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Review Article

Medical Management of Oral Submucous Fibrosis in Its Initial Stages

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Abstract

Oral submucous fibrosis (OSF) is an insidious, chronic, progressive, debilitating disease. It has amalignant potential resulting from progressive juxtaepithelial fibrosis of the oral soft tissues, resulting in increasing loss of tissue mobility, marked rigidity and an eventual inability to open the mouth. The hallmark of the disease being sub mucosal fibrosis that affects most parts of the oral cavity, pharynx and upper third of the oesophagus and its clinical presentation depends on the stage of the disease at detection. As the disease has a spectrum of presentation, the management differs with the various stages of the disease. This articles presents a review of the existing literature pertaining to the effectiveness of medical management of Oral submucous fibrosis in its initial stages.

Keywords: Oral submucous fibrosis (OSF), juxtaepithelial fibrosis, debilitating disease.

INTRODUCTION

Oral submucous fibrosisis (OSF) is a chronic, insidious, disabling disease that involves the oral mucosa, the oropharynx, and the larynx ocassionally. It results in an increasing loss of tissueelasticity with marked rigidity and an eventual inability to open the mouth [1]. The most frequently involved site is buccal mucosa, followed by palate, retromolar region, faucial pillars and pharynx [2]. Numerous terminologies were used to describe this condition. These include Atrophia Idiopathica Mucosae Oris [3], Submucous fibrosis of the palate and pillars [4], Diffuse Oral submucous fibrosis [5], Idiopathic scleroderma of the mouth Sclerosing stomatitis Idiopathic palatal fibrosis Juxta epithelial fibrosis, Asian Sideropenic Dysphagia [6].

Etiopathogenesis

Main contributing factors in the development of oral submucous fibrosis are the use of areca nut, tobacco, and crude lime wrapped in betel leaf [7]. Arecoline which is an alkaloid component of the areca nut, cause the stimulation of fibroblast and gene expression hence leading to increased collagen production. The flavanoids increase the cross-linking of collagen and copper causes the up-regulation of lysyl oxidase and hence stimulating fibrogenesis [6]. Collagen-related genes COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 have been identified as targets of transforming growth factor-b (TGF- b) and induced fibroblasts at an early stage of the disease [8]. These genes play a key role in the homeostasis of collagen in the body. The genetic modulation of different enzymes such as collagenases and lysyl oxidase together with cytokines, namely TGF-b has been implicated in this context. The transcriptional activation of procollagen genes by TGF-b may contribute to increased collagen levels and hence increased expression of procollagen genes and thereby contributing to increased collagen level in oral submucous fibrosis [9]. The role of autoimmunity in oral submucous fibrosis can be confirmed by the presence of circulating immune complexes, their immunoglobulin contents and the detection of various autoantibodies in patients' sera [10]. Anti-nuclear antibodies (ANA) (23.9%), anti smooth muscle (SMA) antibodies (23.9%) and anti gastric-parietal cell (GPCA) (14.7%) were positive in patients with oral submucous fibrosis compared with healthy patients [11]. Increased levels of IgG, IgA and IgM immune complexes and raised serum levels compared with control groups have also been reported [12].

Clinical Presentation

The clinical manifestation of the condition is primarily due to inflammation and fibrosis. Initial manifestations include burning sensation, dry mouth,

blanching oral mucosa, and ulceration. The burning sensation usually occurs while chewing spicy food [13]. Blanching of the oral mucosa is caused by impairment of local vascularity because of increasing fibrosis and results in a marble-like appearance [14]. In some cases, blanching may be associated with small vesicles that rupture to form erosions. In the more advanced stage of the disease, the essential feature is a fibrous band restricting mouth opening and causing difficulty in mastication, speech, swallowing, and maintaining oral hygiene [15].

Management

Numerous treatment protocols have been proposed for the management of oral sub mucous fibrosis. Before the initiation of treatment the patient is advised to completely quit the habit of betel nut chewing and other local irritants, spicy and hot food, alcohol, and smoking. Oral submucous fibrosis in its initial stages can be managed by medical management. However, advanced stages of oral submucous fibrosis should be managed by surgical intervention. This paper deals with the medical management of initial stages of oral submucous fibrosis.

Corticosteroids

Corticosteroids are immunosuppressive agents which can suppress inflammatory reactions, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen [16]. It can be applied topically or via intralesional injections depending upon the clinical stage of the disease. In the early stages when patient presents with the burning sensation, topical corticosteroids in the form of Triamcinolone acetonide 0.1% and Betamethasone – 0.5% are applied locally for 3 months. In the clinical stages with palpable fibrous bands, intralesional injection of Dexametasone – 4mg/ ml, Triamcinolone - 10 mg/ml are given biweekly for 3 months, at multiple sites; parallel to the mucosal surface as possible to avoid unnecessary trauma of the submucosal vessels and subsequent release of hemosiderin, which will stimulate fibroblastic activity [6, 17].

Interferon Gamma

It has immuno-regulatory effect and has anti-fibrotic cytokine effect and hence it plays a key role in altering collagen synthesis. A study revealed that the postoperative immunohistochemistry showed a decreased amount of inflammatory cell infiltrate and an altered level of cytokines compared with the pre-operative lesional tissue [18].

Placental Extracts

They contain nucleotides, enzymes, vitamins, amino acids, and steroids. It is an aqueous extract of human placenta which stimulates the pituitary and the adrenal cortex, and regulates the metabolism of tissues [6]. Intralesional injection of Placenta extract 2.0cc given locally in the predetermined areas, once a week for one month showed improvement in the mouth opening [19].

Immune Milk

It has anti-inflammatory effect and contains vitamins such as Vit. A, C, B1, B2, B6, B12, nicotinic acid pantothenic acid, folic acid, iron, copper and zinc. It is produced from cows immunized with multiple human intestinal bacteria and contains 20-30% higher concentration of IgG type I antibody. It is used in the management of oral submucous fibrosis due to its local and systemic upregulation of fibrogenic cytokines and down regulation of anti fibrotic cytokine and hence has an anti-inflammatory action and modulate cytokine production [20].

Pentoxifylline

It is a tri-substituted methylxanthine derivative. It increases red cell deformability, leukocyte chemotaxis, antithrombin and anti- plasmin activities and has fibrinolytic activity. Pentoxifylline also decreases red cell and platelet aggregation; it also decreases granulocyte adhesion, fibrinogen levels, and whole blood viscosity. Dosage of 400 mg 3 times a day for 7 months showed significant improvement in the symptoms. They have their role in OSF as pathologically occluded blood vessels due to collagen deposition and hypercoagulated status of blood restrict the nutrients and other therapeutic substances from reaching the affected tissue [21, 22].

Enzymes

Enzymes such as collagenase, hyaluronidase and chymotrypsin are being used for the treatment of oral submucous fibrosis. Hyaluronidase by breaking down hyaluronic acid decreases the viscosity of intercellular cement substance [16]. Patients receiving hyaluronidase alone showed a quicker improvement in the burning sensation and painful ulceration produced by the effects of local by-products, although combination of dexamethasone and hyaluronidase provides better long-term results than other regimens [23]. Another study revealed that hyaluronidase is much quicker in ameliorating painful ulceration and burning sensation than dexamethasone, but the effect is short term, although its combination with steroids provide slightly better long term results [24]. Chymotrypsin, an endopeptidase, hydrolyses ester and peptide bonds; therefore have a role in OSF cases as a proteolytic and anti-inflammatory agent [25].

Curcumin

It is a major yellow pigment in turmeric, curry and mustard. It suppresses the expression of extracellular matrix genes in activated hepatic cells by inhibiting connective tissue growth factor gene expression [26]. Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months decreased the number of micronucleated cells observed in both the exfoliated

oral mucosal cells and circulating lymphocytes [6]. The anti-inflammatory, antioxidant and antifibrotic properties of curcumin interfere with the progression of oral submucous fibrosis at multiple stages in the pathogenesis of this complex disease. The antioxidative and scavenger properties of curcumin, make it a very effective chemopreventive agent in the prevention of cancer [16].

Supplements

Vitamin E acts as an antioxidant and prevents the formation of toxic substances and enhances the concentration of Vitamin A. Vitamin A plays a major role in induction and control of epithelial differentiation in mucous secretary and keratinization tissues and maintains the integrity of epithelium [27]. Lycopene is an antioxidant obtained from tomatoes. It has two major biological effects in the form of antioxidative effects and non-oxidative. Acting as potent antioxidants, it inactivates free radicals and attenuates free radicals-initiated oxidative reactions, particularly lipid peroxidation and DNA oxidative damage, thereby preventing tissue damage as well as potential cancerization. The nonoxidative effects are regulation of gap-junction communication (GJC), gene function regulation, hormone and immune modulation, and antiproliferation and prodifferentiation activities [28].

Physiotherapy

It modifies tissue remodeling through promotion of physical movements and heat. Physical exercise regimen like muscle stretching exercise, forceful mouth opening with the help of sticks, tongue movement in the figure of 8, ballooning of mouth, hot water gargling, using mouth gag and acrylic surgical screws aid in the forceful opening of mouth.

CONCLUSION

Choosing the appropriate treatment modality for management of oral submucous fibrosis depends upon the stage of the condition. Management of oral submucous fibrosis in the initial stages should include counseling of patient pertaining to quitting the habit. Medical management should be in the form of topical applications of steroids along with lycopene / multivitamin supplements. Moderate stages of OSMF should be treated with intralesional steroids and enzymes or pentoxifylline. Surgical intervention should be restricted to advanced stages of the disease.

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