Oral submucous fibrosis

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INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic insidious disease sometimes preceded by vesicle formation or stomatitis but always associated with juxta-epithelial inflammatory reaction and fibroelastic changes of the lamina propria with epithelial atrophy. It causes stiffening of the oral mucosa which becomes dry, blanched and leathery in consistency and results in trismus (Fig. 1).

HISTORICAL BACKGROUND

As early as 600 BC Sushruta (cited by Mukherjee and Biswas) described a condition resembling OSMF and named it 'Vidari'. Its features were progressive narrowing of the mouth, depigmentation of the oral mucosa and pain on taking food. In 1952 it was described among Indian migrants in Kenya and was named atrophica idiopathica (tropicum) mucosum oris. In 1953 a report from Bombay (India) gave it the name of submucous fibrosis. Similar cases were reported from Taiwan in 1954 and were called idiopathica scleroderma of the mouth. Since then the disease has been described by various names such as 'submucous fibrosis of the palate and cheek', 'idiopathic palatal fibrosis' and 'sclerosing stomatitis'. It derives its name from the deposition of fibrous tissue in the submucosal layer of the palate, fauces and cheek which cause disabling sequelae. No other part of the body is affected. OSMF is now the most widely accepted and commonly used term to describe this disease.

PREVALENCE

Oral submucous fibrosis is predominantly seen in India (prevalence rate 0.2% to 0.5%), and an estimated 2.5 million people suffer from the disease. The disease is more common in South India and the state of Kerala has the highest prevalence. Epidemiological surveys show...
that the prevalence of OSMF is high in Lucknow (0.51%), Bombay (0.5%) and Trivandrum (1.22%), and low in Darbhanga (0.07%), Srikakulam (0.04%), Bhavnagar (0.2%), Ernakulam (0.4%) and Bangalore (0.18%). Some recent reports indicate an increase in the number of OSMF cases in eastern Uttar Pradesh. In Sevagram (Maharashtra) it comprises 0.97% of all new cases attending the Otorhinolaryngology out-patient department.

Cases of OSMF have been reported among people of Indian origin in Taiwan, Nepal, Sri Lanka, Malaysia, Thailand, Vietnam, Uganda and South Africa. Isolated cases of OSMF have been reported in Indian and Pakistani migrants to the UK, Europe, Africa and in a British woman married to a Pakistani national. OSMF has also been found to occur frequently in workers in the cashewnut industry.

AETIOLOGY

The aetiology of OSMF is obscure. Some of the hypotheses put forward are as follows.

Chronic irritation

It is attributed to a high intake of chillies (capsaicin), and chewing of betel-nut (areca-nut) with lime, ‘pan’ leaves and tobacco with lime. The use of ‘misi’ (a black coloured powder containing washing soda, borax, powdered alum, charcoal of myrobalan and Fullers’ earth in various proportions) for cleaning teeth and colouring the gums, and exposure to volatile oil vapours in the cashewnut industry have also been implicated. These agents are more likely to be risk factors rather than specific aetiological agents. Experimental studies were performed when ingredients of chillies such as capsaicin and arecoline (an extract of areca-nut) were applied to the oral mucosa of healthy Wistar rats. These failed to produce submucous fibrosis in the oral mucosa. However, tissue cultures have revealed that the alkaloid present in areca-nut extract has a collagen stimulating property. Tannins present in areca-nut have been shown to reduce the collagenase-activated collagen degradation products. Vitamin deficiency and streptococcal infection are believed to precipitate OSMF.

Collagen disorder

It was Su who first suggested that OSMF was a collagen disorder. In OSMF changes similar to those of rheumatoid arthritis and scleroderma have been shown on histopathological, electron microscopic, histochemical and enzymatic studies. However, other workers feel that OSMF is a localized collagen disorder similar to idiopathic retroperitoneal or mediastinal fibrosis, or Dupuytren’s contracture. The presence of hyperglobulinaemia, mononuclear cell infiltration in collagen fibres, increased levels of serum mucoproteins and mucopolysaccharides has further supported the collagen nature of OSMF. However, L.E. cells have not been found in cases of OSMF.

Immunological disorder

The occurrence of OSMF in teenagers and in cases without any history of using irritants suggests that an immune mechanism may cause OSMF. Humoral studies have shown consistent hyperimmunoglobulinaemia but the observations on various fractions of immunoglobulins have been inconsistent. Serum IgG levels which have been related to the severity of the disease were found raised in two studies and normal in one. Serum IgM and IgA were found to be normal but in the advanced stages the level of IgA was found to be decreased, whereas other studies have shown raised levels of IgM, IgA, IgD and IgE. Immunofluorescence and immunoperoxidase techniques have demonstrated the presence of immunoglobulins in tissue from OSMF lesions. Cellular immunity in OSMF has revealed an increased absolute null cell count, a decrease in the absolute number of T cells and a normal population of B cells. C3 has been observed to be normal. Salivary studies in patients of OSMF have shown an increased pH, salivary amylase, alkaline phosphatase and potassium, and low to normal levels of calcium. Salivary immunoglobulins have been reported to be within normal limits. The unusual feature of saliva in patients of OSMF is the presence of a heat-labile fibrin producing factor along with an increased level of plasma fibrinogen. The theory of genetic predisposition has been proposed as OSMF runs in families, predominantly Indian and of Indian origin. OSMF has been shown to be associated with HLA A110, DR3, DR7 and probably B7 and haplotypes A10/DR3, B8/DR3 and A10/B8. At present it appears that OSMF has a multifactorial aetiology with a strong interaction between these factors. A possible mechanism is outlined in Fig. 2.
HISTOPATHOLOGY OF OSMF
The squamous epithelium of the oral cavity shows thickening with deep invagination of epithelial rete pegs into the adjacent lamina propria. The submucosal layer reveals increased and dense collagen fibrils with marked hyaline degeneration and the presence of increased PAS-positive material in the connective tissue.\textsuperscript{35,36} Based on the histopathological changes OSMF has been classified into four different stages:\textsuperscript{18}

I. Very early stage showing fine dispersed fibrillar collagen with marked oedema and presence of polymorphs and occasional eosinophils (Fig. 3a)

II. Early stage showing early hyaline degeneration of juxta-epithelial area and a thickened separate collagen bundle (Fig. 3b)

III. Showing moderately hyalinized collagen, adult sized fibroblasts with elongated, spindle shaped nuclei and scanty cytoplasm. The blood vessels are constricted and other cells are similar to those seen in stage II (Fig. 3c)

IV. Advanced stage showing complete hyalinization of collagen in the form of a smooth sheath without any separate bundle being discernible (Fig. 3d).
The presence of refractile eosinophilic material and metachromasia in the ground substance are also described in OSMF. Other changes described are irregularity and detachment of the epithelium with a varying degree of keratosis, parakeratosis and orthokeratosis, a reduction in the number of epithelial layers including atrophic changes and a thinning of the basement membrane which remains intact. Atrophic changes are distinct and important features of OSMF.

EXfoliative CytoLOGY
Cytology of early cases of OSMF shows marked pleomorphism of the cells in the superficial and deep layers of epithelium. In the more advanced stages groups of cells show large nuclei with a distinct nuclear membrane and a rarified centre which does not contain much chromatin. Interpretation is difficult when cells show marked atypia and degeneration. Advanced lesions show only a few cells, some cell shadows and an increase in the number of keratinized squamous cells. Wahi et al. observed large exfoliated cells with a predominance of surface cells and a peculiar rarified chromatin pattern in the nuclei. With an increasing severity of OSMF the nuclear changes become more marked and there is a progressive increase in dyskaryotic changes. Alkaline phosphatase has been found to be raised in the exfoliated cells.
Though the cellular changes are typical of OSMF, they may not help to diagnose a malignant change. Thus exfoliative cytology can only be used as an adjunct and not a substitute for biopsy.

**CLINICAL FEATURES**

OSMF affects a wide age range (10 to 70 years) with the highest reported incidence in patients aged between 30 and 40. However, our studies have shown the most commonly affected age group to be between 20 and 40. The male to female ratio is variable.

The early symptoms are recurrent episodes of vesicular eruption, pin-head sized multiple shallow ulcers, excessive salivation and burning sensation in the mouth, intolerance of hot and spicy foods and a progressive increase in trismus. In the advanced stage, the patient is unable to blow out his cheek or whistle. Impairment of taste is uncommon, being seen in 6.6% of cases while electrogustometry has revealed impairment of taste in 48%. OSMF has an insidious onset of symptoms with an average duration of 2 to 5 years.

The normal, pink and supple mucosa of the oral cavity is replaced by dry, blanched and leathery mucosa. However, black pigmentation of the mucosa has been observed in patients using 'Misi' for dental hygiene.

Different clinical classifications have been used to grade the cases depending upon the severity of the symptoms. Depending on the degree of fibrosis, trismus and ankyloglossia the most common classification divides the cases into the following grades.

I. Mild fibrosis with slight decrease in mouth bite (Fig. 4)
II. Moderate symptoms of disease and fibrosis extending from the cheek and uvula to the palatal area (Fig. 1)
III. Marked involvement of the cheek, uvula and lips with narrow opening of the mouth and ankyloglossia (Fig. 5).

**TREATMENT**

Prevention of OSMF is more important than treatment. Since the aetiology of OSMF remains uncertain, the treatment is aimed at ameliorating the discomfiting symptoms, reducing the fibrosis and improving the mouth bite.

**Systemic treatment**

It is of doubtful value. In the past, gold, arsenic trioxide and large doses of iodide followed by liver extract, high doses of vitamin A and iron preparations have been tried without much success. Corticosteroids have also been used with partial relief of the symptoms.

**Local treatment**

1. **Medical treatment:** Submucosal infiltration of hyaluronidase, fibrinolysin, collagenase, aqueous extract of human placenta, chymotrypsin and various forms of steroids like hydrocortisone, methylprednisolone and triamcinolone either alone or in combination have been used. The most common treatment at present is a combination of 1 ml of hydrocortisone and 1500 IU of hyaluronidase infiltrated submucosally, in the
mouth, at 2 or 3 different sites by a tuberculin syringe, given twice weekly for a total of 24 sittings.59

Hyaluronidase has been found to be an effective palliative for the burning sensation.60 This symptom is produced by the effect of local by-products of hyaluronic acid which is a ground substance in the connective tissue. Hyaluronidase rapidly breaks down the hyaluronic acid and lowers the viscosity of the intercellular cementing substance.60 An initial course of hyaluronidase is followed by the addition of dexamethasone.60 The relief from various symptoms including an improvement in the suppleness of the oral mucosa is temporary and may last from a few months to a few years. A recurrence of the symptoms requires another course of treatment.

2. Surgical treatment: In the past it has involved forcing open the mouth and cutting the fibrous bands under general anaesthesia, which results in more disability.2,20 Covering the raw areas after excising the fibrous band with skin (either full or split thickness) grafts has met with a high rate of failure. As the posterior third of the tongue is not involved by OSMF, a tongue flap pedicle graft based either anteriorly or posteriorly has been used to cover the raw area created after making linear incisions in the retromolar region. This has met with some success.44,61

3. Physical agents: Microwaves at the rate of 2450 per second have been used. This radiation is given by a 'Microwave 200 Unit' for 20 minutes a day at each site with 20 to 25 watts energy for a total of 15 sittings.62 Along with the medical or surgical treatment acrylic moulds of progressively increasing sizes or dental props have been used to help maintain the mouth bite.44,61

OSMF AS A PREMALIGNANT CONDITION

Slow growing squamous cell carcinoma has been observed in 23 to 30 per cent of cases of OSMF.63,64 A routine histopathological examination of the OSMF lesion has revealed histological evidence of carcinoma in 5% to 6% of cases without any clinical evidence of the same.15 Studies in our institution have shown associated carcinoma in less than 1% of cases.

A recent investigation of trace elements in OSMF has revealed raised serum levels of copper and normal levels of zinc. The rise of serum copper level was highest in cases of Stage I OSMF.65

SUMMARY

Oral submucous fibrosis is seen predominantly in India with a prevalence rate of 0.12 to 0.5 per cent. The disease receives its nomenclature from its well developed state which includes the deposition of fibrous tissue in the submucosal layer of the palate, fauces and cheek and causes disabling sequelae without affecting any other part of the body. It probably has a multifactorial aetiology with well defined risk factors such as chewing of betel-nut, 'pan' leaves, tobacco with lime and excess intake of chillies which act either by mechanical irritation, hypersensitivity or by producing chemical burns, with a strong underlying immune mechanism and genetic predisposition. At present there is no curative treatment. The various modalities tried so far include local infiltration of hyaluronidase, cortico-stereoids either alone or in combination with other agents, excision of the fibrotic areas and covering with a myocutaneous tongue flap, microwave diathermy and physiotherapy using acrylic mould screws or dental props to maintain the mouth bite. A regular follow up of these cases is essential as OSMF is known to be precancerous.

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