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Review Article

Journey from Oral Sub mucous Fibrosis (Osmf) to Functional Disease-Free Mouth Opening

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ABSTRACT

Oral Submucous Fibrosis (OSMF) is a potentially malignant disease that causes oral mucosa damage. It is a well-known chronic insidious disease, precancerous condition, an autoimmune and collagen-related disorder with a multifactorial cause associated with betel quid chewing and characterized by gradual hyalinization of the lamina propria. In the large literature available for OSMF, multiple staging systems have already been proposed by various authors. Some of the most essential staging systems are widely utilized in clinical practice, resulting in earlier diagnosis and treatment. The treatment of oral submucous fibrosis has been a source of contention since Schwartz initially described the ailment in 1952. An attempt is made to critically assess and update knowledge of current breakthroughs that increase comprehension of the etiology of the premalignant disease and its medical and surgical care, hence increasing life expectancy. The goal of this research is to present a specific treatment technique that combines surgery and active physiotherapy to increase jaw opening and prevent relapse. The current study made a small effort to maintain adequate, functional disease-free mouth opening and detect any growing malignant change as soon as possible.

Keywords: Pseudoarthrosis tibia, Physiotherapy, Ilizarov's fixation, Case report, etc.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a condition caused by a persistent, insidious change in fibro-elasticity. It is characterized by a burning sensation in the oral cavity, blanching, and stiffening of the oral mucosa and oro-pharynx, which leads to trismus and difficulty in opening the mouth. The symptoms and indicators vary depending on how the lesions grow and how many places are impacted. It is distinguished by a loss of mucosal flexibility and severe fibrosis, as well as juxta epithelial inflammation and increasing laminar hyalinization. Schwartz first reported it in 1952 as a fibrosing disorder of the mouth in five Indian women from Kenya, and he coined the phrase. "Atrophicaidiopathicatropica mucosae oris" [1].

According to recent epidemiological statistics, OSMF is most commonly observed among people living in the Indian subcontinent, surrounding Asian countries, and Asian immigrants in South Africa, Malaysia, and the United Kingdom. It is found among Asians or Asians who have settled in other countries. So an ethnic basis for the sickness was proposed. Oral submucous fibrosis (OSMF) is a premalignant disorder caused mostly by the practice of chewing betel quid-containing areca nut, which is popular among South Asians. Inflammation, increased deposition of submucosal collagen, and the creation of fibrotic bands in the oral and paraoral tissues all contribute to a decrease in mouth opening. OSMF is a well-known potentially malignant

disorder in the oral cavity, and transformation rates as high as 7.6% over ten years have been documented in India.[1] OSMF is more frequent among people aged 20 to 39 [2].

Kumar et al found that greater gutkha consumption was directly associated with malignant changes in oral submucous fibrosis. Several hypotheses have been proposed, suggesting that the etiology of OSMF is complicated. Local irritants such as chili eating, areca nut chewing, tobacco smoking, and chewing are all contributing factors. Systemic factors include anemia (iron deficiency), vitamin deficiencies (B-complex and folate), malnutrition (protein deficit), a hereditary predisposition to the condition, and autoimmune. Currently, areca nut use is thought to be the most important etiological factor in the pathogenesis OSMF. Areca consumption varies by geography and is frequently related to cultural and religious traditions. Areca nuts can be fresh, dried, cooked, or baked. Lime, tobacco, catechu, cloves, saffron, and piper betel leaves may all be used in the recipe. The current review aims to better understand the etiology and pathogenesis of OSMF, with a focus on areca nuts and their contents [3].

Etiopathogenesis

Various epidemiological reviews, case series reports, large-scale cross-sectional investigations, case-control studies, and accomplice and mediation studies provide overwhelming evidence that areca nut is the primary etiological component. Everyday use was prioritized in the function of etiology across time.

A continuing study shows that younger people developed OSMF symptoms in 3.5 years, while older people took 6.5 years from the start of the tendency. The chemical components and alkaloids from areca nut have the most critical role in the etiology of oral fibrosis.

Arecoline, Arecaidine, Guvacine, and Guvacoline are the actual alkaloids found in areca nut. Fibrosis and hyalinization of subepithelial tissue are undoubtedly the most common clinical features of this illness. Later, it was shown that slaked lime Ca $(OH)_2$ causes this impact. Flavonoids, tannins, and catechins can promote fibrosis by blocking the synthesis of collagenase compounds, resulting in insoluble and persistent collagen filaments. The BQ contains alkaloids and flavonoids, which assist digestion. These components and their metabolites are constant stimulants for oral tissues.

TGF-beta

It promotes the genesis of collagen production. COL1A2, COL3A1, COL6A1, COL6A3, and COL7A1 have been identified as TGF-β targets. These are fibroblasts' early-promoting genes. enhanced collagen levels in OSMF are due to enhanced pro-collagen gene expression, which is mediated by TGF-β production. TGF-ß may play an important role in the pathophysiology and malignant progression of OSMF [4].

Lysl Oxidase (LOX)

LOX is a key molecule for converting collagen strands into a stable covalently cross-connected produce fibrillar structure that is resistant to proteolysis. The LOX movement is important for the organization of insoluble collagen due to cross-linking. TGF-β plays a crucial role in the declaration of LOX.

Tannins

Tannin reduces collagen corruption and plays an important role in the etiology of oral submucous fibrosis. Large levels of tannin found in areca nuts reduced collagen corruption by inhibiting collagenases, and the cause of fibrosis was hypothesized to be the combined effect of tannin and arecoline, which reduced debasement and increased collagen production separately.

Copper

Lysyl oxidase is a copper-stimulated chemical enzyme that promotes collagen cross-linking and ECM interaction. The fibroblasts in OSF exhibit increased lysyl oxidase activity as well as certain developmental characteristics. Micronutrients, particularly antioxidant minerals such as selenium, copper, zinc, manganese, and iron, are risk factors for cancer.

Copper is an essential trace element required for the functioning of several key enzymes like cytochrome-c-oxidase, superoxide dismutase, metallothionein and lysyl oxidase. Zinc implicated in modulation of mucosal metallothionein interfering with copper absorption. The serum levels of copper and zinc have been reported to be altered in many malignant and non-malignant conditions but the biochemical derangement in these trace elements and its association with OSMF is poorly understood[5].Several studies have shown that patients with habits have significantly lower serum Mg and Fe levels than normal healthy persons. There was a significant difference in serum zinc levels between patients with and without habits, and with and without OSMF. Altered blood trace element levels have

been recorded in malignant instances and are thought to be useful indicators for malignancies. The serum copper and zinc levels, as well as the copper/zinc ratio, in OSMF patients, can be considered indications of cancer susceptibility.

Genetic factors

Hereditary characteristics play an etiological role. Connective tissue development factor (CTGF/CCN2) is associated with a variety of human fibrotic disorders and has been discovered to be overexpressed in OSMF. Microtrauma may trigger the release of thrombin. Thrombin produced by microtrauma may contribute to the development of OSMF by increasing CCN2 articulation. OSMF patients have higher estimates of human leukocyte antigen (HLA) than the general population. Sirsat demonstrated that capsaicin in chilies causes far-reaching palatal fibrosis in animals [6].

Betel quid has an impact on the immune system, resulting in decreased levels of development factor-β and interferon in mononuclear cells among elderly patients. Lack of iron, nutritional B-complex, minerals, and malnutrients are thought to be etiological variables that inhibit the healing of inflamed oral mucosa, resulting in scarring and fibrosis. Abnormal iron metabolism plays a significant role in OSMF. Microcytic hypochromicity, along with serum iron, has been linked to oral submucous fibrosis.

Lipids are a crucial component of living cells. Cholesterols and triglycerides are lipids that can readily be accumulated in the body. They provide fuel and are an essential component of cell structure. These are key cell membrane components required for a variety of biological tasks, including cell growth and division in both normal and malignant tissues. Lipid status may be a useful sign of early changes in neoplastic cells and can be used as an early diagnostic tool in such cases. It is a simple and economical way of diagnostics [7].

Creatine phosphokinase's diagnostic and prognostic significance as a biomarker in other systemic diseases has been thoroughly proven. Creatine phosphokinase is an enzyme that is secreted in response to muscle injury in several systemic illnesses. As a result, this is employed as a biomarker to assess the severity of muscle injury. Serum urea, uric acid, and creatinine levels are measured as part of a biochemical assessment, which may be useful for proactive management in high-risk groups. It is therefore recommended that biochemical analysis can be useful in mass screening of OSMF patients [8].

Biopsies play a role in the development of OSMF. Radioimmune assays show elevated levels of endothelin and TGF-β-1 in OSMF fibroblasts. As seen by an analysis, there is a decrease in phagocytosis due to decreased cell-mediated immunity, which suppresses T-cell activity via aeroline. Extracellular matrix deposition may increase and continue as a result of a disruption in the equilibrium between matrix metalloproteinase and tissue inhibitors of matrix metalloproteinase.

Classification of OSMF

Kerr et al (2011), proposed a classification system for OSMF:

Grade I – Mild

Any highlights of the infections group of three for OSMF (Depapillation, consuming, whitening, or weathered mucosa) might be accounted for, and inter-incisal opening >35mm.

Grade II - Moderate

The above highlights of OSMF were seen between incisal confinements of mouth opening between 20-35mm.

Grade III – Severe

Above highlights of OSMF and between incisal opening <20mm.

Grade IV A

The above highlights OSMF with conceivably harmful issues on clinical examination

Grade IV B

The above highlights of OSMF with any evaluation of oral epithelial dysplasia on biopsy

Grade V

The above highlights of OSMF with oral squamous cell carcinoma. More et al characterized dependent on clinical and utilitarian parameters.

Clinical staging of OSMF

Stage I

Stomatitis and additional whitening of oral mucosa.

Stage II

Discernable stringy groups in buccal mucosa or potentially oropharynx, with/without stomatitis.

Stage III

Nearness of discernable stringy groups in buccal mucosa or potentially oropharynx, and in some other pieces of oral depression, with/without stomatitis.

Stage IV A

Any of the above stages alongside other possibly dangerous issues, e.g.; oral leukoplakia and Oral erythroplakia.

Stage IV B

Any of the above stages alongside squamous cell carcinoma.

Functional staging of OSMF

M 1

Between incisal mouth opening up to or> 35mm.

M 2

Between incisal mouth opening between 25 to 35mm.

M 3

Between incisal mouth opening between 15 to 25mm.

M 4

Between incisal mouth opening < 15mm. Patil and Maheshwari recommended new characterization dependent on the adaptability of the cheek.

Typical cheek adaptability watched was 35-45mm for males and 30-40mm for females

Grade 1

(Early): cheek adaptability of 30mm or more.

Grade 2

(Gentle): cheek adaptability between 20 to 30mm.

Grade 3

(Moderate): cheek adaptability under 20 mm.

Grade 4

(Extreme): above conditions without simultaneous nearness of potential threatening sores.

Grade 5

(Progressed): Above condition with simultaneous nearness of oral carcinoma.

Management of OSMF

Non-Surgical

Oral submucous fibrosis is noted for its persistent and consistent nature. As a premalignant condition, no treatment can provide a complete cure. Legitimate treatment begins with informing the patient about their condition. Patients should be educated about the concept of sickness, regardless of stopping the predisposition. Gupta et al. treated six OSMF patients with nutrients including A palmitate 2500 IU nutrient E, beta carotene 50 mg, nutrient C, zinc, copper, and manganese.

Copper and zinc play a role in the etiology of OSMF and can also be used as a prognostic indicator. Estimating serum levels of these elements in OSMF patients with regular follow-up may aid in the optimal therapy of these disorders.

Lycopene is the true carotenoid found in tomatoes, and it is thought to have cancer-preventing and chemopreventive capabilities against possibly malignant illnesses. The combination with intralesional steroids and hyaluronidase is quite successful in reducing mouth opening. A variety of glucocorticoids are used in the treatment of OSMF. Hydrocortisone is short-acting, triamcinolone is intermediate-acting, and betamethasone and dexamethasone are long-acting steroids. For 10 weeks, a submucosal infusion of chymotrypsin (500IU), hyaluronidase (1500IU), and dexamethasone (4mg) was administered twice weekly. Pentoxifylline 400 mg, three times daily for seven months, was used as adjuvant therapy for OSMF.

Curcuma, also known as Haldi, turmeric, or Indian saffron, is noted for its soothing and anti-oxidant properties. Curcumin is the primary curcuminoid found in turmeric, accounting for roughly 2-5% of the total. When supplied to patients, an improvement in mouth opening and burning sensation was seen.9 Das discovered that combining with turmeric oil was a fundamentally helpful non-intervention herbal medication.4 Turmeric has a therapeutic effect in patients with OSMF and is regarded a safe, nontoxic, and effective alternative to many conventional treatments due to its unique therapeutic qualities and diverse effects on the body's systems. Its role in treatment is quite promising [10].

Because carcinogenesis is caused by the formation of reactive oxygen species, the administration of non-enzymatic antioxidants, particularly B-carotene, vitamin E, and vitamin C, can effectively prevent it. The levels of these antioxidants fall dramatically as the lesion advances from normal to pre-cancerous and finally to cancer, indicating a considerable increase in oxidative stress throughout the progression of OSMF to oral cancer.

Li and Tang discovered that tea hues play an important impact in reducing blood consistency. Aloe Vera is a powerful wound healer that is used topically at the onset of a lesion. Microalgae that include beta carotene, tocopherols, and phenolic acid have anticancer effects. Shetty et al. used 500 mg of spirulina twice daily as an adjuvant therapy in their study. Surgical intervention for the management of OSMF is decided according to clinical phases. Oral stents can also be used as an adjuvant to prevent relapse.

Surgical Treatment

Medical treatment is palliative therapy, which will not reverse the illness. Surgical treatment has its advantages and disadvantages.

Extraoral flaps

Like a split-thickness skin graft, superficial temporal fascia pedicled flap, temporalis pedicled flap,

nasolabial flap, platysma myocutaneous muscle flap.

Intraoral flaps

Like tongue flap, palatal island flap, buccal pad of fat, microvascular-free flaps, radial forearm free flap, and anterolateral thigh flap

Allografts like

Collagen membrane, alloderm.

The new Temporalis fascia flap procedure releases powerful mouth closure muscles such as masseter and temporalis from their origins and insertions, respectively. The mucosa, pterygomandibular raphe, and buccinator muscle are released intraorally, resulting in a mucomuscular deficit. A well-vascularised superficial temporal fascia flap improves blood flow to the fibroid muscles and mucosa while also providing a healthy substrate for the skin graft. This approach, based on anatomical landmarks and physiological facts, is a successful treatment for oral submucous fibrosis.

The nasolabial method flap provides adaptability and a particular advantage in maintaining the mouth opening throughout time since it is local, easily accessible, and changeable in a single session. Linear closure of the donor site may result in a well-camouflaged scar in the nasolabial fold. Large faults can be closed. Minor issues include increased intercommisure breadth and intraoral hair development. Trismus is commonly treated with workouts that blend active and passive ranges of motion. Management of OSMF using the nasolabial flap procedure and postoperative exercises allows for effective disease-free mouth opening with minimum functional and esthetic deformities at the donor site.

The Platysma myocutaneous muscle flap is simple, adaptable, and might be considered a viable reconstructive option with acceptable visual outcomes. It is an effective treatment option for restoring the optimum buccal mucosa in minor and medium-sized oral cavity deficits ranging from 2 to 4 cm^2.

The buccal fat pad (BFP) flap offers numerous advantages over other types of flaps. The surgical procedure is uncomplicated and has demonstrated a high success rate in a variety of applications. BFP can be utilized for epithelialization without requiring a skin graft. BFP's high vascularity is advantageous when applied in a less vascularized recipient location. However, due to its size, frequent use may be impossible. The flap is delicate, and injury to the vascular pedicle may result in graft loss. Removing too much of the buccal fat pad may result in facial deformity or limited mouth opening. These constraints should be recognized when applying BFP in clinical settings.

The buccal fat pad approach in the therapy of OSMF with postoperative exercise had an essential role in achieving functional disease-free mouth opening and detecting any growing malignant alteration at an early stage.[15]

Pedicled tongue flap surgery has produced relatively promising results. Especially in a nation like India, where the prevalence of OSMF is high due to regular chewing of betel nut and tobacco with lime, a well-formulated protocol like the one we use is quite beneficial.

Post-Operative Physiotherapy

Vigorous mouth-opening exercises are essential for achieving sufficient mouth opening and preventing trismus recurrence after surgery. Oral physiotherapy is normally started three days following surgery, when recovery begins. To achieve maximal mouth opening, wooden tongue spatulas can be put between the molar teeth and gradually raised on a daily basis. For optimal effects, do this for at least 3 minutes, three times every day, for three months. Good patient compliance is required to sustain this level of dedication as well as to discontinue the areca nut habit, which is critical for preventing fibrosis recurrence. Close monitoring for malignant change is important.

Colposcopy - After applying 2% acetic acid, the lesions showed faint pink to orange in hue. The Lugol's iodine application did not result in uniform uptake. It was iodine-negative in some spots. Histopathological investigation found 9 patients with mild dysplasia, 2 with moderate dysplasia, 4 with severe dysplasia, and 11 with symptoms of chronic nonspecific inflammatory reaction.

Laser technology has advanced rapidly over the last few decades, and lasers have found a place in a variety of surgical specialties. Diode lasers have become indispensable in OSMF surgery as an extra modality due to their numerous benefits. Lasers have numerous applications in OSMF surgery, and the introduction of new wavelengths will surely lead to new treatments that can be performed with laser technology.

While dental lasers are still in their early stages, there is no doubt that the field is beginning to acknowledge them as a viable option to traditional procedures. The ErCr: YSGG laser is useful in both hard and soft tissue operations

because the hydro-photonic process allows it to outperform other conventional modalities in a variety of ways. Lasers are commonly used for soft and hard tissue procedures such as maxillary and mandibular frenectomies, lingual frenectomy, operculectomy, gingivectomy around orthodontic brackets, fibroma removal, dilantin hyperplasia treatment, mucocele removal, uncovering tissue around implants, treating aphthous ulcers, cosmetic tissue recontouring, cavity preparations, apicoectomy, and so on. Overall, laser surgery is effective and safe. This example emphasizes the utilization of ErCr: YSGG laser as an innovative and precise way of treatment.

However, we need a larger study with long-term follow-up in similar instances before implementing this method in ordinary clinical practice.

Malignant transformation and molecular markers

OSMF has a malignant transformation rate of 7–30%. Pathogenesis is believed to be complex. The carcinogenic effects of tobacco in combination with areca-nut are well documented, but the International Agency for Research on Cancer's (IARC) second assessment on betel quid designated areca-nut as a "group one carcinogen". Its genotoxic and mutagenic effects are related to polyphenols, alkaloids, and arecanut-specific nitrosamines such as N-nitrosoguvacoline, N-nitrosoguvacine, 3-(N-nitrosomethylamino) propionaldehyde, and 3-(N-nitrosomethylamino) propionitrile.10, 57 Several research have been undertaken in an attempt to uncover molecular markers that can predict malignant transformation in OSMF. Recently, a loss of heterozygosity in 23 "hotspot" loci that modify genes that govern the cell cycle was identified as a key genetic predictor for malignancy in OSMF.

Malignant transformation and precancerous character of Oral Submucous Fibrosis: In 1956, Paymaster observed squamous cell carcinoma in 33% of individuals with oral submucous fibrosis. Pindborg et al found a malignant transformation rate of 4.5% in 66 cases of OSMF during 4-15 years. In Taiwan, the figure is 3.27-8.63%. According to Patel and Maheswari's 2014 study, the figure is 4.6%. [11].

CONCLUSION

The goal of this research is to present a specific treatment technique that combines surgery and active physiotherapy to increase jaw opening and prevent relapse. The current study made a small effort to maintain adequate, functional disease-free mouth opening and detect any growing malignant change as soon as possible.[12]

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