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RESEARCH ARTICLE

A COMPREHENSIVE REVIEW ON ORAL SUBMUCOUS FIBROSIS

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ABSTRACT

Oral submucous fibrosis is an irreversible mucosal change due to hypersensitivity; the attributing factors are mainly divided into local and systemic. Local factors are dietary substances such as Chilies, betel quid (Gutkha) and Areca nut which imparts main contribution for the condition. Systemic factors, nutritional deficiency, autoimmunity, and genetic susceptibility. It is associated with other conditions such as trismus and fibrosis, burning sensation with initiation from an early mucosal inflammation. It is an irreversible condition with high probability of malignant transformation. So, it is imperative to have an insight related to this debilitating disease and its etiology, pathology, and treatment modes and prevention and insight about mechanisms of malignant transformation and to provide and apply possible management and decisively work towards treatment modalities. Hence the present article OSMF reviewed the etiology, pathophysiology, clinical features & management.

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INTRODUCTION

Oral Submucous fibrosis (OSMF) is a common problem in India. The most common symptom is progressive trismus i.e. inability to open the mouth which is due to accumulation of inelastic fibrous tissue in the juxta-epithelial region of the oral mucosa (Wollina, 2015). Progressive trismus in turn impairs mastication and results in poor oral hygiene (Saurabh, 2014). The epithelium overlying the fibrous condensation becomes atrophic in 90% of cases and is the site of malignant transformation in 4.5% of patients (Rajendra, 2014). OSMF is predominantly seen in South Asian inhabitants from India, Bangladesh, Bhutan, Pakistan and Sri Lanka or in people emigrated from South Asia to other parts of the world (Food and Chemical Toxicology, 1986). Occasionally it is seen in Europeans and sporadic cases have been reported from Taiwan, China, Nepal, Thailand and Vietnam. India has seen a marked increase in the occurrence of OSMF in recent years especially in states of Bihar, Madhya Pradesh, Gujarat and Maharashtra (Rachana, 2014). The Younger generation has been found to be suffering more due to their attraction towards different tobacco products and areca nut products available in different multicolored attractive pouches. OSMF is a well-recognized potentially malignant condition in the oral cavity, and the transformation rate as high as 7.6% over a period of ten year have been reported from India (Fareedi, 2014). Currently areca nut use is most important etiological factor in pathogenesis OSMF. The formulation in which areca is consumed varies according to geographical location and often associated with cultural and religious practices. Many treatment protocols for oral sub mucous fibrosis have been proposed to alleviate the signs and symptoms of the disorder. Patient is advised to completely quit the habit of betel nut chewing. The treatment of oral submucous fibrosis includes iron, multivitamins including lycopene, pentoxifylline, local submucosal injections of steroids, hyaluronidase and chylomicrons, aqueous extract of healthy human placenta, and surgical excision of the fibrous bands (Anjana, 2017). The aim of the present review is to understand the etiology and pathogenesis, clinical features and various treatment modalities.

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Definition

Insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded

by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria with epithelial atrophy leading to stiffness of mucosa and causing trismus and inability to eat. - Pindborg JJ & Sirsat SM.

History

- Oral Sub Mucous Fibrosis condition was first designated in ancient Indian Manuscripts by Susruta (An Ancient Indian physician) and main author of the he compendium of Susruta, he described the condition as VEDARI, where patients suffering from inability to open the mouth, burning sensation and pain.
- Schwartz coined the term atrophica idiopathic mucosa oris to describe an oral fibrosing disease, in 1952 based on his observation in 5 Indian women from Kenya, later Joshi coined the term oral sub mucous fibrosis for the condition in 1953.
- The term "submucous fibrosis of the palate and pillars" were coined by Joshi other terminologies suggested including "diffuse oral submucous fibrosis", "idiopathic scleroderma of the mouth", "idiopathic palatal fibrosis", and "sclerosing stomatitis".
- Paymaster in 1956 first described its premalignant nature. The term "submucous fibrosis" was used by Pindborg and Sirsat although they suggested that a more appropriate name would be "juxta epithelial fibrosis. Ramanathan called it an Asian analog of sideropenic dysphagia, when he suggested that OSMF may be a mucosal change secondary to chronic iron deficiency (Pindborg, 1966).

Epidemiology

An etiological and epidemiological study of oral sub mucous fibrosis (OSMF) has been done in North east India. Survey committee selected few cases of OSMF and counterpart control subjects were selected for study in the period of two years. It was observed that Male: Female ratio was 2.7: 1, which clearly illustrates gender prevails based on habit patterns. Maximum number of cases was belonging to age group between 20 to 40 years old, and they were belonging to low or middle socioeconomic class, but not belongs elite social group. Most of the OSMF cases are in the people who consume heavy spices and chilies, whereas control mild spices and chilies are less prone to the disease. The highly addictive and carcinogen substance gutkha was the most commonly used by the OSMF cases only minute per cent did not use any gutkha or other areca nut product whereas maximum per cent control did not have any chewing habit. The OSMF cases used gutkha and other products ranges from > 10 sachets per day and kept in the mouth for considerable minutes and they were using since <5 years. Maximum number of cases they kept in the buccal vestibule or they chewed and swallowed it, only a small number of patients chewed and spitted it out. It was also observed that OSMF developed on one side of the buccal vestibule where they kept chewing and other side was normal. Mucosa on affected side becomes opaque due to submucosal scarring and this condition may progress into squamous cell carcinoma (Ahmad, 2006).

Etiology

Chilies: Chili peppers are the fruits of Capsicum pepper plants, well-known for their scorching flavor. They are usually eaten cooked, or dried and powdered. chilies ingestion leads to hypersensitivity of oral submucosa and thus leads to the condition oral sub mucous fibrosis is a debatable topic. According to one study ingestion of chilies more in Mexico despite that factor incidence rate is lower compares to in India and study[10]. In most patients with oral sub mucous fibrosis, areca nut was chewed alone more frequently than it was chewed in combination with pan (betel leaf plus lime plus betel catechu, with or without tobacco) Especially in Southern parts of India high prevalence of oral cancer and oral submucous fibrosis are common.

Areca Nut: The Areca Nut is the seed of the areca palm, which grows in much of the tropical pacific South east and South Asia. This seed is referred to as betel nut. The Areca Nut contains the tannins area tannin and gallic acid, and fixed oil gum and some amount of terpineol, lignin, various saline substances and three alkaloids – arecoline, arecaidine and gucavaine- all of which has vasoconstrictive properties (Cox, 1996). Arecoline is a nicotinic acid based alkaloid, Arecoline is known to be a partial agonist of muscarinic acetylcholine M1, M2, M3 receptors and M4. There is reasonable evidence in humans for the carcinogenicity of areca nut without tobacco. Areca nut is available as gutkha, pan parag and mawa.

Gutkha: Gutkha is a preparation of crushed areca nut, tobacco, catechu, paraffin wax, slaked lime and sweet or savory flavorings is also one of the commonest causes for OSMF. This product is packed in an individual size packets or sachets and sold across the Indian subcontinent India. Betel quid without tobacco is mostly used in Southeast Asian countries, Taiwan, Myanmar, Thailand, China, Papua New Guinea (Nigam, 2014).

Genetic Susceptibility

Increased likelihood or chance of developing a disease due to presence of one more gene mutations and/or a family history that indicates an increased risk of the disease is genetic susceptibility. Understanding genetic susceptibility and its knowledge has various advantages to understand not only oral sub mucous fibrosis and other prevailing malignant transforming conditions. The major histocompatibility complex (MHC) class I chain-related gene A (MICA) is expressed by keratinocytes and other epithelial cells, and its encoded protein interacts with gamma/delta T-cells localized in the submucosa. The MICA gene has a triplet repeat (GCT) polymorphism in the transmembrane domain resulting in five distinct allelic patterns. A study conducted and analyzed MICA polymorphism in selected number of OSF patients and randomly selected unrelated controls by using the ABI Prism, DNA sequence to analyze the sample DNA PCR products. The results depict that phenotype frequency of allele A6 of MICA in subjects with Oral Sub mucous fibrosis are more than in controls. The risk of OSMF also increases from the polymorphisms of the genes coding for tumor necrosis factor (TNF) alpha. The procollagen genes identified as TNF-β targets are COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 (Tilakaratne, 2016).

Autoimmunity

Based upon human leukocyte antigen HLA associations and circulating immune complexes and autoantibodies a possible underlying autoimmune mechanism with genetic

predisposition has been proposed (Canniff, 2008). An association with human leukocyte antigen HLA as A10, DR3, DR7, and probably B7 and demonstration of autoantibodies along with haplophytic pairs A10/DR3, B8/DR3, and A10/88, has been found in patients with oral sub mucous fibrosis.

High Copper content role in Oral sub mucous fibrosis

High Copper content in dietary substance and consumption is considered as an etiology for OSF and it's been helpful resource for the researchers to determine the role of copper in the formation of fibrous bands due to increased lysyl oxidase activity and this helps in treatment modality. The researcher Rajalalitha in 2006 considered lysyl oxidase to be a key enzyme tilting the balance in the collagen metabolism towards fibrosis (Rajalalitha, 2005). Enforce a restriction on activity of lysyl oxidase either by using a copper chelator or through another inhibitory mechanism may help in reducing the fibrosis by reducing cross-linking of the collagen fibers. lysyl oxidase to be a key enzyme tilting the balance in the collagen metabolism toward fibrosis (Meghji, 1997).

Nutritional Deficiency

Deficiency of minerals and nutrients can affect oral health by various mechanisms. Deficiency of iron in tissues causes improper vascular channel formation and causes reduced vascularity this leads to disturbance in the inflammatory reparative response of the lamina propria and resulting in defective in healing mechanism and scar formation. Thus, combined effect of these factors leads to fibrosis advancement (Typical feature of oral sub mucous fibrosis). One recent research on the same condition has proved that low levels of hemoglobin and serum iron are indicative of iron deficiency anemia (Hegde, 2012). Iron deficiency anemia in patients with oral sub mucous fibrosis could be related to the premalignant nature of this condition.

Oral submucous fibrosis is predominantly a disorder of collagen metabolism. Hydroxyproline is an amino acid found only in collagen, which is unified in the hydroxylated form. Hydroxylation reaction requires ferrous iron and ascorbic acid. Use of iron, for the hydroxylation of proline and lysine, primes to decreased serum iron level. In oral sub mucous fibrosis patients, there is an increase in the production of highly cross-linked insoluble collagen type I loss of more soluble procollagen type III and collagen type VI. The cross-linking of collagen due to the upregulation of lysyl oxidase plays a vital role in the development and progression of the condition. Apart from the mechanism nutritional deficiency also lead to onset of the insidious disease by unpalatable condition, unable to consume proper food and leads to anemia. Though oral sub mucous fibrosis is a benign condition but rate of malignant transformation is higher rate so it's inevitable to have proper knowledge regarding every aspect which affects the condition (Trivedy, 2000).

Molecular Pathogenesis

Collagen is a long-chain amino acid and the most abundant protein in the body. It is composed of the individual amino acids Glycine, Proline, Hydroxyproline and Arginine and in nature is found exclusively in animal tissue, especially bones and connective tissue (Mohammed, 2014). Oral sub mucous fibrosis is considered as collagen disorder. Increase or decrease in collagen production results in an insoluble form of collagen predominantly formed by cross linking of collagen thus leads to fibrosis and by the active involvement of irritants results in the oral sub mucous fibrosis. Synthesis of collagen is mediated by various factors - growth factors, hormones, cytokines, and lymphokines. The mechanisms accountable for the pathogenesis are augmented collagen accretion, increased expression of fibro genic cytokines, genetic polymorphisms and autoimmunity. The increased collagen accumulation results from increased collagen production and stabilization or reduced breakdown of collagen. Fibroblasts are transformed into different phenotypes under the effect of areca nut alkaloids, which secrete more amount of collagen. Expanded fibrosis is also believed to be due to improved cross-linking of collagen through up-regulation of lysyl oxidase activity in oral sub mucous fibrosis fibroblasts. Therefore, oral sub mucous fibrosis is now considered a collagen metabolic disorder. Maintenance of collagen structure is produced by catechin and tannins from the areca nut. Pathogenesis encompasses sub epithelial 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 (Gauri and K. Ranganathan, 2010). Procollagen genes increase collagen production while TIMP and PAI genes prevent collagenase and in that waydeclines collagen degradation, which result in an increase in insoluble form of collagen. The risk of oral sub mucous fibrosis also increases from the polymorphisms of the genes coding for tumor necrosis factor (TNF) alpha. The procollagen genes identified as TNF-β targets are COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1. Oral sub mucous fibrosis is also hypothetical to be an autoimmune disorder. Various studies have found HLA types, raised autoantibodies and immune complexes, which be disposed to show the autoimmune basis of the disease (Tak, 2015).

Clinical Features

Oral sub mucous fibrosis is a chronic, complex, premalignant condition of the oral cavity, characterized by juxta-epithelial inflammatory reaction and progressive fibrosis of the sub mucosal tissues. In the initial phase of the disease, the mucosa feels leathery with palpable fibrotic bands. In the advanced stage, the oral mucosa loses its resiliency and becomes blanched and stiff. The disease is supposed to begin in the posterior part of the oral cavity and gradually spread outward and fibrosis leads to progressive incapability to open the mouth (trismus) due to oral fibrosis and scarring.

Symptoms of oral sub mucous fibrosis include the following (Cox, 1996):

- Progressive inability to open the mouth (trismus) due to oral fibrosis and scarring
- Oral pain and a burning sensation upon consumption of spicy foodstuffs
- Increased salivation
- Change of gustatory sensation
- Hearing loss due to stenosis of the eustachian tubes
- Dryness of the mouth
- Nasal tonality to the voice

- Dysphagia to solids (if the esophagus is involved)
- Impaired mouth movements (e.g., eating, whistling, blowing, sucking)

Oral sub mucous fibrosis is clinically divided into three stages, and the physical findings differ accordingly (Pindborg, 1966).

Very Early (Stage I)

- A finely fibrillar collagen, dispersed with marked edema.
- The fibroblastic response is strong.
- The blood vessels are sometimes normal, but more often they are dilated and congested.
- Inflammatory cells, mainly polymorphonuclear leukocytes with an occasional eosinophil, are present.

Early (Stage II)

- The juxta-epithelial area shows early hyalinization.
- Plump young fibroblasts are present in moderate numbers.
- The blood vessels are dilated and congested.
- Inflammatory cells are mostly mononuclear lymphocytes, eosinophils and an occasional plasma cell.

Moderately Advanced (Stage III)

- The collagen is moderately hyalinized.
- The fibroblastic response is less marked. The cells present being mostly adult fibrocytes
- Blood vessels are normal or constricted.
- Inflammatory exudates consist of lymphocytes and plasma cells, although an occasional eosinophil is seen.

Advanced (Stage IV)

- The collagen is completely hyalinized.
- The hyalinized areas are devoid of fibroblasts.
- Blood vessels are completely obliterated or narrowed.
- Inflammatory cells are lymphocytes and plasma cells.

Staging

J.N Khanna and N.N Andrade developed the classification system for the surgical management of trismus, associated with Oral submucous fibrosis (Khanna, 1995).

- **Group I**: This is the earliest stage and is not associated with mouth opening limitations. It refers to patients with an interincisal distance of greater than 35 mm.
- **Group II**: This refers to patients with an interincisal distance of 26-35 mm.
- **Group III**: These are moderately advanced cases. This stage refers to patients with an interincisal distance of 15-26 mm. Fibrotic bands are visible at the soft palate, and pterygomandibular raphe and anterior pillars of fauces are present.
- **Group IVA**: Trismus is severe, with an interincisal distance of less than 15 mm and extensive fibrosis of all the oral mucosa.
- **Group IVB**: Disease is most advanced, with premalignant and malignant changes throughout the mucosa.

In the vast literature available for OSMF, numerous staging systems are put forward by various authors in the past. Some of the most important staging system which can routinely be used in the clinical practice, and help in early diagnosis and treatment includes: Haider SM, Merchant AT, Fikree FF, Rahbar MH (2000): Clinical and functional staging of OSMF.

Clinical Stage

- Stage-I Faucial bands only
- Stage-2 Faucial and buccal bands
- Stage-3 Faucial, buccal and labial bands

Functional Stage

- Stage-A Mouth opening >20 mm
- Stage-B Mouth opening 11–19 mm
- Stage-C Mouth opening <10 mm

Mathur RM and Jha T (1993) described the OSF staging based on clinical presentation

Stage-1: Early OSMF:

- Mild blanching
- Mouth opening normal
- No restriction in tongue protrusion.
- Burning sensation – only on taking spicy food or hot temperature liquid.

Stage-2: Moderate OSMF

- Moderate to severe blanching.
- Mouth opening reduced by 33%, tongue protrusion reduced by 33%, flexibility also demonstrably decreased.
- Burning sensation even in the absence of stimuli.
- Palpable bands felt.
- Lymphadenopathy either unilateral or bilateral.
- Demonstrable anemia on hematological examination.

Stage-3: Severe OSMF

- Burning sensation very severe, patient unable to do day-today work.
- More than 66% reduction in the mouth opening, cheek flexibility and tongue protrusion. In many, the tongue may appear fixed.
- Ulcerative lesions may appear in cheek.
- Thick palpable bands.
- Lymphadenopathy bilaterally present.

Histopathology

To provide more wide-ranging description of oral sub mucous fibrosis, histopathological features and classification based on those characteristics has been proved beneficial to evaluate and study the microscopic features of oral sub mucous fibrosis. The observed epithelial changes are secondary to changes in connective tissue.

Histopathological Findings (Rooban, 2011)

- Atrophic oral epithelium
- Loss of rete pegs
- Epithelial atypia may be observed hyalinization of collagen bundles

- Fibroblasts decreased and blood vessels obliterated

Histopathologic findings in oral sub mucous fibrosis cases were found to differ depending on the clinical severity of the cases and the site of biopsy.

Differential Diagnosis

The distinguishing of a disease or condition from others that presents similar clinical features. Possible differential diagnosis of oral sub mucous fibrosis based on physical characteristics, appearances, location, color, texture and appearance.

- Amyloidosis
- Generalized Fibromatosis
- Oral manifestations of Scleroderma
- Oral Lichenplanus
- Anemia

Laboratory Findings

There is no accurate laboratory tests are obtainable for oral sub mucous fibrosis, and abnormalities may be associated with secondary nutritional deficiencies. Some studies have reported the following laboratory findings (Saurabh, 2014).

- Decreased hemoglobin levels
- Decreased iron levels
- Decreased protein levels
- Increased erythrocyte sedimentation rate
- Decreased vitamin B complex levels

Another method of diagnosing oral sub mucous fibrosis is typically made on history of areca nut exposure and clinical examination.

Proposed clinical signs (Jayanthi, 1992)

- Whitening of oral mucosa
- Palpable fibrous bands
- Tough leathery texture to the oral mucosa

Mucosal biopsy shows nonspecific in early stages with swelling and acute inflammation. However, in engrained disease, the distinguishing pathology with chronic inflammation and the presence of thick collagen bandsand reduced blood vessels. The surface epithelium is thinned and dysplasia is common. Muscle degeneration is seen in late disease. Barium swallow might be beneficial to assess throat and esophageal involvement. Blood tests possibly will be required to assess nutritional state and for autoimmune conditions. For instance, Complete Hemogram.

Other Diagnostic Methods

Cytologic smears might be performed. A neural network–based oral precancer stage detection method has been proposed to diagnose oral sub mucous fibrosis (Messadi, 2013). The new technique uses wavelet coefficients from transmission electron micrograph images of sub epithelial fibrillar collagen in strong oral submucosa and in oral submucous fibrosis tissues. Presently, oral biopsy for hematoxylin and eosin offers the most definitive diagnosis and is crucial because of the association of oral submucous fibrosis with oral cancer. Some surveys have reported advantage with, immune histochemical 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 pan cytokeratin and high molecular weight cytokeratin, aberrant expression of cytokeratin 8, and decreased expression of cytokeratin's 5 and14 suggest their potential as surrogate indicators for malignant transformation (Messadi, 2013).

Management

The management of oral submucous fibrosis depends on the degree of clinical involvement. If the disease is detected at a very early stage, termination of the habit is enough. Moderate-to-severe oral submucous fibrosis is irreversible. Medical treatment is symptomatic and chiefly intended at improving mouth movements.

Management Methods are given below:

- Patient Education
- Supportive Care
- Surgical Management
- Oral Physiotherapy
- Medical Management

Patient Education

- Instruct patients about the importance of ceasing the habit of chewing betel quid.
- Advise patients that eradicating tobacco from the quid product may lessen the risk of oral cancer.
- Instruct patients to avoid spicy food products.
- Teach patients to eat a complete and healthy diet to avoid malnutrition.
- Educate patients about maintaining proper oral hygiene and scheduling regular oral examinations.
- Intercession studies and public health campaigns in contradiction of oral habits linked to oral sub mucous fibrosis could be the best way of controlling the disease at the community level (Gupta, 2013).
- Educate the community regarding the local adversative effects of chewable mediators.
- Provide information to the patients for patient education resources.

Supportive Care

- Combination of micronutrients and minerals is helpful. And focusing on dietary changes and regulating nutritional deficiencies such as iron and vitamin B complex are proved to be beneficial. Substantial improvement in symptoms was observed.
- Surgical Management
- Surgical management is designated in patients with severe advanced stages of the disease and predominant characteristics of malignancy and in the patients with limited mouth movements as in trismus.

Surgical Methods

- **Simple expurgation of the fibrous bands:** Excision of fibrous bands can result in the hardening of muscle and tissues that may lead to deformity and rigidity and

aggravates the condition. So, it should be followed by the masticatory muscle myotomy and defect formed after excision can be treated by the Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy (Mahajan, 2010).

- **Nasolabial flaps and Lingual pedicle flaps:** Surgery to create flaps is performed only in patients with oral submucous fibrosis with no tongue involvement.
- **KTP-532 Laser:** A KTP laser is a solid-state laser that uses a potassium titanyl phosphate (KTP) crystal as its frequencing doubling device. The KTP crystal is engaged by a beam generated by neodymiumyitriumaluminium garnet (Nd: YAG) laser. This is directed through the KTP crystal to produce a beam in the green visible spectrum with a wavelength of 532 nm. Use of KTP-532 laser release procedure was found to increase mouth opening range in 9 patients over a 12-month follow-up period in one study. The KTP laser works on the principle of selective photothermolysis. By using KTP- 532 laser there is definitive improvement of mouth range in patients (Nayak, 2008).
- **Er,Cr YSGG Laser:** YSGG laser has an active medium of yttrium-scandium-gallium-garnet doped with er-bium and chromium ions and emits free-running pulsed laser energy at a wavelength of 2,780 nm. ErCr:YSGG laser fibrotomy is performed under a local anesthesia. This may be a useful adjunct in managing oral sub mucous fibrosis (Chaudhary, 2011).

Oral Physiotherapy

Another method is physical therapy using muscle stretching exercises for the mouth is useful in stopping further limitation of mouth movements. For example, Heisters jaw exercises by using Heister jaw stretcher. After surgical intervention like nasolabial flap technique followed by heisters jaw exercise (active mouth opening exercise) proves advantageous (Rai, 2011).

Medical Management

Steroids: In patients with reasonable oral submucous fibrosis, weekly submucosal intralesion injections or topical application of steroids may help prevent further damage. Corticosteroids are immunosuppressive agents which are believed to decrease inflammation and collagen formation, thereby reducing the symptoms and resulting in increased mouth opening. Corticosteroids such as hydrocortisone, triamcinolone, dexamethasone and betamethasone have been used in the treatment of OSMF. Steroids suppress inflammatory reactions, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen (Dyavanagoudar, 2009).

Placental Extracts

The basis for using placental extract in patients with oral sub mucous fibrosis originates from its proposed anti-inflammatory effect, and prevents or inhibits mucosal damage. Aqueous placental extract Placentrex topical application is used for efficacy (Raj Kumar, 2017).

Hyaluronidase

Usually 1500 IU hyaluronidase administered as topical application. Combination of topical and systemic steroids shows additive effects and better long-term results (Kakar, 1985).

IFN-Gamma

Intralesional injection of interferon gamma (0.01)-10.0U/ml three times in a day for 6 months are usually preferred. IFN-gamma plays a vital role in the treatment of patients with oral sub mucous fibrosis, as of its immunoregulatory effect. IFN-gamma is also known as antifibrotic cytokine. The principal mechanism behind the IFN-gamma is altering the collagen synthesis, which is useful in treatment of oral sub mucous fibrosis (Haque, 2001).

Lycopene

Lycopene is a non-provitamin A, and treating patients with Lycopene proved beneficial. It is given in the dose of 8 mg twice per day for two months (Kumar, 2007).

Pentoxifylline

Pentoxifylline is a drug is a methylxanthine derivative that has vasodilating properties and was predicted to increase mucosal vascularity. It is given in the dose of 400mg three times in a day for 7 months (Dyavanagoudar, 2009).

Immune Milk

Immune milk is a kind of skimmed milk produced from cows immunized with multiple human intestinal bacteria. It has good anti-inflammatory effect & contains moderate amounts of Vitamin A, C, B1, B2, B6, B12, nicotinic acid, pantothenic acid, folic acid, iron, copper & zinc. Though chemically its identical to commercial milk but it contains 20-30% higher concentration of IgG type 1 antibody. Tai et al., (2001) advocated 45 gms of immune milk powder twice a day, for 3 months and observed a regression of concomitant leukoplakia and erythroleukoplakia in addition to significant improvement in symptoms of OSMF.

Turmeric

Turmeric has been found to inhibit many disease processes through their anti-inflammatory, antioxidant and anticancer properties. In addition, Curcuminoids isolated from turmeric, has been found to have effective antioxidant, DNA-protectant and antimutagen action. A study concluded that usage of turmeric oil daily for 3 months had a beneficial role in treatment of OSMF.

Microwave Diathermy

Microwaves are quasi optical and are applied by radiation. It therefore produces sharp localized deep heat without undue heating of skin and other subcutaneous tissues such as fat and is thus simple to apply with minimum discomfort. Gupta et al., (1980) advocated diathermy daily for 20 minutes at each site of lesion with 20 -25 watts of energy to produce comfortable warmth. Such 15 sittings were given to each patient and found valuable for the moderately advanced stage of OSMF.

Conclusion

Oral sub mucous fibrosis is a chronic fibrosing disease with a progressive and inexorable clinical progression that leads to mucosal stiffness and limited mouth opening. Exposure to dietary substance like Areca nut containing products with or without tobacco is presently believed to most common

etiological factor to oral sub mucous fibrosis. Knowledge about this potentially malignant disorder is very important and used to devise advanced treatment modalities. Research related to oral sub mucous fibrosis has been central in the formation of health policies and which may lead to shed an insight on tobacco usage and prohibition. Oral health providers can contribute to community by encouraging patients to participate in the tobacco anti-addiction programs and encouraging them to quit the habit.

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