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Case Report

Dentistry Section

# Management of Histologically Proven Oral Submucous Fibrosis with Intralesional Steroids and Hyaluronidase- A Report of Two Cases

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## ABSTRACT

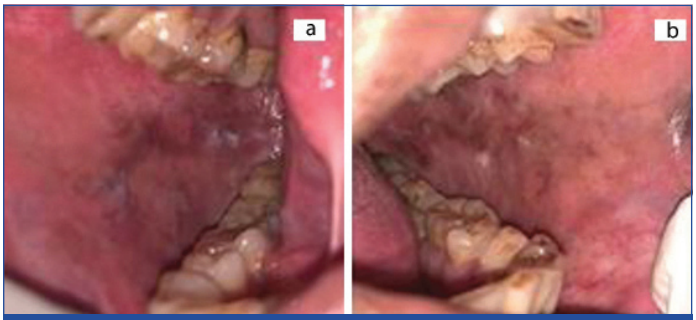
Oral Submucous Fibrosis (OSMF) is a chronic debilitating disease characterised by progressive fibrosis. The disease is predominantly seen in South East Asia and mainly attributed to areca nut chewing habit. The classical presentation includes generalised blanching with palpable fibrotic bands in the oral mucosa. Patients experience severe burning sensation, trismus and difficulty in gustatory functions, thus resulting in compromised nutritional status. The OSMF has been grouped under Oral Potentially Malignant Disorders (OPMD) and has high rates of malignant transformation. Although randomised controlled trials on different treatment modalities have been conducted, currently there is no effective medical management. This paper highlights two cases of OSMF presenting with severe burning sensation and trismus, who underwent incisional biopsy for histopathological confirmation and to rule out dysplasia. Both the patients were treated with dexamethasone and hyaluronidase, biweekly for four weeks. Post-treatment there was significant improvement in the clinical symptoms, thus providing the patients with better quality of life.


**Keywords:** Areca nut, Malignant transformation, Oral potentially malignant disorder

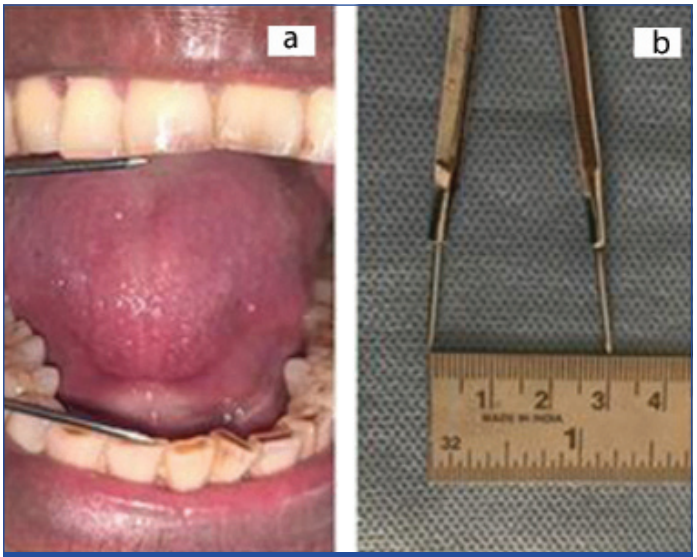
## CASE REPORT

### Case 1

A 41-year-old male patient reported to the Outpatient Department of Oral Medicine and Radiology with a chief complaint of limited mouth opening since four months. On eliciting the personal history, the patient gave history of pan chewing for past four years, 10 times a day, and had habit of keeping it in left buccal mucosa for 15 minutes before spitting it out. The patient gave a Visual Analogue Scale (VAS) score of seven for burning sensation. On examination, there was evidence of generalised blanching [Table/Fig-1a,b], with restricted tongue movements and mouth opening of 30 mm [Table/Fig-2a,b]. On palpation, the buccal mucosa was leathery in texture with evident palpable fibrotic bands bilaterally on the buccal mucosa. A provisional diagnosis of Oral Submucous Fibrosis (OSMF) (Stage II-based on Khanna and Andrade Functional staging [1] was given. Informed consent was obtained from the patient prior to investigative work up. The haematological findings were within normal limits with haemoglobin at 14.4 gm/dL and incisional biopsy was done on the left buccal mucosa. The histopathology report revealed the presence of atrophic stratified squamous epithelium, with underlying connective tissue showing hyalinisation, fibrosis, with few inflammatory cells and absence of dysplasia, correlating with histopathological Grade III based on histopathological grading of OSMF by Pindborg and Sirsat [Table/Fig-3] [2].



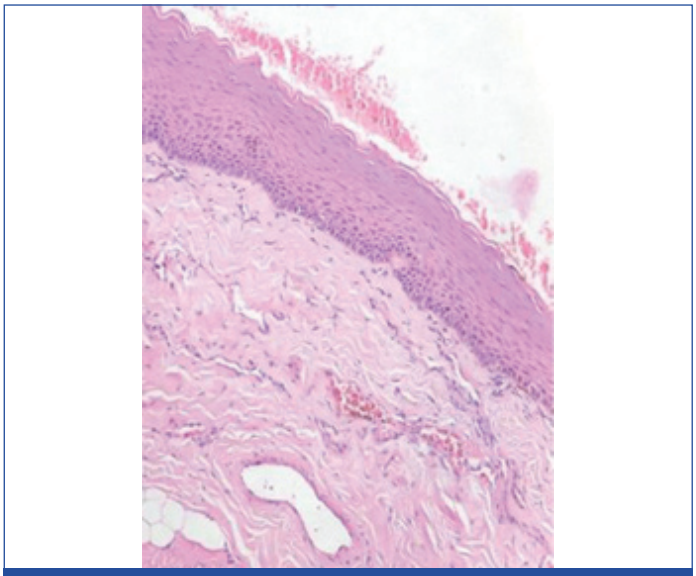

**[Table/Fig-1a-b]:** Image shows blanching of right and left buccal mucosa.




**[Table/Fig-2a-b]:** Pre-treatment image showing mouth opening with an interincisal distance of 30 mm.

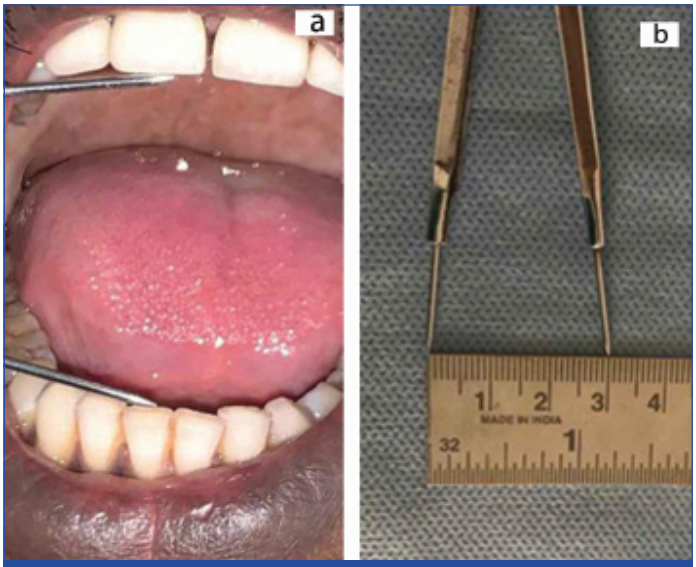
### Case 2

A 40-year-old male patient reported to the Outpatient Department of Oral Medicine and Radiology with a chief complaint of burning sensation to spicy foods and limited mouth opening since one year. Personal history revealed that the patient had pan chewing habit for two years, two times a day, and had habit of keeping it in left and right buccal mucosa for five minutes before spitting. The patient gave a VAS score of eight for burning sensation. On examination there was evidence of generalised blanching of oral mucosa with marble like appearance [Table/Fig-4a-d]. The mouth opening measured as interincisal distance using metallic scale and divider was 30 mm [Table/Fig-5a,b]. Tongue movements were restricted and there was evidence of bud shaped uvula [Table/Fig-6]. On palpation, bilateral fibrous bands were evident bilaterally on the buccal mucosa. A provisional diagnosis of OSMF (Stage II-based on Khanna and Andrade functional staging [1] was given. Patient's consent was obtained



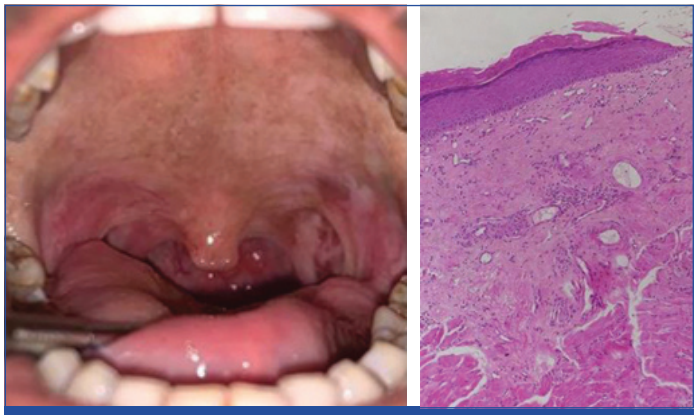
**[Table/Fig-3]:** Histopathological features of Case-1 showing the presence of atrophic stratified squamous epithelium with underlying connective tissue showing hyalinisation, fibrosis, with few inflammatory cells and absence of dysplasia (Magnification: X100).


**[Table/Fig-4a-d]:** Image shows blanching in right and left buccal mucosa; upper and lower labial mucosa.




**[Table/Fig-5a-b]:** Pre-treatment image showing mouth opening and interincisal distance of 30 mm.

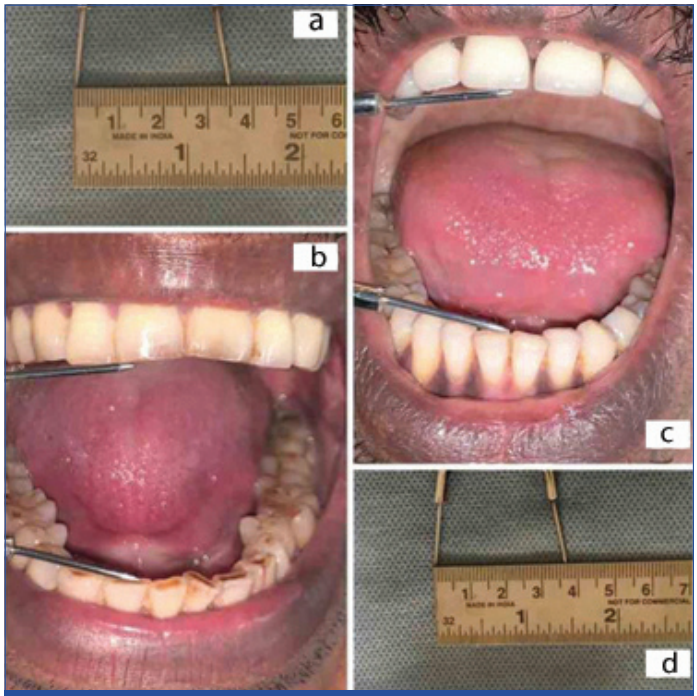
before subjecting to investigations. The haematological parameters were within normal limits with haemoglobin levels at 12.3 gm/dL and incisional biopsy was performed in relation to right buccal mucosa. The histopathology report revealed the presence of orthokeratotic atrophic stratified squamous epithelium, with underlying connective tissue showing hyalinisation, fibrosis, with few inflammatory cells and absence of dysplasia, correlating with histopathological Grade III based on histopathological grading of OSMF by Pindborg and Sirsat [Table/Fig-7] [2]. The differential diagnosis for both the cases, included scleroderma, iron deficiency anaemia and generalised fibromatoses [3], however they were ruled out based on the habit history and classical clinical manifestations of OSMF.



**[Table/Fig-6]:** Bud shaped uvula.
**[Table/Fig-7]:** Histopathological features of Case-2 showing presence of orthokeratotic atrophic stratified squamous epithelium, with underlying connective tissue showing hyalinisation, fibrosis, with few inflammatory cells and absence of dysplasia. (Magnification: X100). (Images from left to right)

**Treatment:** Both the patients were counselled to stop pan chewing habit. The treatment included topical application of 0.1% triamcinolone acetonide twice daily, vitamin B complex tablet, and intralesional injection with 1.5 ml of dexamethasone (4 mg/mL) and hyaluronidase (1500 IU); with 0.5 ml lignocaine HCL, biweekly for four weeks on right and left buccal mucosa in multiple sites, based on James L et al., [4]. Patient was advised mouth opening exercises for 2-3 times a day.

At the end of four weeks, case 1 gave a VAS score of 0 (pre-treatment VAS score-7) and increase in mouth opening as interincisal distance improved to 35 mm (an increase by 5 mm) [Table/Fig-8a,b]; case 2




**[Table/Fig-8a-d]:** a) and b) Post-treatment image showing mouth opening as interincisal distance of 35 mm (case 1); c) and d) Post-treatment image showing mouth opening as interincisal distance of 37 mm (case 2).

gave a VAS score of 0 (pre-treatment VAS score-8) and interincisal distance improved to 37 mm (an increase by 7 mm) [Table/Fig-8c,d]. Both the patients gave a subjective improvement in the tongue movements and the elasticity of the right and left buccal mucosa (measured using divider and scale) improved in both the patients, which was performed based on Reddy V et al., [5]. The patients were asked to continue mouth opening exercises for another six weeks, and the patients were kept under follow-up.

## DISCUSSION

Oral Submucous Fibrosis (OSMF) is a chronic debilitating disease seen in betel nut chewers, characterised by progressive fibrosis. The clinical features include burning sensation, trismus, blanching, palpable fibrotic bands and altered gustatory function. The burning sensation seen in OSMF is mainly attributed to the atrophy of the epithelium, which results in reduction of the distance of intra-epithelial nerve endings from the surface [6]. The areca alkaloids in the betel nut-namely arecoline, arecaidine, guvacine and guvacoline play major role in the pathogenesis of OSMF. Arecoline stimulates fibroblastic proliferation, collagen synthesis and decreases collagen breakdown. Areca nut chewing causes continuous local irritation of the soft tissues of oral cavity, leading to injury related chronic inflammation, oxidative stress and cytokine production. Oxidative stress and subsequent Reactive Oxygen Species (ROS) generation induces cell proliferation and apoptosis; these events lead to preneoplastic changes and subsequently to oral malignancy [7,8].

Various OPMD include oral leukoplakia, erythroplakia, erythroleukoplakia, OSMF, palatal lesions in reverse smokers, oral lichen planus, oral lichenoid reactions, graft versus host Disease (GvHD), oral lupus erythematosus, actinic chelitis of lower lip and some hereditary conditions, such as dyskeratosis congenita and epidemolysis bullosa. Most of these conditions tend to be asymptomatic in early stage and hence early identification is of utmost importance for better prognosis and prevents malignant transformation [9]. High rates of malignant transformation has been reported in OSMF amongst OPMD, with malignant transformation rate of 7-13% [7,8]. The different treatment strategies include local injections of steroids (dexamethasone or betamethsone), placental extracts, hyaluronidase, lycopene, pentoxyphylline, IFN-gamma, colchicine, Vitamin A and other anti-oxidants. However, it has been seen that various treatment modalities have limited efficacy with currently no single effective treatment available [10]. Previous studies indicate that the anti-inflammatory effect of steroids along with breakdown of inter-cementing substance by hyaluronidase has proven symptomatic relief in OSMF [4,11]. The current report highlights two cases of histologically proven cases of OSMF treated with dexamethasone and hyaluronidase resulting in substantial symptomatic relief at four weeks post treatment.

Steroids namely dexamethasone, betamethasone, hydrocortisone, triamcinolone which have been employed in the management of OSMF, have proven anti-inflammatory action. Steroids further reduce the fibroblastic proliferation and the collagen deposition [11]. The symptomatic relief resulting in reducing the burning sensation and increasing the mouth opening in both the cases could be attributed to the potent anti-inflammatory and antifibrotic effect of steroids. Hyaluronidase has the potency to break the inter-cementing substance (hyaluronic acid); the combination with steroid has provided better results in symptomatic improvement among OSMF patients [12]. Despite steroids being conventional treatment regimen for different clinical stages of OSMF, a study by Borle RM et al., showed increased fibrosis with repeated steroid injections and has favoured conservative approach for OSMF in the form of topical application of betamethasone, chewable vitamin A tablets and iron supplements [13]. An unusual case of bilateral buccal space abscess and a case of central serous chorioretinopathy were observed after intralesional steroid injections in OSMF patients [14]. Hence, it is mandatory to consider the possibility of such rare side effects during the entire course of treatment and a thorough evaluation of medical history is necessary before the initiation of treatment. Some of the contraindications include hypersensitivity to steroids or hyaluronidase, medically compromised patients including uncontrolled diabetes, hypertension and pregnant women [15,16].

In a report of three cases, intralesional injection of steroids along with hyaluronidase resulted in a significant relief of symptoms [17]. Study done by Tilekaratne WM et al., employed intralesional injections of 40 mg of prednisolone on 116 patients in histologically proven cases of OSMF with mouth opening less than 30 mm. The study showed that around 60% of cases had 5 mm or <5 mm improvement of mouth opening at one year follow-up from the first dose, after being treated at monthly intervals for a period of six months. The improvement in mouth opening after corticosteroid administration has been correlated with the anti-inflammatory and upregulation of immune mediated fibrolytic pathways [18]. It has been observed in a study that intralesional triamcinolone acetonide (40 mg/mL; 1 mL) showed superior clinical improvement compared with intralesional placental extract (placental extract 2 mL) after 10 weeks of therapy [19]. The current case report highlights good clinical response of reduced burning sensation and improvement in mouth opening after four weeks post-treatment with intralesional dexamethasone and hyaluronidase. With currently no effective medical management for OSMF, steroids along with hyaluronidase play a promising role in symptomatic relief for patients thus reducing the morbidity associated with the disease.

## CONCLUSION(S)

Currently, management of OSMF with respect to alleviation of burning sensation and trismus is challenging. Intralesional dexamethasone with hyaluronidase aids in symptomatic relief and improvement in mouth opening, resulting in better nutritional intake. Oral physiotherapy during the treatment and adequate follow-up of such patients helps in monitoring them for any malignant transformation, thus enhancing the quality of life of OSMF patients.

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