	0.27
Gupta et al (1998)[11]	Gujarat, India/ Indians	10.9
Mathew et al (2008)[12]	Southern India/ Indians	2

ETIOLOGY

Several etiological factors, such as chilly consumption, nutritional deficiency states, areca nut chewing, genetic susceptibility, autoimmune and collagen disorders, have been suggested to be involved in the pathogenesis of OSMF.

However, areca nut is considered to be the strongest risk factor for OSMF. The amount, frequency, and duration of chewing areca nut are clearly related to the development of this disease.[15,16] Areca nut is an endosperm of the fruit of the *A. catechu* tree. Areca nut contains tannins of which gallotannic acid and D-catechol are important. It also contains several alkaloids, of which arecoline is most abundant, and arecaidine, guvacine, arecolidine, and guvacoline are found in small quantities. The most predominant polyphenols are catechin, flavonoids, flavan-3,4-diols, leucocyanidins, hexahydroxyflavans, and tannin. Minor polyphenols include epicatechin, gallic acid, gallotannic acid, D-catechol, and phlobatannin. The increasing use of pan masala/gutka (a mixture of tobacco, areca nut, and beetle quid) seems to be associated with an earlier age of onset of OSMF. The direct contact of the quid mixture with oral tissues results in their continuous irritation by various components, including biologically active alkaloids, tannins, catechins, and copper.[17] Areca nuts also contain trace elements like copper, bromide, vanadium, manganese, and chlorine, thus exposing betel quid users to increased concentrations of potentially hazardous compounds.[18,19]

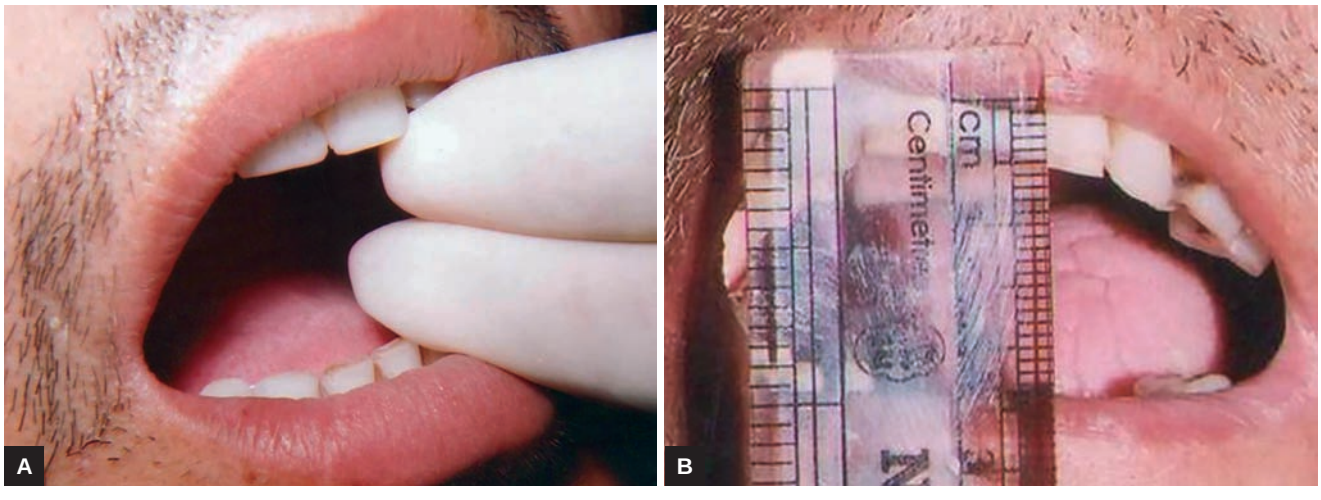
Pathogenesis

The pathogenesis of OSMF is not well established, although a number of possible mechanisms have been suggested. Pathogenesis is believed to involve a juxtaepithelial inflammatory reaction and fibrosis in the oral mucosa, probably due to increased cross-linking of collagen through the upregulation of lysyl oxidase activity.[20] Lysyl oxidase enzyme appears to take part in the initial steps of converting soluble monomers of collagen and elastin into insoluble fibers in the extracellular matrix. Excessive collagen deposition results from the effects of areca nut, which increases collagen production (e.g., stimulated by arecoline, arecaidine) and decreases collagen degradation.[21-23] Tannins from areca nuts increase collagen fiber resistance to collagenase.[24]

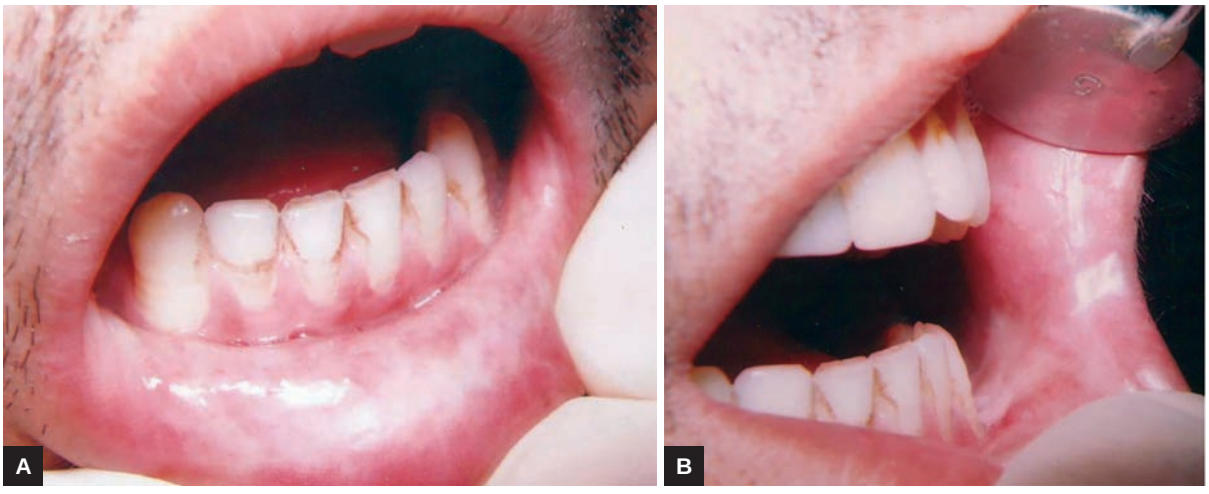
Areca nuts contain high copper concentrations, which get liberated during consumption of areca nut. The processed form of betel nut, i.e., the freeze-dried products (pan masala, gutka, mawa), contains higher concentration of copper as compared with the raw form; this may be because of the copper that is added as a preservative.[25,26] The average daily intake of copper by adults from diet in developing countries is between 0.6 and 1.6 mg/day.[27] An adult Indian, chewing areca nut daily, consumes over 5 mg of copper/day.[28] Copper plays an important role in the pathogenesis of OSMF because it stimulates collagen synthesis in oral fibroblasts and also causes upregulation of lysyl oxidase enzyme.[29,30] Furthermore, elevated serum and tissue copper levels are associated with duration of areca nut chewing and severity of OSMF.[20,31]

Clinical Features

The period between initiation of the chewing habit and the development of clinical symptoms of OSMF varies tremendously, ranging from a few months to several decades depending on the type of areca nut consumed, duration and practice of the habit, individual susceptibility, and other factors. Early symptoms include burning sensation, especially on consuming spicy foods. Increasing pain and discomfort is associated with vesicles and ulcerations.[32] There is an increased salivation with a subsequent xerostomia and defective gustatory sensation. The involved tissues become blanched, opaque, and adopt a marble-like appearance (Figs 1A and B). The



Figs 1A and B: Extraoral photograph showing reduced mouth opening



Figs 2A and B: Intraoral photograph showing blanched fibrosed oral mucosa and restricted mouth opening

figures depict blanching caused by impairment of local vascularity because of increasing fibrosis oral mucosa.

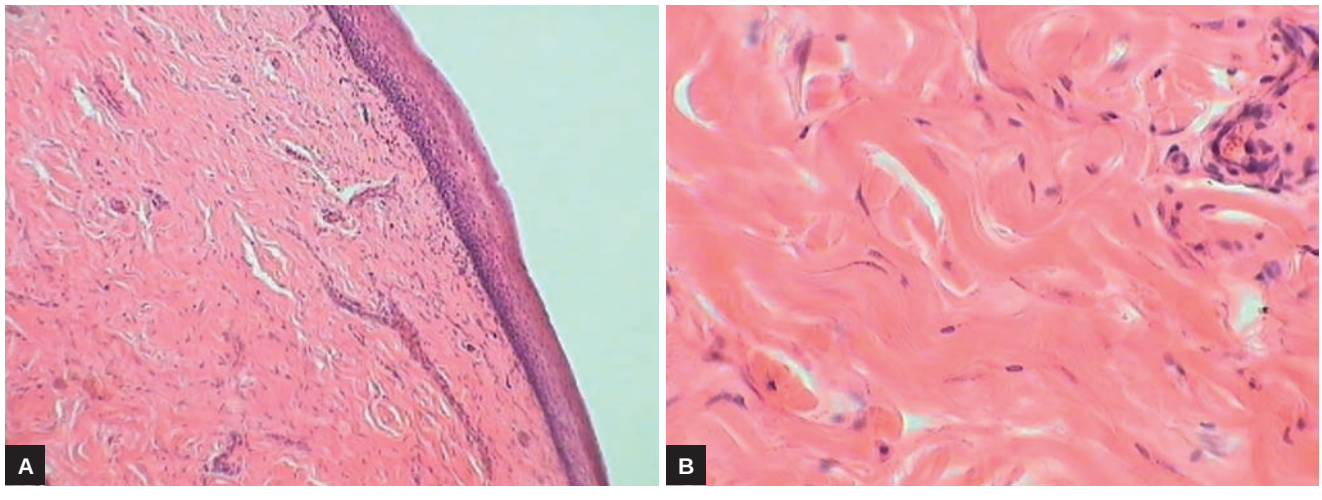
In the more advanced stage of the disease, the essential feature is a thick fibrous band, which may be palpated in the posterior buccal mucosa and around entire rima oris (Figs 2A and B). The figures depict restricting mouth opening (trismus) and causing difficulty in mastication, speech, and swallowing. The severity of trismus can be graded by measuring the interincisor opening or mouth opening. The mouth opening is categorized into stage I (>3 cm), stage II (2–3 cm), and stage III (<2 cm).[33,34] Fibrosis makes cheeks thick and rigid. The tongue becomes progressively less mobile and there may be an associated atrophy of papillae of the tongue. Hard palate involvement includes extensively blanched mucosa.[32]

Pathology

It is generally agreed that the pathological alteration in OSMF begins in the lamina propria and the epithelium responds only secondarily to it.[35] Based on the histopathological appearances of stained (hematoxylin and eosin) sections, the surgical specimens from OSMF can be grouped into four clearly definable stages: Very early, early, moderately advanced, and advanced. The early stages of OSMF are characterized by juxtaepithelial inflammation, including edema, large fibroblasts, and an inflammatory infiltrate, consisting primarily of neutrophils and eosinophils.[36] Later, collagen bundles with early hyalinization are seen.[37] In more advanced stages, OSMF is characterized by the formation of thick bands of collagen and hyalinization extending into the submucosal tissues and decreased vascularity. Muscle degeneration may also be seen in advanced stages.[38] The epithelium frequently becomes atrophic and loses melanin (Figs 3A and B).

Management

So far, there does not seem to be any satisfactory treatment for OSMF, although some conservative and surgical interventions may result in improvement.[39] Reduction or



Figs 3A and B: Histology of buccal mucosa biopsy showing atrophic epithelium with thick bands of collagen bundles and decreased vascularity

Table 2: Treatment modalities for OSMF

Nutritional support[40,41]	Micronutrients and minerals, e.g., Vitamins A, B complex, C, D, and E, iron, copper, calcium, zinc, magnesium, selenium, lycopene
Local drug delivery[42-44]	Local injections of dexamethasone, hyaluronidase, chymotrypsin, and placental extract
Physiotherapy[43,45,46]	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
Surgical management[43,47,48]	Submucosal resection of fibrotic bands, myotomy, coronoidectomy

even elimination of the habit of areca nut chewing is an important preventive measure. At least in the early stages of OSMF, it could probably slow down the progress of the disease. Currently, intralesional steroids and hyaluronidase are the main treatment modalities. Various treatment modalities for OSMF are summarized in Table 2.[40-48]

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