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Oral submucous fibrosis and Recent advances

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Abstract

Oral submucous fibrosis (OSMF) is a chronic, potentially malignant disorder of the oral cavity characterized by progressive fibrosis of the submucosal tissues. Recently, due to advances in the field of diagnostic pathology, advanced diagnostic aids are used to guide the dentist about the nature of disease and its prognosis. Management of OSMF has also seen changes These advancements have aimed to improve treatment outcomes, relieve symptoms, and prevent the malignant transformation of the condition.

Keywords: OSMF, diagnosis, management, recent, advances

Introduction

Oral Submucous Fibrosis (OSMF) is an Oral potentially malignant disorder. It is a collagen metabolism disorder. (1) A number of definitions have been proposed by a number of researchers. (2) The ancient medical literature has evidence of definitions by Sushruta where it was popularly known as 'Vidari'. J.Schwartz in 1952 also fondly described it as Atropicaidiopathica (tropica) Mucosae Oris in five Indian migrant women. (3,4) However, it wasPindborg who coined the term OSMF and gave an extensive definition of the same. (5) The epidemiology of OSMF is dependent on the socio-demographic factors of the population. (6) OSMF is a disease of middle age group. Usually, patients are 20-40 years of age and this is progressing towards younger age group. In India, the prevalence of OSMF is 0.2-2.3% in males and 1.2-4.6% in females.(7)Males are found to be more affected due to easy habit acquisition.(8)Regionally, it is more prevalent in the South-east Asia India, Sri Lanka, Maldives, Bangladesh, Myanmar, Taiwan and various islands in South Pacific contributing to more than half of the global prevalence.

The etiology of OSMF is multifactorial. A number of surveys suggests that areca nut is the main etiologic factor with a dose-dependent relationship. (8) There are many other local factors like capsaicin, tobacco, spicy foods and alcohol have synergistic effects. Systemic factors like iron, Vitamin B12 deficiency, anemia, genetic predisposition are also contributory. (9)These

etiologic factors directly dictate the pathogenesis pf OSMF. This review provides an overview of OSMF with recent advances in diagnosis and management.

Pathogenesis

Although the pathogenesis of OSMF is one of the most researched area, its pathogenesis is still obscure. (10) There are a number of proposed mechanisms for the same:'

OSMF -a collagen metabolism disorder

Disturbance in collagen turnover is central to pathogenesis of OSMF. Arecanut which is a causative factor for OSMF contains alkaloids and flavonoids. The alkaloids are responsible for collagen synthesis whereas flavonoids decrease the activity of collagenase-the enzyme responsible for breakdown of collagen. The net effect is increased collagen production and decreased collagen degradation. (5,11) In an interesting study, the qualitative properties of collagen were assessed with hstopathological grading of OSMF. Picrosirius red staim was used to locate collagen fibers. The submucosa exhibited a denser arrangement of collagen fibers, indicating the initiation of fibrosis in that region. The progressive histopathological grades showed an elevated presence of perpendicular type III fibers, implying their involvement in the fibrotic process. (12)

Effect of arecanut alkaloids on fibroblasts

Alkaloids have direct effect on proliferation of fibroblast which in turn increase the production of collagen. When mixed with slaked lime, arecanut is converted to are cadine which stimulated fibroblasts. (8) This phenomenon may arise from the clonal selection of a specific cell population within the modified tissues, influenced by local factors such as interleukin-1 released by inflammatory cells.(13)

Collagen stabilization

The presence of Areca flavonoids, tannins, and catechins can lead to increased fibrosis by promoting the formation of a more resilient and insoluble collagen structure through the inhibition of collagenase enzyme activity.(13) Type I collagen which is normally present in the oral cavity is completely replaced by type III collagen which is more resilient. (14,15) At a molecular level also, there is excess of alpha 1 chain than alpha 2 chains. Hence the collagen structure becomes more stable and less prone to degradation. (16)

1. Nutritional deficiency

Nutritional deficiencies like iron, vitamin, protein, etc are seen frequently in OSMF pa6tients. (17) Hydroxyproline, an amino acid exclusively present in collagen, is integrated into collagen in its hydroxylated form, specifically as 4-hydroxyproline. This process relies on the presence of iron and ascorbic acid. The decline in iron levels might be attributed to iron utilization in the fibrotic process.(18)

Molecular pathogenesis

Many biological pathways are active in the pathogenesis of OSMF. ROS (reactive oxygen species) activate various components within the cellular signalling network, including receptors, receptor-activated protein kinases, nuclear transcription factors, growth factor receptors, Janus kinase (JAK), SRC kinase, RAS signalling, mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, and nuclear factor-κβ (NF-κβ). These pathways are involved in EMT. (19) Arecoline induces the growth factors (TGFβ, CTGF, bFGF) and downregulates BMP7 as a negative regulator of fibrosis. (20–22) The equilibrium between MMPs and TIMPs that is responsible for maintaining collagen is also disrupted. Many studies reported decreased

concentration of MMPs while TIMPs is increased hence stabilising the collagen. (23,24) The detailed discussion of molecular pathogenesis of OSMF is beyond the scope of this article.

Diagnosis

The clinical presentation of OSMF is very characteristic and diagnosis is usually done by oral examination. Reduced mouth opening is one of the findings with which patient reports to the dentist. Other signs such as ulcers, xerostomia, blanching of oral mucosa, etc. are also commonly present. In advanced cases the upper aerodigestive tract also has strictures. (25) The fibrous bands are progressive and makes opening of mouth difficult. Many researchers have proposed various classifications based on the clinical features observed. The classification proposed by More et al. presents the clinical and functional staging of OSMF. This system of classification is appropriate for Indian population(4)

There are many definitive methods to diagnose OSMF. One of the methods is the gold standard histopathological examination. A solid biopsy is performed which is wedge shaped from the most representative site. The findings can be aptly described as mucosal and submucosal changes. Mucosal changes include atrophy of the epithelium, loss of rete ridges and liquefactive degeneration of basal layer. Rarely, pigment incontinence can be seen. Submucosa is very characteristic. Diffuse fibrosis in the submucosa with a chronic inflammatory infiltrate is the hallmark of OSMF.(26)

Exfoliative cytology although of little use, is a quick chairside investigation. In a study evaluating cellular features of OSMF, the keratinised cells and intermediate buccal cells were stained green to blue in colour and the cytoplasm appeared creased. The detection of a higher quantity of intermediate cells may suggest the initial occurrence of atrophic alterations. As only a small number of cases exhibited inflammatory cells, abnormal chromatin patterns, and perinuclear halo, these cellular transformations might be related to the overall health status of the patient and may not be exclusive to OSMF.(27)In a recent study conducted by Jaitley et al., it was observed that patients with OSMF demonstrated a reduction in cytoplasmic diameter and an elevation in nuclear diameter. These alterations were determined to be early signs indicating the potential for malignancy in the lesions. (28) The pathogenesis of OSMF is molecular and many pathways are involved in the pathogenesis. In 77% of cases, PCNA was positive. (29)

Cyclophilin A (CYPA) was identified as a biomarker and a target for gene intervention in OSF through proteomic two-dimensional electrophoresis (2-DE).(30) NCOA7 is a potential biomarker in detecting malignant transformation of OSMF. Interestingly, HIF1α was elevated in fibroblasts of betel quid chewed. Use of Ultrasonography (USG) in OSMF gave promising results. It is a non-invasive method to grade the degree of fibrosis. The elastography score represents the relative elasticity ratio between areas that appear normal and areas that appear abnormal. In OSF where tissue elasticity is reduced due to fibrosis, this method gives promising results. (32)autofluorescence spectroscopy, optical coherence tomography (OCT), and Fourier transform infrared spectroscopy (FTIR) were used in patients who do not undergo biopsy for OSF diagnosis. Auto fluorescence spectroscopy functions on the principle that when tissues are excited to a suitable wavelength, intrinsic fluorophores rise to various fluorescence emission spectra. By the means of optical coherence tomography, the measurement of epithelial thickness and the standard deviation (SD) of A-mode

scan intensity within the laminar propria layer prove to be effective diagnostic indicators for OSF.(33)

Management

Asper the definition by Pindborg, OSMF is a chronic disease. (34) Conservative treatments usually are of little benefit. (35)Habit intervention remains the central point of OSMF treatment. Patientn education regarding ill effects of arecanut and measures should be taken to stop its usage. Nevertheless,for the ease of understanding the treatment of OSMF can be divided as: conservative therapy, pharmacotherapy and surgical intervention.

1. Conservative therapy

For mild cases of OSMF i.e., mouth opening greater than 25 mm conservative therapy can nbe considered. Physiotherapy such as using mouth props, various splints, jaw stretching exercises have proved to be beneficial in early stages of OSMF. (32) Physiotherapy has shown promising results in a long run and can be used when other resources are limited. (37)

2. Pharmacotherapy

A lot of research has been done to find the medicinal treatment of OSMF. Some of these aim at reversal of the disease process while some provide symptomatic control.

- Steroids have been the drug of choice in treatment of OSMF since a long time. Their anti-inflammatory property has proved to be highly beneficial. Commonly used steroids are hydrocortisone, triamcinolone, methylprednisolone, betamethasone, dexamethasone and clobetasol propionate. They can be used topically or as intralesional injections. (38,39)
- Interferon gamma:This cytokine is recognized for its anti-fibrotic properties, as it promotes the production of collagenase in the oral epithelium and the underlying lamina propria, while inhibiting the proliferation of fibroblasts.(40)
- Herbal extracts: Herbal medicines such as colchicine,(41) basil, turmeric, (42) aloe vera(43), lycopene (44) are vastly researched to aid in treatment of OSMF. All of them have satisfactory results in a long term.
- Iron supplements: Iron is essential for epithelial turnover. Deficiency of Iron leads to atrophic epithelium.

  Numerous research studies have indicated a decline in haemoglobin and serum ferritin levels in OSMF, with the iron content being depleted during collagen synthesis.(45) Hence iron supplements can be beneficial in treatment of OSMF.
- Fibrinolytic therapy: The fibrosis in OSMF can be broken down by the means of proteolyticenzymes such as hyaluronidase, collagenase, and chymotrypsin and have proved to be successful. (46)

3. Surgical treatment

- Treatment of patients with advanced stages of OSMF is a challenging task. Surgical treatment of OSMF primarily aims to increase the mouth opening. (47) The prognosis of surgical interventions have been debatable. The treatment options for OSMF essentially involveexcision of the fibrous bands, excision of bands with myotomy either with or without coronoidectomy, and covering the exposed area with various materials such as skin grafts, fresh amnion, collagen membrane, buccal fat pad, local flaps, or vascularized free flaps. This is followed by proactive post-operative jaw physiotherapy, incorporating antioxidants and ensuring proper nutrition. Regular follow-ups are essential to maintain oral opening and promptly identify any potential malignant changes. (48) In a

systematic review, it is observed that lasers such as Diode, KTP-532, ErCr:YSGG have proved to be promising in treatment of OSMF.

4. **Stem Cell Therapy**

- Researchers have investigated the potential of stem cell-based approaches, particularly mesenchymal stem cell (MSC) transplantation, to reverse fibrosis and facilitate tissue regeneration in OSMF. MSCs possess immunomodulatory and regenerative properties, making them a prospective therapeutic option for OSMF. However, further investigation is necessary to establish their effectiveness and safety.(49)

5. **Targeted Therapies**

- The management of OSMF has witnessed the emergence of molecular targeted therapies. These therapies focus on specific signaling pathways involved in fibrosis, such as the transforming growth factor-beta (TGF-β) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. In preclinical studies, drugs targeting these pathways have demonstrated potential by disrupting the fibrotic process and potentially impeding the progression of the disease.(25)

Conclusion

In recent years, significant strides have been made in both diagnosing and managing oral submucous fibrosis (OSMF). Cutting-edge diagnostic techniques, including optical coherence tomography (OCT) and confocal microscopy, have emerged as promising non-invasive methods for detecting OSMF-related changes in the oral mucosa at an early stage. These innovative technologies play a crucial role in facilitating timely diagnosis and monitoring disease progression. Moreover, the field of pharmacological interventions has witnessed remarkable progress, broadening the array of treatment options for OSMF. Antioxidants, immunomodulators, and collagen cross-linking agents have been extensively studied for their potential in alleviating symptoms and modulating the fibrotic process. Surgical interventions have also evolved, with techniques such as laser therapy offering minimally invasive alternatives to enhance mouth opening and foster tissue regeneration. However, further advancements and optimization of care necessitate continued research and clinical trials in order to refine these innovative approaches and benefit individuals affected by OSMF.

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