Oral Submucous Fibrosis

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Updated: Jan 18, 2012

Background

In 1952, Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease he discovered in 5 Indian women from Kenya.[1] Joshi subsequently coined the termed oral submucous fibrosis (OSF) for the condition in 1953.[2]

Oral submucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). Oral submucous fibrosis results in marked rigidity and an eventual inability to open the mouth.[3, 4] The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx.[5]

The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing, the main component of betel quid. Betel quid chewing is a habit practiced predominately in Southeast Asia and India that dates back for thousands of years. It is similar to tobacco chewing in westernized societies. The mixture of this quid, or chew, is a combination of the areca nut (fruit of the *Areca catechu* palm tree, erroneously termed betel nut) and betel leaf (from the *Piper betel,* a pepper shrub), tobacco, slaked lime (calcium hydroxide), and catechu (extract of the *Acacia catechu* tree).[3] Lime acts to keep the active ingredient in its freebase or alkaline form, enabling it to enter the bloodstream via sublingual absorption. Arecoline, an alkaloid found in the areca nut, promotes salivation, stains saliva red, and is a stimulant.

The ingredients and nomenclature of betel quid vary by region as detailed below[6, 7] :

- Pan: This is freshly prepared betel quid (with or without tobacco).
- Gutka (gutkha, guttkha, or guthka): This is a manufactured version of betel quid with tobacco sold as a single-use sachet. It is primarily used on the Indian subcontinent (ie, India, Pakistan, Bangladesh). Betel quid without tobacco is mostly used in Southeast Asian countries (ie, Taiwan, Myanmar, Thailand, China, Papua New Guinea, Guam).
- Pan masala: This is a commercially manufactured powdered version of betel quid without tobacco used in the Indian subcontinent.
- Pan Parag: It is a brand name of pan masala and gutka used in India.
- Mawa (kharra): This is a crude combination of areca, tobacco, and lime.
- Mainpuri tobacco: Popular in parts of northern India, Mainpuri tobacco is a mixture of areca nut, tobacco, lime, and various condiments. Depending on local preferences, sweeteners or spices (ie, cardamom, saffron, clove, anise seed, turmeric, mustard) are also added as flavorings.

In most patients with oral submucous fibrosis, areca nut was chewed alone more frequently than it was chewed in

combination with pan (ie, betel leaf plus lime plus betel catechu, with or without tobacco)[4] or had a higher areca nut content.[8]

Pathophysiology

The pathogenesis of the disease is not well established, but the cause of oral submucous fibrosis is believed to be multifactorial. A number of factors trigger the disease process by causing a juxtaepithelial inflammatory reaction in the oral mucosa. Factors include areca nut chewing, ingestion of chilies, genetic and immunologic processes, nutritional deficiencies, and other factors.

Areca nut (betel nut) chewing

The areca nut component of betel quid plays a major role in the pathogenesis of oral submucous fibrosis.[9] In a 2004 study, a clear dose-dependent relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of oral submucous fibrosis.[10] Smoking and alcohol consumption alone, habits common to areca nut chewers, have been found to have no effect in the development of oral submucous fibrosis,[11] but their addition to areca nut chewing can be a risk for oral submucous fibrosis.[11] Commercially freeze-dried products such as pan masala, guthka, and mawa have higher concentrations of areca nut per chew and appear to cause oral submucous fibrosis more rapidly than self-prepared conventional betel quid, which contains smaller amounts of areca nut.[8]

Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150%.[12] In one study, arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated in a variety of fibrotic diseases, in a dose-dependent manner in persons with oral submucous fibrosis.[13]

In 3 separate but similar studies, keratinocyte growth factor-1, insulinlike growth factor-1, and interleukin 6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up-regulated in persons with oral submucous fibrosis due to areca quid chewing, and arecoline may be responsible for their enhanced expression.[14, 15, 16] Further studies have shown that arecoline is an inhibitor of metalloproteinases (particularly metalloproteinase-2) and a stimulator of tissue inhibitor of metalloproteinases, thus decreasing the overall breakdown of tissue collagen.[17]

Insertion/deletion 5A polymorphism in the promoter region of the matrix metalloproteinase-3 gene, which results in alteration of transcriptional activities, has also been found in persons with oral submucous fibrosis but not in those with oral squamous cell carcinoma.[18] Conversely, insertion/deletion 2G polymorphism in the promoter of the matrix metalloproteinase-1 gene has been implicated in oral squamous cell carcinoma but not oral submucous fibrosis.[19]

Flavanoid, catechin, and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation.[20] This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown.[4] Oral submucous fibrosis remains active even after cessation of the chewing habit, suggesting that components of the areca nut initiate oral submucous fibrosis and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen.[21] Chewing areca quid may also activate NF-kappaB expression, thereby stimulating collagen fibroblasts and leading to further fibrosis in persons with oral submucous fibrosis.[22]

Areca nuts have also 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 persons with oral submucous fibrosis by stimulating fibrogenesis through up-regulation of copper-dependent lysyl oxidase activity.[23] Further, a significant gradual increase in serum copper levels from precancer to cancer patients has been documented,[24] which may have a role in oral fibrosis to cancer pathogenesis.

Ingestion of chilies

The role of chili ingestion in the pathogenesis of oral submucous fibrosis is controversial. The incidence of oral submucous fibrosis is lower in Mexico and South America than in India, despite the higher dietary intake of chilies.[25] A hypersensitivity reaction to chilies is believed to contribute to oral submucous fibrosis.[4] One study

demonstrated that the capsaicin in chilies stimulates widespread palatal fibrosis in rats,[26] while another study failed to duplicate these results.[27]

Genetic and immunologic processes

A genetic component is assumed to be involved in oral submucous fibrosis because of the existence of reported cases in people without a history of betel nut chewing[9, 28] or chili ingestion.[28] Patients with oral submucous fibrosis have been found to have an increased frequency of HLA-A10, HLA-B7, and HLA-DR3.[4]

An immunologic process is believed to play a role in the pathogenesis of oral submucous fibrosis.[29, 30] The increase in CD4 and cells with HLA-DR in oral submucous fibrosis tissues suggests that most lymphocytes are activated and that the number of Langerhans cells is increased. The presence of these immunocompetent cells and the high ratio of CD4 to CD8 in oral submucous fibrosis tissues suggest an ongoing cellular immune response that results in an imbalance of immunoregulation and an alteration in local tissue architecture.[31] These reactions may be the result either of direct stimulation from exogenous antigens, such as areca alkaloids, or of changes in tissue antigenicity that lead to an autoimmune response.[31]

Further, the major histocompatibility complex class I chain–related gene A (*MICA*) is expressed by keratinocytes and other epithelial cells and interacts with gamma/delta T cells localized in the submucosa. *MICA* has a triplet repeat (GCT) polymorphism in the transmembrane domain, resulting in 5 distinct allelic patterns. In particular, the phenotype frequency of allele A6 of *MICA* in subjects with oral submucous fibrosis is significantly higher and suggests a risk for oral submucous fibrosis.[32]

Some authors have demonstrated increased levels of proinflammatory cytokines and reduced antifibrotic interferon gamma (IFN-gamma) in patients with oral submucous fibrosis, which may be central to the pathogenesis of oral submucous fibrosis.[33]

Nutritional deficiencies

Iron deficiency anemia, vitamin B complex deficiency, and malnutrition are promoting factors that derange the repair of the inflamed oral mucosa, leading to defective healing and resultant scarring.[4] The resulting atrophic oral mucosa is more susceptible to the effects of chilies and betel nuts.

Other significant factors

Some authors have found a high frequency of mutations in the *APC* gene and low expression of the wild-type *TP53* tumor suppressor gene product in patients with oral submucous fibrosis, providing some explanation for the increased risk of oral squamous cell carcinoma development in patients with oral submucous fibrosis.[9] Other studies have suggested that altered expression of retinoic acid receptor-beta may be related to the disease pathogenesis.[34]

Epidemiology

Frequency

United States

Oral submucous fibrosis is rare in the United States and is found only in the immigrant members of the South Asian population who chew betel nuts.

International

Worldwide, estimates of oral submucous fibrosis indicate that 2.5 million people are affected, with most cases concentrated on the Indian subcontinent, especially southern India.[3] The rate varies from 0.2-2.3% in males and 1.2-4.57% in females in Indian communities.[4] Oral submucous fibrosis is widely prevalent in all age groups and across all socioeconomic strata in India. A sharp increase in the incidence of oral submucous fibrosis was noted after pan parag came onto the market, and the incidence continues to increase. Oral submucous fibrosis also occurs in other parts of Asia and the Pacific Islands.[3] Migration of endemic betel quid chewers has also made oral

submucous fibrosis a public health issue in many parts of the world, including the United Kingdom, South Africa, and many Southeast Asian countries.[35]

Mortality/Morbidity

Oral submucous fibrosis has a high rate of morbidity because is causes a progressive inability to open the mouth, resulting in difficulty eating and consequent nutritional deficiencies. Oral submucous fibrosis also has a significant mortality rate because of it can transform into oral cancer, particularly squamous cell carcinoma, at a rate of 7.6%.[4]

Race

Oral submucous fibrosis occurs on the Indian subcontinent, in Indian immigrants to other countries, and among Asians and Pacific Islanders as a result of the traditional use of betel quid endemic to these areas.[3]

Sex

The male-to-female ratio of oral submucous fibrosis varies by region, but females tend to predominate. In a study from Durban, South Africa, a distinct female predominance was demonstrated, with a male-to-female ratio of 1:13.[36] This was later confirmed by others, with a male-to-female ratio of 1:7.[37] In addition, a female predominance in areca nut chewing was also noted in this region. Studies in Pakistan reported a male-to-female ratio of 1:2.3.[4]

Conversely, a case-control study of 185 subjects in Chennai, South India revealed a male-to-female ratio 9.9:1.[11] In Patna, Bihar (also in India), the male-to-female ratio was 2.7:1.[38] With the onset of new commercial betel quid preparations, trends in sex predominance and age of occurrence may shift.

Age

The age range of patients with oral submucous fibrosis is wide and regional; it is even prevalent among teenagers in India. In a study performed in Saipan, 8.8% of teenagers with a mean age of 16.3 years (± 1.5 y) were found to have oral submucous fibrosis.[39] Generally, patient age ranges from 11-60 years[4, 38] ; most patients are aged 45-54 years and chew betel nuts 5 times per day.[4]

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Disclosure: Nothing to disclose.

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Disclosure: AMGEN Consulting fee Consulting; AMGEN Grant/research funds Investigator; Genentech Grant/research funds investigator; Centocor Consulting fee Consulting; Abbott Grant/research funds investigator; Abbott Consulting fee Consulting; Novartis investigator; Pfizer Grant/research funds investigator; Celgene Consulting fee DMC Chair; NIAMS and NHLBI Grant/research funds investigator

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Disclosure: Nothing to disclose.

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