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Complication Of Intralesional Hyaluronidase Injection DuringTreatment Of Oral Submucous Fibrosis: A Case Report

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ABSTRACT

Aims and background: Oral submucous fibrosis (OSMF) is a potentially malignant condition of oral cavity. Optimal dosage of local injection of corticosteroids with hyaluronidase is an effective treatment.

Case description: A 34 years' old male, diabetic patient reported with reduced mouth opening. He had a tobacco chewing habit. He was thoroughly examined and diagnosed with OSMF. Due to diabetes, he was advised only hyaluronidase injection. After 4 sessions of intralesional injection, he started developing facial edema after every session that subsided within 48-72 hours.

Conclusion: The present report is to discuss a complication of intralesional hyaluronidase therapy.

Clinical significance: Hyaluronidase can be administered without corticosteroid in OSMF patients with diabetes keeping in mind the adverse reactions that could happen and how to manage them when encountered.

Keywords: OSMF, Hyaluronidase injection, Corticosteroid & Hyaluronidase injection in OSMF, OSMF Treatment, Oral Submucous Fibrosis

INTRODUCTION

Oral submucous fibrosis (OSMF) is a potentially malignant condition of oral mucosa, characterized by juxta-epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues. Pindborg in 1966 defined OSMF as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. It is associated with juxta-epithelial inflammatory reaction followed by fibroelastic changes in the lamina propria layer, along with epithelial atrophy which leads to rigidity of the oral mucosa proceeding to trismus and difficulty in mouth opening." [1] The etiological factors of the disease, like alkaloids present in areca nut(arecoline, arecaidine, guvacine, and guvacoline), capsaicin in chilies, micronutrient deficiencies of iron, zinc, and essential vitamins. For example, Arecoline, the most potent of these alkaloids and is a major cause of OSMF activates fibroblasts, which are key cells in the OSMF microenvironment, and increases collagen synthesis by hence causing the progressive loss of mucosal elasticity and restricted mouth opening. [2]

CASE REPORT

A 34 year old male patient reported with the complaint of inability to open the mouth since last 1 year. Patient was apparently alright 1 year back since when he has been noticing a reduction in his mouth opening with a persistent burning sensation while eating hot and even mildly spicy food. Patient gives history of areca nut chewing habit for over 10 years. He is under regular medication for uncontrolled Diabetes Mellitus.

On examination,
Inspection:

- Interincisal opening = 19mm [Figure 1]
- Blanching of both right and left buccal mucosae [Figure 2a & 2b]
- Depapillated tongue with glossy appearance noted
- Poor oral hygiene

- Complete intraoral examination was not possible due to insufficient mouth opening

Palpation:

- Thick vertical palpable fibrous bands noted in relation to the left and right buccal mucosae.

Provisional diagnosis: Oral Submucous Fibrosis Stage III

Investigations:

- Blood investigations: Complete Blood count, Fasting Blood glucose, Postprandial blood glucose, HbA1C

The blood reports were under normal range except for fasting and postprandial blood glucose which were measured as 180 mg/dl and 271 mg/dl respectively. HbA1C was reported as 7.0.

Advised treatment:

- To stop all oral deleterious habits
- Oral antioxidants given twice daily for 3 months.
- Intralesional Hyaluronidase injection 1500 IU to be given once in 3 days for 10 sittings.

Complication: After 2 doses of Intralesional hyaluronidase injection, the patient presented with swellings in both right and left cheeks. The surfaces of the swellings were of normal skin colour. The swellings were non-tender and soft in consistency. [Figure 3]

As treatment for the swelling (which were considered to be hypersensitivity reaction), anti-histaminic (LEVOCETRIZINE) tablets were prescribed twice daily for 5 days. The patient reported that the swelling subsided within the next 48 hours.

Intralesional hyaluronidase was continued as mentioned in the treatment plan.

Similar episodes occurred till the 5th dosage and the same treatment plan was followed to treat the swelling.

After 6 doses of intralesional hyaluronidase, interincisal mouth opening was measured to be 24mm. [Figure 4]

After 10 doses, the interincisal mouth opening was found to be 26mm. [Figure 5] Patient was kept on monthly follow up for the next 6 months.

Discussion:

As of 2017, India is the world's largest producer of areca nuts, or betel nuts, accounting for 54.07% of the world's output. Areca nut or Supari is consumed across all age groups (15 and above) in India.[3] Oral submucous fibrosis can occur at any age. It's most commonly seen in adults between 25 and 35 years. In India, the prevalence increased over the past four decades from 0.03% to 6.42%.[4]

Early diagnosis and prompt treatment of OSMF becomes very critical due to its high malignant transformation rate, which is up to a staggering 30%. Kerr et al. in the year 2011 suggested a comprehensive classification system for OSMF based on clinical features: (Table 1)[1]

Treatment:

- Cessation of habit
- Antioxidants - Carotenoids

    - Lycopene which acts via reducing the inflammatory process seen in OSMF by reduction of reactive oxygen species and modifies the expression of certain genes that play a key role in collagen deposition and collagen degradation[5]

- Intralesional Hyaluronidase + Corticosteroids (most commonly used, currently)
    - Hyaluronidase breaks down hyaluronic acid, which is the ground substance in connective tissue. This lowers the viscosity of intercellular cement substance and activates plasmatic mechanisms. Hyaluronidase is an endoglycosidase that breaks down hyaluronic acid into monosaccharides by cleaving its glycosidic bonds; additionally, to some extent, it also breaks down other acid mucopolysaccharides in the connective tissue[6]
    - Corticosteroids, such as dexamethasone and betamethasone, acts as an immune suppressive agent by its antagonistic activity on the soluble factors released by the sensitized lymphocytes succeeding the activation by nonspecific antigens. It additionally muzzles the inflammatory reaction. Thus, fibrosis is prevented by a decrease in fibroblastic proliferation and deposition of collagen. [7]
- Intralesional placental extracts
- Surgical treatment – in severe cases

Now in cases of uncontrolled blood glucose levels, dexamethasone can impose problems in the patient. (Figure 6)
Hence it was avoided in this case as it is a relative contraindication in diabetes.[8] Patient has been kept on follow up and till date no other adverse effects have been reported after completion of 10 sittings of intralesional hyaluronidase other than the ones which were encountered in the beginning. The interincisal mouth opening continues to be at 26mm which signifies a successful treatment.

Conclusion:
Many case reports suggest Hyaluronidase as dermal fillers have caused local hypersensitivity reactions leading to swelling, erythema and itching. Several drugs act as antagonists to hyaluronidase, including anti-inflammatory drugs (such as ibuprofen, aspirin, diclofenac), anti-histamines, mast cell stabilizers, Vitamin C, flavonoids, and anti-oxidants. [9] The discussed case also stands out to be the result of a hypersensitivity reaction. Hence it can be

concluded that only intralesional hyaluronidase can be administered to uncontrolled diabetes patients with Oral Submucous Fibrosis along with a commonly used antihistamine medication to avoid any unnecessary side effects, to achieve the desired results.

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Table legend

Table 1: Classification of OSMF by Kerr et al in 2011

GRADE	FEATURES
Grade 1– Mild	Any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported – and inter-incisal opening >35 mm Any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported – and inter-incisal opening >35 mm Any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported – and inter-incisal opening >35 mm Any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported – and inter-incisal opening >35 mm Any features of the disease triad for OSMF (burning, depapillation, blanching or leathery mucosa) may be reported – and inter-incisal opening >35 mm
Grade 2 – Moderate	Above features of OSMF + inter-incisal limitation of opening 20–35 mm
Grade 3 – Severe	Above features of OSMF + inter-incisal opening <20 mm
Grade 4A	OSMF + other potentially malignant disorder on clinical examination
Grade 4B	OSMF with any grade of oral epithelial dysplasia on biopsy
Grade 5	OSMF + Oral squamous cell carcinoma (OSCC)

Figure legend :

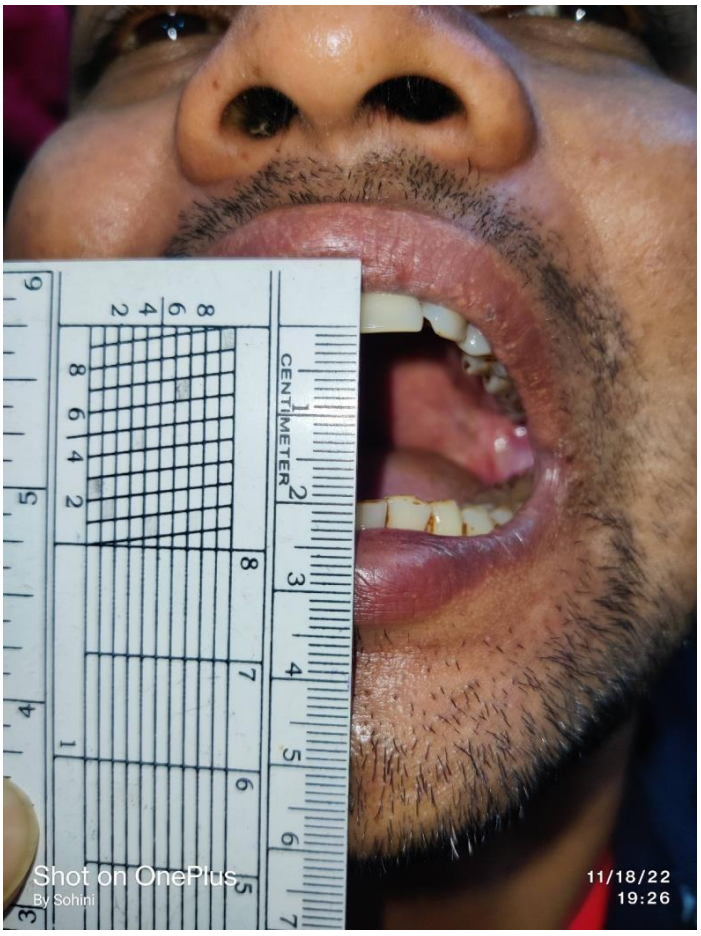

Figure 1: Interincisal mouth opening 19mm

Figure 2a & 2b: Blanched appearance of both buccal mucosae with thick white bands in the retromolar region

Figure 3: Swelling after 2 doses of intralesional hyaluronidase

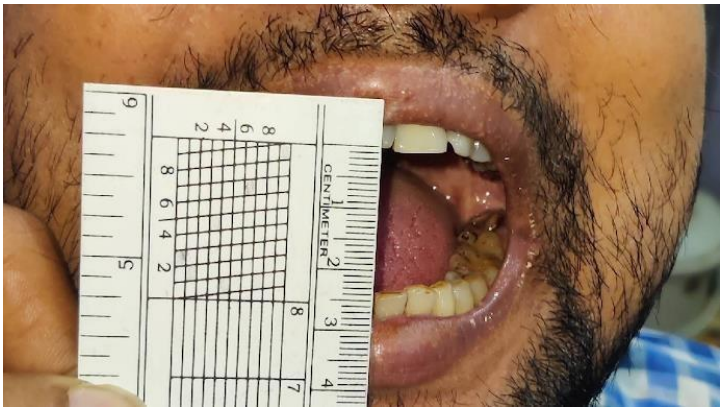

Figure 4: Interincisal mouth opening 24mm after 6 doses

Figure 5: Interincisal mouth opening 26mm after 10 doses

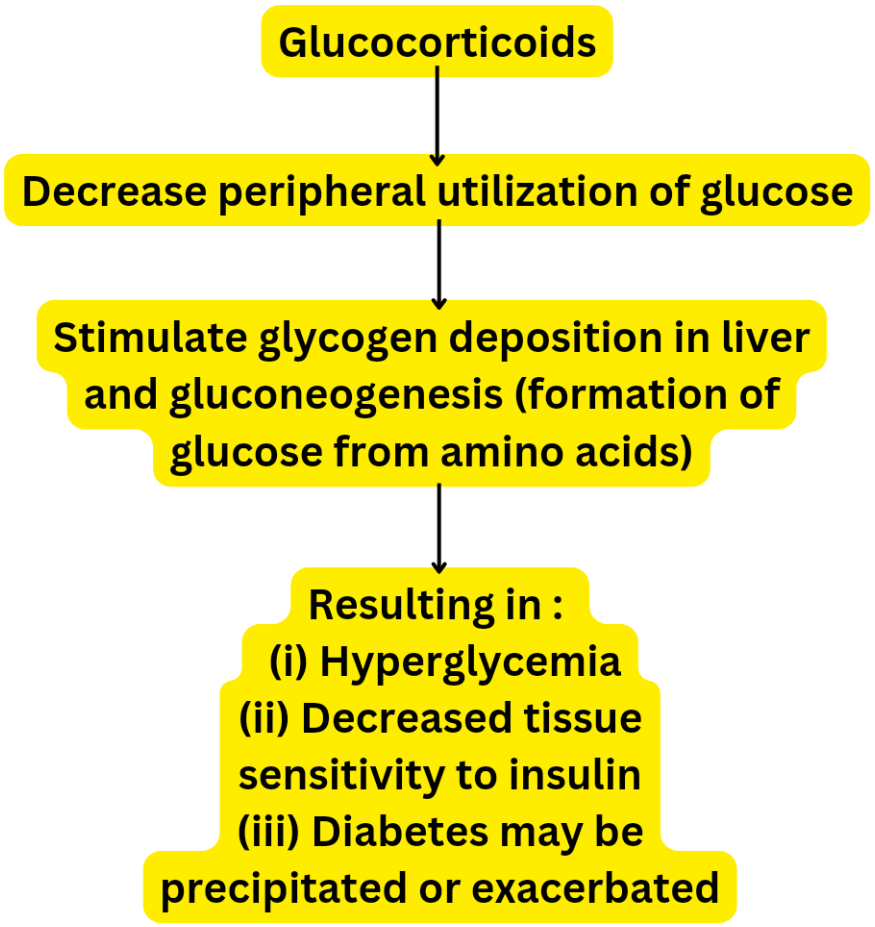

Figure 6: Role of Glucocorticoid in Hyperglycemia