

Tacrolimus-Induced Gingival Enlargement: A Case Report

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Abstract: Gingival enlargement poses functional as well as cosmetic problems. It affects the quality of life by interfering with mastication, speech, occlusion and maintaining optimal oral hygiene. Gingival enlargement induced by cyclosporine A has been well documented in the literature. Only few studies, however, have associated the occurrence of such condition with the use of tacrolimus. A case of 48 years old female patient presented with a generalized gingival enlargement is reported. A medical history revealed a hepatic transplantation and a current immunosuppressive therapy based on tacrolimus. In this case report, surgical excision of the enlarged gingival tissues was presented. The findings of the present case suggest that tacrolimus immunosuppressive therapy may induce gingival enlargement in some patients. Hence, obtaining a thorough medical history is critical to reach a definite diagnosis.

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1. Introduction

Gingival enlargement poses functional as well as cosmetic problems. The enlargement can be localized or generalized, mild or severe. It usually starts at the interdental papillae that increases in size and appears to coalesce with the adjacent papilla resulting in a lobulated appearance.⁽¹⁾ It is more commonly seen on the anterior segments of the oral cavity.⁽¹⁾ The enlargement may extend to cover the labial surfaces of the teeth causing an esthetically unpleasant appearance.

Gingival enlargement can be seen in patients medicated with anticonvulsants, immunosuppressants and calcium channel blockers.⁽²⁾ Several immunosuppressive drugs have been developed to increase the success rate of organ transplantation. Cyclosporine A is an immunosuppressive agent that is administered primarily for the purpose of preventing organ transplant rejection in the human body. Cyclosporine A-induced gingival enlargement, an undesirable side effect, is well documented in the literature, with prevalence ranges from 25% to 81% with or without drug associations.⁽³⁾

Another immunosuppressive agent, tacrolimus, showed a strong potential to substitute the use of cyclosporine A in cases of transplanted organs.^(3,4) It has been suggested that tacrolimus may be even more effective than cyclosporine A in preventing acute and chronic rejection of liver transplants.⁽⁴⁾ It has a variety of major side effects similar to those induced by administering cyclosporine A including nephrotoxicity, neurotoxicity and the induction of diabetic state.

Only few studies associated the occurrence of gingival overgrowth with the use of tacrolimus,⁽⁴⁻⁶⁾

although at less frequency and severity than with cyclosporine A.^(3,4,7-9) In fact, other studies suggested that tacrolimus is not associated with gingival overgrowth.^(7, 10, 11) Some other reports have demonstrated that a switch from regimens based on cyclosporin A to tacrolimus could reduce the prevalence of gingival overgrowth.^(12, 13) Furthermore, there have been reports that conversion from cyclosporin A to tacrolimus could even cause regression of gingival overgrowth⁽¹²⁾ and in some cases complete resolution.⁽¹⁴⁾

The microbiological profile of subjects with gingival enlargement has been poorly investigated. The presence of specific periodontal pathogen seemed to be associated with gingival enlargement.⁽¹⁵⁾ A study showed a higher frequency of *T.forsythia* especially in those medicated with tacrolimus.⁽¹⁵⁾

The objective of this report is to present the clinical findings and the periodontal management of a patient with a generalized gingival enlargement attributed to tacrolimus immunosuppressive therapy.

2. Case report

A 48-year-old African American female patient came to the department of Periodontics at Case School of dental medicine for examination of gingival enlargement (Fig.1). The patient's chief complaint was that she cannot eat properly and the gingiva is not looking good. Medical history showed that the patient had undergone a liver transplant three years ago and she is taking tacrolimus as an immunosuppressant since then. Upon clinical examination, a generalized fibrotic gingival enlargement was observed. The patient demonstrated a fair oral hygiene. Minimum local factors and minimal bleeding on probing with 4

to 6 mm probing depths throughout the entire dentition were observed as well. A periodontal diagnosis of gingival enlargement associated with an

immunosuppressive drug (tacrolimus) was proposed, since it is the only immunosuppressive drug the patient had after the liver transplant.



Figure 1: Pre-operative photographs.

After a consultation with the patient's physician, it was decided to do a gingivectomy. Following administration of local anesthesia, an internal bevel full mouth gingivectomy was performed to the patient except at the anterior upper area where an external bevel was used (Fig.2). Post operative instructions were given too.



Figure 2: A photograph of the surgical procedure.

Three months follow up showed an excellent response to the surgery (Fig.3). Reinforcement of oral hygiene measures was done. The patient was placed on 4- months recall intervals to monitor any changes in her gingival condition.



Figure 3: Three months post-surgical photograph.

4. Discussion

It is usually uncommon to see gingival enlargement in patients taking tacrolimus immunosuppressive drug. This patient was on tacrolimus since she had the liver transplant.

Several risk factors were shown to be associated with the development and severity of gingival enlargement in immunosuppressed subjects. These

risk factors may include demographic variables, pharmacological variables and periodontal variables.⁽¹⁶⁾ The major risk factor for this condition seems to be a concomitant medication with calcium channel blockers.⁽³⁾ The prevalence and the severity of the gingival enlargement increased in those taking calcium antagonists along with tacrolimus.^(4,10) It has been postulated that the use of calcium channel

blockers may have a synergetic effect on gingival tissues when associated with calcineurin inhibitors such as cyclosporine A and tacrolimus. ^(17, 18) Previous medication with cyclosporine A is another significant risk in subjects treated with tacrolimus. ^(4, 5, 15) Also, time since transplant was associated with gingival enlargement. ⁽¹⁹⁾ Moreover, there is a significant correlation between the severity of the enlargement and the level of oral hygiene. ⁽²⁰⁾ A study revealed that gingival inflammation, represented by papillary bleeding index, was a variable associated with tacrolimus induced gingival overgrowth. ⁽¹⁹⁾

Tacrolimus induces increases in fibroblast and collagen tissue, in parallel with increased severity of overgrowth during long-term treatment. The exact mechanism of tacrolimus-induced gingival overgrowth during long periods of treatment is not known. It was speculated that gingival overgrowth could result from a gradual sensibilization of the gingival fibroblasts, as well as of the gingival epithelium. Long term tacrolimus therapy may have a direct or indirect action on gingival fibroblasts as well as on collagen metabolism via cytokines, growth factors and the consequent activity of matrix metalloproteinases (MMPs). ⁽²¹⁾

Treatment usually includes surgical periodontal therapy either gingivectomy or the flap technique. At six months, flap surgery offered no advantage over conventional gingivectomy with respect to the rate of recurrence but those who were treated with laser showed less recurrence. ⁽²²⁾ However, a recurrence of the condition is expected leading to the need of repeated surgical interventions especially in those with poor oral hygiene. The plaque control should be emphasized as a first step in the treatment. It is suggested that good oral hygiene and frequent professional removal of plaque decrease the degree of gingival enlargement and improves overall gingival health. However, patient education about improving plaque control along with the removal of local factors seems insufficient to prevent gingival overgrowth. ⁽²³⁾ Non surgical therapy includes the possibility of discontinuing the drug or substituting the medication with another. These possibilities should be discussed with the patient's physician. In this case report, a full mouth conventional gingivectomy was performed after a consultation with the patient's physician.

A thorough medical history is essential for every patient to achieve an accurate diagnosis and excellent treatment.

Conclusion

Gingival enlargement may be caused by tacrolimus immunosuppressive agent. A thorough medical history is a prerequisite for optimal standard of care.

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