Oral Submucous Fibrosis, a Clinically Benign but Potentially Malignant Disease: Report of 3 Cases and Review of the Literature

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SOMMAIRE

La fibrose sous-muqueuse buccale (FSMB) est une affection précancéreuse que l'on associe principalement à une pratique répandue chez les Asiatiques du Sud – la chique de bétel contenant de la noix d'arec. Cette affection se caractérise par une inflammation, un dépôt accru de collagène dans la sous-muqueuse et la formation de bandes fibreuses dans les tissus buccaux et parabuccaux, qui ont pour effet de limiter de plus en plus l'ouverture de la bouche. La FSMB a récemment été observée chez des immigrants d'Asie du Sud vivant au Canada, au Royaume-Uni et en Allemagne. Les dentistes des pays occidentaux devraient se familiariser davantage avec cette affection, qui semble en progression due à la migration des populations. Cet article passe en revue la littérature sur la FSMB et expose 3 cas représentant différents stades de l'affection, pour aider les dentistes à poser un diagnostic précoce et réduire la morbidité et la mortalité associées à cette affection.

Pour les citations, la version définitive de cet article est la version électronique : www.cda-adc.ca/jcda/vol-74/issue-8/735.html

Oral submucous fibrosis (OSF) is a disease mainly associated with the chewing of areca nut, an ingredient of betel quid, and is prevalent in South Asian populations. It causes significant morbidity (in terms of loss of mouth function as tissues become rigid and mouth opening becomes difficult) and mortality (when transformation into squamous cell carcinoma occurs). The introduction of chewing tobacco containing areca nut into the market has been associated with a sharp increase in the frequency of OSF.[1] According to Statistics Canada,[2] in 2006 about 1.26 million people in Canada identified themselves as South Asians. With an increase in immigration from South Asia, there will likely be an increase in the frequency of OSF in western countries (**Table 1**) including Canada.[3–15] In this article, we review the literature on OSF and present 3 cases to increase awareness of this condition among Canadian dentists.

Literature Review

Etiology

The strongest risk factor for OSF is the chewing of betel quid containing areca nut. The amount of areca nut in betel quid and the frequency and duration of chewing betel quid are clearly related to the development of OSF.[16] The direct contact of the quid mixture with oral tissues results in their continuous irritation by various components, including biologically active alkaloids (arecoline, arecaidine, arecolidine, guvacoline, guvacine, flavonoids (tannins and catechins) and copper.

Table 1 Summary of oral submucous fibrosis cases reported in western countries

Country	Ethnic origin of patient	Number of cases reported
Canada[3]	India	2
Canada[4]	India	1
Canada[5]	India	3
United Kingdom[6]	Bangladesh	1
United Kingdom[7]	Bangladesh	1
United Kingdom[8]	India (2) Pakistan (1)	3
France[9]	India	1
Germany[10]	India	1
Russia[11]	Greece	1
Melbourne, Australia[12]	India	1
South Africa[13]	India	14
Durban, South Africa[14]	Not mentioned	6
Not available[15]	Saudi Arabia	1

Other factors, such as genetic and immunologic predisposition, probably also play a role as OSF has been reported in families (both children and adults) whose members are not in the habit of chewing betel quid or areca nut.[17]

Pathogenesis

The pathogenesis of OSF is not well established, although a number of possible mechanisms have been suggested (**Fig. 1**). Pathogenesis is believed to involve juxta-epithelial inflammatory reaction and fibrosis in the oral mucosa, probably due to increased cross-linking of collagen through up-regulation of lysyl oxidase activity.[18]

Fibrosis, or the build up of collagen, results from the effects of areca nut, which increases collagen production (e.g., stimulated by arecoline, an alkaloid) and decreases collagen degradation.[19,20] Thus, OSF is now considered a collagen metabolic disorder.[16]

Clinical Features

The period between initiation of the chewing habit and the development of clinical symptoms of OSF 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. The symptoms and signs of OSF are due to inflammation and, primarily, fibrosis.

The most common initial symptoms and signs are a burning sensation, dry mouth, blanching oral mucosa and ulceration. The burning sensation usually occurs while chewing spicy food. Blanching of the oral mucosa is caused by impairment of local vascularity because of increasing fibrosis and results in a marble-like appearance. Blanching may be localized, diffuse or reticular. In some cases, blanching may be associated with small vesicles that rupture to form erosions. Patients complain that these vesicles form after they eat spicy food, suggesting the possibility of an allergic reaction to capsaicin. These features can be observed at all stages of OSF.

In the more advanced stage of the disease, the essential feature is a fibrous band restricting mouth opening and causing difficulty in mastication, speech, swallowing and maintaining oral hygiene. Development of fibrous bands in the lip makes the lip thick, rubbery and difficult to retract or evert; a band around the lips gives the mouth opening an elliptical shape. Fibrosis makes cheeks thick and rigid. When a patient blows a whistle or tries to inflate a balloon, the usual puffed-out appearance of the cheeks is missing. In the tongue, depapillation of mucosa around the tip and lateral margins may occur with blanching or fibrosis of the ventral mucosa. Fibrosis of the tongue and the floor of the mouth interfere with tongue movement. Hard palate involvement includes extensively blanched mucosa.

Fibrosis may extend posteriorly to involve the soft palate and uvula. The latter may appear shrunken and, in extreme cases, budlike. Gingival involvement is relatively uncommon and is characterized by fibrosis, blanching and loss of normal stippling. In rare cases of extensive involvement, there may be loss of hearing due to blockage of Eustachian tubes and difficulty swallowing because of esophageal fibrosis.

Pathology

The initial pathology of OSF is characterized by juxta-epithelial inflammation including edema, large fibroblasts and an inflammatory infiltrate, consisting primarily of neutrophils and eosinophils.[21] Later, collagen bundles with early hyalinization are seen and the acute inflammatory infiltrate contains more chronic cell types, such as lymphocytes and plasma cells, occasionally resembling lichenoid mucositis.

In more advanced stages, OSF is characterized by formation of thick bands of collagen and hyalinization extending into the submucosal tissues and decreased vascularity. The epithelium lining frequently becomes thin and loses melanin or becomes hyperkeratotic. Occasionally dysplastic changes occur in the epithelium. Inflammation and fibrosis of minor salivary glands can also be seen. Muscle degeneration will occur in advanced stages of OSF.

Treatment

No known treatment for OSF is effective, although some conservative and surgical interventions may result in improvement.[7,22] Currently, intralesional steroids are the main treatment modality. These are injected into the fibrotic bands weekly for 6–8 weeks with regular monitoring of mouth opening. Patients are advised to do mouth-opening exercises, for example, by placing ice cream sticks in their mouth and gradually increasing the number. Hyaluroni-

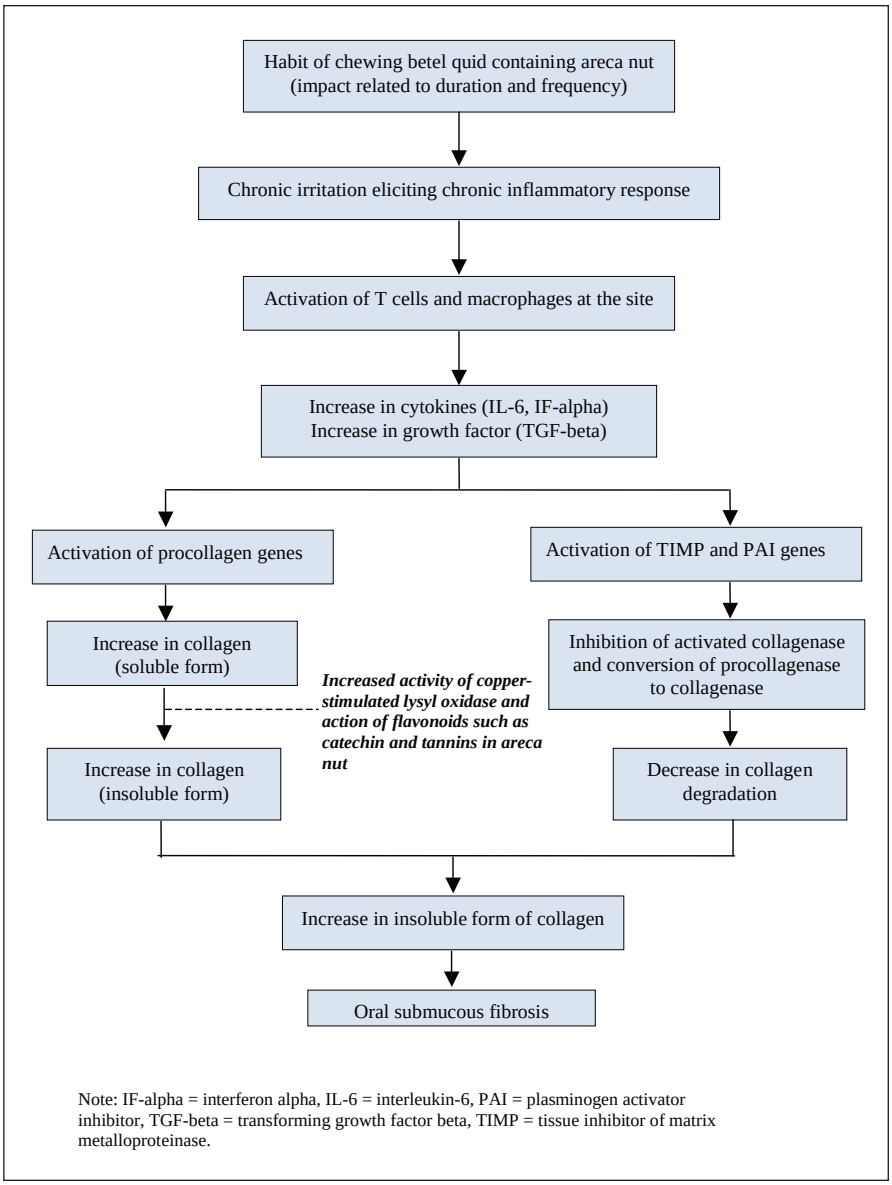

Figure 1: Etiopathogenesis of oral submucous fibrosis.

dase,[23] which facilitates the breakdown of connective tissue, can be combined with the steroids for injection.

The list of other treatment modalities (**Table 2**)[23–31] is extensive and includes use of micronutrients and minerals, carbon dioxide laser, pentoxifylline, lycopene, immunized milk, interferon gamma, turmeric, hyalase, chymotrypsin and collagenase. As fibrosis cannot be reversed, when mouth opening is severely limited surgical interventions, such as myotomy, coronoidectomy[32] and excision of fibrotic bands, are required. Reconstruction using such techniques as buccal pad flap, superficial temporal flap and forearm flap, can also be performed.[22,33,34] Alternative procedures, such as insertion of an oral stent, physiotherapy, local heat therapy, mouth exercises using acrylic carrots and ice cream sticks, have been tried with variable rates of success.

In most cases, depending on the stage of disease and extent of oral involvement, therapy consisting of a combination of the above-mentioned drugs and surgery might be useful.

Outcome

Outcomes of OSF are characterized by 2 features: the persistence of the disease and its potential to become malignant.

OSF does not regress spontaneously or on cessation of areca nut chewing. Once the disease is present, it either persists or becomes more severe with involvement of additional areas of the oral mucosa.[35]

OSF is strongly associated with a risk of oral cancer, although the biology underlying this association is still unresolved.[36] OSF may cause atrophy in the epithelium, increasing carcinogen penetration. Studies suggest that dysplasia is seen in about 25% of biopsied OSF cases and the rate of transformation to malignancy varies from 3% to 19%.[37]

Case Reports

Case 1

A 23-year-old man presented with a complaint of a burning sensation in the buccal mucosa while chewing spicy food, but no other systemic or dermatologic problem. The patient reported a habit of chewing dried areca nut powder 3–4 times a day for the past 2–3 years. He occasionally mixed calcium oxide with the areca nut powder and drank alcohol (approximately 750 mL of local undistilled alcohol) on weekends for the previous 5 years. His mouth opening was normal. Intraoral examination revealed that his entire oral mucosa was pale, especially the buccal mucosa, which showed areas of erosion (**Fig. 2**), and the hard palate, which was completely blanched. His tongue, uvula and soft palate were normal. No fibrotic bands were palpable in the oral cavity.

A biopsy of the buccal mucosa showed nonspecific ulcer and mucositis consisting of prominent fibroblasts, increased vascularity, edema and an inflammatory infiltrate that included numerous neutrophils and eosinophils. Although histologic evidence alone was not specific, it was highly consistent with OSF when considered in combination with the patient's chewing habit and clinical

Table 2 Treatment modalities for oral submucous fibrosis

Treatment	Treatment details
Micronutrients and minerals[24]	Vitamin A, B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium and others
Milk from immunized cows[25]	45 g milk powder twice a day for 3 months
Lycopene[26]	8 mg twice a day for 2 months
Pentoxyfilline[27]	400 mg 3 times a day for 7 months
Interferon gamma[28]	Intralesional injection of interferon gamma (0.01–10.0 U/mL) 3 times a day for 6 months
Steroids[29]	Submucosal injections twice a week in multiple sites for 3 months
Steroids[29]	Topical for 3 months
Hyalase + dexamethasone[23]	—
Placental extracts[23]	—
Turmeric[30]	Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months
Chymotripsin, hyaluronidase and dexamethasone[31]	Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks

presentation. A diagnosis of early OSF was made. This patient was advised to stop chewing areca nut and return for follow-up in 1 month. He did not return until 8 months later, when he had developed difficulty in mouth opening. He had not stopped chewing areca nut although he reported a reduction in frequency of use.

Case 2

A 43-year-old woman presented with a complaint of progressive difficulty in opening her mouth over the past 2 years. She had a longstanding habit of chewing fresh areca nut (4–5 pouches a day for 20–25 years). Examination revealed that her lips were thin and her mouth opening was limited to about 26 mm (average normal opening is 40 mm). There was erosion at the corners of her mouth (**Fig. 3**). The entire oral mucosa was pale, with focal blanched areas (**Fig. 4**). The tongue was devoid of papillae and extensive fibrosis had occurred on its ventral surface and the floor of the mouth (**Figs. 3** and **5**). The patient could not stick out her tongue or touch the hard palate with the tip of her tongue.

Thick fibrotic bands were palpable bilaterally on the buccal mucosa. Intraoral examination was problematic as it was difficult to retract the patient's fibrotic cheeks. During examination the mirror often stuck to the oral mucosa, suggesting dry mouth. When the patient was asked to blow out air with closed lips, the usual puffed-cheek appearance was not seen, suggesting loss of cheek elasticity. General examination was normal.

A diagnosis of OSF at a moderately advanced stage was made based on the characteristic oral features: generalized blanching of mucosa, extensive fibrosis and limited mouth opening.

Case 3

A 60-year-old man, with diagnosed OSF of 10 years duration, reported to our clinic for evaluation of a swelling in his cheek and on the floor of the mouth apparent for the past 6 months. The patient had begun treatment with intralesional steroids 10 years earlier on diagnosis of OSF. However, after a few visits, he ceased treatment and continued to chew areca nut over subsequent years.

His mouth opening was restricted to about 16 mm. His oral cavity was fully blanched and the buccal mucosa completely fibrotic. The uvula was fibrotic and deformed (**Fig. 6**). The tongue was completely devoid of papillae. A diagnosis of OSF at an advanced stage was made based on the habit and the classical clinical presentation.

In addition to the above changes, 2 masses were noted. One mass (about 3 × 2 cm) with an irregular margin was located on the right buccal mucosa extending from the corner of his mouth to the molar area. It was firm on palpation and fixed to the underlying tissues. The mucosa surrounding the mass was indurated. The other mass, about 1 cm in diameter, was on the floor of the mouth, in the lingual sulcus of the right mandibular premolar region. Its surface had numerous small finger-like projections (**Fig. 7**). On palpation, the swelling was firm and fixed to the underlying structures; however, a panoramic radiograph revealed no bony involvement. Biopsies of both masses revealed squamous cell carcinoma.

Discussion

The 3 cases reported here represent different stages of OSF. In the first case, the disease was at a very early stage and the patient showed the classical clinical presentation of burning sensation, ulceration, localized areas of pale and blanching mucosa and a habit of chewing areca nut. This case illustrates the importance of clinical information, as a diagnosis of early-stage OSF cannot be based on histology alone but rather on a combination of histology, chewing habit and clinical information. It is critical to provide the

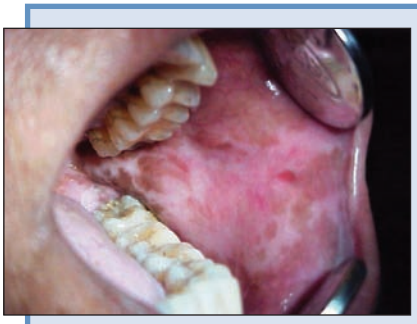

Figure 2: Case 1. Intraoral photograph of the buccal mucosa showing blanched oral mucosa with erosions in the initial stages of oral submucous fibrosis.

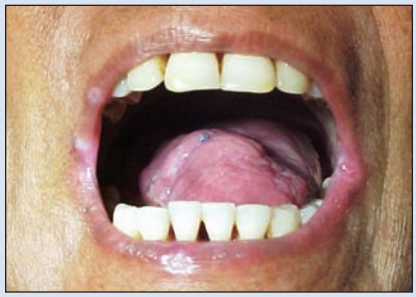

Figure 3: Case 2. Extraoral photograph showing reduced mouth opening with atrophied lips and erosions at the corners of the mouth.

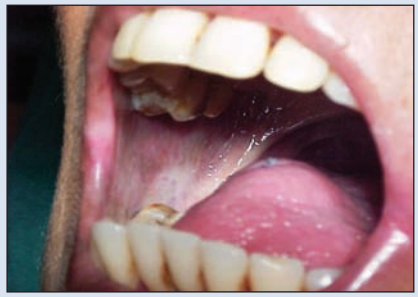

Figure 4: Case 2. Intraoral photograph showing blanched fibrosed oral mucosa and restricted mouth opening.

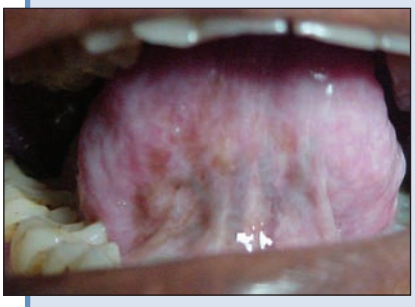

Figure 5: Case 2. Intraoral photograph showing extensive blanching and fibrosis of the ventral surface of the tongue.

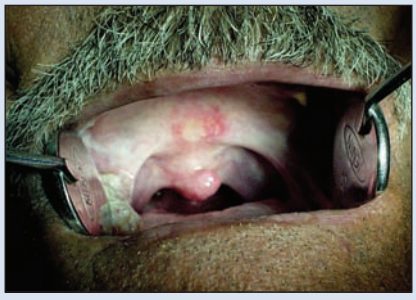

Figure 6: Case 3. Intraoral photograph showing fibrosed and deformed uvula and a small ulcer in the palate.

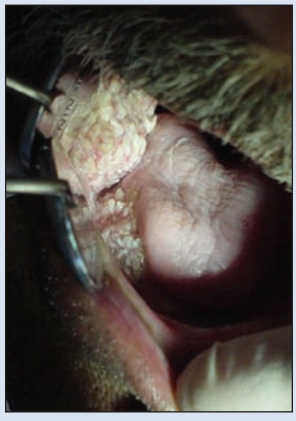

Figure 7: Case 3. Intraoral photograph showing 2 proliferative growths in the buccal mucosa and sulcus (because of restricted mouth opening, it was impossible to obtain a high-quality image).

pathologist with clinical information. In the second case, the disease was at a more advanced stage, and the patient showed diffuse blanching and fibrosis of the oral mucosa. In the third case, an advanced stage of OSF, the patient had diffuse oral fibrosis and severely limited ability to open his mouth. In addition, 2 late-stage squamous cell carcinomas were found, a disease associated with a poor survival rate in the late stages.

The rate of development of OSF varied among the 3 patients. The first patient developed early OSF after only 2–3 years of chewing areca nut, whereas the second developed the disease only after more than 20 years of using areca nut. The first patient went on to experience difficulty in mouth opening in a short time (8 months) despite a reduction in areca nut use.

The cases illustrate the relentless progression of OSF and its significant morbidity and mortality; they also emphasize the importance of close follow-up of such cases. Because of the significant cancer risk among these patients, periodic biopsies of suspicious regions of the oral mucosa are essential for early detection and management of high-risk oral premalignant lesions and prevention of cancer. Dentists can play an important role in both the education of patients about the perils of chewing betel quid and in the early diagnosis of high-risk premalignant lesions and cancer.

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***Acknowledgements:** Dr. Auluck is a PORT fellow (Psychosocial Oncology Research Trainee) supported by a grant from the Canadian Institutes of Health Research/National Cancer Institute of Canada.*

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The authors have no declared financial interests.

This article has been peer reviewed.

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