

Rare phenomena of tacrolimus-induced gingival hyperplasia

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Abstract

In the modern world, men and women are very much concerned about their esthetic appearance. The gingival perspective of esthetics is more often concerned with the soft tissue envelope surrounding the teeth. Gingival enlargement/overgrowth is numerous in nature and often poses a clinical challenge by altering the function, resulting in poor oral health of an individual. Tacrolimus, an immunosuppressive drug, has been broadly used for organ-transplant rejection. It results in much less severe hypertension, hypertrichosis and gingival overgrowth compared to cyclosporine and calcium channel blocker-induced gingival enlargements. However, there is scanty literature available regarding the tacrolimus-induced gingival enlargements. Therefore, the present case report with a 6-month follow-up period describes the execution of the proper treatment plan and surgical protocol for the management of a severe case of generalized gingival enlargement attributed to tacrolimus-induced therapy following renal transplant.

Keywords: Cyclosporine, drug-induced gingival overgrowth, immunosuppressants, kidney transplantation, tacrolimus

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INTRODUCTION

The gingival enlargements often results in esthetic and cosmetic problems. The first drug-influenced gingival enlargement reported was produced by Dilantin.^[1] The incidence of gingival enlargement ranges from 3% to 84.5%.^[2,3] Cyclosporine A-induced gingival enlargement is well documented in the literature, with a prevalence of 25%–81%.^[4] Another immunosuppressive drug – tacrolimus is used as an alternate for organ transplantation, which also was reported to reduce the prevalence of gingival enlargement.^[5,6] The present case report with a 6-month follow-up period describes the management of a severe case of generalized gingival enlargement (tacrolimus).

CASE REPORT

A 21-year-old male patient reported to the department of periodontics with a complaint of bad breath and swelling of the gums for the past 2 weeks of his visit. The patient was apparently normal before 2 weeks after which he noticed spontaneous bleeding from gums while brushing. His medical history revealed that the patient had undergone a renal transplant 1 year ago and was under tacrolimus medication since then. The patient had no deleterious habits and his vitals were normal.

On extraoral examination, there were no gross facial asymmetry and no palpable lymph nodes seen. The intraoral examination revealed the presence of generalized,

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soft, edematous, fibrotic enlargement of the gingiva, involving the marginal, attached and the interdental papilla. The patient demonstrated a poor oral hygiene. Profuse bleeding on probing with a pocket depth varying between 6 and 8 mm throughout the dentition was observed. The hard tissue examination revealed congenitally missing – 12; nonvital – 11; Ellis Class II# in relation to 21. Based on the clinical parameters, it was diagnosed as a case of generalized grade III gingival enlargement [Figure 1a-c].

The treatment was planned accordingly and was initiated with a Phase I nonsurgical therapy, which included supra- and sub-gingival scaling and root planing and prescribed with 0.2% chlorhexidine mouthwash twice daily for 2 weeks. This was followed by the re-evaluation of Phase I therapy by the end of 2 weeks' interval.

Surgical excision of the lesion has been planned. The patient was explained about the surgical procedure, and written informed consent form was obtained. With the administration of 2% lignocaine (adrenaline 1:80,000 dilution), an external bevel incision has been given till the crest of the bone with no. 15 blade [Figure 2a]. A tissue obtained from the region of 43 and 44 was stored in formalin and sent for histopathological examination [Figure 2b].

Histopathological examination

The tissue specimen measuring about 0.6 cm × 0.7 cm × 0.3 cm was taken from the region of 43 and 44 and sent for biopsy. The histopathological examination with hematoxylin and eosin stain revealed the presence of stratified squamous parakeratinized epithelium of varying thickness showing hyperplasia in many areas. The underlying connective tissue was fibrous, and numerous areas of hyalinization were seen [Figure 3a]. The histopathological image [Figure 3b] shows the dispersion of chronic inflammatory infiltrates predominantly lymphocytes along with blood vessels and red blood cells in the connective tissue. With the above mentioned histopathological findings, it is suggestive of inflammatory fibrous hyperplasia.

The full-mouth gingivectomy was performed using an external bevel incision [Figure 4a-c]. Adequate amount of hemostasis was achieved, and a periodontal dressing (Coe-Pak) was given [Figure 4d]. Amoxicillin 500 mg – 15 tablets for 5 days and analgesic (tramadol and acetaminophen) – 6 tablets for 3 days were prescribed in reference with the physician's consent. Postoperative instructions were given. The patient was recalled after a period of 2 weeks and assessed. The patient was evaluated at the end of 3 months [Figure 5] and at 6 months [Figure 6]. By the end of 6 months, there was



Figure 1: (a) Clinical image showing a baseline photograph. (b) Baseline clinical photograph – right side. (c) Baseline clinical photograph – left side

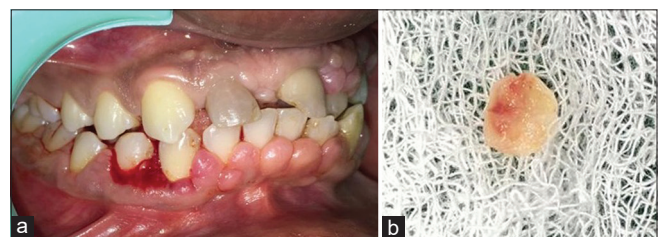


Figure 2: (a) Clinical image showing a gingival tissue harvested from 43, 44 region. (b) Harvested gingival tissue sent for histopathological analysis

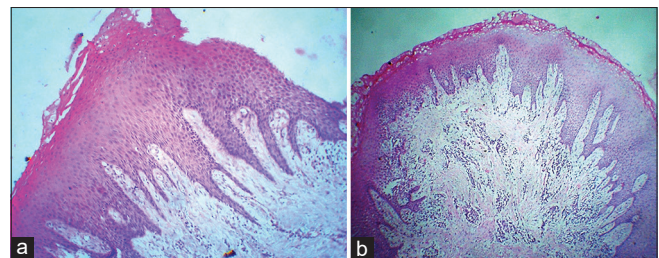


Figure 3: (a) Histopathological image (H&E stain, ×100) (×10). It clearly depicts the presence of stratified squamous parakeratinized epithelium of varying thickness showing hyperplasia. The connective tissue is fibrous and numerous areas of hyalinization are seen. (b) Histopathological image showing the dispersion of chronic inflammatory infiltrate predominantly lymphocytes throughout the connective tissue with blood vessels and red blood cells

complete resolution of the inflammation and reduction in pocket probing depth, and the patient was more satisfied by the outcome.

DISCUSSION

Drug-induced gingival hyperplasia results as a consequence of administration of antiepileptics, immunosuppressants and calcium channel blockers therapy. Greenberg *et al.*^[7] conducted a study of 115 patients who underwent kidney transplants and found a gingival overgrowth rate of 53% among those treated with cyclosporine. However,



Figure 4: (a) Clinical image showing the gingivectomy procedure in relation to anterior teeth. (b) Clinical image showing the gingivectomy procedure in relation to posterior teeth (3rd quadrant). (c) Clinical image showing the gingivectomy procedure in relation to posterior teeth (2nd quadrant). (d) Periodontal dressing (COE-PAK)



Figure 5: Postoperative clinical photograph – 3 months' follow-up



Figure 6: Postoperative clinical photograph – 6 months' follow-up

gingival enlargements were found to be greater in those who were medicated with both cyclosporine and calcium channel blockers. To overcome all these drawbacks, another immunosuppressive drug, tacrolimus which is found to be an alternative drug to cyclosporine, has been used extensively to prevent organ-transplant rejections. Hernández *et al.*^[6] in their case report found that the gingival enlargements almost disappeared by the substitution of cyclosporine with that of the tacrolimus. Even though tacrolimus is found to be nephrotoxic, it resulted in much less severe hypertension, hypertrichosis

and gingival overgrowth. The exact mechanism of this gingival hyperplasia is not known. It was hypothesized that the long-term use of the drug may have a direct or indirect impact on gingival fibroblasts and collagen metabolism. Treatment usually includes surgical therapy either with gingivectomy or the flap technique. However, Alzahrani and Awad^[8] in their case report found that tacrolimus-induced therapy resulted in gingival overgrowths in some patients. The present case report also coincides with those findings wherein the patient was under tacrolimus medication as an immunosuppressant to prevent organ-transplant rejection. Some authors claim that inflammation is a prerequisite for gingival enlargement, which could be prevented by mechanical and chemical plaque control. The recurrence of these conditions might result with poor oral hygiene, and hence, patient motivation and reinforcement of oral hygiene measures are to be taken care of.

CONCLUSION

Tacrolimus, an immunosuppressive drug, has been extensively used for organ-transplant rejection. In the present case report, tacrolimus-induced therapy resulted in gingival overgrowth; however, its exact mechanism is not known. It would be admissible if newer molecular and diagnostic approaches come into existence to identify and explore the possible risk factors associated with prevalence and severity of the disease. More number of cases series and case reports are needed to be documented to support this evidence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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