Oral Stent loaded with 0.1% Tacrolimus for management of Pemphigus Vulgaris

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Abstract

Pemphigus vulgaris is a mucocutaneous disorder, commonly affecting older individuals, predominantly in women. It is characterized by bullae formation, shows positive Nikolsky's sign. We present a case of pemphigus vulagaris in a 70 year old lady who was treated with topical tacrolimus. On clinical examination, multiple eroded areas with bleeding seen on buccal mucosa, labial mucosa, hard palate. For treatment, prednisolone was prescribed orally for 1 month, along with alternate topical application of 0.05% clobetasol propionate and 0.1% tacrolimus ointment for 6 months. Satisfactory healing with no recurrence of lesion was noted. Hence topical tacrolimus can be used as adjuvant therapy along with corticosteroid for treating and preventing recurrence of pemphigus vulgaris.

Keywords: Clobetasol Propionate, Corticosteroids, Oral Stent, Pemphigus vulgaris, Tacrolimus.

Keymessage- Tacrolimus is a immunosuppressant drug that acts by suppression of production of autoantibody towards own antigen. It can be used along with corticosteroid drugs for treating pemphigus vulgaris. Although further studies are require to assess the potency of the drug.

Introduction

Pemphigus is a chronic autoimmunonue inflammatory disease which affects oral mucosa and skin. Around 0.1-0.5 patients per million population is affected by pemphigus[(1)]. It commonly occurs in 5th-6th decade of life. Female predilection is present with male to female ratio 1:2[(2)]. Clinical subtypes of pemphigus are pemphigus vulgaris, pemphigus vegetans pem-phigus foliaceous, pemphigus erythematosus, para- neoplastic pemphigus. Among all of these subtypes most common is the pemphigus vulgaris which occurs in 80% of the cases[(3)]. Lesions of oral mucosa most commonly occurs on buccal mucosa followed by palatal, labial and lingual

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mucosa, gingival lesions manifests as desquamative gingivitis. In many cases oral involvement is followed by skin lesions[4]. For management of pemphigus, corticosteroid both systemic and topical are mainly used, along with steroids immune-suppressive drugs like azathioprine, cyclopho-sphamide, tacrolimus are also used. We are discussing a case of pemphigus vulgaris that was successfully treated by tacrolimus along with corticosteroids.

Case history

A 70 year old lady reported with a chief complain of ulcers in the mouth along with difficulty in swallowing food since 30 days. History of the present illness reveals she was apparently alright 30 days back when she noticed ulcerations on multiple sites within the mouth. The size and number of the lesions increased with time. and intermittent bleeding was associated with the lesions which occurred mostly while brushing and chewing coarse food. Patient gave history of pain which was mild to moderate in intensity, intermittent in frequency, non-progressive type that initiates on consumption of hot and spicy food which remains for 2-3 minutes and then subsides on its own. No history of any skin involvement. Patient did not take any medication and reported to departmental OPD for treatment. A review of medical and family history was non-contributory. Patient was married, she had mixed dietary habit, bowel and micturition was normal. The patient had adequate appetite and undisturbed sleeping pattern. No history of any adverse habit. She brushes her teeth once daily with toothbrush and fluoridated toothpaste in horizontal motion for approximately 2 minutes.

Patient was well oriented to person place and time, her vitals were within the normal range. No signs of pallor, icterus, clubbing, cyanosis, koilonychia, lymphadenopathy, edema. Extraoral examination revealed apparently symmetrical face, no abnormality was noted in TMJ, salivary glands, lymph nodes were non-palpable. Intra-oral examination of soft tissue revealed ulcerative and eroded lesions on bilateral buccal mucosa extending from retro-commissure region to retromolar region along the line of occlusion. Erosions were evident on lower labial mucosa as well. Erosive areas were seen on hard palate and gingiva. Ulcers were shallow had irregular borders covered by pseudomembrane with bleeding points, shown in (Fig. 1). On palpation, sloughing of pseudomembrane, bleeding on slight provocation with tenderness was noted. No enduration of the borders of the ulcers. Nikolsky"s sign showed a positive reaction. Hard tissue examination showed presence of generalized attrition, stains and calculus. The clinical presentation of chronic multiple oral ulcer with positive Nikolsky's sign led to provisional diagnosis of pemphigus vulgaris.

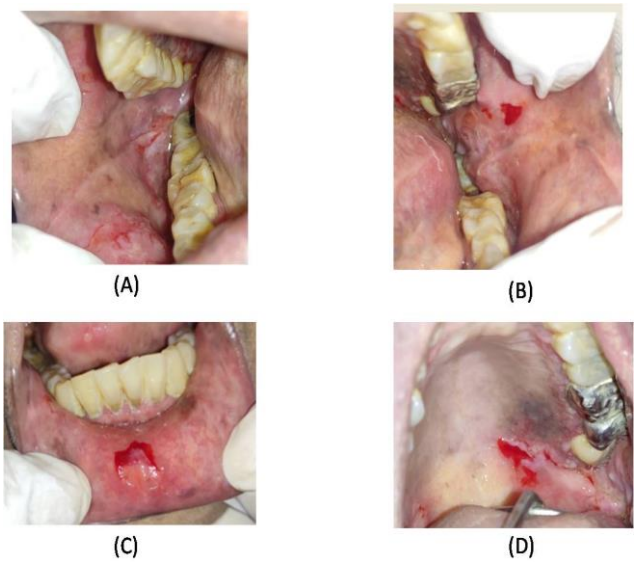

Figure 1: (A) Right buccal mucosa (B) Left Buccal mucosa (C) Lower lip (D) Hard palate ; At first visit

Differential diagnosis, investi-gation and treatment

Differential diagnosis mucous membrane pemphigoid, bullous lichen planus, chronic ulcerative stomatitis, recurrent herpes lesion.

Routine blood investigation showed reduced hemoglobin levels. Incisional biopsy of perilesional areas was done on buccal mucosa and lower lip. Tissue specimen was sent for histopathological examiation and direct immune-fluorescence test. Histopathological examination showed evidence of intra-epithelial suprabasilar split with presence of Tzanck cells. Direct immunofluorescence test showed presence of positive IgG antibodies with fine granular fish net like appearance in epithelium, shown in (Fig.2). Based on clinical examination , histopathological and direct immunofluorescence investigations a final diagnosis of pemphigus vulgaris was given.

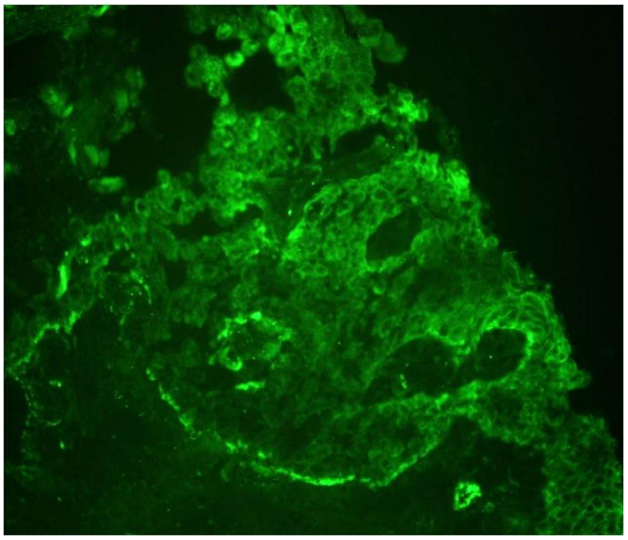

Figure 2: Direct immunofluorescence of tissue specimen showing presence of positive IgG antibodies with fish net like appearance of epithelium.

Treatment plan included systemic and topical corticosteroid application. Prednisolone 60 mg/day for 7 days was prescribed, intralesional dexamethasone 4 mg injection was given biweekly

for 4 weeks. Topical alternate application of 0.05% clobetasol propionate and 0.1% Tacrolimus 3-4 times daily was given. Tacrolimus (0.1%) ointment was prepared by mixing 0.1% w/w tacrolimus powder with orabase. Topical clobetasol (0.05%) ointment was prepared by mixing 0.05% w/w clobetasol propionate with orabase. For oral stent fabrication, maxillary and mandibular arch impression was taken and cast was prepared. Soft acrylic splint was fabricated in the Biostar machine (Fig.3). Occlusal stent has several advantages, salivary clearance of the medicine will be less, medicament will be in contact with the lesion for longer period of time. Patient was instructed to apply topical tacrolimus and clobetasol alternately on the stent and wear it overnight. For symptomatic relief sucralfate oral suspension was prescribed.

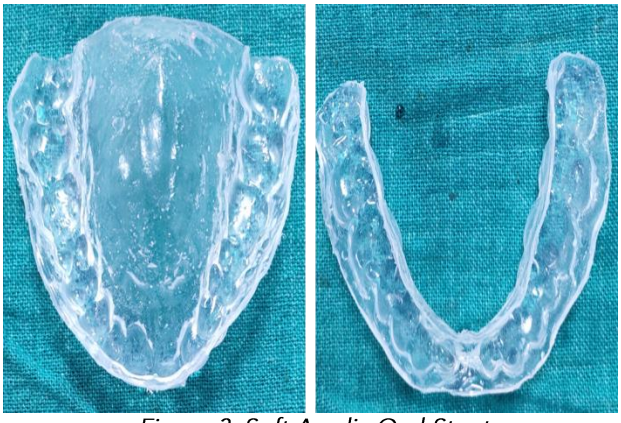

Figure 3: Soft Acrylic Oral Stent

Outcome and follow-up

Follow-up was scheduled weekly for 6 months. After 7 days, on the first follow up, 50 percent reduction of lesion and symptoms were noted, dose of prednisolone was reduced to 40 mg/day for the next 7 days. On 2nd follow-up, further reduction in symptoms along with decrease in extent and number of the lesion was noted. Dose of prednisolone was tapered to 20 m g/day for next 7 days. On third follow-up 90 percent reduction of lesions was evident, shown in (Fig. 4). Prednisolone and sucralfate was stopped and patient was advised to continue alternate topical application of clobetasol propionate and tacrolimus for 6 month, no new lesions were noted.

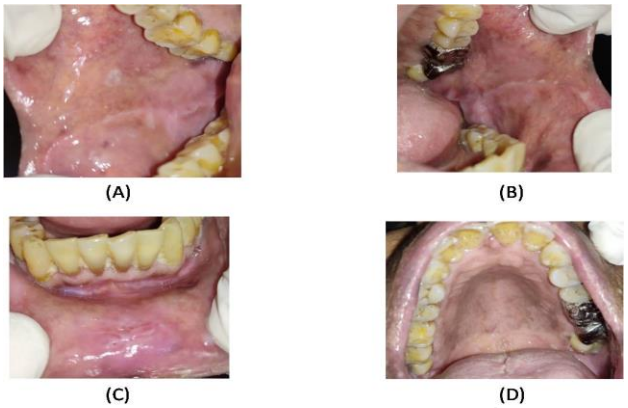

Figure 4: (A) Right buccal mucosa (B) Left Buccal mucosa (C) Lower lip (D) Hard palate ; On 3rd follow-up

Discussion

Pemphigus vulgaris is a mucocutaneous disorder affects skin and oral mucosa. It is characterized by bullae, irregular erosions and ulcers. Mucosa adjacent the lesions show positive Nikolsky's sign. Pemphigus vulgaris pathogenesis is related to autoimmunity. Desmoglein 1 & 3 proteins are present in between keratinocytes; they acts as intercellular bridge and helps in maintaining the structural integrity of the epithelium. Autoantibodies generated against demoglein 1 & 3, results in acantholysis which leads to bullae formation.

Corticosteroid has been used mainly for treating pemphigus, but many cases of recurrence of the lesion has been encountered. Immunosuppressive drug like tacrolimus has been used recently for treating pemphigus vulgaris. Tacrolimus was formerly known as FK 506. It is a macrolide antibiotic produced from fermentation broth of Streptomyces tsukubaensis. The mechanism of action of tacrolimus is given in (Fig.5). Tacrolimus inhibits the production of IL-2 and IFN-γ which inhibits differentiation of $CD4^+$ T helper cells into $CD8^+$ t cells and B-lympholyctes, thus autoantibody production against desmoglein 1 & 3 is restricted.

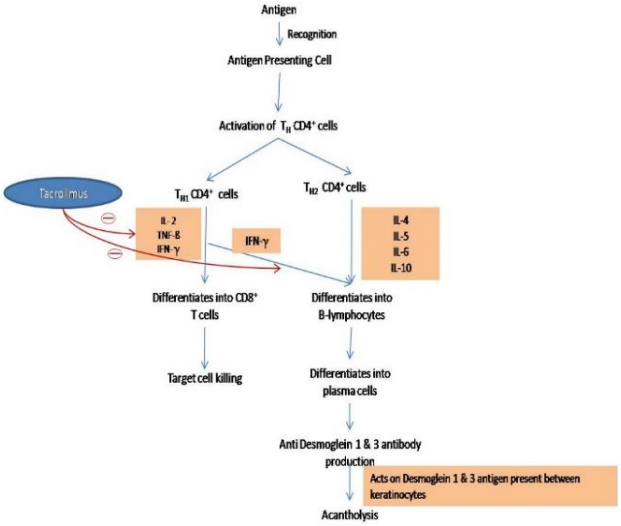

Figure 5: Mechanism of action of Tacrolimus

In the present case report 0.1% tacrolimus ointment was prescribed for topical application. No recurrence of the lesion was noted and patient had no side effects. In a study conducted by Ujiie et al (2019)[5] they prescribed prednisolone only for treating pemphigus vulgaris but recurrence of lesion was noted. In a randomized control trial conducted by Dastgheib et al[6], pemphigus vulgaris was treated successfully by tacrolimus. Assessment of levels of serum desmoglein 1 & 3 after topical tacrolinus was done by Saad et al[7] which showed reduced autoantibody levels in serum. Tacrolimus inhibits phosphatase activity of calcineurin that prevents the gene transcription of proinflammatory cytokines like IL-2, IL- 3, IL-5 , IFN- γ that inhibits proliferation of B lymphocytes. This results in inhibition of antigen specific IgG antibodies and also suppress antigen

presentation[8]. Use of only corticosteroids can cause recalcitrant pemphigus, if it is used along with immunosuppressive drug can show lesser recurrence of the lesion. In a comparartive study conducted by Hidemi et a[9] , they compared the efficacy of tacrolimus ointment with topical corticosteroid for treating atopic dermatitis; topical tacrolimus showed better efficacy than corticosteroid.

Conclusion

Topical tacrolimus application with regular follow-up can be prescribed as an adjuvant therapy along with systemic and topical corticosteroid for managing cases of pemphigus vulgaris.

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