Oral submucous fibrosis and its dermatological relation

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ABSTRACT

Oral submucous fibrosis is a chronic insidious disease and is well-recognized as a premalignant condition. It is a collagen related disorder associated with betel quid chewing and characterized by progressive hyalinization of the submucosa. The oral submucous fibrosis needs to be differentiated from scleroderma showing oral manifestations, as these diseases have different pathogenesis and prognostic aspects. The patients of oral submucous fibrosis can approach the dermatologist. The aim of this article is to present concise overview of the disease and its dermatological relation.

Key words: Fibrous bands, oral submucous fibrosis, scleroderma

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INTRODUCTION

Submucous fibrosis is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Oral submucous fibrosis (OSMF) has also been previously described as idiopathic scleroderma of mouth, idiopathic palatal fibrosis, sclerosing stomatitis and juxta-epithelial fibrosis.[1] The hallmark of the disease is submucosal fibrosis that affects most parts of the oral cavity, progressive trismus due to rigid lips, cheeks, pharynx and upper third of the esophagus leading to dysphagia.[2]

The disease is mainly seen in Asian countries and the prevalence is more in India.[2] OSMF was first reported by Schwartz in 1952 while examining five Indian women from Kenya, which he called as "atrophica idiopathica (tropica) mucosae oris".[3,4] Later in 1953, Joshi from Mumbai re-designated the condition as OSMF, implying predominantly its histological nature.[3] Its precancerous potential was first reported by Paymaster in 1956. Rao in 1962 suggested that OSMF is a localized condition of collagen disease.[5,6]

Pindborg in 1966 defined OSMF as "an insidious chronic disease affecting any part 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 fibroblastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating."[6]

OSMF is regarded as a condition as it affects different regions of the oral cavity as well as pharynx. Prevalence of OSMF is 2.01% and malignant transformation rate of 2.3-7.6% has been reported in the literature. Genomic instability and altered keratinocyte phenotype has been reported to play an important role in malignant transformation.[7-10]

The main differential diagnosis of OSMF is oral features of scleroderma, which is a disorder of the connective tissue characterized by fibrosis of the skin, blood vessels and visceral organs.[11]

ETIOLOGY

The factors that have been discussed as possible etiological factors to date are areca nut, capsaicin in chillies, micronutrient deficiencies of iron, zinc and essential vitamins. A possible autoimmune basis to the disease with demonstration of various auto-antibodies and genetic predisposition with specific human leukocyte antigen (HLA) has also been proposed. However, from the available scientific literature, it is clear that the regular use of areca nut/betel nut is the major etiological factor.[4,12-15]

Four alkaloids are responsible for the pathologic effects of the areca nut, of which arecoline is the main agent. The other alkaloids present in areca nut are arecoline, arecaidine, guvacine and guvacoline. Arecoline undergoes nitrosation and leads to the formation of areca nut specific nitrosamine namely nitrosoguvacoline, nitrosoguvacine and 3-methyl nitrosominopropionitrile. These nitrosamines alkylate deoxyribonucleic acid (DNA) and metabolism of these areca nut specific nitrosamine lead to formation of cyanoethyl, which binds with o'methyl guanine in DNA. Prolonged exposure to this chemical irritant leads to malignant transformation.[2]

A dose-dependent relationship was observed for both frequency and duration of chewing areca nut (without tobacco) in the development of OSMF.[12,16] In a study carried out by Ali *et al*. highest incidence of OSMF with increasing severity was associated with those who chew areca nut more than 10 packets/day for more than 5-10 min.[17] The severity and the time taken for the development of the disease may also vary according to the preparation of areca nut consumed. The commercially freeze dried products such as pan masala, gutkha and mawa (areca and lime) have high concentrates of areca nut per chew and appear to cause OSMF more rapidly than by self-prepared conventional betel quid.[12,18]

PATHOGENESIS

The disease is multifactorial but the exact pathogenesis is not well-established.[19] The mechanisms responsible for the pathogenesis are increased collagen accumulation, increased expression of fibrogenic cytokines, genetic polymorphisms and autoimmunity. The increased collagen accumulation results from increased collagen production and stabilization or decreased breakdown of collagen.[2]

Fibroblasts are changed into different phenotypes under the influence of areca nut alkaloids, which secrete more amount of collagen. Increased fibrosis is also thought to be due to increased cross-linking of collagen through up-regulation of lysyl oxidase (present in copper which is present in betel nut) activity in OSMF fibroblasts. Thus, OSMF is now considered a collagen metabolic disorder. Stabilization of collagen structure is produced by catechin and tannins from the areca nut.[16,20]

Pathogenesis involves subepithelial inflammatory reaction and fibrosis in the oral mucosa. Due to chronic irritation from areca nut chewing, T cells and macrophages are activated at the site which increases cytokines (interleukin-6, interferon alpha) and growth factors (transforming growth factor beta) at the site. This activates procollagen genes, tissue inhibitor of matrix metalloproteinase (TIMP) and plasminogen activator inhibitor (PAI) genes. Procollagen genes increase collagen production while TIMP and PAI genes inhibit collagenase and thereby decreases collagen degradation, which result in an increase in insoluble form of collagen.[2,16]

The risk of OSMF also increases from the polymorphisms of the genes coding for tumor necrosis factor (TNF) alpha. The procollgen genes identified as TNF-β targets are COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1. Lastly OSMF is also thought to be an autoimmune disorder. Various studies have found HLA types, raised autoantibodies and immune complexes, which tend to indicate the autoimmune basis of the disease.[2]

The etiology of scleroderma is unknown. Immunologic studies suggest that the pathogenesis of the disease is autoimmune with antibodies directed against the endothelium.[21]

CLINICAL FEATURES

OSMF is preceded by symptoms such as burning sensation of the oral mucosa, ulceration and pain. The characteristic features of OSMF are loss of pigmentation of oral mucosa, leathery texture and blanching of oral mucosa, depapillation and reduced movement of tongue, progressive reduction of mouth opening and sunken cheeks. The changes of OSMF are similar to those of systemic sclerosis (scleroderma) but are limited to oral tissue.[22]

Blanching may be localized, diffuse or reticular and is caused by impairment of the local vascularity because of increasing fibrosis of the oral mucosa and results in a marble-like appearance [Figure 1]. Blanching may be associated with small vesicles that rupture to form erosions. Patients usually 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 OSMF.[16]

In the more advanced stage of the disease, the essential feature is a fibrous band restricting mouth opening [Figure 2]

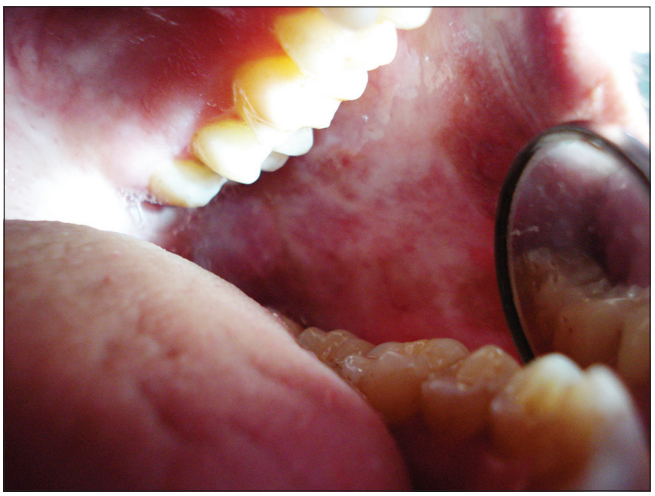

Figure 1: Blanching seen over left buccal mucosa

and causing difficulty in mastication, speech, swallowing and maintaining oral hygiene. Fibrosis may extend posteriorly to involve the soft palate and uvula. The uvula may appear shrunken and in extreme cases, budlike [Figures 3 and 4]. It was found that betel quid chewing habit has a dose-response effect on OSMF and the bands form initially in the fauces, followed by buccal and labial areas. Fibrosis makes cheek thick and rigid and fibrosis of the tongue [Figure 5] and the floor of the mouth interfere with tongue movement. Hard palate involvement includes extensively blanched mucosa.[13,16,23]

OSMF needs to be differentiated from oral manifestations of scleroderma and the pale mucosa with pigmentation seen in anemia.[24] In scleroderma, tongue, soft palate and larynx are the intraoral structures usually involved. The tongue becomes stiff and board-like and may result in dysphagia and the gingival tissues are pale and unusually firm.[20,25,26] The microstomia often develops as a result of increased collagen deposition in the perioral tissues. Characteristic furrows radiating from mouth produce a "purse string" appearance. Another important feature of scleroderma is widening of the periodontal ligament space.[20,25,27,28]

It differs from the other examples of pathological fibrosis (e.g. juvenile aggressive fibromatoses, abdominal desmoids) in that it harbors with it a definite tendency to induce the overlying epithelium to undergo neoplastic transformation, at least in a small proportion of cases.[29]

HISTOPATHOLOGY

The initial pathology of OSMF is characterized by juxta-epithelial inflammation including edema, large fibroblasts. The inflammatory infiltrate primarily contains neutrophils and eosinophils. Later, collagen bundles with early hyalinization are seen and inflammatory infiltrate becomes more chronic consisting of lymphocytes and plasma cells. Epithelium may show atrophic changes and dysplastic features[16,30,31] [Figure 6].

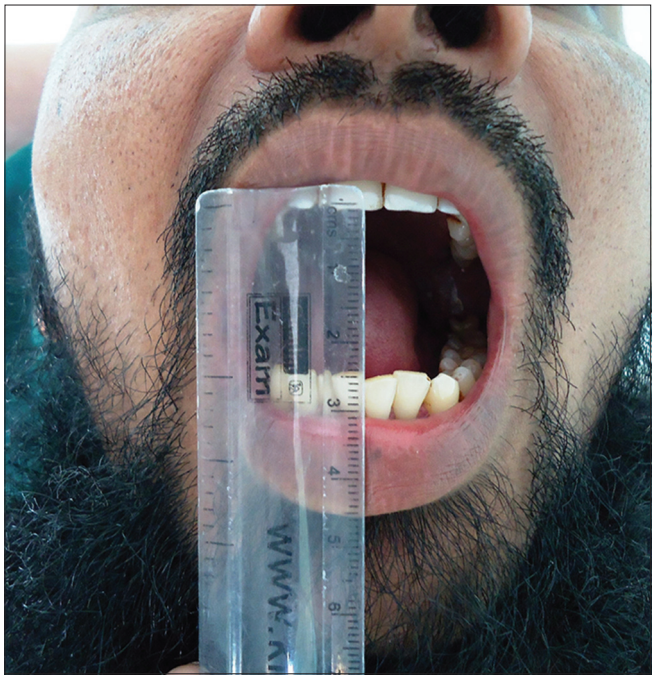

Figure 2: Decreased mouth opening in oral submucous fibrosis patient

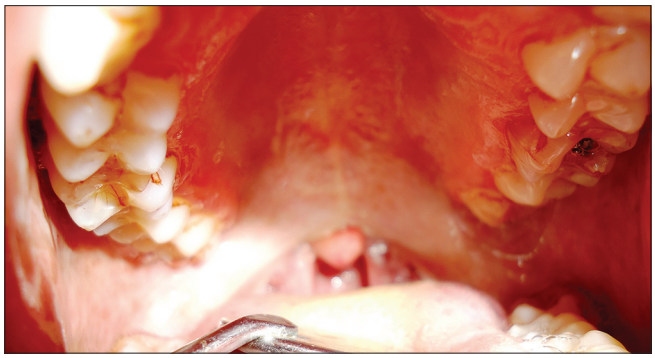

Figure 4: Soft palate showing blanching and shrunken uvula seen in the posterior part

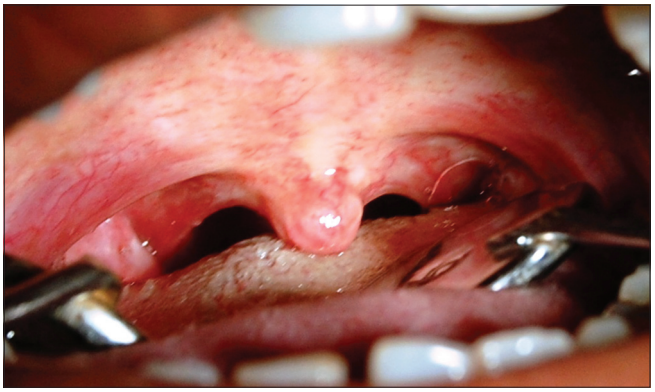

Figure 3: Soft palate and faucial pillars showing redness

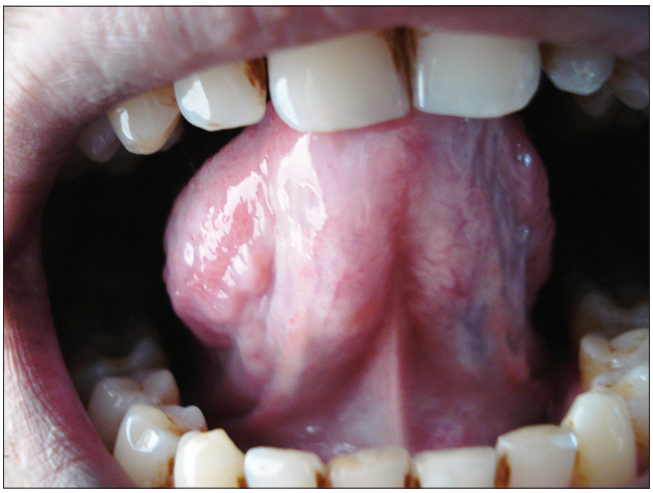

Figure 5: Blanching seen on ventral surface of tongue, floor of mouth and restricted movements of tongue

In more advanced stages, OSMF is characterized by formation of thick bands of collagen fibers and hyalinization extending deep into the submucosal tissues and decreased vascularity [Figure 7]. Collagen fibers may orient horizontally or vertically. Inflammation and fibrosis of minor salivary glands and muscle degeneration will occur in advanced stages of OSMF.[16,24,32,33] [Figures 7 and 8].

Histologically, OSMF shows features similar to scleroderma with few differences. In scleroderma, the epidermis may be normal, flattened or atrophic with loss of the rete ridges. At first the dermis is edematous, with swelling and degeneration of the collagen fibrils, which become homogeneous and eosinophilic. There may be a scanty perivascular lymphocytic infiltrate and small blood vessels may show intimal thickening.[20,27]

STAGING

Various classifications and staging systems have been put forward by various researchers based on clinical and/or histopathological aspects.[6,34] Most recently proposed classification is by More *et al*. in 2012:[22]

Clinical staging

- Stage 1: (S1) – Stomatitis and/or blanching of the oral mucosa
- Stage 2: (S2) – Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, with/without stomatitis
- Stage 3: (S3) – Presence of palpable fibrous bands in buccal mucosa and/or oropharynx and in any other parts of oral cavity, with/without stomatitis
- Stage 4: (S4) – (A) Any one of the above stage, along with other potentially malignant disorders, e.g. oral leukoplakia, oral erythroplakia, etc., (B) Any one of the above stage along with oral carcinoma.

Functional staging

M1: Inter-incisal mouth opening up to or >35 mm
M2: Inter-incisal mouth opening between 25 mm and 35 mm
M3: Inter-incisal mouth opening between 15 mm and 25 mm
M4: Inter-incisal mouth opening <15 mm
Examples: S1M1, S2M3, S2M4, S3M4, S4AM2, S4BM3.

PREVENTIVE MEASURES

As the OSMF is a progressive disease an important step to avoid progression of OSMF is to stop the habit completely.[17] The important step in preventing the OSMF is to decrease the habit of chewing areca nut by decreasing its availability in the market. The easy availability of areca nut products in various social places should be stopped.

MANAGEMENT

Complete stoppage or even reduction of the habit of areca nut chewing is the most important aspect of management. The management suggested for the OSMF is as follows:[3]

Nutritional support

Micronutrients, high proteins, calories and vitamins are the main nutritional support required for the management of the condition.[3,35,36]

Immunomodulatory drugs

Local and systemic glucocorticoids and placental extracts are the most commonly used. These also prevent or suppress inflammatory reaction by decreasing fibroblastic proliferation and deposition of collagen, thereby decreasing fibrosis.[3]

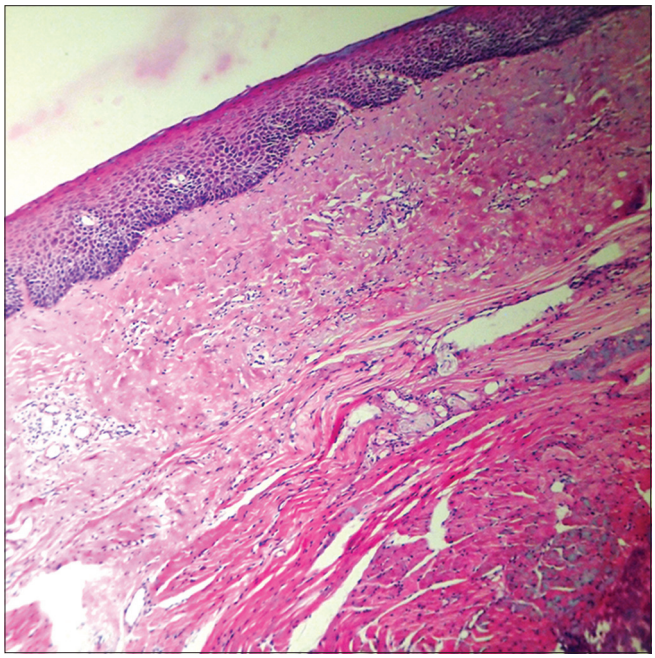

Figure 6: Histopathological picture showing early changes in the oral submucous fibrosis (H and E, ×100)

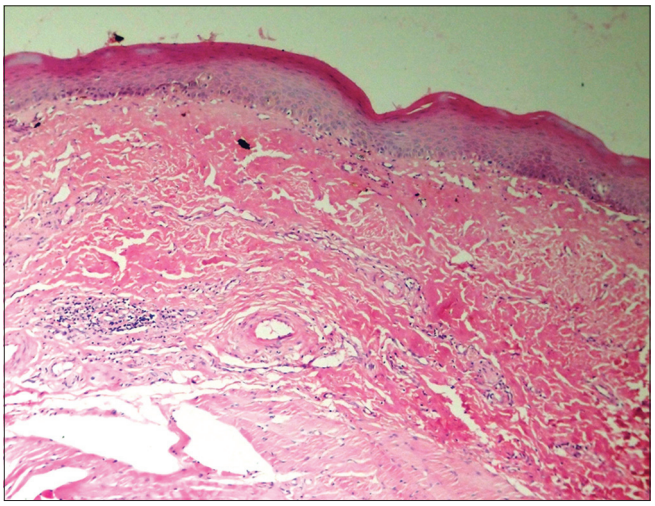

Figure 7: Histopathological picture of advanced stage oral submucous fibrosis showing atrophied epithelium, increased fibrosis and hyalinization of submucosal tissues (H and E, ×100)

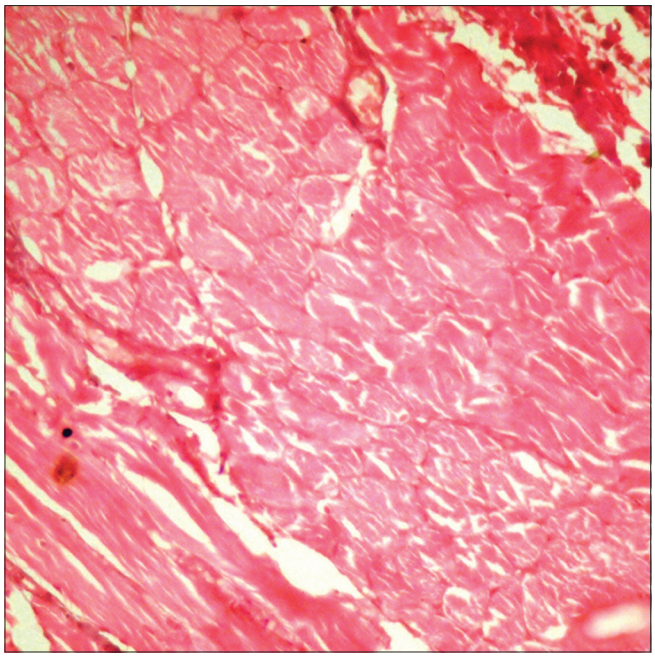

Figure 8: Histopathological picture of advanced oral submucous fibrosis showing muscle degeneration (H and E, ×400)

Physiotherapy

This includes measures such as forceful mouth opening, blowing and heat therapy. These measures have been commonly used and the results have been described as satisfactory.[3,33]

Local drug delivery

Local injection of corticosteroids and placental extract have also been tried, in addition to hyaluronidase, dexamethasone, collagenase, interferon-λ, antifibrotic cytokine and like substances which break down intercellular cement substances and also decreases collagen formation.[3,36,37]

Combined therapy

Combined therapy of peripheral vasodilators (nylidrin hydrochloride), vitamin D, E and B complex, iodine, placental extract, local and systemic corticosteroids and physiotherapy can produce a high success rate in OSMF management.[3,18]

Surgical management

Measures such as forcing the mouth open and cutting the fibrotic bands have resulted in more fibrosis and disability. Submucosal resection of fibrotic bands and replacement with a partial thickness skin or mucosal graft has been attempted. Procedures such as bilateral temporalis myotomy have also been tried.[3,36,38]

CONCLUSION

It is possible that the patients of OSMF can approach the dermatologist and it is important for the dermatologist to know the clinical manifestations of OSMF, its etiology and pathogenesis; for the proper diagnosis and management of the condition. So, that the condition can be diagnosed at the earlier stages and can benefit the patient.

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