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Review Article

ORAL SUBMUCOUS FIBROSIS – A BRIEF REVIEW

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A R T I C L E I N F O

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A B S T R A C T

Oral submucous fibrosis (OSF) is a debilitating, potentially cancerous oral condition, caused primarily by chewing areca nut and its mixtures, as demonstrated by numerous epidemiological studies and other corroborative evidence. The condition may sometimes extend beyond the mouth to the oesophagus.OSF is well established as a condition with high malignant potential and is considered irreversible. It results in limited mouth opening which may leads to, chewing, swallowing, and speech problem. It is a characterized by juxta epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues such as lamina propira and deeper connective tissues.OSF is quite common in Indian subcontinent due to various oral habits like chewing tobacco, chewing pan masala etc. Early diagnosis is very important to prevent the lesion to be malignant. Herein, I have briefly discussed the historical perspective, definition, epidemiology, etiopathogenesis, clinical features, histopathological features in general along with different treatment modalities of OSF.

INTRODUCTION

Cancers of the head and neck region account for only 5% of all cancers reported yearly involving the human body, of which 30 % occur in the oral cavity. Over 95% of these cancers are squamous cell carcinomas[1]which usually develop from preexisting potentially malignant disorders.

Oral sub mucous fibrosis (OSF), one of the premalignant disorders is seen primarily in the Indian subcontinent and in Southeast Asia.[2]The prevalence rates in India ranges from 0.2% to 1.2%.[3]

The disease is considered to be a multifactorial one but the exact etiology is unknown. A positive association between betel nut chewing and onset of oral sub mucosal fibrosis have also been noted.[4, 5] Hypersensitivity to capsaicin, nutritional and vitamin deficiencies have been mentioned as possible etiological factors.[5-8] Probably genetic and environmental factors associated with immunological alterations may influence its development.[9]

The most frequently affected locations are the buccal mucosa and the retro molar areas. However, involvement of the soft palate, palatal fauces, uvula, tongue and labial mucosa are also reported. Common initial symptoms are burning sensation of the oral mucosa associated with vesiculation and /or ulceration, excessive salivation, pigmentation changes, recurrent stomatitis, defective gustatory sensation and dryness of mouth.

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The earliest and the most common clinical sign is blanched, stiff oral mucosa associated with vertical fibrous band[10] which is pathognomic feature of OSF.

The characteristic histopathological features of OSF revealed the presence of atrophic surface epithelium with hyalinization and homogenization of the subepithelial connective tissue associated with a variable numbers of inflammatory cell infiltration.[10] Epithelial dysplasia was found in 10-15% cases[11] while long term follow-up studies depict 7.6 %[12] malignant transformation.

A thorough comprehensive and complete description regarding OSF is depicted below including its historical perspective, definition, epidemiology, etiopathogenesis, clinical features, histopathological features and different treatment modalities of OSF.

Historical Perspective

In ancient history of medicine it was Sushruta (2500-3000 B.C.) , who first described about a condition known as 'VIDARI' in his classification on mouth and oral maladies that resembles to sub mucous fibrosis. [13]

In 1952, J. Schwartz describe an oral fibrosing disease in five Indian women from Kenya and coined the term "***atrophica idiopathica (tropica) mucosa oris"*** .[14]

S.G. Joshi subsequently coined the termed oral sub mucous fibrosis (OSF) for the condition in 1953.[15]

Definition

Pindborg and Sirsat in 1966 described OSF as "An insidious, chronic, disease affecting any parts of the oral cavity and sometimes 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 oral mucosa and causing trismus and inability to eat."[16]

WHO in 1978 described OSF as "Slowly progressive disease in which fibrous bands form the oral mucosa leading to severe restriction of the movements of the jaw including tongue. [17]

Epidemiology

Epidemiological surveys reveal, the prevalence rate in India varying from 0.2%-1.2%.[3]Incidence rates are available only from India. Gupta *et al* reported incidence in North-Western India of 2.6 and 8.5 per 100,000 per year for males and females respectively.[15]

Etiopathogenesis

In 1995, P.R.Murthy described arecoline (the active component of betel nut) which stimulates fibroblast to increase the production of collagen manifold (approx. 150%). In addition, arecoline is an inhibitor of metalloproteinases and a stimulator of tissue inhibitor of metalloproteinases thereby decreasing the overall degradation of collagen.[18]Caniff et.al[19]and Pindborg[20] considered the disease to be a form of hypersensitivity to capsaicin, an irritant in chilies. Nutritional and vitamin deficiencies have been mentioned as possible aetiological factors.[7]

Rajalalitha and Vali, in 2005 depicted the initial events of the disease process.[21]

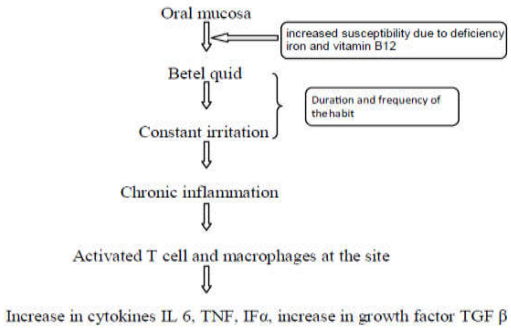

Figure 1 Initial Pathway In Pathogenesis of OSF

Ekanayaka RP, Tilakaratne in 2013 depicted the possible molecule and pathways involved in the pathogenesis of Oral Submucous Fibrosis.[22]

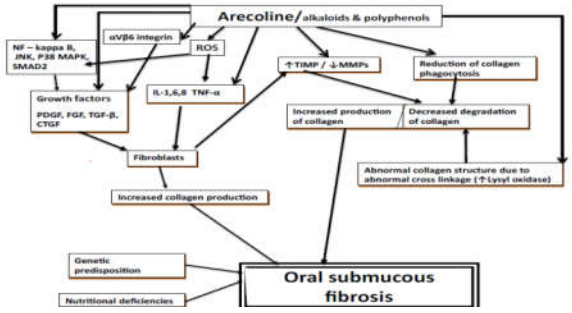

Figure 2 Possible Pathways in Pathogenesis of OSF

Serum zinc levels are decreased in patients with OSF which can act as indicator for malignant transformation. Copper can up regulate the expression of enzyme lysyl oxidase leading to fibrosis. Copper can stabilize enzyme activity by increasing its half-life. N terminus of exon-1 of lysyl oxidase molecule has copper binding site and this interaction may upregulate the expression of these enzymes. This event leads to crossing of collagen and elastin making it lessdegradable.[23-25]

Evidences suggest that collagen-related genes are altered due to ingredients in the quid. The genes COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 have been identified as definite TGF-β targets and induced in fibroblasts at early stages of the disease. The transcriptional activation of these procollagen genes by TGF-β suggests that it may contribute to increased collagen levels in OSF (Rajalalitha& Vali, 2005).[26]

Clinical Features

In relation to the distribution of the disease process, Paymaster in 1952, noticed of its limitation in the younger persons.[26]

Pindborg in 1966, reported of distribution of OSF among all age group ranging from 10 years to 77 years.[27]

There is no specific sex predilection in OSF. (Joshi, 1953[28]; Pindborg 1968[29])

However, Schwartz[30] (1952) and Rao[31] (1962) found female sex predilection. In 1981 Bhonsle *et al* stated that the most common sites of occurrence of OSF were tongue, buccal mucosa and lips.[32]

In Desa's (1957) opinion, the earliest consistent symptom of OSF was soreness of mouth with burning sensation ((stomatopyrosis), enhanced by eating food spiced with chilies.[32]

A R Kerr *et al* in 2011 narrated the high variability in the severity and permutation in the signs and symptoms of OSF.[33] Ranganathan K *et al* (2001)[34] divided OSF based on mouth opening as follows:

- Group I Only symptoms, with no demonstrable restriction of mouth opening.
- Group II Limited mouth opening 20 mm and above.
- Group III Mouth opening less than 20 mm.
- Group IV OSF advanced with limited mouth opening. Precancerous or cancerous changes seen throughout the mucosa.

Rajendran R (2003)[34] reported the clinical features of OSF as follows

- Early OSF Burning sensation in the mouth. Blisters especially on the palate, ulceration or recurrent generalized inflammation of oral mucosa, excessive salivation, defective gustatory sensation and dryness of mouth.
- Advanced OSF Blanched and slightly opaque mucosa, fibrous bands in buccal mucosa running in vertical direction. Palate and faucial pillars are the areas first involved. Gradual impairment of tongue movement and difficulty in mouth opening.

Histopathological Features

Rajendran *et al*. (1993) in a study of 10 cases of OSF noted microscopically atrophy of epithelium, atypia and absence of any basement membrane damage.[35]Kokila Ganganna *et al*.

described (J. Oral Maxillofac Pathol. 2012 May-Aug),the changes in OSF are mainly due to increased collagen deposition in connective tissue, subsequent to which there are changes in epithelium.[34]

Classifications Based on Histopathological Features of OSF

Pindborg JJ and Sirsat SM (1966) were the first to divide OSF depending only on histopathological features alone are as follows[34]

- **Very early stage** Finely fibrillar collagen dispersed with marked edema. Plump young fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorph nuclear leukocytes with occasional eosinophils are found.
- **Early stage** Juxtra-epithelial area shows early hyalinization. Collagen still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils and occasional plasma cells.
- **Moderately advanced stage** Collagen is moderately hyalinised. Thickened collagen bundles are separated by slight residual edema. Fibroblastic response is less marked. Blood vessels are either normal or compressed. Inflammatory exudate consists of lymphocytes and plasma cells.
- **Advanced stage** Collagen is completely hyalinised. A smooth sheet with no separate bundles of collagen is seen. Edema is absent. Hyalinised area is devoid of fibroblasts. Blood vessels are completely obliterated or narrowed. Inflammatory cells are lymphocytes and plasma cells.

Utsimomiya H, TilakratneWm, Oshiro K *et al* (2005) histologically divided OSF based on the concept of Pindborg and Sirsat and modified it as follows [34]

- **Early stage** Large number of lymphocytes in sub epithelial, connective tissue, zone along with myxedematous changes.
- **Intermediate stage** Granulation changes close to the muscle layer and hyalinization appears in sub epithelial zone where blood vessels are compressed by fibrous bundles. Reduced inflammatory cells in sub epithelial layer.
- **Advanced stage** Inflammatory cell infiltrate hardly seen. Number of blood vessels dramatically small in sub epithelial zone/Marked fibrous areas with hyaline changes extending from sub epithelial to superficial muscle layers. Atrophic, degenerative changes start in muscle.

Malignant Transformation of OSF

The precancerous nature of OSF was first mentioned by Paymaster (1956) who observed the development of slowly growing Squamous Cell Carcinoma (SCC) in one third of his patients in the Tata Memorial Hospital, Bombay.[36] Malignant transformation rate of OSF was found to be in the range of 7-13%. According to long term follow-up studies malignant transformation rate of OSF is 7.6% over a period of 17 years was reported (Murti *et al*., 1885).[12]

Ekanayaka RP, Tilakaratne[22] in 2013 depicted the possible events in malignant transformation of Oral Submucous Fibrosis.

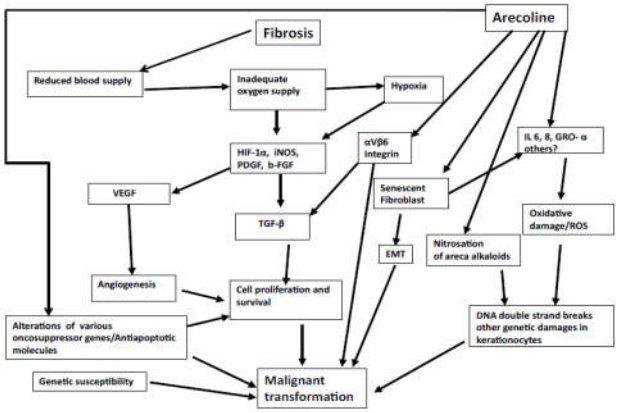

Figure 3 Possible Events in Malignant Transformation of OSF

Different Treatment Modalities

Quitting the habit of taking pan masala and other tobacco related products is most important to further progression of the OSF.

Intralesional: injection of corticosteroid, placental extract and hyaluronidase is very important in breaking collagen and helps in improvement of the condition.

The combination of local injections including, chymotrypsin, hyaluronidase, and dexamethasone, give better results than with one drug alone or combination of dexamethasone with chymotrypsin or dexamethasone with hyaluronidase alone. Combined therapy with nilydrin hydrochloride (peripheral vasodilator), vit D, E, B –complex, iodine, placental extract, local and systemic corticosteroids and physiotherapy claims a success rate of 62% in OSF.

Surgical management- surgical management including the forceful mouth opening and surgical removal of fibrotic bands have resulted in more fibrosis and disability. A new surgical technique consisting of excision of surgical band and submucosal placement of fresh human placental grafts, followed by local injection of dexamethasone was recommended for advanced cases.[37]

Table 1 Different Treatment Regimen in OSMF[37]

Treatment	Modalities
Steroids(topical)	⇨ To be applied locally at site of lesion
Steroids(intralesional)	⇨ Submucosal injection twice a week in multiple sites for 3 months at the site of lesion
Combination of chymotrypsin, hyaluronidase and dexamethasone	⇨ Chymotrypsin(5000LU) Hyaluronidase(1500LU) Dexamethasone(4mg) Twice weekly submucosal injection for 10 weeks.
Turmeric	⇨ Alcoholic extract of turmeric (3g), turmeric oil (600mg), turmeric oleoresin (6oomg) for 3 months. Lycopene14 8 mg twice a day for 2 months.
Interferon gamma	⇨ Intralesional injection of interferon gamma(.01-10 U/ml thrice a day for 6 ,months

CONCLUSION

Oral submucous fibrosis ia a chronic premalignant disorder with marked morbidity of the patient in terms of speech, food intake and mastication, being characterized by progressive fibrotic changes of the entire oral mucosa and its sequale

thereafter. The diagnosis of OSF provisionally made based on the presenting signs and symptoms. Most of the time the diagnosis of OSF were made upon the clinical presentation of burning sensation, difficulty in chewing and difficulty in mouth opening and blanching of oral mucosa. Later on the Histolopathgical evaluation is the definitive procedure for confirmation of oral submucous fibrosis. In order to prevent the condition like OSF a total restriction on the pan masala as well as other related products is needed.Thus,the entire gamut of historical perspective, definition, epidemiology, etiopathogenesis, clinical features, histopathological features and different treatment modalities of OSF are discussed herewith.

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