International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 21-12-2019; Accepted: 23-01-2020; Published: 26-02-2020
www.medicalsciencejournal.com
Volume 6; Issue 2; 2020; Page No. 186-191

Assessment of factors underlying the occurrence of oral Submucous Fibrosis in Patients from Jharkhand Region

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Abstract
Oral sub mucous fibrosis (OSMF) is an insidious, chronic fibrotic change affecting any part of oral mucosa and has been considered as potentially malignant disorder. OSMF is a chronic disease of oral mucosa characterised by inflammation and progressive fibrosis of the lamina propria and deeper connective tissues, followed by stiffening of mucosa resulting in difficulty in opening the mouth. The diagnosis of OSMF is made on clinical grounds. Habitual chewing of gutkha (mixture of dry areca nut, tobacco and other chemical in trace for flavouring) and other areca nut quid plays a major role in the aetiology of the disease. Gutkha is very commonly used by younger generation and has become extremely popular acting as a main cause of OSMF. Hence based on above findings the present study was planned for Assessment of Factors Underlying the Occurrence of Oral Submucous Fibrosis in Patients from Jharkhand Region.

The present study was planned in Department of Oral Medicine, Diagnosis & Radiology, Vananchal Dental College & Hospital, Farathiya, Garhwa, Jharkand, India. Total 40 cases of the patients from age group 20 – 60 years of both the sexes were included in the present study. The patients were evaluated for the various parameters. The questionnaire included the basic socio demographic variables of all patients along with presence of habit of areca nut or gutkha chewing or having spicy food, symptoms like burning sensation in mouth on intake of hot and spicy food, and altered salivation. Clinical examination showed blanching and stiffness of oral mucosa and soft palate, palpable bands chiefly in buccal mucosa, and sometimes vesicle formation and ulceration.

The data generated from the present study concludes that correlation between functional and histological staging suggests that individuals with clinically advanced OSMF had extensive fibrosis histologically. Also early recognition with accurate staging of the disease and appropriate treatment planning is of utmost importance to prevent the malignant transformation and to improve the quality of life of the patient.

Keywords: Oral Submucous Fibrosis, OSFM, gutkha, pan masala, etc

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. Oral submucous fibrosis is a chronic, complex, premalignant (1% transformation risk) condition of the oral cavity, characterized by juxta-epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues (the lamina propria and deeper connective tissues). As the disease progresses, the jaws become rigid to the point that the person is unable to open the mouth. The condition is remotely linked to oral cancers and is associated with areca nut and / or its by-products chewing, majorly practiced in South and South-East Asian countries. The incidence of OSMF has also increased in the western countries due to the changing habits and constant migrating population.

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 [6]. 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 [7, 8].

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 [9].

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.

The areca nut component of betel quid plays a major role in the pathogenesis of oral submucous fibrosis. 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. 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, but their addition to areca nut chewing can be a risk for oral submucous fibrosis. 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 [9].

Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150%. 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 [10].

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.

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 [11].

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. 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 [12].

Flavanoid, catechin, and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation. This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown. 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. Chewing areca quid may also activate NF-kappaB expression, thereby stimulating collagen fibroblasts and leading to further fibrosis in persons with oral submucous fibrosis [13].

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. Further, a significant gradual increase in serum copper levels from precancer to cancer patients has been documented, [14] which may have a role in oral fibrosis to cancer pathogenesis.

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. A hypersensitivity reaction to chilies is believed to contribute to oral submucous fibrosis. One study demonstrated that the capsaicin in chilies stimulates widespread palatal fibrosis in rats, while another study failed to duplicate these results [15].

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 or chili ingestion. 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. 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. 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 [16].

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 [17].

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 [18].

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. The resulting atrophic oral mucosa is more susceptible to the effects of chilies and betel nuts.

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. Other studies have suggested that altered expression of retinoic acid receptor-beta may be related to the disease pathogenesis [19].

The term oral submucosal fibrosis derives from oral (meaning mouth), submucosal (meaning below the mucosa of the mouth), and fibrosis (meaning hardening and scarring). Chewable agents, primarily betel nuts (Areca catechu), contain substances that irritate the oral mucosa, making it lose its elasticity. Nutritional deficiencies, ingestion of chilies, and immunologic processes may also have a role in the development of oral submucous fibrosis.

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. 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. The rate varies from 0.2-2.3% in males and 1.2-4.57% in females in Indian communities. 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. 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 [20].

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].

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. This was later confirmed by others, with a male-to-female ratio of 1:7. 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 [15]. In Patna, Bihar (also in India), the male-to-female ratio was 2.7:1. [43] With the onset of new commercial betel quid preparations, trends in sex predominance and age of occurrence may shift.

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 [44]. Generally, patient age ranges from 11-60 years [4]; most patients are aged 45-54 years and chew betel nuts 5 times per day [4].

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].

No treatment is effective in patients with oral submucous fibrosis, and the condition is irreversible. Reports claim improvement of the condition if the habit is discontinued following diagnosis at an early stage [21].

Patients with oral submucous fibrosis have an increased risk of developing oral cancer. The malignant potential and the origin of cancer are attributed to the generalized epithelial atrophy associated with oral submucous fibrosis. Tobacco is the component of the quid believed to be most associated with cancer development. However, the carcinogenic property of the areca nut was discovered after noticing that cancer occurred in patients who chewed the nut without tobacco. In vitro, betel nut extracts increase the rate of cell division, reduce cell cycle time, induce DNA strand breaks, and induce unscheduled DNA synthesis [22]. Whether the use of tobacco in addition to areca nuts is responsible for the increased risk of oral cancer is controversial because evidence is conflicting.

Instruct patients regarding the importance of discontinuing the habit of chewing betel quid. Inform patients that eliminating tobacco from the quid product may reduce the risk of oral cancer. Instruct patients to avoid spicy foodstuffs. Instruct patients to eat a complete and healthy diet to avoid malnutrition. Instruct patients regarding maintaining proper oral hygiene and scheduling regular oral examinations. Intervention studies and public health campaigns against oral habits linked to oral submucous fibrosis may be the best way of controlling the disease at the community level. Educate the community regarding the local adverse effects of chewable agents, which although not inhaled, are still not harmless.

Oral sub mucous fibrosis (OSMF) is an insidious, chronic fibrotic change affecting any part of oral mucosa and has been considered as potentially malignant disorder. OSMF is a chronic disease of oral mucosa characterised by inflammation and progressive fibrosis of the lamina propria and deeper connective tissues, followed by stiffening of mucosa resulting in difficulty in opening the mouth. The diagnosis of OSMF is made on clinical grounds. Habitual chewing of gutkha (mixture of dry areca nut, tobacco and other chemical in trace for flavouring) and other areca nut quid plays a major role in the aetiology of the disease. Gutkha is very commonly used by younger generation and has become extremely popular acting as a main cause of OSMF. Hence based on above findings the present study

was planned for Assessment of Factors Underlying the Occurrence of Oral Submucous Fibrosis in Patients from Jharkhand Region.

Methodology

The present study was planned in Department of Oral Medicine, Diagnosis & Radiology, Vananchal Dental College & Hospital, Farathiya, Garhwa, Jharkand, India. Total 40 cases of the patients from age group 20 – 60 years of both the sexes were included in the present study. The patients were evaluated for the various parameters. The questionnaire included the basic socio demographic variables of all patients along with presence of habit of areca nut or gutkha chewing or having spicy food, symptoms like burning sensation in mouth on intake of hot and spicy food, and altered salivation. Clinical examination showed blanching and stiffness of oral mucosa and soft palate, palpable bands chiefly in buccal mucosa, and sometimes vesicle formation and ulceration.

Participants included were individuals with classic features of OSMF such as mucosal blanching, burning sensation, hardening of mucosa, presence of fibrous bands, and inability to open mouth completely. Patients undergoing treatment for OSMF, immunocompromised/debilitated patients, and those with temporomandibular joint problems were excluded from the study.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Table 1: Grading system for OSMF

Features	Grade 1 (Very early stage)	Grade 2 (Early stage)	Grade 3 (Moderately advanced stage)	Grade 4 (Advanced stage)
Symptoms	Burning sensation, dryness of mouth, vesicle formation or ulceration	Burning sensation, dryness of mouth	Burning sensation, dryness of mouth	Burning sensation, dryness of mouth
Spicy food	Irritation	Irritation	Irritation	Irritation
Mucosal colour	No changes in mucosal colour	Mucosa is blanched and loses its elasticity	Blanched opaque leather-like mucosa	Blanched opaque leather-like mucosa
Fibrosis	No fibrosis, bands palpable	No clear-cut fibrotic bands	Vertical fibrotic bands on buccal mucosa making it stiff	Thick fibrotic bands occurring at both the buccal mucosa in retromolar area and at the terygomandibular raphe
Mouth opening	Mouth opening normal	Slight restriction of mouth opening	Considerable restriction of mouth opening	Very little mouth opening
Tongue	Tongue protrusion normal	Tongue protrusion normal	Tongue protrusion not much affected	Restricted tongue protrusion
Eating and speaking	-	-	Difficulty in eating and speaking	Eating and speaking very much impaired
Oral hygiene	-	-	Poor oral hygiene	Very poor oral hygiene

Results & Discussion

Oral submucous fibrosis (OSF) is “an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibro-elastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat [23-24].

Oral submucous fibrosis is an “insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx, occasionally preceded by vesicle formation, always associated with fibrous bands and juxtaepithelial inflammatory reaction followed by a fibroelastic change of lamina propria with epithelial atrophy leading to stiffness of oral mucosa, trismus and inability to eat.” The WHO definition for an oral precancerous condition stated as “A generalized pathological state of the oral mucosa associated with a significant increased risk of oral cancer”, gives an appropriate description of OSMF.

Oral submucous fibrosis (OSF) is a chronic, progressive, scarring disease, that predominantly affects the people of South-East Asian origin. This condition was described first by Schwartz [25] while examining five Indian women from Kenya, to which he ascribed the descriptive term "atrophia idiopathica (tropica) mucosae or is". Later in 1953, Joshi [26] from Bombay (Mumbai) redesignated the condition as oral submucous fibrosis, implying predominantly its histological nature. The WHO definition for an oral precancerous condition - "a generalized pathological state of the oral mucosa associated with a significantly increased risk of' cancer," accords well with the characteristics of OSF.

A study from Delhi reported the prevalence of areca nut use to be 11.74% among high school students [9]. A similar study was done by Goel *et al*., [27] which showed that commercial areca nut consumption was 40% among OSF patients; Ahmad *et al*. [28] showed that 69% were consuming gutkha. Other studies have reported an increased prevalence in the consumption of areca nut and areca nut-based products, which are addictive and psychoactive in nature [28-30]. The findings of Babu *et al*., among OSF patients in Hyderabad, showed that people were more addicted to gutkha than any other related areca nut and tobacco products such as pan, pan masala and raw areca nut. They found a strong association between gutkha chewing and OSF and pointed that gutkha consumption led to OSF. [31]

Table 1: Age & Sex of Patient

Age	No. of Cases
15 – 25 years	8
26 - 30 years	10
31 – 40 years	7
41 – 50 years	7
51 – 60 years	5
Above 60 years	3
Total	40
Males	38
Females	2
Total	40

Table 2: Oral Habits

Sr. No.	Habits	No. of patients
1.	Areca nut	34
2.	Gutkha chewing	29
3.	Spicy food	18
	Total 40	40

Table 3: Functional staging

Functional staging	No. of Cases
Group I Very early case - mouth opening >36 mm	3
Group II Early case - mouth opening 26-35 mm	22
Group III Moderately advanced cases - mouth opening 15-25 mm	10
Group Iva Advanced cases - mouth opening 2-15	4
Group IVb Advanced cases with premalignant changes and malignant transformation	1
Total 40	40

Table 4: Histological Stage

Histological staging	No. of Cases
Stage 1	4
Stage 2	10
Stage 3	20
Stage 4	6
Total 40	40

A male predominance in OSF cases was reported by Sinor *et al*. [32] in India. Male predominance in our study can be due to easy accessibility for males to use areca nut and its products more frequently than females in our society along with the changing lifestyles of youngsters.

There is compelling evidence to implicate the habitual chewing of areca nut with the development of OSF. It occurs predominantly in the Indian subcontinent where the habit is more prevalent. The frequency of this habit in population affected by OSF ranged from 35% to 100% (Bhonsle RB *et al* 1987) [33]. This has been reported to be higher among OSF patients than in the general population. In a study of 100,000 villagers in Maharashtra (India), 4.2% of females who chewed areca nut and did not use tobacco, suffered from OSF. Thus chewing areca nut may be an important factor in the aetiology of OSF.

A vascular response due to inflammation, apart from the connective tissue repair process, has been very commonly found in OSF. Normal, dilated and constricted blood vessels have been seen often in combination, in the same section. Apparent narrowing of the smaller vessels appears first in the upper mucosa and spreads gradually to the larger, deeper vessels. Persistent dilation has also been seen in many moderately advanced and advanced biopsies. A rise in mast cells occurs in the earlier stages of the tissue reaction but in advanced stages, the counts are less in number. The inflammatory cells seen are mainly lymphocytes and plasma cells. The connective tissue in advanced stages is characterized by submucosal deposition of extremely dense and avascular collagenous tissues with variable numbers of chronic inflammatory cells. Epithelial dysplasia without carcinoma is found in l 0 to 15 % of cases submitted for biopsy and carcinoma is found in at least 5 percent of sampled cases. The excessive fibrosis in the mucosa seems to be the primary pathology in OSF and the atrophic changes in the epithelium secondary.

The alkaloid present in areca nut, Arecoline, is converted to arecadaine, which stimulates fibroblastic activity in oral mucosa resulting in [34] excessive collagen deposition seen in OSMF. This finding proves to be areca nut chewing habit in various forms, which is addictive and psychoactive in nature. Evidence from other studies shows that areca nut chewing suppresses hunger and reduces appetite during working hours or until people find time to have food. Sullivan and his colleagues found that people chewed it to get energy rather than for its psychotropic effects. But nevertheless, areca nut is the 4 most addictive substance in the world and is associated with a [35-36] dependence syndrome. This habit was seen especially in young males as they got exposed to these products at an early age through their friends and colleagues, or resorted to it in a hope to overcome stress and tension. Financial independence also acted [2] as a contributing agent.

Conclusion

The data generated from the present study concludes that correlation between functional and histological staging suggests that individuals with clinically advanced OSMF had extensive fibrosis histologically. Also early recognition with accurate staging of the disease and appropriate treatment planning is of utmost importance to prevent the malignant transformation and to improve the quality of life of the patient.

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