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CLINICAL ASSESSMENT OF OCCURRENCE OF ORAL SUBMUCOUS FIBROSIS IN PATIENTS FROM PATNA DENTAL COLLEGE & HOSPITAL

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Abstract:
Oral submucous fibrosis is a chronic progressive scarring disease of oral cavity and oropharynx characterized by epithelial atrophy and juxta epithelial inflammatory reaction with progressive fibrosis of the lamina propria and deeper connective tissue. The resulting stiffness of the oral mucosa then causes a progressive decrease in mouth opening. Hence based on above findings the present study was planned for Clinical Assessment of Occurrence of Oral Submucous Fibrosis in Patients from Patna Medical College & Hospital.
The present study was planned in Department of Oral Pathology, Patna Dental College & Hospital, Patna. Total 50 cases of the patient diagnosed with the Oral Sub mucous Fibrosis (OSMF) were evaluated in the present study. History, examination and investigation of patients were done in detail as per predesigned proforma. Histopathological examination of biopsy tissue from oral mucosa was done in patients who had taken pre-therapy and post-therapy (if and when required). X-ray of temporomandibular joint was requested (whenever needed).
OSMF is a commonly occurring and widely spread premalignant condition increasingly affecting the youth. The occurrence of OSMF in gutkha chewers is far faster and more severe as compared in other forms of areca nut products chewers. The easy availability and promotions of these areca nut products especially gutkha and pan masala outside the schools colleges and social places has impacted younger population in India which has led to the increased occurrence of OSMF.
Keywords: Oral Submucous Fibrosis, OSFM, gutkha, pan masala, etc.

Introduction:

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.[1][2] The condition is remotely linked to oral cancers and is associated with areca nut or betel quid chewing, a habit similar to tobacco chewing, is practiced predominantly in Southeast Asia and India, dating back thousands of years.

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 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 term oral submucosal fibrosis derives from oral (meaning mouth), submucosal (meaning below the mucosa of the mouth), and fibrosis (meaning hardening and scarring). [4] 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. [3]

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. [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. [7]

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. 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. [8] This was later confirmed by others, with a male-to-female ratio of 1:7. [9] 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. 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 ; most patients are aged 45-54 years and chew betel nuts 5 times per day. [10]

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%. 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. [11]

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. [25] In

vitro, betel nut extracts increase the rate of cell division, reduce cell cycle time, induce DNA strand breaks, and induce unscheduled DNA synthesis. 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. [12]

A neural network–based oral precancer stage detection method has been proposed. [7] This new technique uses wavelet coefficients from transmission electron micrography images of subepithelial fibrillar collagen in healthy oral submucosa and in oral submucous fibrosis tissues. These wavelet coefficients are used to choose the feature vector, which, in turn, can be used to train an artificial neural network. This trained network is able to classify normal and oral precancer stages (less advanced and advanced) after obtaining the image as an input. This technology is not readily available but could theoretically be used as an adjunct to hematoxylin and eosin histologic evaluations.

Currently, oral biopsy for hematoxylin and eosin provides the most definitive diagnosis and is crucial because of the association of oral submucous fibrosis with oral cancer. Some authorities have reported benefit with immunohistochemical techniques such as Masson trichrome staining when pathology involved muscle. Alteration of cytokeratin expression, as is seen in leukoplakia and oral cancer, has also been noted in oral submucous fibrosis. Increased intensity of staining for pancytokeratin and high molecular weight cytokeratin, aberrant expression of cytokeratin 8, and decreased expression of cytokeratins 5 and 14 suggest their potential as surrogate markers for malignant transformation. [13]

Dense bundles and sheets of collagen, thick bands of subepithelial hyalinization extending into the submucosal tissues (replacing fat or fibrovascular tissue), decreased vascularity, no edema, and inflammatory cells (lymphocytes and plasma cells) are found. Oral submucous fibrosis is generally characterized by diffuse hyalinization of the subepithelial stroma with pigment incontinence from the overlying epithelial melanin. [58] Other histologic findings include an atrophic epithelium and intercellular edema, with or without hyperkeratosis, parakeratosis, or orthokeratosis; epithelial dysplasia (25% of patients who underwent biopsy); squamous cell carcinoma histologically identical to typical squamous cell carcinomas; chronic inflammation and fibrosis in the minor salivary glands in the area of quid placement; and atrophy of the underlying muscle. Ultrastructural changes in oral submucous fibrosis include an increase in collagen type I; however, fibrils retain the normal structure. [14]

Oral submucous fibrosis is a chronic progressive scarring disease of oral cavity and oropharynx characterized by epithelial atrophy and juxta epithelial inflammatory reaction with progressive fibrosis of the lamina propria and deeper connective tissue. The resulting stiffness of the oral mucosa then causes a progressive decrease in mouth opening. Hence based on above findings the present study was planned for Clinical Assessment of Occurrence of Oral Submucous Fibrosis in Patients from Patna Medical College & Hospital.

Methodology:

The present study was planned in Department of Oral Pathology, Patna Dental College & Hospital, Patna. Total 50 cases of the patient diagnosed with the Oral Sub mucous Fibrosis (OSMF) were evaluated in the present study. History, examination and investigation of patients were done in detail as per predesigned proforma. Histopathological examination of biopsy tissue from oral mucosa was done in patients who had taken pre-therapy and post-therapy (if and when required). X-ray of temporomandibular joint was requested (whenever needed).

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.

Patients were divided into four groups according to severity, following the criteria from a study done by Ranganathan et al. [15] The criteria taken was mouth opening as follows.

Grade I: Only symptoms, with no demonstrable restriction in mouth opening

Grade II: Limited mouth opening. 20 mm and above

Grade III: Mouth opening less than 20 mm.

Grade IV: OSMF advanced with limited mouth opening. Precancerous or cancerous changes seen throughout the mucosa.

Following was the inclusion and exclusion criteria for the present 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 pterygomandibular 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 (OSMF). OSMF is a peculiar, chronic progressive, insidious, irreversible, crippling disease of the oral cavity characterized by fibrotic change and severe burning sensation with restricted opening of the mouth. [16] The disease affects most part of oral cavity as well as the upper-third of the esophagus. [17] The disease is characterized by blanching and stiffness of oral mucosa, trismus, and burning sensation in the mouth. It also produces hypomobilty of the soft palate and tongue, and loss of gustatory sensation. Occasionally there can be mild hearing impairment due to blockade of the Eustachian tube. [18-20] Malignant transformation rate of OSMF was found to be in the range of 7-13%. [21] According to long-term follow-up studies a transformation rate of 7.6% over a period of 17 years was reported. [22]

The disease is predominantly seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan, China, and among other Asiatics, with a reported prevalence ranging up to 0.4% in Indian rural population. [23] As a result of transmigration of populations, an increasing number of cases are being seen in other countries. [24] A study conducted in 2002 indicates that more than 5 million people in India have OSMF (0.5 % of Indian population), [25] the figure that must have increased sharply by now. It has been suggested that consumption of chillies, nutritional deficiency, chewing of areca nut, genetic susceptibility, altered salivary constituents, autoimmunity, and collagen disorders may be involved in the pathogenesis of this condition. [26] Teenagers and youths are getting more attracted to commercially available areca nut products like Gutkha and pan masala due to wide publicity, marketing and easy availability of such products. [27]

Table 1: Age & Sex of Patient

Age	No. of Cases
10 – 20 years	8
21 – 30 years	12
31 – 40 years	12
41 – 50 years	6
51 – 60 years	7
Above 60 years	5
Total	**50**
Males	39
Females	11
Total	**50**

Table 2: Oral Habits

Sr. No.	Habits	No. of patients
1.	Areca nut	31
2.	Gutkha chewing	30
3.	Spicy food	22

Table 3: Distribution as per Clinical Grades

Sr. No.	Mouth opening (in mm)	No. of patients
I	>40	2
II	31-39	2
III	21-30	16
IV	<20	30

Table 4: Sign & Symptoms

Signs and symptoms	Grade I	Grade II	Grade III	Grade IV	Total
Burning sensation to hot and spicy food	1	3	19	23	46
Dryness of mouth	0	2	9	11	22
Presence of white fibrous bands	0	2	20	25	47
Limitations of mouth opening	1	2	5	10	18
Restricted tongue movement	0	0	6	4	10

The occurrence of OSMF was seen significantly in those having one or the other forms of areca nut. This occurrence has shown that the products which leach out from areca nut would be responsible for the development of OSMF. [28] People having tobacco alone have never been seen to have OSMF. This was also observed in our study that there was no synergistic effect on development of OSMF in those consuming tobacco along with gutkha or in those consuming alcohol, tobacco, and gutkha simultaneously. If tobacco would have been a causative factor for OSMF then other forms of tobacco like cigarette, bidi, pipe smoking should have manifested OSMF as one of the clinical feature. In the areca nut chewers the lysyl oxidase activity is upregulated to alter fibroblast metabolism producing more collagen. This may add to the conclusion of the occurrence of OSMF due to the products leaching out from areca nut causes OSMF and not from those leaching out from tobacco. [29]

The pathogenesis of OSMF involves the mechanical as well as chemical trauma to the oral mucosa. The dry areca nut pieces present in gutkha and pan masala causes microtrauma to the oral mucosa. The traumatized mucosa undergoes chronic inflammation due to repeated microtrauma and irritation. This causes the oxidative stress and cytokines production due to chronic inflammation. The hypothesis that dense fibrosis and less vascularity of the corium, in the presence of an altered cytokine activity creates a unique environment for carcinogens from both tobacco and areca nut to act on the epithelium is widely being accepted. The alkaloid like arecoline, arrecadine guaccine, tannins, catechins, leaches out in saliva from areca nut and acts on the chronically inflamed mucosa. Increased amount of cytokines produced in oral mucosa like fibroblast growth factor, transforming growth factor and platelet-derived growth factor increases the production of collagen in the submucosal region. Also the inhibitory cytokine in collagen-production interferon-alpha is decreased in oral mucosa which leads to decreased degradation of collagen. Alkaloid leached out from areca nut acts on the fibroblast and induces the phenotypic changes, which leads to the decreased capacity of fibroblasts to degrade and remodel the collagen fibers in the submucosal region. This leads to the increased amount of collagen fibers in the submucosal region of oral cavity leading to OSMF. [30]

Haider et al.[31] studied the clinical and functional grading of 228 OSF patients and concluded that the bands formed initially in the fauces, followed by the buccal and labial areas. This is accompanied by an increase in the severity of the disease as measured by restriction in the ability to open the mouth. In the present study, the site of biopsy chosen was most characteristic of the condition, showed presence of vertical fibrous palpable bands and in most cases was the posterior buccal mucosa. This seems to be the reason for the shift of some of the patients in clinical Stage II to histopathological Grade III. When the correlation of functional staging with histopathological staging was done, a significant correlation was observed between them. Studies on qualitative analysis of collagen distribution in different stages of OSMF using Picrosirius red stain under polarized microscopy by Ceena et al.,[32] Modak et al.,[33] and Radhika et al.[34] found that tight packing of collagen fibers in OSMF progressively increased as the disease progressed from early to advanced stages, and it was observed that

comparison of functional and histological stages was a reliable indicator of the severity of the disease than clinical staging. However, Rooban et al.,[35] Goel et al.,[36] and Gajendra et al.[37] in their studies did not find significant correlation between clinical staging of mouth opening and histological grading of fibrosis. The possibility of a difference in the severity and extent of fibrosis in different regions of the oral mucosa and involved muscles was considered as contributory factors for this variation. Use of different staging systems, exclusion criteria, and biopsy technique could be a reason for the different results. However, a lack of uniform classification regarding clinical, functional, and histological changes of the condition cannot be overemphasized.

Conclusion:

OSMF is a commonly occurring and widely spread premalignant condition increasingly affecting the youth. The occurrence of OSMF in gutkha chewers is far more faster and more severe as compared in other forms of areca nut products chewers. The easy availability and promotions of these areca nut products specially gutkha and pan masala outside the schools colleges and social places has impacted younger population in India which has led to the increased occurrence of OSMF.

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