

Oral submucous fibrosis: an update

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Abstract: Oral submucous fibrosis (OSF) is a premalignant condition caused by betel chewing. It is very common in Southeast Asia but has started to spread to Europe and North America. OSF can lead to squamous cell carcinoma, a risk that is further increased by concomitant tobacco consumption. OSF is a diagnosis based on clinical symptoms and confirmation by histopathology. Hypovascularity leading to blanching of the oral mucosa, staining of teeth and gingiva, and trismus are major symptoms. Major constituents of betel quid are arecoline from betel nuts and copper, which are responsible for fibroblast dysfunction and fibrosis. A variety of extracellular and intracellular signaling pathways might be involved. Treatment of OSF is difficult, as not many large, randomized controlled trials have been conducted. The principal actions of drug therapy include antifibrotic, anti-inflammatory, and antioxidant radical mechanisms. Potential new drugs are on the horizon. Surgery may be necessary in advanced cases of trismus. Prevention is most important, as no healing can be achieved with available treatments.

Keywords: betel nut, betel quid, oral disease, squamous cell carcinoma, tobacco, fibrosis

Introduction

Oral submucous fibrosis (OSF) is a premalignant disorder associated with the chewing of areca nut (betel nut). The habit is prevalent in South Asian populations but has been recognized nowadays also in Europe and North America. OSF causes significant morbidity. After transformation into squamous cell carcinoma (SCC), it is also responsible for mortality. The combination of areca nut and tobacco has led to a sharp increase in the frequency of OSF.¹

Definition and clinical manifestations of the disease are summarized in Table 1. The initial presentation of OSF is inflammation. Inflammation is followed by hypovascularity and fibrosis visible as blanching of the oral mucosa with a marble-like appearance. Blanching may be localized, diffuse, or reticular. In some cases, small vesicles may develop that rupture and form erosions.¹

In the later advanced stage of OSF, a fibrous band that restricts mouth opening (trismus) is characteristic. It causes further problems in oral hygiene, speech, mastication, and possibly swallowing. Development of fibrous bands in the lip leads to thickening and rubbery appearance. It becomes difficult to retract or evert the lips, which transform into an elliptical shape. A cross-sectional study in 325 patients in Karachi, Pakistan demonstrated a strong association among labial bands, bands in the fauces, and buccal bands. On the other hand, buccal bands had a weaker association to labial bands.²

Table I Histopathological classifications of oral submucous fibrosis

Very early (stage I)	Early (stage II)	Moderately advanced (stage III)	Advanced (stage IV)
A finely fibrillar collagen, dispersed with marked edema The fibroblastic response is strong	The juxta-epithelial area shows early hyalinization Plump young fibroblasts are present in moderate numbers	The collagen is moderately hyalinized The fibroblastic response is less marked, the cells present being mostly adult fibrocytes	The collagen is completely hyalinized The hyalinized areas are devoid of fibroblasts
The blood vessels are sometimes normal, but more often they are dilated and congested	The blood vessels are dilated and congested	Blood vessels are normal or constricted	Blood vessels are completely obliterated or narrowed
Inflammatory cells, mainly polymorphonuclear leukocytes with an occasional eosinophil, are present	Inflammatory cells are mostly mononuclear lymphocytes, eosinophils, and an occasional plasma cell	Inflammatory exudates consist of lymphocytes and plasma cells, although an occasional eosinophil is seen	Inflammatory cells are lymphocytes and plasma cells

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).^{3–5} Fibrosis makes cheeks thick and rigid. The cheek flexibility may also be used to classify the severity of OSF. Three categories have been suggested: cheek flexibility >30 mm, 20–30 mm, and <20 mm.¹

Clinical features of advanced OSF include the loss of puffed-out appearance of cheeks when a patient blows a whistle. Fibrosis of tongue and mouth impairs tongue movement and leads to depapillation and blanching of mucosa.¹

Fibrosis may also affect the soft palate and uvula, whereas gingival involvement is relatively uncommon. Sometimes the blockage of Eustachian tubes impairs hearing, and esophageal fibrosis causes problems in swallowing.¹

Epidemiology

Approximately 600 million persons are betel chewing, with a hot spot throughout the Western Pacific basin and South Asia. This makes betel the fourth most-consumed drug after nicotine, ethanol, and caffeine.^{6,7}

Betel is composed of the areca nut (*Areca catechu*), the fresh leaf of betel pepper (*Piper betle*), spices, and calcium hydroxide (lime) (Figure 1A and B). Pan or paan masala is a quid of piper betel leaf.⁸ Mawa is a mixture of tobacco, lime, and areca nut. Chewing tobacco or guthka became very popular, and betel chewers often also used guthka. However, guthka has recently been officially banned from the Indian market,^{9–11} but chewing tobacco-containing betel quid has become one of the most popular habits in South Asia.¹² Since there is a lot in common between the various areca nut mixtures (pan, mawa) we will not differentiate between them. Betel is now widely available in the Western world as well.¹³

OSF subjects are younger and have shorter histories of chewing compared to chewers without OSF. OSF does not disappear after cessation of the habit but remains permanent.¹⁴

A study from Gujarat has shown that the prevalence of OSF is increasing – from 0.16% (1967) to 10.9% (1998). About 85% of patients were younger than 35 years.¹⁰ In 2005, the OSF prevalence among visitors at a dental school in Manipal, India was estimated as 2%, with a preference for



Figure 1 Handmade and commercial forms of betel.

Notes: (A) Typical ingredients of hand-made betel quid: green *piper betel* leaves (left), areca nut (lower right), slaked lime (upper left), and a mixture of spices (upper right). (B) Some commercial brands ready to use.

male sex and an age range of 40–60 years.¹⁵ The prevalence of OSF in an aboriginal community of southern Taiwan was 17.6%. Although the betel quid in Taiwan does not contain any tobacco, in contrast to India and Pakistan, a significant association with oral mucosal lesions was still identified.¹⁶

In a study from Allahabad, India, 239 OSF patients were studied; 46% were in their 3rd decade of life. The most common affected site was buccal mucosa (20.8%), followed by palate (17.7%). Trismus was observed in 37.2% of patients, 25.9% suffered from burning sensations, 22.5% reported excessive salivation, and 14.2% suffered from recurrent oral ulcerations.³

Grading OSF in relation to addiction habits demonstrated a dependence from years of addiction and frequency of chewing betel and tobacco. Most patients with stage I OSF were addicted for at least 3–5 years, whereas the majority of patients with stage III OSF had consumed betel and tobacco products for 8–10 years or more with a frequency of 6–10 times per day. Trismus was seen more often in stage II and III OSF, but a clear correlation between the severity of trismus and OSF staging was missing.³

Major constituents of areca nuts

Areca nuts contain a great variety of substances. In the light of OSF, the most interesting compounds are those that are water or ethanol soluble. The alkaloid fraction contains arecoline, arecaidine, guvacine, guvacoline, arecolinidine, and others. 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, phlobatannin, and others. Furthermore, nitrosamines have been identified in areca nuts. Areca nuts also contain trace elements like copper, bromide, vanadium, manganese, chlorine, and calcium.¹⁷ Betel quid chewers are exposed to increased concentrations of potentially hazardous compounds such as arsenic, cadmium, copper, and lead.¹⁸

Pathogenic factors in precancerous and cancerous lesions induced by betel chewing

The relationship of OSF to chewing of areca nut/quid or pan masala has been directly related to OSF, whereas chewing or smoking tobacco did not increase the risk for OSF.¹⁹ In a case–control study from Kerala, India, betel quid alone increased the odds ratio for OSF to 56.2.²⁰

Extracellular matrix and fibroblast changes

The most obvious changes occur in the extracellular matrix of the submucous tissue layer. Fibrosis is associated with quantitative and qualitative alterations of collagen deposition within the subepithelial layer of the oral mucosa. This is partly due to marked deficiencies in collagen and fibronectin phagocytosis by fibroblasts caused by betel nut alkaloids (arecoline, arecaidine).²¹ On the other hand, tannins from areca nuts increase collagen fiber resistance to collagenase.²²

In vitro, areca nut extract suppresses the synthesis of [³H] proline and the growth and attachment to collagen of oral fibroblasts in a dose-dependent manner.²³ Pretreatment of oral mucosa fibroblasts with other areca nut compounds such as buthionine sulfoximine or diethyl maleate potentiates the cytotoxic effects.²⁴ Overexpression of stress protein colligin was found in 70% of OSF patients. It has been suggested that colligin may contribute to the increased deposition of collagen I and thereby to fibrosis development in oral submucosa.²⁵ CD34 – a marker of mucosal vascular endothelium – and basic fibroblast growth factor are both increased in OSF and demonstrate an association to the stage of fibrosis.²⁶

Arecoline – the major compound of areca nut – can induce various growth factors in OSF fibroblasts in vitro, like insulin-like growth factor-1 and keratinocyte growth factor-1, and basic protein cystatin C,^{27–29} but inhibits proinflammatory cytokines like interleukin-6.³⁰ Arecoline stimulates another key molecule in the regulation of fibrosis – the hypoxia-inducible factor-1 α – in a dose-dependent manner.³¹

Copper

Copper is implicated in the pathogenesis of fibrotic disorders because it stimulates collagen synthesis in oral fibroblasts.³² Elevated serum copper levels are associated with duration of betel nut chewing and severity of OSF.³³

Areca nuts contain high copper concentrations compared to other nuts, and copper becomes liberated during chewing. Mass absorption spectrometry of buccal mucosa detected a mean tissue copper level of 5.5 ± 2.9 $\mu\text{g/g}$ in patients with OSF compared with 4 ± 1.9 $\mu\text{g/g}$ in controls. Copper has been detected in the epithelium and the connective tissue of the OSF specimens.³⁴ Copper levels are significantly higher in commercial areca nut products compared with raw areca nut.³⁵

Immune system

Betel quid affects the immune system. The levels of transforming growth factor (TGF)- β and interferon (IFN)- γ are

lower in mononuclear cells from OSF patients than from controls.^{36,37}

Antioxidant status and cytokines

Glutathione S-transferases (GST) are part of the antioxidant system. GSTT1 and GSTM1 null phenotypes increase the risk of OSF.³⁸ Reduced glutathione levels in betel quid users are related to raised levels of the proinflammatory interleukin-6.³⁹ Diminished levels of superoxide dismutase but increased levels of malondialdehyde – a lipid peroxidation product – have been detected in OSF.⁴⁰

The role of tobacco addition

Several surveys show an increase in the incidence of OSF when areca nut and tobacco consumption are combined. A relative risk of 489 has been reported for OSF in consumers of areca nut/tobacco compared with nonusers.⁴¹ The consumers of mixed products are often younger.^{10,42} OSF develops faster in these patients (after 2.7 years) than in betel quid chewers (after 8.6 years). Cancerous transformation appeared at an early age.⁴³

Both genotoxicity and carcinogenicity of areca nut and betel quid with or without tobacco admixture are well documented. Nitrosamines, reactive oxygen species, and depletion of endogenous anti-oxidant capacity are the dominant contributors.^{38,44} Esophageal subepithelial fibrosis is seen more frequently in patients who had consumed areca nut and tobacco for longer than 5 years.⁴⁵

Changes in gene expression and activity

More recently, the expression profiles of genes in OSF and normal oral mucosa have been studied more intensively. In one study, 14,500 genes were analyzed using gene chip arrays. The study demonstrated 716 genes were upregulated and 149 genes were downregulated in OSF. The gene expression profiles of normal controls and OSF patients were clearly distinct, in particular the genes involved in immune response, inflammatory response, and TGF- β -induced epithelial-mesenchymal transition.⁴⁶

In a comprehensive analysis of water-soluble and ethanol-soluble areca nut constituents, it was demonstrated that both alkaloid and polyphenol fractions induced TGF- β signaling in human keratinocytes. Involved genes included *TGF- β 2*, *SMAD-3*, matrix metalloproteinase (*MMP*)1, *MMP2*, and *MMP9*, and others. In contrast, no TGF signaling was induced in fibroblasts.⁴⁷

It can be assumed that direct effects on epithelial cells with TGF- β activation can suppress antifibrogenetic

cytokines, including bone morphogenetic protein-7 and stimulated fibroblast activity. Both OSF and oral SCC development are quite complex and it is unlikely that a single factor is responsible.⁴⁸

Related conditions in oral submucous fibrosis

Betel nut chewers are also prone to benign and malignant diseases other than OSF. These diseases can occur intraorally, but also in the descending parts of the gastrointestinal tract, like esophagus or liver. Malnutrition and hepatitis virus infection are independent risk factors.⁴⁹

Betel chewing leads to blood-red saliva that stains teeth and gingiva. The teeth may become red-brown to nearly black (Figure 2).^{1,13} Betel chewer's mucosa (BCM) is characterized by a brownish-red discoloration and an irregular epithelial surface (Figures 3 and 4). The prevalence of BCM reaches up to 60% with a preference for female sex. The epithelium is often hyperplastic (Figure 4). In contrast to OSF, BCM is not premalignant.⁵⁰⁻⁵²

Oral leukoplakia and OSF are clinically distinct premalignant states that precede the development of oral SCC. Oral leukoplakia is an early sign of mucosal damage. It can appear as macular, plaque-like, erosive, or verrucous lesion with a homogeneous or speckled white appearance. Erythroplakia would be the reddish counterpart that poses a greater risk for malignant transformation into invasive SCC (Figure 5).^{1,53}

In more-advanced OSF, fibrosis is a hallmark leading to impairment in mouth opening, speaking and swallowing (Figures 6 and 7).^{1,2}

Oral cancer, in particular oral SCC, has been linked to areca nut chewing. The most common symptoms are related



Figure 2 Dental staining and irregular cobble-stone pattern of oral mucosa.



Figure 3 Blanching of buccal mucosa in oral submucous fibrosis.

to later stages of cancer, like odynophagia, oral ulcers, or ulcer pain.⁵⁴ Patients with oral SCC and OSF are younger, show a higher grade of tumor differentiation, and a lower incidence of nodal and extracapsular spread (Figure 8).⁵⁵

Oral cancer accounts for up to 40% of all malignancies in Asia.^{56,57} Tobacco smoking and chewing betel quid containing tobacco are the major risk factors for oral cancer, whereas betel quid without tobacco significantly increased oral cancer risk in only one study.⁵⁸ OSF makes oral cancer 19.1 times more likely.^{8,59}

Attempts have been made to identify specific molecular events as prognostic markers to identify oral precancerous



Figure 4 Redness and irregular cobble-stone appearance in oral submucous fibrosis. **Note:** In such cases a biopsy is recommended to exclude initial oral squamous cell carcinoma.



Figure 5 Blanching present on soft palate of patient with oral submucous fibrosis.

lesions with higher malignant potential. The expression of TGF- α and epidermal growth factor-receptor was upregulated in oral leukoplakia, OSF, and oral SCC relative to normal oral mucosa.⁶⁰

Arecoline is considered the most important etiological factor, but addition of peroxynitrite (a reaction product of cigarette smoking) and nicotine acted as a synergistic effect on the arecoline-induced cytotoxicity and glutathione depletion.^{1,61-64} Other factors associated with malignant transformation of OSF have been identified (Table 2).⁶⁵⁻⁷⁷

Esophageal involvement is the most common extraoral manifestation in betel nut chewers. Esophageal abnormalities were seen more frequently in patients who had consumed a combination of areca nut and tobacco; the esophagus may also be involved in about two-thirds of patients.⁴⁵



Figure 6 Decreased mouth opening in patient with advanced-stage oral submucous fibrosis.

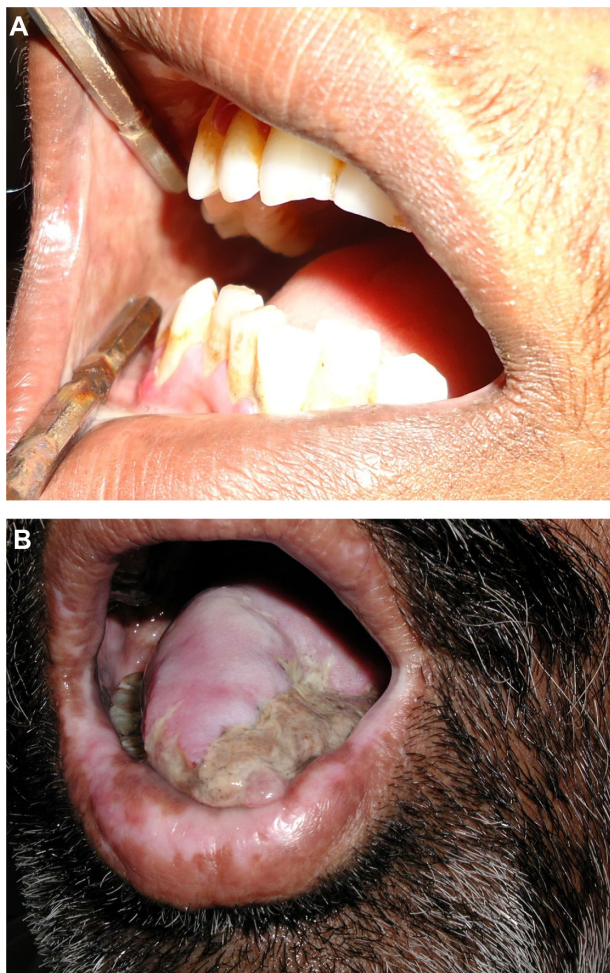


Figure 7 Advanced-stage oral submucous fibrosis.

Notes: (A) Severe decreased mouth opening and blanching seen on buccal mucosa. (B) Leukoplakia of the tongue; a biopsy is indispensable to exclude cancer of the tongue.

Associated visceral organ involvement has not been observed.⁷⁸ Cancer of the esophagus is another possible manifestation, in particular in patients who had been using fermented betel nut with any form of tobacco.⁷⁹

A recent meta-analysis investigated case-control studies and cohort studies from Asia. The authors found an odds ratio for esophageal SCC of 3.05 in areca nut chewers, which was further increased by additional tobacco smoking to 6.79.^{80,81} Betel quid chewing is an independent risk factor of hepatocellular carcinoma.⁸²

Recently, evidence has been gained for the association of areca nut chewing and systemic inflammation. In an observational study of 1,112 chewing individuals and 556 controls, the areca nut chewers had an odds ratio of 3.23 for C-reactive protein higher than 10 mg/dL. This might be linked to an increased risk for metabolic diseases, hypertension, and cardiovascular disease.^{83,84} A possible link between betel



Figure 8 Oral squamous cell carcinoma in a patient with oral submucous fibrosis.

quid chewing and cardiovascular disease could be arecoline. Arecoline is capable of blocking the high-density lipoprotein receptor with a higher affinity than cholesterol. Inhibition of cholesterol endocytosis may contribute to atherosclerosis.⁸⁵

A recent meta-analysis of betel quid and risk of cardiovascular disease concluded that betel quid poses a greater risk than tobacco.⁸⁶ Another meta-analysis concluded that betel quid is associated with two major disorders of metabolic syndrome – diabetes mellitus and central obesity.⁸⁷

Diagnostics

The hallmark of diagnosing OSF is clinical and histological. Clinically, one or more of the following symptoms should be present:

- Blanching of oral mucosa defined as a persistent, white, marble-like appearance of the oral mucosa, which may be localized, diffuse or reticular
- Tough, leathery texture of the mucosa
- Palpable, whitish, fibrous bands.

This should be accompanied by histopathological investigations. OSF is characterized by epithelial atrophy with loss of rete ridges and hyalinization of the lamina propria and the underlying muscle (Table 1).¹

The initial pathology of OSF is characterized by mixed inflammation and edema, and large fibroblasts (Figure 9). Later, collagen bundles with early hyalinization are seen, and the inflammatory infiltrate contains lymphocytes and plasma cells, occasionally resembling lichenoid mucositis.⁸⁸

In more-advanced stages, OSF is characterized by formation of thick bands of collagen and hyalinization extending into the submucosal tissues and decreased vascularity (Figure 10A and B). The epithelium becomes thinner

Table 2 Factors associated with malignant transformation of oral submucous fibrosis

Molecules	Description	Findings	References
0(6)-methylguanine-DNA	Methyltransferase DNA repair enzyme	Low levels associated with advanced oral SCC and lymph node involvement	65
Mutations of p53	Tumor suppressor gene	Degree of p53 staining increased with morphologic transformation of epithelial cells, associated with progression of oral SCC	66–72
p16INK4alpha/p19ARF mutations	p16 regulated G1 proliferation	p53 independent pathway of tumorigenesis	68
MDM2-P2 promoter	Transcriptional target of p53	Elevated levels of MDM2 protein in dysplastic lesions and oral SCCs	72
C-jun	Protooncogene	Chronic stimulation by areca nut and arecoline leading to oral SSC	73
mtDNA mutations	Mitochondrial DNA	Contributor to the early phase of oral carcinogenesis	74
HSP70	Heat shock protein	Significant correlation of HSP70 expression with consumption of betel and tobacco; in patients with premalignant lesions median transition time (pre malignancy to malignancy) was significantly shorter in HSP70 overexpressing cases; oral cancer patients with elevated levels of HSP70 showed decreased median disease-free survival time	75
HSP27	Heat shock protein	Increased in betel nut-induced oral SCC due to direct action of arecoline	76

Abbreviation: SCC, squamous cell carcinoma.

or hyperkeratotic. Inflammation and fibrosis of minor salivary glands may develop. Muscle degeneration will occur in advanced stages of OSF.^{1,82,89} In vivo autofluorescence from buccal mucosa seems to be an interesting noninvasive tool to differentiate normal mucosa from OSF and early carcinoma.⁸²

Prevention and treatment

Betel nut chewing is a major risk factor for health, with the propensity for the development of malignancies of the

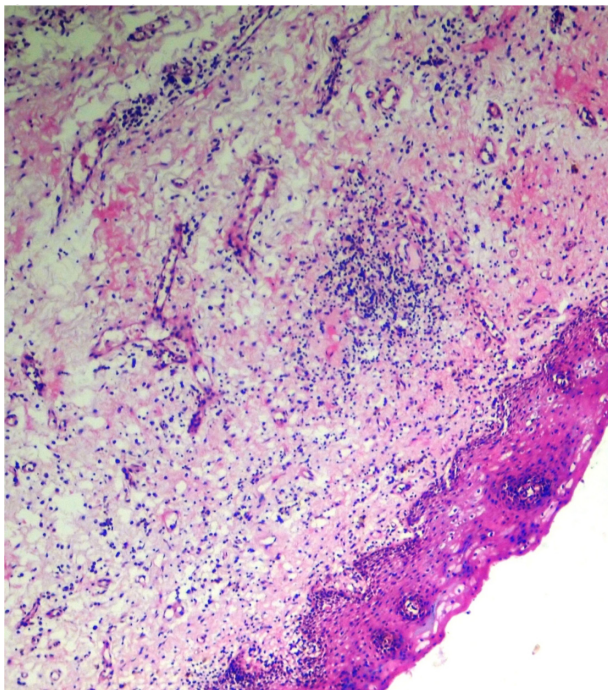


Figure 9 Histopathological picture showing initial stage of oral submucous fibrosis. **Note:** Hematoxylin and eosin staining, $\times 10$.

gastrointestinal tract. The combination of risk factors like betel nut and tobacco chewing, tobacco smoking, and alcohol increases the risk of severe disease like oral SCC. Health education will probably have an influence on this habit. Lessons learned from tobacco smoking, however, argue against rapid changes due to education and information alone.

Asian immigrant communities are growing in Western countries. Some authors have suggested implementation of an oral cancer screening by health care providers. On the other hand, the concept of screening of an asymptomatic patient is not well understood by many immigrants.⁹⁰ Physicians and dentists in the Western world should know about OSF to make an early diagnosis that will help to reduce morbidity and mortality.^{91,92}

Conventional therapies in the treatment of OSF are empirical and symptomatic in nature. The major targets of treatment can be summarized as:

- anti-inflammatory
- oxygen radical-scavenging
- antifibrotic.¹

In many cases, combined drug treatment is performed, although controlled clinical trials are completely lacking. In other patients, depending on severity of disease, physical therapy and/or surgery is added to drug therapy.⁹³

Here we will focus on pharmacological therapies, although patients might benefit from physical therapy in conjunction with drug treatment. The more advanced OSF is, the more limited the efficacy of pharmacological treatment. Patients may benefit from surgery or laser surgery in such situations.^{94–96}

During the early inflammatory phase of OSF, corticosteroids are of potential benefit, as suggested by in vitro studies.

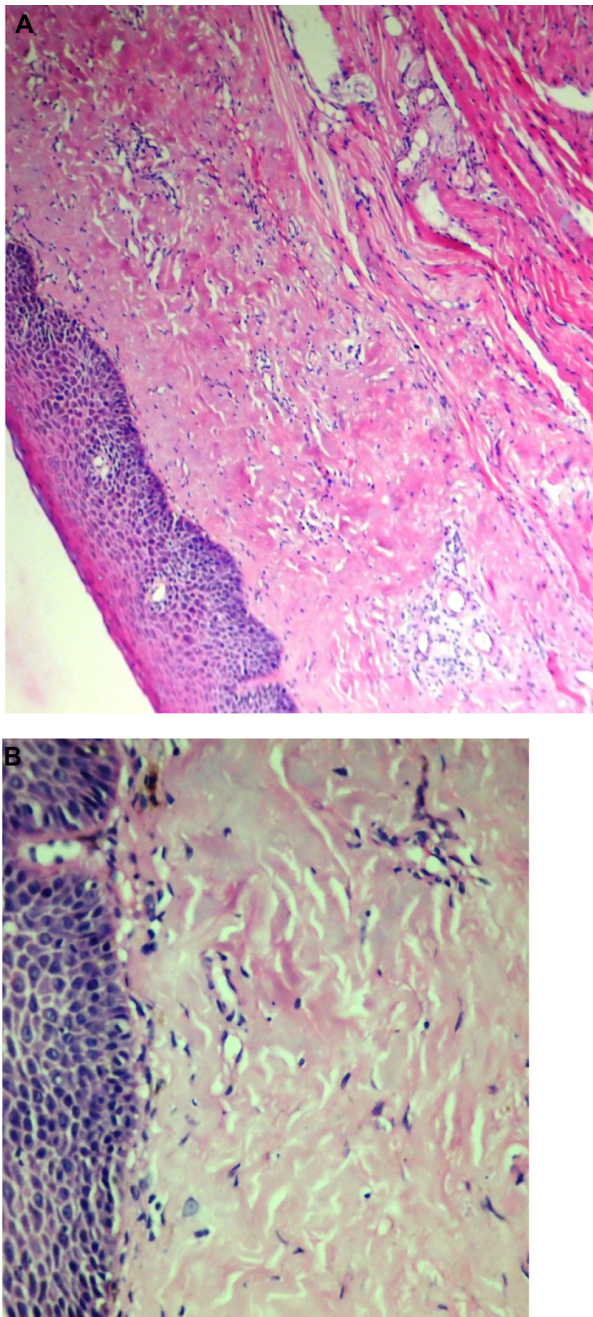


Figure 10 Histopathological picture showing advanced stage of oral submucous fibrosis.

Notes: (A) Hematoxylin and eosin staining, $\times 100$. (B) Closer view (hematoxylin and eosin staining, $\times 400$).

OSF has also been treated with hyaluronidase, chymotrypsin and collagenase, pentoxifylline, nylidrin hydrochloride, iron, and lycopene among others, but the level of evidence for any of these attempts is low.⁹⁴

A 6-week course of intralesional injections of 4 mg dexamethasone/mL and 1,500 U hyaluronidase twice weekly improved trismus and other clinical parameters associated with fibrosis. In addition, autofluorescence of the affected

mucosa normalized for collagen and nicotinamide adenine dinucleotide (reduced form) spectra.⁹⁶

A combination of micronutrients and minerals was evaluated in a single-arm study. Significant improvement in symptoms was observed after 1–3 years of treatment. The interincisor distance was stable in 49% of patients and improved in 41%, and leukoplakia regressed.⁹⁷

Oxitard is a phytopharmacological complex of antioxidant activity. In a group of 120 OSF patients, efficacy of oxitard two capsules per day was compared to topically applied 0.5% aloe vera three times daily for 3 months. Subjective symptoms like burning pain and difficulty in swallowing, and mouth opening and tongue protrusion were significantly more improved with oxitard.⁹⁸

Lactoferrin is a biologically active compound of bovine milk. Lactoferrin can also be produced by recombinant technology. The compound is not only immune modulating, resulting in increased antiviral and antibacterial activity of intestinal mucosa, but improves cancer surveillance and has anti-inflammatory effects.⁹⁹

IFN- γ that inhibits the collagen synthesis was given intralesionally in an open uncontrolled study. IFN- γ treatment showed improvement in the patient's mouth opening with a net gain of 8 ± 4 mm (42%) of interincisor distance 6 months later. Histochemical investigations demonstrated effects on inflammation and collagen metabolism in favor of antifibrotic activity.¹⁰⁰

Standardized treatment of OSF does not exist, but some interesting and promising drugs are available (Table 3).^{93,98,101–107} Controlled, prospective multicenter trials seem to be necessary. Careful monitoring of these patients is mandatory so as not to overlook early and treatable stages of oral SCC. Whenever SCCs develop, there is no special treatment but standard surgical, radiotherapeutic, and chemotherapeutic therapy like in other SCCs.

There are a number of potentially beneficial drugs that have yet not been studied systematically in OSF.

1. Modulating agents (antiproteinase, anti-inflammatory) seem to be of interest in gingivitis and periodontitis.¹⁰²
2. Antifibrotic compounds: synthetic drugs that show antifibrotic activities include angiotensin receptor blockers, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) inhibitors.¹⁰⁸ Protein kinase inhibitors have shown potential to decrease lung fibrosis by interaction with key enzymes, eg, focal adhesion kinase and protein kinase B.¹⁰⁹ Small interfering RNA, statins (simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin), peroxisome proliferation-activated

Table 3 Treatment of oral submucous fibrosis (controlled trials)

Treatment(s)	Outcome	References
Cessation of betel quid chewing	Common sense	No studies at all
Oxirtard twice daily orally	Better than aloe vera gel three times/day	98
Aloe vera gel topical	Better than hyaluronidase + dexamethasone submucous injection	101
Triamcinolone acetonide + salvianolic acid B submucous injections	Better than triamcinolone or salvianolic acid alone	102
Isoxuprine 10 mg four times/day + physiotherapy	Better than physiotherapy alone	103
Pentoxifylline 400 mg/day	Better than placebo	93
Hydrocortisone acetate/ hyaluronidase versus triamcinolone acetonide/ hyaluronidase	Equal efficacy	104
Physiotherapy five times/week	Better than no treatment or local injections with hyaluronidase and steroids	105
Lycopene 16 mg/day	Better than placebo	106
Immunized milk + physiotherapy	Better than physiotherapy alone	107

receptor gamma antagonists and prostaglandins are capable of blocking the profibrotic activity of connective tissue growth factor CCN2.¹¹⁰ In patients with psoriatic arthritis, TNF- α inhibitors exert a hepatoprotective effect and prevent liver fibrosis in vivo.¹¹¹

There is an increasing list of herbal antifibrotic compounds, including quercetin, baicalein, baicalin, wogonin, salvianolic acid B, and emodin, that suppress collagen I expression at both the mRNA and protein levels and also decrease smooth muscle actin expression in vitro.¹¹² Some of the flavones like wogonin, baicalein, and baicalin also show anticancer activities and are oxygen radical scavengers.¹¹³

3. N-acetyl cysteine inhibits collagen gene transcription, and production of collagen in oral mucosal cells in vitro. Furthermore, this compound has a positive impact on intracellular glutathione reserve thereby reducing redox stress to mucosal cells. The compound is not cytotoxic in vitro.¹¹⁴
4. Cyclo-oxygenase (COX)-2 inhibitors might be of some benefit during the inflammatory stage of the disease since both immunohistochemistry of OSF lesions and in vitro experiments with buccal mucosal fibroblasts exposed to arecoline demonstrated an upregulation of COX-2.¹¹⁵

Available data are summarized in Table 4. There is a need for controlled prospective trials in OSF and for preventive programs as well.

Table 4 Potential compounds for pharmacological treatment of oral submucous fibrosis

Compound(s)	Effect(s)	Remarks
Vitamins	Oxygen radical scavengers	In conjunction with other treatments
Flavons	Oxygen radical scavengers	In conjunction with other treatments
Pentoxifyllin, isoxuprine	Anti-inflammatory, improves microcirculation	In conjunction with other treatments
Corticosteroids	Anti-inflammatory	In early stages
TNF- α inhibitors, HMG-CoA inhibitors, ACE inhibitors, angiotensin receptor blockers	Antifibrotic	Not yet proven in OSF
N-acetyl cysteine	Anti-inflammatory, anti-oxidant	Not yet proven in OSF
Protein kinase inhibitors	Antifibrotic	Not yet proven in OSF
Immunized milk	Anti-inflammatory	Uncontrolled trials
Lactoferrin	Anti-inflammatory	Not yet proven in OSF

Abbreviations: ACE, angiotensin-converting enzyme; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; OSF, oral submucous fibrosis; TNF, tumor necrosis factor.

Author contributions

Dr Verma, Dr Ali and Dr Patil have investigated the patients shown herein. All four authors fulfilled the following four conditions: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors report no conflicts of interest in this work.

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