Cancer Association of South Africa (CANSA)

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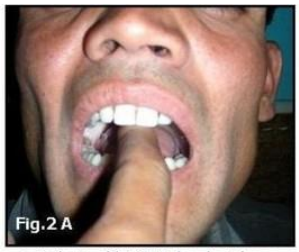
Fact Sheet
on
Oral Submucous Fibrosis

Introduction

Oral submucous fibrosis (OSF) is a chronic, complex potential potent pre-cancerous condition characterised by juxta-epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Approximately 20% of patients may develop oral cancer.



A: Patients with OSMF showing trismus (mouth opening 1 finger)

B: Blanching and fibrosis in OSMF

C: Malignancy of buccal mucosa

D: Tongue malignancy

[Picture Credit: Oral Submucous Fibrosis]

As the disease progresses, the jaws become rigid to the point that the sufferer is unable to open his/her mouth. The condition is linked to oral cancers and is associated with areca nut chewing, the main component of betel quid. Areca nut or betel quid chewing, a habit similar to tobacco chewing, is practiced predominantly in Southeast Asia, India, and east Africa dating back thousands of years.
(Wikipedia).

Areca Nut

The **areca nut** is the seed of the areca palm (Areca caechu), which grows in much of the tropical Pacific, Asia, and parts of east Africa. It is commonly referred to as *betel nut*, as it is often chewed wrapped in betel leaves (paan). The term areca originated from a South Asian word 'root' during the 18th century, when Dutch and Portuguese sailors took the nut to Europe.

[Picture Credit: Areca Nut)

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The habit has many harmful effects on health. The International Agency for Research on Cancer (IARC) concluded that chewing areca nut is carcinogenic (cancer causing) to humans. Various compounds present in the nut, most importantly arecoline, contribute to histologic changes in the oral mucosa. As with chewing tobacco, its use is discouraged. (Wikipedia).

Causes and Risk Factors of Oral Submucous Fibrosis (OSF)

A number of risk factors seem to contribute to the juxtaepithelial inflammatory disease process in the oral mucosa leading to OSF. A strong association has been observed with areca nut chewing with or without tobacco and OSF.

The other factors that are considered to be responsible are capsaicin in chilies and micronutrient deficiencies of iron, zinc and essential vitamins.

An increase in the frequency of this disease, especially among the young, has been reported in India due to the increase in the use of commercially prepared areca nut preparations without betel leaf (*pan masala*). A genetic predisposition for the development of this disease has also been reported.

The areca nut, which contains alkaloids, such as arecoline, and other chemicals, such as catechin and tannin, plays a major role by stimulating production of collagen fibres and making them less susceptible to the action of collagenase. It is suggested that components of the areca nut also affect gene expression in the fibroblasts leading to the production of greater amounts of normal collagen. Areca nut has been shown to have a high copper content, and chewing areca nuts for 5–30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in OSF by stimulating fibrogenesis through up-regulation of lysyl oxidase activity.

It is not clear if a hypersensitivity reaction to chilies plays any role in the development of OSF. Iron deficiency anaemia, vitamin B complex deficiency, and malnutrition are implicated in the pathogenesis of OSF leading to deranged repair processes of the inflamed oral mucosa, contributing to defective healing and scarring. The resulting atrophic oral mucosa is more susceptible to the effects of areca nut and alcohol. An immunologic process and a genetic component are assumed to be involved because of reported cases in non–areca nut chewers. Increased levels of pro-inflammatory cytokines and reduced antifibrotic interferon have also been demonstrated in patients with OSF.
(IARC Screening Group).

Oral Submucous Fibrosis (OSF) Incidence in South Africa

A review of research related to oral submucous fibrosis (OSF) among South Africans of Indian descent shows a certain uniqueness compared to other countries. In South Africa the betel habit is more common among women, only 60% of chewers prefer the betel quid while the rest like the nut by itself, the majority of chewers prefer the baked (black) nut variety and a minority add tobacco to their chew. This pattern reflects in the distribution of OSF and the practice of the habit by OSF subjects. Compared to chewers without OSF, OSF subjects are younger and have shorter histories of chewing. Yet the profile of systemic diseases were similar among subjects with and without OSF.

The habit as practised in South Africa also determines the pattern of oral squamous carcinomas. They are more common in women, with buccal mucosa cancers being the most frequent. The latter are commonly found in subjects not using any tobacco, indicating the carcinogenicity of the areca nut. It was also shown that oral cancer can develop in chewers without an intermediate precancerous OSF phase. A follow-up of OSF cases after cessation of the habit revealed that once present the disease is permanent. An analysis of cultured OSF fibroblasts demonstrated a permanent shift to larger cells theoretically capable of producing larger amounts of collagen. Thus the agents in the nut could be the initiators of the disease and its permanent character the result of a phenotypic alteration in cells from changes in gene expression.
(van Wyk).

Incidence of Oral Submucous Fibrosis in South Africa
The National Cancer Registry (2013) does not provide information regarding Oral Submucous fibrosis.

According to the National Cancer Registry (2013) the following number of cancer of the mouth cases was histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	342	1:403	0,95%
Asian males	10	1:516	1,16%
Black males	174	1:534	1,62%
Coloured males	45	1:364	1,07%
White males	114	1:241	0,57%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	191	1:1 109	0,52%
Asian females	12	1:563	1,12%
Black females	77	1:2 125	0,49%
Coloured females	30	1:688	0,73%
White females	73	1:492	0,46%

The frequency of histologically diagnosed cases of cancer of the mouth in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	2	6	8	39	104	117	42	16
Asian males	0	0	1	0	2	2	1	0
Black males	2	4	4	21	52	57	11	7
Coloured males	0	1	1	6	16	11	4	1
White males	0	0	0	10	29	40	21	6

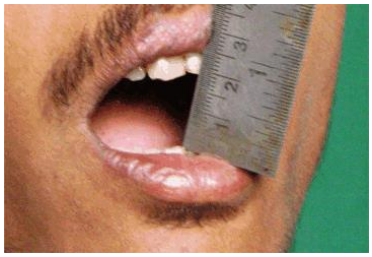
Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	1	4	9	15	31	51	35	22
Asian females	0	0	1	0	3	4	2	1
Black females	1	3	7	6	23	17	7	7
Coloured females	0	0	1	5	9	8	4	1
White females	0	1	0	4	14	19	21	10

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for ‘all males’ and ‘all females’, however, always reflect the correct totals.

Signs and Symptoms of Oral Submucous Fibrosis (OSF)
The first symptom of oral submucous fibrosis is a burning sensation in the mouth especially when eating spicy food, sometimes also with small blister formation. The mouth may feel dry with ulcers.

On examination, even at an early stage, the oral mucosa looks white in a marble-like pattern, either diffusely throughout the mouth or in localised areas, or in a netlike pattern.

In later stages fibrosis develops:



[Picture Credit: Mouth Opening Reduced]

- mouth cannot be opened as wide as normal, affecting eating and swallowing, speaking and dental hygiene.
- tongue becomes smooth, white and cannot move easily.
- the cheeks feel thick and firm and cannot 'puff out'.
- lips become rubbery and thick with an elliptical shape.

In very severe cases, the fibrosis extends to the soft palate, throat and oesophagus. The uvula may shrink and become distorted in shape. Difficulty may occur with swallowing and the Eustacian tubes to the ear may be blocked, affecting hearing.

Although most of the inside of the mouth can become fibrotic, the gums are uncommonly affected. Involvement on just one side of the mouth has been reported when the betel quid is habitually held in one specific site. The pattern of involvement is also affected by whether the quid is swallowed after chewing, or spat out. Swallowing exposes the soft palate, throat and oesophagus to the betel quid and therefore these areas at the back of the mouth are more likely to be affected than in those who spit the quid out. Those who spit it out are more likely to have involvement of the lips and areas towards the front of the mouth.

There is an increased risk of developing squamous cell carcinoma in the thinned oral mucosa. The risk has been estimated to be as high as 1 in 5 in some reports.
(DermNet NZ).

Diagnosis of Oral Submucous Fibrosis (OSF)
The differential diagnosis for Oral Submucous Fibrosis includes Lichen Planus, Scleroderma, and Squamous Cell Carcinoma. The conclusion that an individual may present with Oral Submucous Fibrosis may be achieved using several different modalities to confirm a diagnosis. In a study conducted by Chiu *et al*., A total of 296 subjects were recruited, including 123 Oral Submucous Fibrosis patients whose condition had not yet progressed to malignancy as well as 173 betel quid chewers who did not demonstrate existing Oral Submucous Fibrosis. The subjects were given a questionnaire and had their maximal mouth opening recorded. The distance between upper and lower incisor edges was measured with the following results.

Normal mouth opening in healthy individuals ranges from 40-50mm. According to the questionnaire subjects with a maximum mouth opening of less than 35mm complained of trismus (87.3%), burning sensation (76.0%), and xerostomia (72.25%). Subjects with a maximum mouth opening greater than 35mm complain of burning sensation (68.2%) followed by trismus (54.5%) and xerostomia (54.5%). Although this is not a confirmation of

the disease, it does provide researchers with better understanding of its pathogenesis. A biopsy is the ultimate determining factor and should be performed to rule out Squamous Cell Carcinoma (Vanessa M Cook).

Treatment of Oral Submucous Fibrosis (OSF)

Medical Treatment - the treatment of patients with oral submucous fibrosis depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with oral submucous fibrosis present with moderate-to-severe disease. Moderate-to-severe oral submucous fibrosis is irreversible. Medical treatment is symptomatic and predominantly aimed at improving mouth movements. Treatment strategies include the following:

- Steroids: In patients with moderate oral submucous fibrosis, weekly submucosal intralesional injections or topical application of steroids may help prevent further damage.
- Placental extracts: The rationale for using placental extract in patients with oral submucous fibrosis derives from its proposed anti-inflammatory effect, hence, preventing or inhibiting mucosal damage. Cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human placental extract (Placentrex) has shown marked improvement of the condition.
- Hyaluronidase: The use of topical hyaluronidase has been shown to improve symptoms more quickly than steroids alone. Hyaluronidase can also be added to intralesional steroid preparations. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone.
- IFN-gamma: This plays a role in the treatment of patients with oral submucous fibrosis because of its immunoregulatory effect. IFN-gamma is a known antifibrotic cytokine. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with oral submucous fibrosis, and intralesional injections of the cytokine may have a significant therapeutic effect on oral submucous fibrosis.
- Lycopene: Newer studies highlight the benefit of this oral nutritional supplement at a daily dose of 16 mg. Mouth opening in 2 treatment arms (40 patients total) was statistically improved in patients with oral submucous fibrosis. This effect was slightly enhanced with the injection of intralesional betamethasone (two 1-mL ampules of 4 mg each) twice weekly, but the onset of effect was slightly delayed.
- Pentoxifylline: In a pilot study, 14 test subjects with advanced oral submucous fibrosis given pentoxifylline at 400 mg 3 times daily were compared to 15 age- and sex-matched diseased control subjects. Statistical improvement was noted in all measures of objective (mouth opening, tongue protrusion, and relief from fibrotic bands) and subjective (intolerance to spices, burning sensation of mouth, tinnitus, difficulty in swallowing, and difficulty in speech) symptoms over a 7-month period. Further studies are needed, but this could be used in conjunction with other therapies.

The role of these treatments is still evolving. The US Food and Drug Administration has not yet approved these drugs for the treatment of oral submucous fibrosis.

Surgical treatment - is indicated in patients with severe trismus (means being unable to open the mouth completely. It can be caused by muscle, nerve or joint damage) and/or biopsy

results revealing dysplastic or neoplastic changes. Surgical modalities that have been used include the following:

- Simple excision of the fibrous bands: Excision can result in contracture of the tissue and exacerbation of the condition.
- Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy: Trismus (means being unable to open the mouth completely. It can be caused by muscle, nerve or joint damage) associated with oral submucous fibrosis may be due to changes in the temporalis tendon secondary to oral submucous fibrosis; therefore, skin grafts may relieve symptoms.
- Nasolabial flaps and lingual pedicle flaps: Surgery to create flaps is performed only in patients with oral submucous fibrosis in whom the tongue is not involved.
- Use of a KTP-532 laser release procedure was found to increase mouth opening range in 9 patients over a 12-month follow-up period in one study.
- ErCr:YSGG laser fibrotomy, performed under a local anaesthesia, may be a useful adjunct in managing oral submucous fibrosis.

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